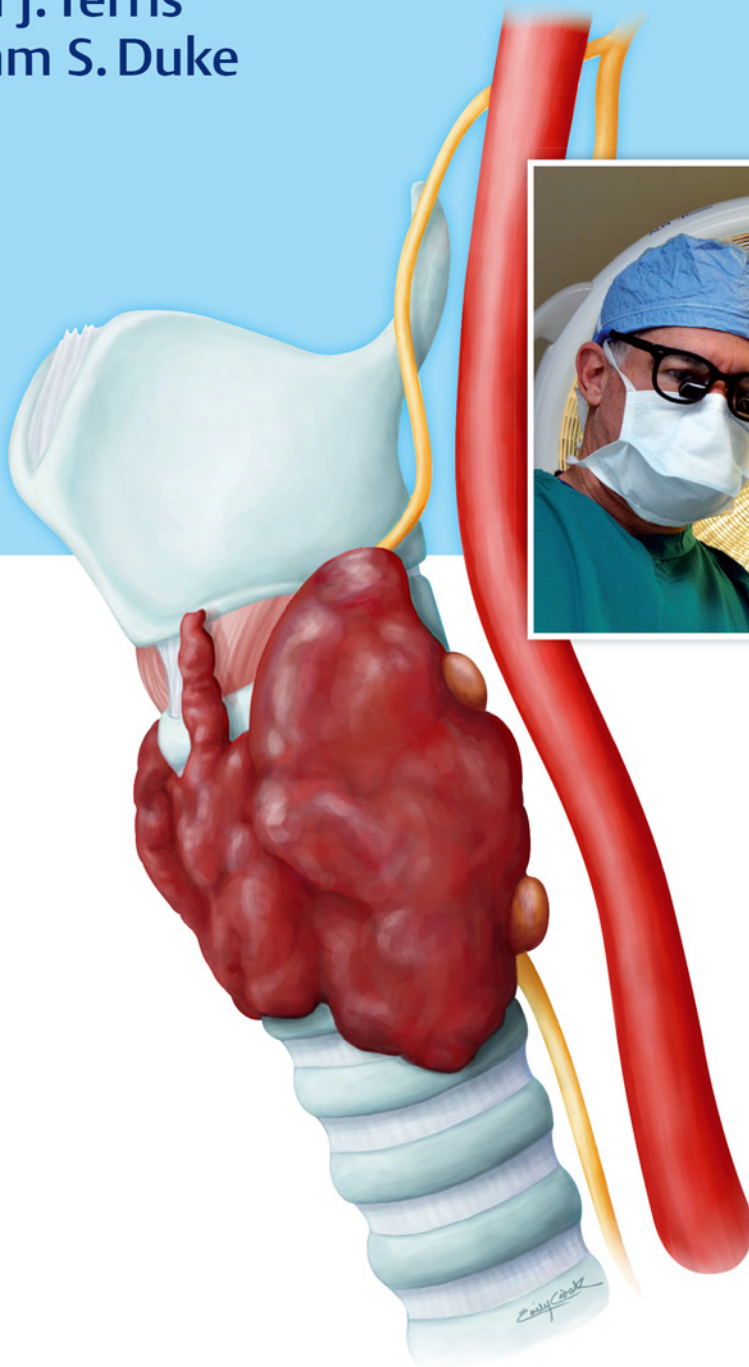


Thyroid and Parathyroid Diseases

Medical and Surgical Management

David J. Terris
William S. Duke

Second Edition



 Thieme

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David J. Terris, MD, FACS

Professor of Otolaryngology–Head and Neck Surgery
Surgical Director, GRU Thyroid and Parathyroid Center
Georgia Regents University
Augusta, Georgia

William S. Duke, MD

Assistant Professor of Otolaryngology–Head and Neck Surgery
Associate Surgical Director, GRU Thyroid and Parathyroid Center
Georgia Regents University
Augusta, Georgia

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Thieme Publishers Delhi
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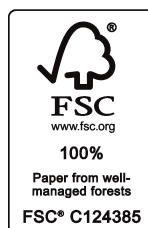
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Dedicated to my family and friends, who have endured countless inconveniences and sacrifices on behalf of my academic and clinical pursuits. To my students, residents, and fellows, who have served as my most important source of inspiration to innovate. And to my patients, who have bestowed upon me the privilege of both caring for them and learning from them.

– *DJT*

For my wife, whose love supports me; for my children, who inspire me; for my mother, who sacrificed so much for me; and for my patients, who continuously teach me.

– *WSD*

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Foreword

I was honored to be asked by Dr. David J. Terris and Dr. William S. Duke to write this Foreword for the second edition of their superb book *Thyroid and Parathyroid Diseases: Medical and Surgical Management*. The first edition had been published in 2008, and much new information is currently available warranting the publication of this new edition. The editors of the book are experienced thyroid and parathyroid surgeons who have recruited a talented group of authors with extensive experience in the medical and surgical management of thyroid and parathyroid disorders. The book includes six chapters concerning the basic science and clinical aspects of thyroid and parathyroid disorders. It is well organized and presents new information regarding the molecular biology, physiology, imaging, indications for operation, and new medical and surgical treatments.

Thyroid nodules are common, and palpable nodules occur in about 4 percent of the population. Thyroid cancer is the most rapidly increasing cancer in the USA and Europe, the sixth most common cancer in women, and the second most common cancer in women under 40 years of age. Because of detection by ultrasound or by other scans done for non-thyroid reasons, there is a marked increase in the identification of thyroid cancer. Controversy continues regarding the extent of thyroidectomy and node resection for low risk papillary thyroid cancers and even for whether thyroid resection is necessary for patients with small (less than 1 cm) tumors.

Thyroid and parathyroid operations have advanced impressively during the past 150 years. Today minimally invasive thyroid and parathyroid operations are being done routinely. The death rate from thyroidectomy has decreased from about 40 percent in 1850 when the French Academy of Medicine condemned thyroid operations to less than one

percent currently. Newly developed molecular studies are helping to determine whether indeterminate thyroid nodules warrant removal. Minimally invasive procedures and remote access surgery are being performed by some expert surgeons in this field. In medical centers in Japan some patients with small papillary thyroid cancers are being followed without removal. In these cases tumor growth or the development of nodal metastases is uncommon. Most patients having thyroid and parathyroid operations are discharged within one day of thyroidectomy or parathyroidectomy. Serious complications following thyroid and parathyroid operations include postoperative bleeding, recurrent laryngeal or external laryngeal nerve injury or permanent hypoparathyroidism. The complication rate by experienced surgeons is less than one percent.

Since the first NIH guidelines meeting in 1990 regarding the management of patients with “asymptomatic” hyperparathyroidism, more evidence supports surgical correction of this disorder even when there are few or no apparent adverse clinical manifestations.

Dr. Terris and Dr. Duke and their colleagues have done a great service to the endocrine surgical community and their patients by editing an outstanding book that is up to date regarding all aspects of thyroid and parathyroid disorders. Although further new information and treatments will certainly occur, their book is an excellent reference and reflects today’s state of the art regarding the management of patients with thyroid and parathyroid disorders.

Orlo H. Clark, MD, FACS
Emeritus Professor of Surgery
University of California San Francisco
San Francisco, California

Preface

After nearly a hundred years of essentially unchanged management strategies, the discipline of head and neck endocrine surgery suddenly experienced revolutionary changes at the turn of the century, prompting the publication of the first edition of *Thyroid and Parathyroid Diseases: Medical and Surgical Management*, which introduced cutting edge advances in thyroid and parathyroid surgery to audiences around the world. Just six years later, many of the novel techniques introduced in the first edition are now routinely incorporated in both tertiary and community-based practices, and the wheels of innovation have continued to turn.

This second edition is therefore a response to these continued innovations, as well as a reflection of our growing understanding of the complex pathophysiology of the thyroid and parathyroid glands. All chapters are either new or completely rewritten, yet we have endeavored to maintain the straightforward and readable style of the initial work.

Several new topics and concepts are introduced, representing important information that is critical to providing state-of-the-art care for patients with thyroid and parathyroid disease. These topics include molecular advances in the management of thyroid disease, emerging nerve monitoring techniques, modern application of rapid intraoperative assessment of parathyroid hormone levels, evolving central neck imaging, and remote access endocrine surgery, and they are explored in detail by international thought leaders from multiple disciplines who complement critical review of the current medical literature with a wealth of personal experience.

It is with great pleasure that we present this second edition of *Thyroid and Parathyroid Diseases*. We hope that this work inspires and guides every provider, from medical student to seasoned endocrine practitioner, in their effort to provide the highest quality care to those in need.

Contributors

Sara Ahmadi, MD, ECNU

Assistant Professor
Department of Medicine
University of Texas Health Science Center
San Antonio, Texas

Victor J. Bernet, MD

Chair, Division of Endocrinology
Mayo Clinic
Assistant Professor
Mayo Clinic College of Medicine
Jacksonville, Florida

Paul W. Biddinger, MD

Professor of Pathology
Chief, Section of Anatomic Pathology
Medical College of Georgia
Georgia Regents University
Augusta, Georgia

Wendy B. Bollag, PhD

Professor of Physiology
Georgia Regents University
Research Career Scientist
Charlie Norwood VA Medical Center
Augusta, Georgia

Steven R. Bomeli, MD

Clinical Instructor of Otolaryngology–Head and Neck
Surgery
GRU Thyroid and Parathyroid Center
Georgia Regents University
Augusta, Georgia

Richard B. Cannon, MD

Department of Otolaryngology–Head and Neck Surgery
University of Utah Health Sciences Center
Salt Lake City, Utah

Katrina Chaung, MD

Ear, Nose and Throat Centers of Texas
Dallas, Texas

Herbert Chen, MD, FACS

Professor of Surgery
Chairman, Department of Surgery
Fay Fletcher Kerner Endowed Chair
University of Alabama-Birmingham (UAB) School of
Medicine
Surgeon-in-Chief
UAB Medicine
Birmingham, Alabama

Gerard M. Doherty, MD

Utley Professor and Chair of Surgery
Professor of Medicine
Boston University
Surgeon-in-Chief, Boston Medical Center
Boston, Massachusetts

William S. Duke, MD

Assistant Professor of Otolaryngology–Head and Neck
Surgery
Associate Surgical Director, GRU Thyroid and Parathyroid
Center
Georgia Regents University
Augusta, Georgia

Ramon E. Figueroa, MD, FACS

Professor of Radiology
Chief of Neuroradiology Section
Department of Radiology and Imaging
Georgia Regents University
Augusta, Georgia

Bruce Curtiss Gilbert, MD

Assistant Professor of Neuroradiology
Georgia Regents University
Augusta, Georgia

Megan R. Haymart, MD

Assistant Professor of Medicine
Division of Metabolism, Endocrinology, and Diabetes and
Hematology/Oncology
University of Michigan
Ann Arbor, Michigan

Susan J. Hsiao, MD, PhD

Assistant Professor of Pathology and Cell Biology at CUMC
Columbia University Medical Center
New York, New York

Jason P. Hunt, MD, FACS

Director, Head and Neck Surgery
Associate Professor of Otolaryngology–Head and Neck
Surgery
University of Utah Health Sciences Center/Huntsman
Cancer Institute
Salt Lake City, Utah

Kenneth H. Hupart, MD, FACP

Chairman of Medicine
Coney Island Hospital
Brooklyn, New York
Clinical Associate Professor of Medicine
Albert Einstein College of Medicine
Bronx, New York
Affiliate Full Clinical Professor
St. John's University College of Pharmacy and Allied Health
Professions
Queens, New York

Carlos M. Isales, MD

Professor of Neuroscience and Regenerative Medicine,
Orthopaedic Surgery, Medicine and Cell Biology and
Anatomy
Vice-Chair, Departments of Neuroscience and Regenerative
Medicine and Orthopaedic Surgery
Georgia Regents University
Augusta, Georgia

Jacqueline Jonklaas, MD, PhD

Associate Professor of Medicine
Director, Clinical Research Unit
Georgetown University
Washington, DC

Dipti Kamani, MD

Director of Research
Division of Thyroid and Parathyroid Surgery
Department of Otolaryngology
Massachusetts Eye & Ear Infirmary
Boston, Massachusetts

Galimat Khaidakova, MD

Department of General Surgery
University of Arkansas for Medical Sciences
Little Rock, Arkansas

Daniel Kwon, MD

Chief Resident, Otolaryngology-Head and Neck Surgery
Loma Linda University School of Medicine
Loma Linda, California

Brian Lang, MBBS(Hons), MS(HK), FRACS, FCSHK, FHKAM

Clinical Associate Professor and Chief, Division of Endocrine
Surgery
Department of Surgery
University of Hong Kong
Queen Mary Hospital
Hong Kong, China

James A. Lee, MD

Associate Professor of Surgery
Columbia University Medical Center
New York, New York

Jennifer Leonard, MD, PhD

Senior Resident
Department of Surgery
Mayo Clinic
Rochester, Minnesota

Chung-Yau Lo, MS, FRCS (Edin.), FACS

Honorary Professor
Department of Surgery
The University of Hong Kong
Queen Mary Hospital
Hong Kong, China

Gabriele Materazzi, MD

Department of Surgery
University of Pisa
Pisa, Italy

Rosemarie Metzger, MD, MPH, FACS

Staff, Section of Endocrine Surgery
Endocrinology and Metabolism Institute
Cleveland Clinic
Cleveland, Ohio
Surgical Director
Thyroid Center
Cleveland Clinic Florida
Weston, Florida

Paolo Miccoli, MD

Department of Surgery
University of Pisa
Pisa, Italy

Radu Mihai, MD, PhD, FRCS

Consultant Endocrine Surgeon
Honorary Senior Clinical Lecturer
Department of Endocrine Surgery
Oxford University Hospitals NHS Trust
Churchill Cancer Centre
Oxford, United Kingdom

Mira Milas, MD, FACS

Professor of Surgery
Director of Endocrine Surgery
Department of Surgery
Oregon Health & Science University
Portland, Oregon

Michele N. Minuto, MD, PhD

Assistant Professor of Surgery
Department of Surgical Sciences
University of Genoa
Genoa, Italy

Rahul Modi, MBBS, MS

Clinical Research Fellow
Division of Thyroid and Parathyroid Surgery
Department of Otolaryngology
Massachusetts Eye & Ear Infirmary
Boston, Massachusetts
Assistant Professor
Department of Otolaryngology–Head and Neck Surgery
Bharati Vidyapeeth Deemed University Medical College
Pune, Maharashtra, India

Jeffrey F. Moley, MD

Professor of Surgery
Chief, Endocrine and Oncologic Surgery
Associate Director, The Alvin J. Siteman Cancer Center
Washington University School of Medicine
St. Louis, Missouri

Luc G.T. Morris, MD, MSc, FACS

Adler Junior Faculty Chair
Head and Neck Service
Department of Surgery
Memorial Sloan Kettering Cancer Center
New York, New York

Yuri E. Nikiforov, MD, PhD

Professor of Pathology
Vice Chair for Molecular Pathology
Director, Division of Molecular & Genomic Pathology
Department of Pathology
University of Pittsburgh
Pittsburgh, Pennsylvania

Salem I. Noureldine, MD

Postdoctoral Fellow
Division of Head and Neck Endocrine Surgery
Department of Otolaryngology–Head and Neck Surgery
Johns Hopkins University School of Medicine
Baltimore, Maryland

Sarah C. Oltmann, MD

Assistant Professor
Department of Surgery
University of Texas Southwestern Medical Center
Dallas, Texas

Latha V. Pasupuleti, MD

Endocrine Surgery Fellow
Clinical Instructor in Surgery
Columbia University Medical Center/NY Presbyterian
Hospital
New York, New York

Gregory W. Randolph, MD, FACS, FACE

Director, General Division and Thyroid and Parathyroid
Surgical Divisions
Massachusetts Eye & Ear Infirmary
Member, Endocrine Surgical Service
Massachusetts General Hospital
Associate Professor of Otolaryngology and Laryngology
Harvard Medical School
Boston, Massachusetts

Sara L. Richer, MD, FACS

Northeast Medical Group
Bridgeport, Connecticut

Anatoly P. Romanchishen, MD, PhD, MScD

Professor of Surgery and Oncology
Chief of Hospital Surgery Department of Saint-Petersburg
State Pediatric Medical University
Chief of Saint-Petersburg Center of Endocrinology and
Oncology
Honored Doctor of Russian Federation
Saint Petersburg, Russia

David S. Rosenthal, MD, FACP, FACE

Zaki Hossein Center for Hypertension, Diabetes, and
Vascular Disease
Division of Endocrinology, Diabetes, and Metabolism
Nassau University Medical Center
East Meadow, New York
Assistant Professor of Clinical Medicine (Endocrinology)
The State University of New York
Stony Brook, New York
Assistant Clinical Professor
St. John's University College of Pharmacy and Allied Health
Professions
Queens, New York

Maisie L. Shindo, MD, FACS

Professor and Director, Head and Neck Endocrine Surgery
Department of Otolaryngology–Head and Neck Surgery
Oregon Health & Science University
Portland, Oregon

Alfred Simental Jr., MD, FACS

Chairman, Otolaryngology–Head Neck Surgery
Loma Linda University School of Medicine
Loma Linda, California

Michael C. Singer, MD, FACS

Director, Division of Thyroid and Parathyroid Surgery
Department of Otolaryngology–Head and Neck Surgery
Henry Ford Health System
Detroit, Michigan

Robert C. Smallridge, MD

Deputy Director, Mayo Clinic Cancer Center
Alfred D. and Audrey M. Petersen Professor of Cancer
Research
Professor of Medicine
Mayo Clinic
Jacksonville, Florida

Russell B. Smith, MD

Professor of Otolaryngology–Head and Neck Surgery
University of Nebraska Medical Center
Omaha, Nebraska

Brendan C. Stack Jr., FACS, FACE

Professor
UAMS Thyroid Center
Department of Otolaryngology–Head and Neck Surgery
University of Arkansas for Medical Sciences
Little Rock, Arkansas

David L. Steward, MD

Professor
Department of Otolaryngology–Head and Neck Surgery
University of Cincinnati College of Medicine
Cincinnati, Ohio

Alice L. Tang, MD

Department of Otolaryngology–Head and Neck Surgery
University of Cincinnati College of Medicine
Cincinnati, Ohio

David J. Terris, MD, FACS

Professor of Otolaryngology–Head and Neck Surgery
Surgical Director, GRU Thyroid and Parathyroid Center
Georgia Regents University
Augusta, Georgia

Geoffrey B. Thompson, MD

Professor of Surgery
Senior Associate Dean of Faculty Affairs
Mayo Medical School
Section Head, Endocrine Surgery
Mayo Clinic
Rochester, Minnesota

Ralph P. Tufano, MD, MBA, FACS

Charles W. Cummings MD Professor
Co-Director, Johns Hopkins Hospital Multidisciplinary
Thyroid Tumor Center
Director, Division of Head and Neck Endocrine Surgery
Department of Otolaryngology–Head and Neck Surgery
The Johns Hopkins University School of Medicine
Baltimore, Maryland

R. Michael Tuttle, MD

Endocrinology Service
Professor of Medicine
Joan and Sanford I. Weill Medical College of Cornell
University
Memorial Sloan Kettering Cancer Center
New York, New York

Brian R. Untch, MD

Gastric and Mixed Tumor Service
Head and Neck Service
Department of Surgery
Memorial Sloan Kettering Cancer Center
New York, New York

Emanuela Varaldo, MD

Assistant Professor of Surgery
University of Genoa
Genoa, Italy

Jaime L. Wiebel, MD

Fellow in Metabolism, Endocrinology, and Diabetes
University of Michigan
Ann Arbor, Michigan

Jennifer Yu, MD

Department of Surgery
Barnes-Jewish Hospital
Washington University School of Medicine
St. Louis, Missouri

Part 1

Anatomy, Physiology, and Pathology of the Thyroid Compartment

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1 The History and Evolution of Techniques for Thyroid Surgery

Sara L. Richer, Dipti Kamani, Radu Mihai, Anatoly P. Romanchisen, and Gregory W. Randolph

1.1 Introduction

Thyroidectomy has evolved from a barbaric, high-mortality procedure to an elegant operation, the epitome of the surgeon's art. It was primarily the pioneering work of Kocher, rewarded with the 1908 Nobel Prize, that catalyzed this evolution. This chapter reviews the evolution of thyroidectomy, from the bloody goiter resection of the early centuries to the innovative, patient-centered, refined thyroidectomy of today.

1.2 The Normal and Enlarged Thyroid: Initial Misunderstandings

The initial interest in the thyroid gland was fostered by the large glands endemic in the first and second centuries. Goiters (Latin *guttur* = throat) were recognized in China as early as 2700 BC and then again by the Romans in the Alps in the first 3 centuries AD. The normal thyroid gland was not recognized until the Renaissance. Around 1500 Leonardo da Vinci drew the thyroid as a globular, bilobate structure, which he regarded as two glands, filling the empty spaces in the neck. In 1543 Andreas Vesalius of Padua described two "glandulae larynges" which, he thought, lubricated the larynx. Bartholomaeus Eustachius of Rome, who also described the adrenal glands, described a single "glandulam thyroideam" (Latin for "shield-shaped") with an isthmus connecting its lobes, but his work was not published until the 18th century. In 1656 Thomas Wharton of London described and named "glandula thyroideis." The onset of goiter in the young adult at that time led to speculation that goiter formation was associated with sexual maturity. In the late 18th century microscopy revealed colloid-filled vesicles within the gland. Caleb Hillier Parry of Bath, England, who also described exophthalmic goiter, speculated that the thyroid provided a reservoir to prevent engorgement of the brain.^{1,2}

1.3 Setons, Bootlaces, and Prison: Early Days of Thyroid Surgery

Celsus and Galen have been credited with operating on goiters in the first and second centuries, but it was not until AD 500 in Baghdad that Abdul Kasan Kelebis Abis performed the first recorded goiter excision.

Roger Frugardi, in the Italian School of Salerno, provided the first credible description of operation for goiter in approximately 1170. At this time, if a large goiter failed to respond to medication (including iodine-containing marine products), two setons were inserted at right angles, with the help of a hot iron, and manipulated toward the surface twice daily until they had cut through the flesh. Another technique for goiters that projected anteriorly consisted of making a skin incision, grasping the tumor with a hook, then dissecting the skin from the goiter. The exposed pedunculated portion of the goiter would be

ligated en masse with a bootlace and removed. During such procedures the patients were tied down to a table and held firmly. In 1718 German surgeons wrote an account of thyroid surgery that differed little from that of Frugardi's.

In 1646, Wilhelm Fabricius reported the first thyroidectomy using a scalpel. This technical advance was ironically and unfortunately associated with a poor outcome. The patient died and the surgeon was imprisoned. Pierre-Joseph Desault of Paris is the first surgeon to publish an account of a successful removal of a goiter, which he performed in 1791. He used a vertical incision to isolate and ligate the superior and inferior thyroid arteries before cutting them and dissecting the thyroid from the trachea using the scalpel. He packed the wound, which suppurated and healed in a month. Guillaume Dupuytren followed in Desault's footsteps and in 1808 performed the first "total thyroidectomy."

Attempts to suppress the gland by ligation of the superior thyroid artery were first used by William Blizard in 1811. Although relatively simple due to the lateral approach, this operation fell into disuse because of its minimal long-term benefit.

In the mid-19th century, William Halsted of Baltimore, in his monumental *Operative Story of Goitre*, could trace accounts of only 8 thyroid operations in which a scalpel had been used between 1596 and 1800, and only 69 further cases until 1848. In the 1850s, a variety of incisions were performed for thyroidectomy: longitudinal, oblique, Y-shaped. After the skin incision, most surgeons performed blunt dissection, and their control of bleeding was inadequate. Despite significant perioperative blood loss, bloodletting was performed for postoperative complications. Typically the wound was left open, and the dead spaces were packed or left to fill with blood. At this time the mortality after thyroid surgery was as high as 40%. Not surprisingly, the French National Academy of Medicine condemned any operative procedures on the thyroid gland, and Samuel David Gross, a prominent American surgeon, wrote in 1866, "No honest and sensible surgeon would ever engage in it!"

Throughout most of the 19th century the results of thyroid operations were so poor that most surgeons restricted their practice to very simple procedures, which could be grouped in three categories:

1. Noncutting operations: setons and bristles were inserted, and cysts were punctured and injected with iodine or other irritants. Deaths from hemorrhage, inflammation, or air embolus were not uncommon.
2. Enucleation and bootlace ligation of goiters.
3. Cutting operations with removal of thyroid tissue: these typically included ligation of thyroid arteries and division of superficial muscles and fascia.

1.4 The 19th Century Revolution: Kocher's Thyroidectomy

The 19th century marked a revolution in all fields of surgery, triggered by the introduction of general anesthesia and aseptic



Fig. 1.1 Nikolai Pirogoff.



Fig. 1.2 Albert Theodor Billroth. (Used with permission from Randolph GW. *Surgery of the Thyroid and Parathyroid Glands*. New York, NY: Elsevier; 2003)

technique. In 1846, William Morton's demonstration of ether's efficacy at Massachusetts General Hospital marked the beginning of surgical anesthetics. The first recorded thyroid operation with anesthesia was performed in 1847³, when Nikolai Pirogoff, of Saint Petersburg, Russia, employed ether for a thyroid operation on a 17-year-old girl, whose central goiter compressed the trachea (► Fig. 1.1). Despite such progress, many surgeons at this time continued to manage patients without anesthesia.

One of the most distinguished surgeons of the 19th century, Albert Theodor Billroth, was involved in the new era of thyroid surgery (► Fig. 1.2). In the early 1860s, while holding the chair of surgery in Zurich, he performed 20 thyroidectomies. Billroth, described by William Halstead as a rapid thyroid operator, courageously reported his initial results, documenting a 40% mortality rate due to intraoperative hemorrhage and postoperative sepsis. After abandoning thyroid surgery for more than a decade, he was again attracted to this field while working in Vienna. By then antisepsis had become more established, and he achieved an impressive mortality rate of only 8% for thyroidectomy. Billroth's technique at that time involved division of the sternocleidomastoid muscle, incision and drainage of any thyroid cysts, arterial ligation, and the use of aneurysmal needles for controlling hemorrhage.

Despite Billroth's pioneering work, Theodor Kocher's name dominates the history of thyroid surgery (► Fig. 1.3). Kocher's 1872 appointment as chair of surgery in Bern, Switzerland, marks the beginning of an illustrious career, during which

he performed more than 5,000 thyroidectomies. Kocher represented a new style of thyroid surgeon. With meticulous attention to the details of surgical technique, hemostasis, and antisepsis, he reported a reduction in mortality from more than 12% in the 1870s to 0.2% in 1898.

Kocher's important contributions to thyroid surgery include the concept of total thyroidectomy, capsular dissection, and the demonstrated benefit of being a high-volume surgeon. All of these concepts remain important in the modern era. Subtotal thyroidectomy was the mainstay operation prior to Kocher's realization that this subtotal operation led to goiter recurrence. His capsular dissection, with its emphasis on precise dissection and meticulous hemostasis, was a grand change from the earlier bloody, barbaric surgery. With experience and attention to detail, he was able to spare the recurrent laryngeal nerve and parathyroid glands, despite the unknown function of these structures at the time.^{4,5}

Kocher's technique involved a collar incision, which bears his name today. He also contributed to the understanding of thyroid physiology. His observations of "cachexia strumipriva," the consequences of total removal of the thyroid gland, contributed to the recognition that the thyroid is essential for normal growth, development, and metabolism. In 1908, Dr. Kocher was awarded the Nobel Prize for medicine for his work on the physiology, pathology, and surgery of the thyroid gland.

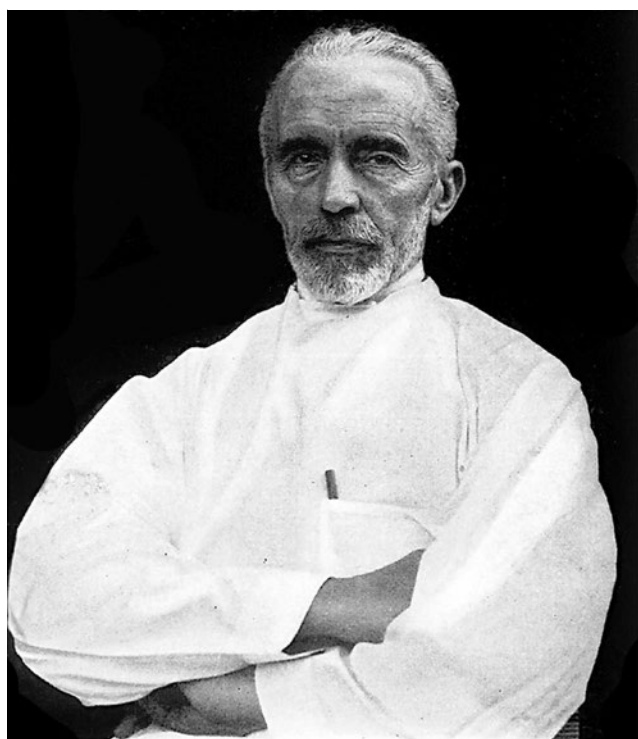


Fig. 1.3 Theodor Kocher. (Used with permission from Randolph GW. *Surgery of the Thyroid and Parathyroid Glands*. New York, NY: Elsevier; 2003)

1.5 The 20th Century: Maturity of Thyroid Surgery

In the late 1890s, European advances in thyroid surgery were adopted in the United States by William Halsted of Baltimore, the Mayo brothers of Rochester, George Crile of Cleveland, and Frank Lahey of Boston. The well-known medical clinics that bear their names were initially financially fueled by high-volume thyroid surgery, made safe and practical through the techniques of Kocher.

At the turn of the 20th century, Thomas Peel Dunhill of Melbourne began work on the treatment of thyrotoxicosis. He introduced the technique of total lobectomy with contralateral subtotal thyroidectomy, subsequently referred to as the Dunhill procedure. He advocated pericapsular dissection performed in a staged manner under local anesthesia, and later under light general anesthesia. He achieved a mortality of only 3% while operating on severely thyrotoxic patients. In London, the same operation at this time was associated with 30% mortality. Interestingly, at the time of Dunhill's initial presentation of results in these patients to the Royal Society of Medicine in London, the society's chairman was James Berry, who described the eponymous ligament that overlies the recurrent laryngeal nerve close to its entry point into the larynx. After the First World War, Dunhill moved to London. In 1919, the *British Journal of Surgery* published his seminal article providing a detailed surgical technique for thyroidectomy, which remains true to form today.⁶ In that same year, Sistrunk described his radical operation for thyroglossal tract lesions, including the resection of the middle third of the hyoid bone.

1.6 Refinement of Thyroidectomy in the 21st Century

Fortunately, issues of postoperative mortality are no longer central to thyroidectomy. The technically challenging issues in thyroid surgery are dominated by postoperative hypocalcemia and voice changes. The cosmetic outcome has also become of increasing importance for a public with high expectations for aesthetic, no-risk surgery. Advanced energy devices and intraoperative nerve monitoring have replaced the setons of old. The trend toward minimally invasive surgical approaches and patient selection for thyroid cancer operations are now the topics of debate.

1.7 Outcomes

Postoperative hypocalcemia and tetany were recognized as early as the mid-19th century, and the careful capsular dissection introduced by Kocher has helped to reduce its incidence. Data have shown that surgeons performing more than 100 thyroid surgeries yearly have superior outcomes.⁷ In today's literature, permanent hypoparathyroidism occurs in less than 2% of patients operated on by high-volume surgeons.

Identification of the recurrent laryngeal nerve (RLN) during thyroidectomy has been advocated for more than 2 decades, finally putting to rest Crile's doctrine of vulnerability, which held that a dissected nerve was an injured nerve. The RLN must be identified and traced up to the entry point in the larynx for one to ascertain that the nerve has not been damaged during the procedure. Intraoperative neural monitoring can provide additional intraoperative functional information and has application in neural identification, aids in neural dissection, and provides prognostic information regarding postoperative function.⁸ An injury rate of 1 to 5% is generally quoted in expert series, although this likely underestimates the rates of paralysis occurring when quality registers report on all surgeons' results.

1.8 Modern Day Technology

The growing understanding of the thyroid gland, surrounding structures, and postoperative management pushed the envelope in regard to new surgical techniques. After the advent of laparoscopic abdominal surgery the public desired minimally invasive techniques with the thyroid as well. Energy devices, such as the Harmonic Scalpel (Ethicon EndoSurgery) or Ligasure systems (Covidien), are linked with newer, minimal-access approaches. Vessel control can be achieved with these devices, along with shorter operative time, decreased mean intraoperative blood loss, and less postoperative pain.^{9,10} To improve nerve outcomes, surgeons have employed magnifying lenses, and even a surgical microscope, to facilitate accurate dissection in the vicinity of the RLN, with the proper intent to decrease transient nerve palsies.¹¹ The endoscope provides another tool for magnification. Terris et al were able to demonstrate a very low rate of nerve injury with the endoscope, likely because of the magnified visualization.¹²

The intraoperative nerve monitor has been used for the past 2 decades in thyroid and parathyroid surgery and is increasingly employed by surgeons today. Recently, continuous vagal

monitoring has been shown to be safe and to prevent RLN paralysis.^{13,14} As the surgeon recognizes electromyographic changes from the continuous monitoring, the surgical maneuver can be aborted prior to nerve damage. Preservation of the external branch of the superior laryngeal nerve (EBSLN) has recently gained attention because injury may be a commonly underestimated morbidity following thyroid surgery. The traditional nerve monitor can be safely used for EBSLN mapping, improving the rate of identification well beyond visualization alone.^{15,16} Improved surgeon awareness and a new endotracheal tube may help facilitate preservation and decrease postoperative concerns about vocal performance.¹⁷

1.8.1 What Is Minimally Invasive Thyroid Surgery?

Decades after the advent of laparoscopic abdominal surgery, several enthusiasts have explored the possibility of using similar equipment and techniques during thyroid surgery. Minimally invasive thyroid surgery seeks to provide a safe and effective operation through a smaller incision. With avoidance of drain use and less postoperative pain, even outpatient surgery has been performed. Two paths emerged from the advent of minimally invasive thyroidectomy. One is a truly minimally invasive approach through video-assisted or nonendoscopic techniques, and another involves remote access techniques, which are not truly minimally invasive because they involve extensive dissection, but they avoid the cervical scar.

Minimally Invasive Approaches

Minimally invasive open surgery involves a central cervical incision smaller than Kocher's 6 cm incision but using techniques similar to those of the conventional operation, aided by energy devices for meticulous hemostasis. Placement of incisions in natural skin creases can improve the cosmetic result.

In Sidney, Delbridge described the technique for minimal-access thyroidectomy (MAT) as an extension of the approach used for minimally invasive parathyroidectomy. In short, a 2.5 cm lateral transverse incision is made directly over the nodule or over the middle of the thyroid lobe, straddling the medial margin of the sternocleidomastoid (SCM) muscle. The SCM is then retracted laterally, and the space posterior to the strap muscles is opened to expose the thyroid gland. This was presented as a safe and feasible surgical procedure that provides an alternative to open thyroid surgery in appropriately selected cases.

Video-Assisted Thyroidectomy

In 1998, in Pisa, Miccoli introduced the minimally invasive video-assisted thyroidectomy (MIVAT or VAT). This gasless procedure is carried out through a 15 mm central incision above the sternal notch. A 5 mm 30° endoscope is inserted through the skin incision. Dissection is performed under endoscopic vision using conventional and endoscopic instruments and techniques. Nodules smaller than 35 mm and early-stage papillary carcinoma are amenable to this operative technique.¹⁸ Reports of MIVAT revealed that patients' satisfaction with their scars

was higher, postoperative pain in the first and second days after surgery was lower, the postoperative hospital stay was shorter, and there were no significant differences in complications compared with those undergoing conventional thyroidectomy. This technique has been shown to be as effective as conventional thyroid surgery at removing thyroid cancer.¹⁹

Endoscopic Thyroid Surgery

Purely endoscopic neck surgery was first reported by Gagner for parathyroid surgery.²⁰ His central endoscopic approach used a 5 mm incision made slightly anterior to the sternal notch with CO₂ insufflation at 8 to 12 mm Hg pressure and additional trocars at the midline and SCM border. Significant improvements in endoscopic instrumentation (e.g., miniscopes, miniature instruments) have encouraged others to adopt these endoscopic techniques for thyroidectomy. In Marseille, an endoscopic thyroidectomy based on a lateral approach was used, similar to that used for minimally invasive parathyroidectomy.²¹ A plane was developed between the carotid sheath laterally and the strap muscles medially, allowing exposure for identification of the RLN and parathyroid glands.²¹

The indications for endoscopic thyroidectomy have expanded as reports have been published on its use for bilateral neck exploration, lymph node dissection in the central and lateral compartments, and thyroid nodules greater than 3 cm.^{22,23,24,25,26} The applications for endoscopic surgery will likely continue to increase as more surgeons adopt the technique in high-volume centers.

Extracervical Thyroidectomy

The desire to avoid neck scars after thyroidectomy has encouraged some authors to use incisions placed outside the cervical region. These various approaches include chest/breast, axillary, combined axillary and areolar, postauricular, or oral cavity access points.^{27,28,29} These approaches are not minimally invasive; they all require a great amount of dissection, but they do avoid a neck scar. Initially favored in Asian societies because of a cultural aversion to neck scars and the predominance of hypertrophic scarring, North American centers have attempted these procedures to appeal to patients now seeking "scarless" surgery. These remote access approaches were initially endoscopically assisted, but they have now incorporated robotic techniques.

In 2000, Ohgami and colleagues described a remote-access hemithyroidectomy using CO₂ insufflation and endoscopes through incisions on the parasternal border of one breast and along the superior margins of both areolas.³⁰ The breast was subject to hypertrophic scarring, and other access points were sought. Ikeda and colleagues described the endoscopic axillary approach in 2001.³¹ This approach takes significantly longer than conventional thyroidectomy, and the narrow operative field and potential morbidity related to CO₂ insufflation are some of the limitations.³⁰

The use of the da Vinci surgical robot (Intuitive Surgical, Inc.) was first described in 2009 in South Korea by Kang³² and colleagues.³³ This uses the axillary approach in a manner similar to the endoscopic transaxillary approach and was initially embraced with enthusiasm in North America. However,

because of economic considerations and complications, such as excessive blood loss, brachial plexus injury, and esophageal perforations, this approach was largely abandoned in the United States.

A relatively new addition to thyroid surgery approaches is the robotic facelift thyroidectomy. This avoids the cervical scar and was found to be safe and feasible in experienced hands. Patient selection is important because the thyroid disease should be unilateral, without thyroiditis or concerning malignancy.³⁴ Although a longer operation than conventional thyroidectomy, the cosmetic outcome has been favorable.

Patient Selection

There is debate about which patients should undergo surgical intervention. Previously, thyroid lobectomy was undertaken for indeterminate nodules on fine-needle aspiration. New genetic expression classification has decreased the number of patients undergoing lobectomy for diagnostic purposes and will likely continue to do so.³⁵

As the incidence of small papillary carcinomas has increased worldwide and the number of thyroidectomies has increased, patient selection has now begun with some patients opting for observation rather than surgical intervention.³⁶ Certainly the observation of these indeterminate and malignant nodules will continue to be the focus of further study.

Many patients readily prefer and seek out “minimally invasive” or “small incision” surgery because they intrinsically assume that such options, if being offered, are as safe as or safer than the previous standard approaches and are of proven benefit. The safety profiles of these minimally invasive techniques must continue to be scrutinized as the modern thyroid surgeon pioneers new techniques. The words of Theodor Billroth remain as valid as ever: “Only the man who is familiar with the art and science of the past is competent to aid in its progress in the future.”³⁷

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2 Developmental and Surgical Anatomy of the Thyroid Compartment

Alice L. Tang and David L. Steward

2.1 Introduction

Central neck surgery can be complicated by congenital anomalies, neoplastic conditions, and ectopia. A fundamental understanding of the embryological development of structures within the thyroid compartment is paramount for performing safe central neck surgery, and surgeons who operate in this region should be facile in exercising applied embryology to the benefit of their patients.

2.2 Embryology of the Thyroid Gland

The thyroid gland, which is the first endocrine organ in the body to form, begins its development during the third week of gestation. It results from the fusion of two structures: the medial and lateral thyroid anlagen. The medial thyroid anlage is

derived from the primitive pharynx. The lateral thyroid anlagen arise from neural crest cells that form embryonic transient structures called the ultimobranchial bodies. Parafollicular cells (C cells) also originate from the paired ultimobranchial bodies.^{1,2,3,4}

The medial thyroid anlage begins its formation from a diverticulum (either single or paired), which forms immediately caudal to the primordium of the tongue (tuberculum impar). Development of this structure occurs between the second and third pharyngeal arch at the foramen cecum and originates from an invagination of epithelial cells from the floor of the primitive pharynx (► Fig. 2.1). After this initial invagination, the medial thyroid anlage takes form and begins its descent by penetrating the underlying mesoderm during the fifth to seventh week of gestation. At about the same time of descent, the hyoid bone, derived from the first pharyngeal pouch, begins to take form from the condensation and chondrification of the mesoderm. Of particular importance is the route of the medial

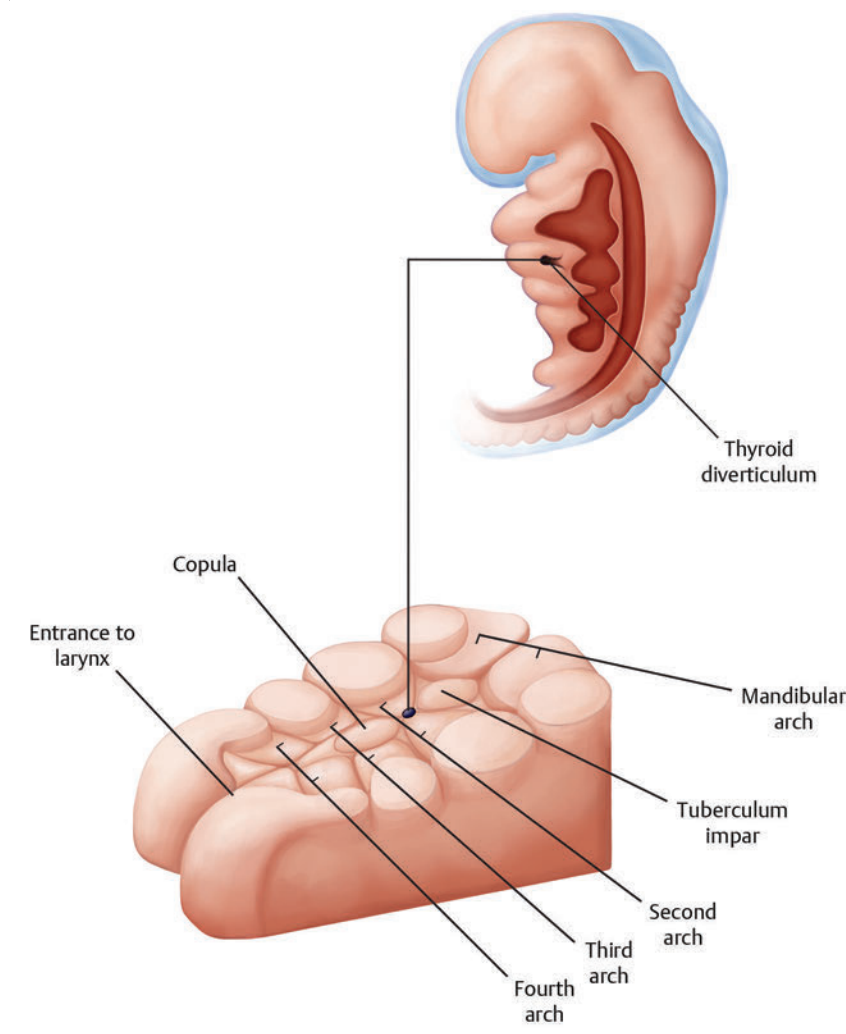


Fig. 2.1 Embryological origin of the thyroid gland, showing the thyroid diverticulum forming caudal to the tuberculum impar.

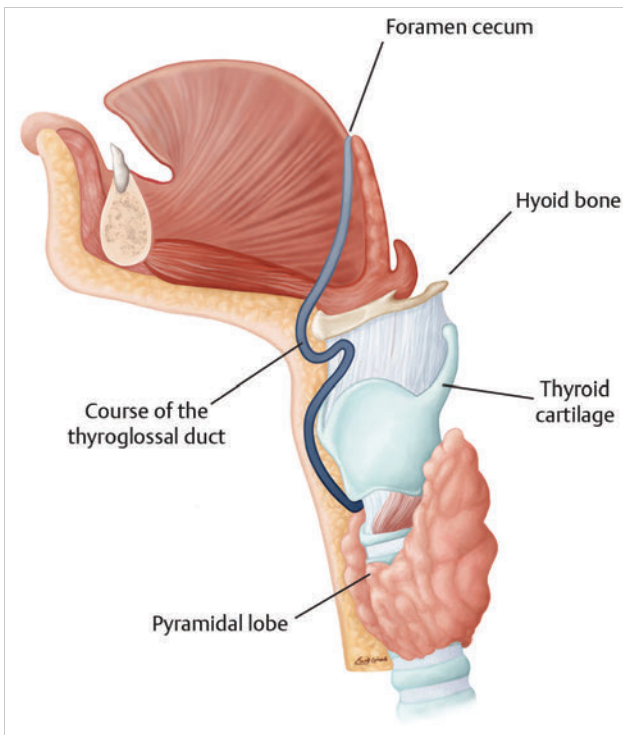


Fig. 2.2 Route of normal thyroid migration from its embryological origin at the foramen cecum to its final position in the anterior neck.

thyroid anlage migration and its relationship to surrounding structures (► Fig. 2.2). The medial thyroid anlage begins posteriorly and most commonly continues anterior to the hyoid and primordial pharyngeal gut. During the migration, the medial thyroid anlage remains attached to the base of the tongue by a continuous lumen, the thyroglossal duct.⁵ As the embryo enlarges and undergoes differentiation, this original diverticulum breaks in two, and the proximal part retracts and disappears. By the seventh week of gestation, the primitive thyroid gland reaches its final destination anterior to the trachea between the second and fifth tracheal ring. The thyroglossal duct loses its lumen by the eighth week as the thyroid reaches its normal position.^{2,3,6}

Although the medial thyroid anlage contributes to the bulk of the thyroid gland, the paired lateral thyroid anlagen (formed from the ultimobranchial bodies) contribute a small but important portion of the final thyroid gland. During the fifth week of development, at the level between the fourth and fifth pharyngeal pouches, cells detach from the pharyngeal wall and fuse with the posterior aspect of the main body of the thyroid as it descends into the neck. These cells originate from neural crest cells and differentiate into the parafollicular cells (C cells), which secrete calcitonin.² Ultimately, the fusion between the medial thyroid anlage and the paired lateral thyroid anlagen produces thickenings of the gland known as the tubercles of Zuckerkandl. The tubercles of Zuckerkandl serve as consistent landmarks for the recurrent laryngeal nerve (RLN), which mostly runs medial and deep to the tubercles on both sides.⁷

Thyroid follicles begin to form at 8 weeks of gestation from epithelial plates. After initial formation, growth continues by budding or division of primary follicles. By the fourth month,

follicles can be seen at various stages of development, and during this time they experience the greatest growth in number. Colloid is visible during the 12th week of gestation. Iodide is incorporated into the follicles to mark the beginning of thyroid hormone synthesis, which is then secreted into the fetal circulatory system.^{3,6}

The normal adult thyroid gland weighs approximately 10 to 20 g and is typically located anterior to the trachea, midway between the thyroid cartilage and the suprasternal notch. A fibrous capsule developed from the deep cervical fascia envelops the gland by dividing into an anterior and a posterior sheath. The thyroid gland is further covered anteriorly by superficial cervical fascia, strap muscles, and the platysma. Laterally, the deep cervical fascia is loosely adherent to the gland. On the posterior portion of the gland, the deep cervical fascia condenses to form a thick suspensory ligament (ligament of Berry), which causes the thyroid to be strongly fixed to the trachea and larynx. In effect, this suspensory ligament facilitates the movement and elevation of the gland as seen during swallowing. The final thyroid gland consists of two lobes, which lie on both sides of the trachea, with a central midline isthmus connecting the lobes. The lobes are typically 4 cm from superior to inferior, 2 cm in width, and 2 to 4 cm in thickness. The isthmus usually measures 1.25 cm. Thyroid disease will often significantly change these dimensions. A pyramidal lobe is present in about 50% of people and is usually connected to the isthmus or one of the lobes.^{4,8}

2.3 Congenital Thyroid Anomalies

Ectopic thyroid tissue is functioning thyroid tissue that exists at any point along the path of migration other than the typical location anterior to the trachea. The majority of aberrant thyroid tissue resides in the midline of the neck along the thyroglossal tract. Lateral neck ectopia is rare and is thought to be derived from abnormal lateral thyroid anlage migration. Ectopic thyroid tissue is reported to occur in 1 of 100,000 to 300,000 people without thyroid disease, and in approximately 1 of 4,000 to 8,000 patients with thyroid disease. Females have a higher predilection for thyroid ectopia than males.^{9,10}

2.3.1 Lingual Thyroid

The lingual thyroid is relatively rare and, because the majority of cases are asymptomatic, the true incidence is not known. Although rare, this entity accounts for 90% of all ectopic thyroid tissue.⁹ Lingual thyroid results when the medial thyroid anlage fails to migrate inferiorly into the neck. In 70% of cases, a lingual thyroid is associated with the absence of the normal cervical thyroid. If both locations have thyroid tissue present, usually the lingual thyroid is the only functional tissue. Most patients present with an asymptomatic mass at the back of the tongue, and the diagnosis is confirmed with a radioisotope scan showing increased uptake in the foramen cecum.^{4,8,9,10} The lingual thyroid is usually associated with hypothyroidism given that functional ectopic thyroid tissue is usually unable to meet the physiological demands of the body. As a result, the lingual thyroid can hypertrophy from thyroid-stimulating hormone stimulation and become symptomatic, provoking dysphagia, dysphonia, dyspnea, or a sensation of choking.⁵ Adults can

experience sleep apnea and respiratory difficulty, and in children the presence of a large base of tongue lingual thyroid can cause upper airway obstruction requiring surgical removal. In general, though, asymptomatic lingual thyroid tissue can be left alone without the need for surgical intervention. The lingual thyroid has a low incidence of malignant conversion, with papillary thyroid carcinoma being the most common to develop.¹¹

2.3.2 Thyroglossal Duct Remnant

The thyroglossal duct usually obliterates by the eighth week of development, but remnants of this attenuated lumen can persist into adulthood.¹² These remnants can present as a cyst or a sinus tract that can develop anywhere along the course of the descent of the thyroid anlage. Anomalies of the thyroglossal duct are the most common congenital neck masses in children.

The most common presenting symptom is a nontender palpable neck mass.¹³ The lesions usually appear in the midline or just off the midline between the hyoid bone and the isthmus of the thyroid and measure approximately 2.5 to 3 cm.¹² A thyroglossal duct cyst may not be apparent until it becomes infected or spontaneously ruptures, usually after an upper respiratory tract infection. There does not appear to be a gender predilection, and most patients will present before age 20.¹² Because the thyroglossal duct cyst is usually firmly fixed to the hyoid bone and tongue musculature, swallowing will classically raise the neck mass in a predictable fashion.

Historically, thyroglossal duct cysts were treated with incision and drainage. Recurrence rates with this method of treatment were >50%.¹³ Currently, the standard treatment for a thyroglossal duct cyst is the Sistrunk procedure, in which the cyst is meticulously dissected out along with the central portion of the hyoid bone, where the cyst is anchored, and a cuff of tissue at the base of the tongue. This extensive dissection reduces the recurrence rate to around 5%.¹³ Postoperative infections are associated with higher recurrence rates.¹³ Thyroid carcinoma can develop within a cyst, especially if the individual has received low-dose irradiation to the head and neck region in the past. Thus all specimens should undergo histological examination.

2.4 Vascular Supply of the Thyroid

2.4.1 Thyroid Gland Vasculature

The thyroid is an extremely vascular gland. Its main arterial blood supply comes from the paired superior and inferior thyroid arteries. The origin of the superior thyroid artery (STA) is variable but most commonly will arise from the external carotid artery.^{4,14} It can also arise from the bifurcation of the common carotid artery and internal carotid artery, although this is seen less frequently.¹⁴ The STA travels along the external surface of the inferior constrictor muscle and enters into the thyroid gland posteromedially near the upper pole of the lobe.^{4,15} The artery may branch prior to entering the thyroid gland. Gupta et al proposed a simple classification of STA branching patterns: type I (two major branches), type II (trifurcation of the artery), and type III (no branching following its origin from the common carotid).¹⁴ If the STA trifurcates, these branches may join with

vessels on the contralateral side through the isthmus and with the inferior thyroid artery (ITA).

The ITA has a variable distribution and is absent on one side (usually the left) in approximately 0.2 to 6% of cases.¹⁶ After branching from the thyrocervical trunk off the subclavian artery, it ascends posterior to the carotid sheath and has a variable relationship with the sympathetic chain. Prior to entering the gland, the ITA divides into an upper and a lower branch.^{15,17} The upper branch goes to the posterior aspect of the gland, and the lower branch to the lower pole of the gland. There can be anastomoses with the STA as well as with the contralateral ITA across the midline.

An aberrant ITA (thyroid ima artery) is an inconsistent vessel arising from the aortic arch or the brachiocephalic, right common carotid, or internal thoracic artery.⁴ When present, it usually arises on the right side, ascending in front of the trachea.

The thyroid gland is drained by large veins that exhibit extensive cross filling from both sides of the thyroid through a valveless venous plexus (► Fig. 2.3).¹⁸

On each side of the gland, three veins arise: the superior, middle, and inferior thyroid veins. Contralateral thyroid veins join through the connective tissue of the lobules of the gland and anastomose behind the capsule. The superior thyroid vein, which drains the upper two-thirds of the ipsilateral thyroid lobe, accompanies its corresponding artery and emerges from the upper pole of the thyroid. It primarily empties into the internal jugular; however, in some cases the superior thyroid

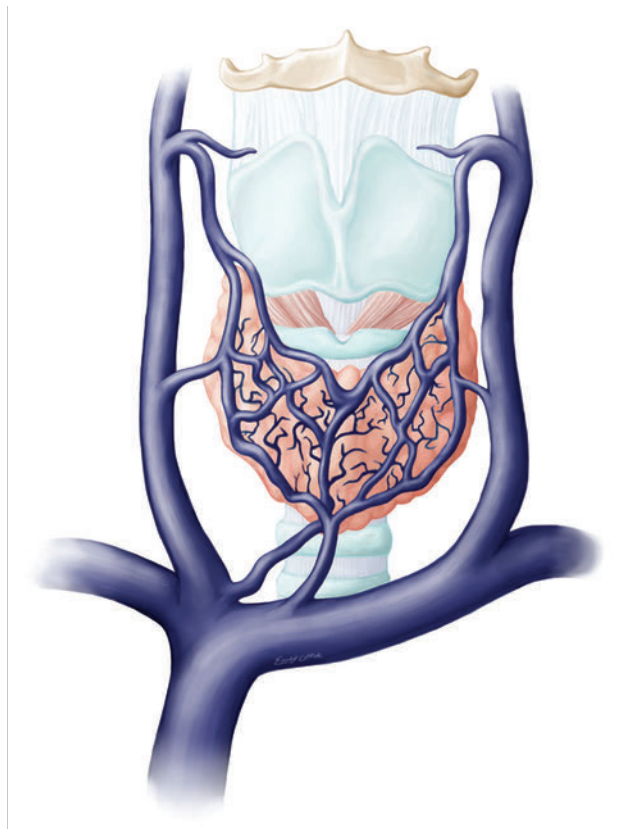


Fig. 2.3 Venous drainage of the thyroid gland. In addition to the superior, middle, and inferior thyroid veins, there is an extensive network of valveless veins within the gland that connect the two lobes.

vein will terminate into the linguofacial trunk and common facial vein.¹⁹

The middle thyroid vein is present in approximately 38% of dissected lobes and in 62% of patients.²⁰ In their prospective study of 394 consecutively dissected thyroid lobes Dionigi et al found that the middle thyroid vein is more likely to be present in patients with hyperthyroidism and large goiters.²⁰ The authors advise that positive identification of the middle thyroid veins in these particular situations can prevent inadvertent injury and excessive bleeding. Like the superior thyroid vein, the middle thyroid vein typically drains the superior two-thirds of the thyroid into the internal jugular vein (a few centimeters below the superior thyroid vein) after crossing the common carotid artery anteriorly.¹⁸ The middle thyroid vein is more commonly found on the right side.²⁰

The paired inferior thyroid veins emerge from the lower portion of the gland and have abundant cross filling with the contralateral vein. Krausen wrote that these veins are the “ultimate guardians of the trachea” because this plexus of veins in the pretracheal fat is frequently the source of bleeding during and after anterior neck surgeries.²¹ There can be a variable number of branches (at least one and up to five) from the inferior thyroid vein, and these branches can terminate into the left brachiocephalic vein, the right brachiocephalic vein, or both vessels.^{19,21} These veins can form a confluence to drain into the thyroid ima vein that ultimately will flow into the innominate vein.²¹

2.4.2 Lymphatics

The efferent lymphatic vessels of the thyroid travel along with the venous drainage of the gland. There are specific drainage patterns for the superior, lateral, and inferior portions of the gland. The lymphatics from the superior portion of the gland and the isthmus drain into the Delphian, or prelaryngeal, lymph nodes and the jugular lymph nodes. The lymphatics from the lateral portion of the gland drain along with the middle thyroid vein through lymph node levels II through IV. The lymphatics draining the inferior portion of the gland follow the inferior thyroid veins and drain to pretracheal, paratracheal (level VI), and lower jugular (level IV) regions as well as the level VII nodes in the anterior mediastinum (► Fig. 2.4).

The thyroid gland also has an intraglandular lymphatic network that connects the two lobes of the gland. This subcapsular network facilitates the spread of tumor within the gland.

2.5 The Recurrent and Superior Laryngeal Nerves

2.5.1 Recurrent Laryngeal Nerve

Identification of the recurrent and superior laryngeal nerves is a cardinal principle during central neck surgery. A complete understanding of these nerves and their relationship to nearby structures is necessary to avoid inadvertent injury that can have temporary or permanent consequences, including dysphonia, dysphagia, and dyspnea.

Originating from the medulla oblongata, the vagus nerve begins its course by exiting the skull through the jugular

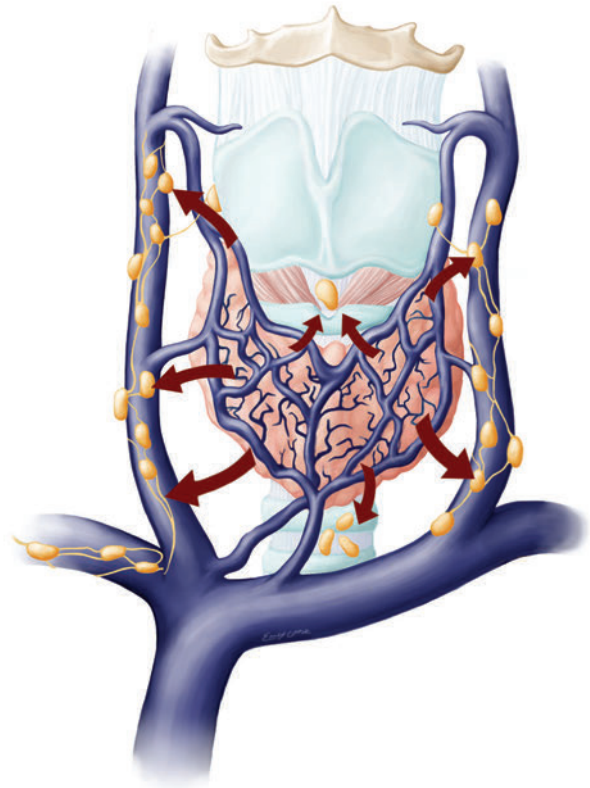


Fig. 2.4 Lymphatic network of the thyroid gland. Lymphatic drainage parallels the venous drainage of the gland.

foramen. As the vagus nerve traverses the neck, the superior laryngeal nerve (SLN) and the RLN branch off to innervate the larynx. The course of the RLN is determined by the descent of the heart and great vessels during embryological development. On the right side, the recurrence of the nerve loops around the fourth arch (right subclavian artery) then ascends the neck to innervate the larynx.⁴ In rare cases, if the right fourth arch is absorbed, the right RLN does not get pulled down into the chest and thus passes directly into the larynx (nonrecurrent laryngeal nerve).²² In normal development, the right RLN exits the vagus at or just superior to the level of the subclavian artery.²³ After its recurrence around the subclavian artery, the right RLN travels cranially toward the tracheoesophageal groove but generally does not reside in the groove until its most distal segment.^{22,23} The left RLN branches from the vagus as it enters the thorax. It then recurs around the sixth aortic arch (ligamentum arteriosum) and travels superiorly toward the tracheoesophageal groove. It travels either on the trachea, in the tracheoesophageal groove, or in the adjacent fat and connective tissue.^{4,23}

The RLN enters the larynx posterior to the cricothyroid joint and provides motor, sensory, and parasympathetic innervation. Motor innervation is provided by the anterior branch of the RLN, which innervates the thyroarytenoid, lateral cricoarytenoid, posterior cricoarytenoid, and transverse arytenoid muscles. The only laryngeal muscle not innervated by the RLN is the cricothyroid muscle. Sensory innervation is provided by the posterior branch of the RLN, which supplies sensation to the vocal cords and to the subglottic region.^{22,24} Branching

patterns prior to entering the larynx can vary.²² Ardito et al found that 27.6% remain unbranched along the RLN entire course, whereas 70.6% bifurcated and a smaller proportion of nerves trifurcated during its ascent.²⁴ Kandil et al prospectively evaluated 137 RLNs intraoperatively and found that, overall, only 34% had extralaryngeal bifurcation with motor fibers exclusively located in the anterior branch and sensory fibers in the posterior branch.²⁵

The RLN exhibits variability in its course, and most anatomists describe these variations relative to three key landmarks: the ITA, the tracheoesophageal groove, and Berry's ligament. The relationship of the RLN to the ITA is often used when trying to identify the nerve, despite the great variability in this relationship. The artery typically arises lateral to the nerve and then courses medial to the gland. In early studies, Hollinshead demonstrated that, on the right side, the RLN passed between the main or minor branches of the ITA 50% of the time and posterior to the artery approximately 25% of the time.²⁶ On the left side, the RLN passed posterior to the ITA 50% of the time and passed anterior to the artery in 10 to 12% of cases.²⁶ Subsequent studies have reported more variability between these two important structures. A study of 21 cadavers by Monfared et al found that, on the right side, the RLN was seen to pass between ITA branches in 50% of cadavers, deep to the ITA in 28% of cases, and anterior to the ITA in 21% of cases.²³ On the left side, it was seen to pass deep to the ITA in 50% of cadavers, in between ITA branches in 28% of cases, and anterior to the ITA in 21% of cases.²³ In an updated intraoperative series by Ardito et al, the authors observed that, in 61%, the right RLN was deep to the ITA, 12% traveled in front of the ITA, and 27% went between branches of the ITA.²⁴ On the left side, 77.4% were deep, 20.5% were between the branches, and 1.9% passed in front of the ITA.²⁴ It is clear from these studies that the relationship between the RLN and ITA is highly inconsistent, and surgeons should be aware that, although the ITA can be used as a landmark, its relationship with the RLN is quite variable.

The RLN's course in relation to the tracheoesophageal groove is more variable on the right side than on the left.²⁴ The RLN also has a relationship with Berry's ligament and passes through it in 25% of cases and deep to it 75% of cases.²⁷ Despite these variations, the most consistent location of the RLN is near its insertion.

The studies of Shindo et al examined how best to locate the RLN surgically.²⁸ Their approach was to locate the RLN distally as it approached the cricothyroid joint, identifying the nerve just below Berry's ligament. The study showed that, during the initial search for the distal segment of the RLN, the dissection of the right RLN can be directed toward a triangle located 15 to 45° from the tracheoesophageal groove where the nerve can be expected to be found 78% of the time.²⁸ On the left side, the nerve was found in the area of a 0 to 30° angle to the tracheoesophageal groove in 77% of cases.²⁸

A nonrecurrent laryngeal nerve can result secondary to a vascular anomaly as mentioned previously. During embryological development, there are multiple vascular consequences that result if a segment of the fourth aortic arch disappears: a left-sided aortic arch with a right subclavian artery, the absence of the innominate artery, and a retroesophageal subclavian artery.^{6,29} As a result, the arterial segment around which the right RLN recurs is absent, leading to branching of the nerve

from the vagus in the cervical region varying from the level of the superior lobe to the thyroid cartilage.^{4,6} This is a rare variation, occurring in approximately 0.63% of patients on the right and 0.04% of patients on the left.²⁹ Diagnosis is made preoperatively, either incidentally on chest X-ray, ultrasound, CT scan, or barium swallow, or by suspicion, with a clinical history of impairment with swallowing (called dysphagia lusoria).

2.5.2 Superior Laryngeal Nerve

After the vagus nerve exits the jugular foramen, one of its first branches is the SLN. The SLN originates from the nodose ganglion and travels inferiorly posterior to the internal carotid artery. About 1.5 cm caudal to the bifurcation of the common carotid artery, the SLN divides into an internal branch (IBSLN) and an external branch (EBSLN).³⁰ The IBSLN enters the larynx by passing through the thyrohyoid membrane and provides sensation to the portion of the larynx above the vocal folds. The EBSLN provides motor innervation to the cricothyroid muscle. The cricothyroid muscle produces a rocking motion at the cricothyroid joint, increasing the tension in the vocal ligaments and raising the vocal pitch. Damage to the EBSLN causes a subtle change in vocal pitch and a decreased vocal range.³¹

The course of the EBSLN is highly variable, both in its relation to the STA and the inferior constrictor muscle. Multiple classification systems have been published regarding this relationship, including the Cernea classification, the Kierner classification, and the Friedman classification.^{32,33,34} Studies by Cernea et al describe the classification scheme as follows: type 1, the EBSLN crosses the STA > 1 cm cranial to the upper pole of the thyroid, type 2A crosses the STA < 1 cm cranial to the upper edge of the thyroid gland, and type 2B crosses the superior thyroid pedicle below the edge of the upper border of the superior pole.³² Following the publication of the Cernea classification, Kierner et al added a fourth type, which describes the EBSLN as running dorsally to the superior thyroid pole (► Fig. 2.5).^{34,35} The studies of Friedman et al describe the variable course of the EBSLN in relation to the inferior constrictor muscle and the classification is based on the terminal aspect of the EBSLN.³³ In these studies, the EBSLN is classified into three types. Type 1 runs its entire course superficial or lateral to the inferior constrictor, descending with the STA until it terminates into the cricothyroid muscle. Type 2 penetrates the inferior constrictor in the lower portion of the muscle ~ 1 cm proximal to the inferior constrictor–cricothyroid junction. Type 3 travels its entire course under the inferior constrictor to the cricothyroid muscle after diving underneath its most superior fibers of the constrictor (► Fig. 2.6).³³

Positive identification of the EBSLN during thyroid surgery can avoid unintentional injury and has been shown to reduce the incidence of permanent voice changes.³¹ Identification of the SLN can be achieved by approaching the larynx within "Joll's space"—the sternothyroid–laryngeal triangle.³⁰ To achieve visualization of this space, the superior thyroid pole is retracted inferiorly and laterally. The space is then defined by the cricothyroid muscle medially, the retracted superior pole laterally, and the sternothyroid muscle anteriorly. With delicate dissection into this space, the EBSLN can be exposed, visualized, and preserved.³¹ The nerve is usually seen running along the inferior constrictor muscles or piercing the cricothyroid muscle.

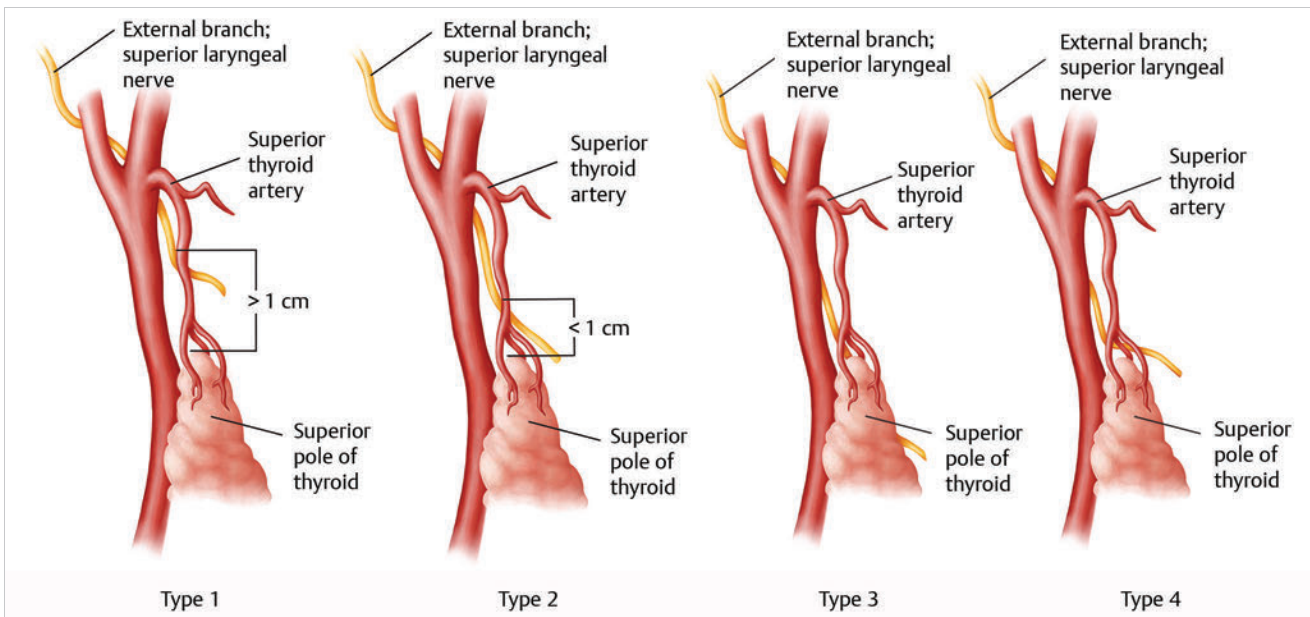


Fig. 2.5 Kierner classification of the possible courses of the external branch of the superior laryngeal nerve (EBSLN).

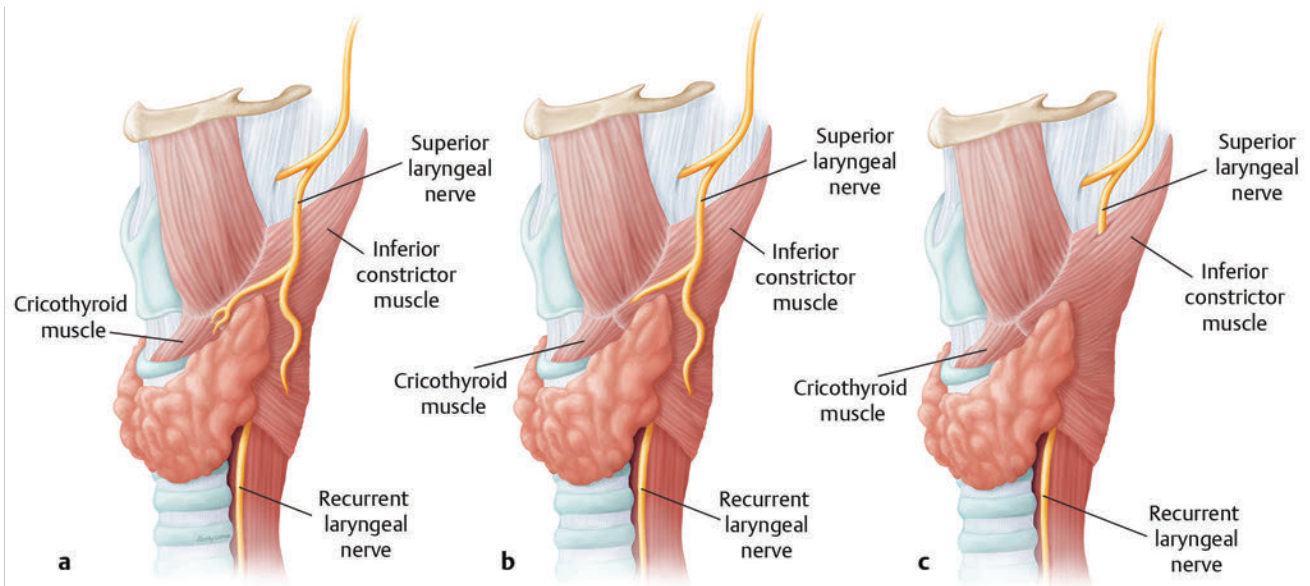


Fig. 2.6 (a) Type 1 variant of the course of the external branch of the superior laryngeal nerve (EBSLN). EBSLN courses superficial to the inferior constrictor muscle. (b) Type 2 variant: EBSLN courses underneath the inferior constrictor muscle for part of its course. (c) Type 3 variant: EBSLN courses entirely deep to the inferior constrictor muscle.

2.6 The Parathyroid Glands

2.6.1 Embryology of the Parathyroid Glands

Beginning in the fifth week of embryological development, the parathyroid glands start to form from the endoderm of the third and fourth pharyngeal pouches. The superior parathyroid glands are derived from the fourth pharyngeal pouch, migrating a short distance medially and inferiorly to ultimately reside near the dorsal aspect of the superior thyroid lobe on each side.

The inferior parathyroid glands share an embryological origin with the thymus gland. From the third pharyngeal pouch, the ventral aspect of the pouch will form the thymus gland, whereas the dorsal aspect of the pouch forms the inferior parathyroid glands. Together, the primordial thymus and inferior parathyroid glands, known as the thymic parathyroid, migrate medially and inferiorly a longer distance toward the superior mediastinum. The two structures eventually separate as the thymus enters the anterior mediastinum.¹⁵ The inferior parathyroid glands settle at the level of the inferior thyroid lobe on each side at the posterior and lateral aspect of the thyroid gland.

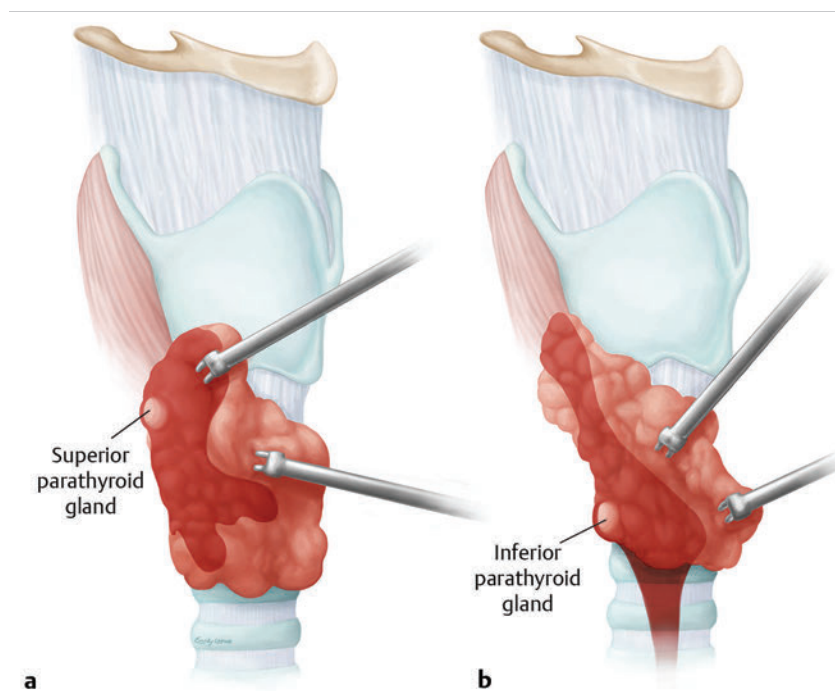


Fig. 2.7 The most common location of the superior parathyroid (a) and the inferior parathyroid glands (b). Shaded areas detail the most common distribution sites of the glands.

2.6.2 Location of Parathyroid Glands and Anomalous Development

Superior parathyroid glands are more consistent in their location given their shorter migration pattern. In a dissection of 160 cadavers, Wang evaluated the locations of normal parathyroid glands. The most common location is at the cricothyroid junction posteriorly (77%).^{15,36} In this location, the superior parathyroid glands tend to be in a 2 cm diameter area centered 1 cm above the intersection of the RLN and ITA.¹⁵ The superior gland migration patterns extend to retropharyngeal, retrolaryngeal, retroesophageal, and posterior mediastinum locations. Parathyroid glands may be ectopically located within the thyroid gland itself. An intrathyroid ectopic location is defined as a parathyroid gland surrounded on all sides by thyroid tissue. This intrathyroid localization occurs most likely due to superior parathyroid fusion with the ultimobranchial bodies during embryological development.⁶

Because of the distance the inferior parathyroid glands must migrate, there is greater variability in their location and a higher degree of ectopia than with the superior glands. Approximately 61% of the inferior parathyroid glands are found inferior, lateral, or posterior to the lower pole of the thyroid gland.³⁷ In the Wang series, the most common location was found to be anterior or posterolateral to the surface of the lower pole of the thyroid (42%).³⁶ Because vessels are prominent in this region, inferior parathyroid glands tend to be hidden by these structures. The inferior parathyroid glands are also commonly found in the thyrothymic ligament or the cervical portion of the thymus. As previously stated, the inferior glands migrate with the thymus. The descent of the thymus extends from the angle of the mandible to the pericardium, and ectopic inferior glands can lie anywhere along that path of descent. If the inferior glands fail to separate from the thymus during their descent or separation is delayed, the

inferior glands may have ectopic locations within the superior mediastinum (► Fig. 2.7).³⁶

Certain migration characteristics are often observed that can help to identify superior and inferior glands. The plane of the parathyroid gland in relation to the RLN is one such characteristic.³⁸ The superior parathyroid glands are located dorsal to the RLN, and the inferior parathyroid glands are ventral to the RLN.

Supernumerary parathyroid glands result secondary to accessory parathyroid fragments, which occur when the pharyngeal pouches separate from the pharynx. They are most often found at the level of the lower poles of the thyroid lobes or in the thymus. Supernumerary parathyroid glands may also be situated in the middle mediastinum at the level of the aortopulmonary window or lateral to the jugulocarotid axis. Such locations are most likely secondary to fragmentation of the superior parathyroid rather than migration of pathological parathyroid tissue. Intravagal parathyroid tissue has also been documented with a frequency of ~6%.³⁹

2.6.3 Parathyroid Gland Anatomy

Normal parathyroid glands typically weigh 55 to 60 mg and are approximately 3 to 8 mm.⁴ The parathyroid gland is often oval shaped with a yellow-brown color. Parathyroid vascular supply is primarily from the ITA. Although there is a wide variation in the location of the parathyroid glands, they are generally symmetric, with 80% symmetry for the superior parathyroid glands and 70% for the inferior parathyroid glands.³⁷

2.7 The Thymus

The thymus is derived from the ventral wing of the third pharyngeal pouch and migrates into the mediastinum during development. Due to this migration, accessory thymic tissue can be found in the neck anywhere along its path of descent,

from the superior thoracic aperture to the thyroid cartilage or higher. The thymus continues to grow through childhood until puberty. By adulthood, the gland has atrophied considerably and can be difficult to locate and identify.

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3 Physiology of the Thyroid Gland

David S. Rosenthal and Kenneth H. Hupart

3.1 Introduction

The mature thyroid gland lies anteriorly, inferiorly, and laterally to the laryngeal thyroid cartilage in the neck. The shape of this cartilage, reminiscent to some of an ancient Greek shield (*thur-eos*), is the source of the name *thyroid*, which was used for the first time in 1656 by Thomas Wharton.¹

Although Graves' disease findings were first documented at the end of the 18th and beginning of the 19th centuries, it was only near the close of the 19th century, with the publication of the report of the Myxoedema Commission of the Royal Society of London,² that the thyroid gland's function began to be understood. The concept that a very small gland was capable of producing an "internal secretion" that could regulate animal and human metabolism stems from this period.

We now know that the thyroid gland concentrates iodide, synthesizes and stores the iodine-rich hormones tetraiodothyronine, also referred to as thyroxine and l-thyroxine (T₄), and triiodothyronine (T₃), and releases them into the circulation by highly regulated processes. These hormones have effects in most cells of the body, controlling oxidative metabolism and the expression of many genes that are specific to differentiated cells.

This chapter reviews the physiology of the thyroid, from its cell structure and organization, to its cellular processes and the regulation of its secretion. It also introduces how the measurement of hormones from the thyroid axis can aid in the diagnosis of thyroid diseases, and reviews how special circumstances in normal physiology, such as aging, pregnancy, and diet, can affect the function of the thyroid hormone axis and the tests that we use to measure that function.

3.2 The Cellular Structure of the Thyroid

The secretory functions of the thyroid are carried out by two distinct cell types of differing origin. The classic thyroid hormones T₃ and T₄ are products of the follicular cells. These are embryologically derived from the endoderm of the primitive foregut in the region of the posterior pharynx at the base of the tongue. They migrate to their mature position along a tubular stalk, the thyroglossal duct, which ultimately is reabsorbed and disappears.³ Follicular cells, the bulk of the thyroid secretory cell population, form follicles that are the basic secretory and storage units for thyroid hormone. Follicles are composed of tightly adherent cuboidal to columnar epithelial cells, which form a "picket fence" structure around a lumen. Each cell is oriented with a basolateral membrane adjacent to the microvasculature and an apical border composed of microvilli (the "brush border") extending into the lumen. The microvilli increase the surface area between the cells and the lumen, which contains thyroglobulin. It is here that iodide (I⁻), which has been concentrated within the follicular cell cytoplasm, is combined with the thyroglobulin to form the active thyroid hormones (► Fig. 3.1).

Interspersed between the follicles are the parafollicular C cells, which produce the calcium-modulating hormone calcitonin. Embryologically, C cells are of neural crest origin. They form bilaterally from the ultimobranchial bodies, which are derived from the fourth pharyngeal pouches and then migrate to lie in their mature position between the follicles (see ► Fig. 3.1).⁴

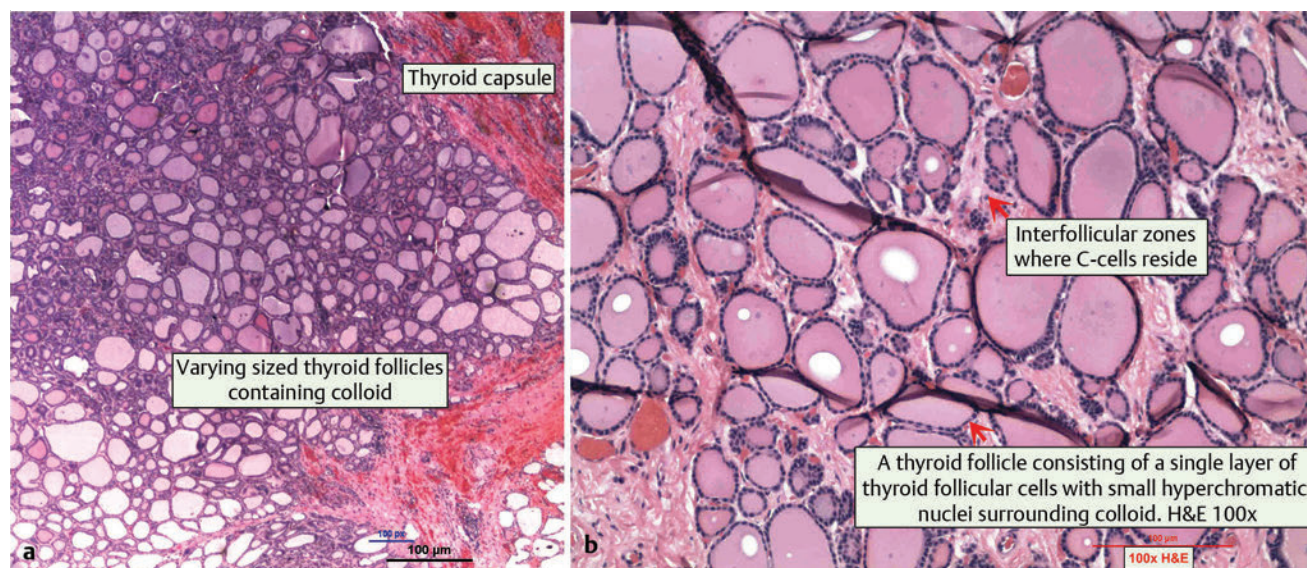


Fig. 3.1 Cellular architecture of the thyroid. (a) Low-power hematoxylin-eosin (H&E)-stained view of thyroid showing follicles with central colloid and thyroid capsule. (b) Medium-power H&E stained view of thyroid. Note varying sized follicles composed of a single layer of epithelial cells surrounding a central colloid matrix containing thyroglobulin. C cells lie in the interfollicular zones. (Courtesy of Lester Freedman, MD, Department of Pathology, Nassau University Medical Center.)

3.3 Thyroid Hormone Synthesis and Release

Thyroid hormones are the only iodine-containing human hormones and require an adequate dietary supply of this environmentally scarce element for their biosynthesis. Iodide (I^-) is the essential rate-limiting substrate for thyroid hormonogenesis. Sophisticated biomechanisms have evolved for the uptake and concentration of iodide into the thyroid follicular cell, its insertion into tyrosine to form mono- and diiodotyrosine (MIT and DIT) and their subsequent coupling into the thyroid hormones T3 and T4 (► Fig. 3.2).

The sodium (Na)/iodide symporter (NIS), a 643 amino acid 108 kDa dimerized transmembrane glycoprotein, is located at the basolateral membrane of the thyroid follicular cell adjacent to the microvasculature.^{5,6} It is an adenosine triphosphate (ATP)-driven active transport protein that simultaneously transports Na^+ and I^- (in a 2:1 ratio) into the cytoplasm. This concentrates I^- against an electrochemical gradient and results in an intra- to extracellular I^- concentration ratio of up to 40:1.⁷ NIS activity, demonstrable as early as the onset of fetal thyroid hormonogenesis at about the 12th week of gestation,⁸ is stimulated by thyrotropin-stimulating hormone (TSH) of pituitary origin and inhibited by anions, such as thiocyanate (SCN^-) and perchlorate (CLO_4^-).⁹ Importantly, when excessive iodine exposure leads to high intrathyroidal I^- concentrations, a block of I^-

oxidation and organification occurs, leading to reduced hormone synthesis (the Wolff–Chaikoff effect).¹⁰ It has been proposed that this same increased intrathyroidal I^- concentration also inhibits NIS activity, resulting in decreased I^- transport into the cytoplasm, thereby reducing intrathyroidal I^- levels and enabling an “escape” from the Wolff–Chaikoff effect.¹¹ In this manner, I^- itself is able to autoregulate NIS activity. While crucial to thyroid function, NIS activity has also been identified in other tissues, such as the lactating breast, salivary glands, stomach, and small intestine.⁹ NIS-mediated iodine uptake and concentration within the follicular cell is the basis for thyroid radioiodine diagnostic testing as well as treatment of those differentiated thyroid cancers expressing adequate NIS activity. Recent reports have suggested that facilitation of radioiodine treatment by upregulation of poor NIS expression may be possible in some tumors with the use of tyrosine kinase inhibitors.¹²

From the follicular cell cytoplasm, I^- is further translocated across the apical cell brush border membrane into the follicular lumen. The characterization of the apical membrane transporter(s) is yet to be fully defined but is thought to involve the transmembrane transporter pendrin (also known as the sodium-independent chloride/iodide transporter),¹³ a 780 amino acid 115 kDa glycoprotein, and possibly other anion transport channels, such as anoctamin-1.¹⁴ As is true for NIS, pendrin activity is stimulated by TSH. Mutations in the gene encoding pendrin have been linked to Pendred syndrome of

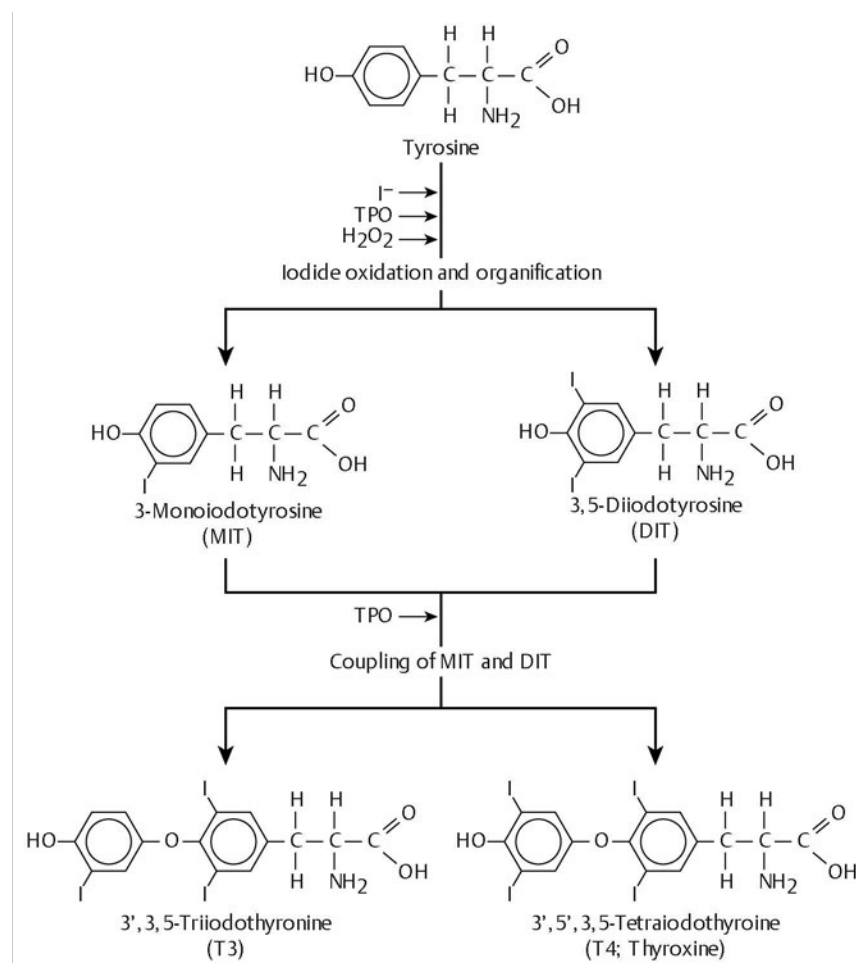


Fig. 3.2 Iodoamines in thyroid hormone synthesis. Tyrosine residues in the follicular thyroglobulin colloid are iodinated at the 3- and 5-positions of their phenyl rings by oxidation and organification of I^- catalyzed by TPO in the presence of H_2O_2 to form inactive MIT and DIT. TPO then further couples MIT and DIT by placing an ether bond between two rings into the active thyroid hormones T3 and T4. H_2O_2 , hydrogen peroxide; TPO, thyroperoxidase; MIT, monoiodotyrosine; DIT, diiodotyrosine; T3, triiodothyronine; T4, tetraiodothyronine, l-thyroxine.

goiter, hypothyroidism, sensorineural hearing loss, and impaired I^- organification.^{15,16}

Within the lumen at the apical border, I^- is oxidized and then organified¹⁷ onto tyrosyl residues at their 3- and 5-phenyl ring positions within the colloid matrix, which is composed of the rough endoplasmic reticulum (RER)-processed 660 kDa dimerized glycoprotein thyroglobulin.¹⁸ This oxidation and organification is catalyzed by the heme-containing apical enzyme thyroperoxidase (TPO) in the presence of hydrogen peroxide (H_2O_2), resulting in the formation of the biologically inactive MIT and DIT.¹⁹ The required H_2O_2 is generated by the calcium-dependent 180 to 190 kDa glycoprotein dual oxidases DUOX1 and DUOX2, which are co-localized with TPO at the apical border.^{20,21} DUOX activity is upregulated by TSH and low I^- concentrations and downregulated by high I^- concentrations. This has been proposed as a partial explanation of the Wolff–Chaikoff phenomenon.²² TPO then further catalyzes the coupling of MIT and DIT by placing an ether bond between two phenyl rings, forming the active thyroid hormones T3 and T4, which are still attached to the thyroglobulin protein backbone.¹⁷ TPO enzymatic activity is also stimulated by TSH, whereas it is inhibited

by the antithyroid thionamide drugs propylthiouracil (PTU), methimazole (MMI), and its metabolic precursor carbimazole (CBZ).²³ This thionamide inhibition of TPO activity forms the basis for the oral antithyroid drug treatment of hyperthyroidism.

The iodothyronines (T3, T4, MIT, and DIT) remain stored within the thyroglobulin colloid reservoir until needed and are then brought into the cytoplasm by endocytosis and proteolytically hydrolyzed within lysosomes. The resulting T3 and T4 are secreted into the vasculature through the basolateral membrane by the active transmembrane monocarboxylate transporter 8 (MCT8).²⁴ MCT8 is expressed in many tissues, including thyroid, brain, kidney, heart, and skeletal muscle. The Allan–Herndon–Dudley syndrome of mental retardation, hypotonia/dystonia, and abnormal thyroid hormone levels has been linked to a loss-of-function mutation in the gene encoding MCT8.^{25,26} Those MIT and DIT residues remaining in the cytoplasm undergo dehalogenation by the enzyme DEHAL1, with the liberated I^- recycled into the colloid for further hormonogenesis.²⁷ The complex intracellular pathways accomplishing these tasks are shown schematically in ► Fig. 3.3.

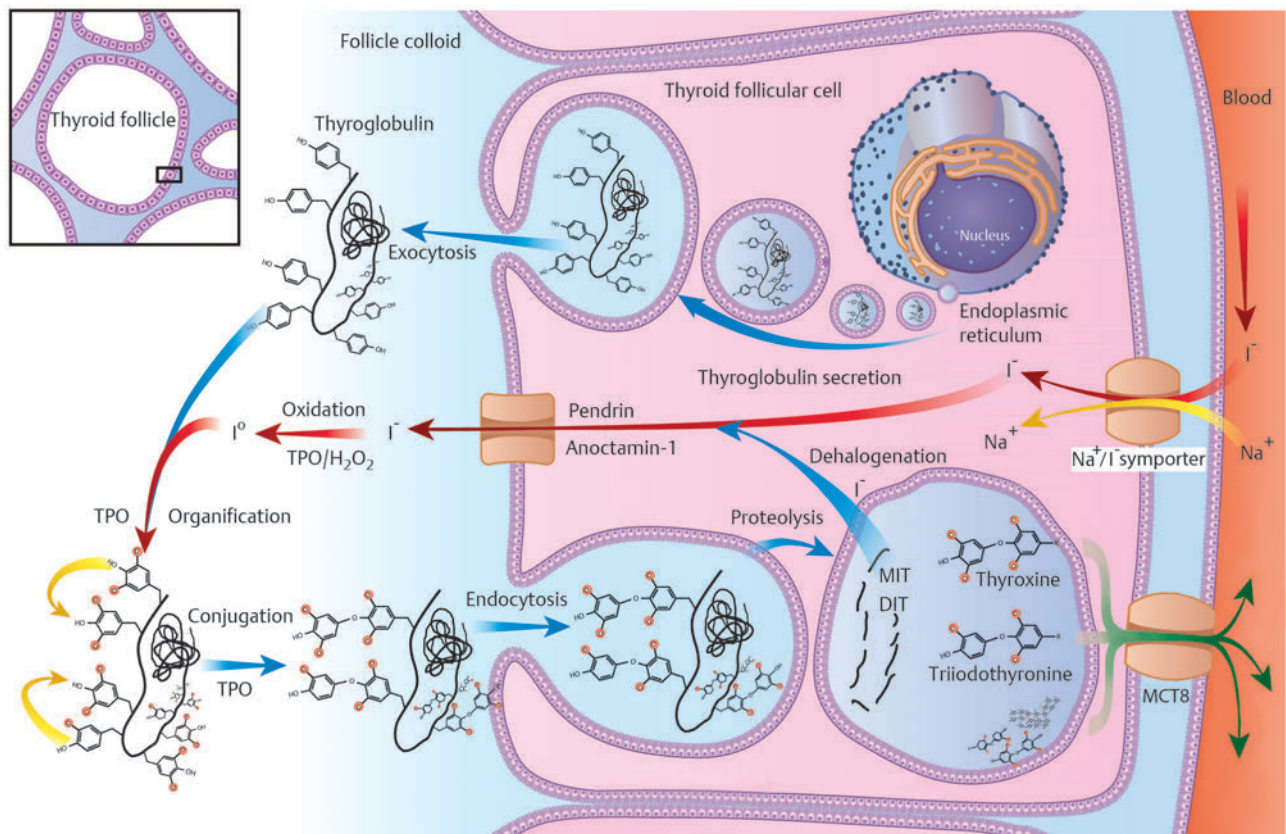


Fig. 3.3 Intracellular pathways for the synthesis and release of thyroid hormone by follicular cells. The basolateral membrane of the follicular cell abuts the microvasculature, whereas the apical brush border faces the follicle lumen containing the colloid matrix. The colloid contains TG, which had originated in the ER before being transported into the lumen. NIS, at the basolateral membrane, actively concentrates I^- from the blood across the membrane into the cytoplasm, from where it is transported by pendrin and anoctamin-1 across the apical brush border. This enables intraluminal oxidation of I^- , catalyzed by TPO in the presence of H_2O_2 , and its subsequent TPO-mediated organification onto tyrosyl moieties within the TG, forming MIT and DIT. TPO further couples MIT and DIT into the active thyroid hormones T3 and T4. These are stored within the colloid until needed, at which time they are brought back into the cytoplasm by endocytosis and proteolytically hydrolyzed by lysosomes into T3 and T4 secretory products. These are actively transported across the basolateral membrane into the microvasculature by MCT8. I^- resulting from dehalogenation of residual MIT and DIT reenters the cytoplasmic I^- pool for reuse. TG, thyroglobulin; ER, endoplasmic reticulum; NIS, sodium/iodide symporter; TPO, thyroperoxidase; MIT, monoiodotyrosine; DIT, diiodotyrosine; T3, triiodothyronine; T4, tetraiodothyronine, l-thyroxine; MCT8, monocarboxylate transporter 8.

T4 and T3 are secreted by the thyroid in molar proportions variously calculated as 14:1,²⁸ or more recently as 17:1.²⁹ However, this direct thyroidal secretion accounts for only 20% (~6 µg) of the circulating T3, whereas the other 80% (~25 µg) is the result of peripheral conversion of T4 to T3 by 5'-deiodination of T4.²⁸

3.4 Thyroid Hormone Deiodination

Secreted T4 may be considered a prohormone and is converted to the active T3 form by deiodination at the 5' position on its outer phenyl ring. This is accomplished by the selenodeiodinases type 1 (D1) and, more robustly, by the higher-affinity type 2 (D2). Deiodination at the 5 position on the inner ring is accomplished by type 3 (D3), and to a lesser extent by D1, and leads to the inactive molecule reverse T3 (► Fig. 3.4). These significantly tissue-specific deiodinases maintain thyroid hormone homeostasis and regulate thyroid-mediated intracellular activity. They are all structurally similar membrane-bound proteins of 29-33 kDa. D1 and D3 have a transmembrane domain at the cell surface, whereas D2 is located at the endoplasmic reticulum. All have their functionally active centers in the cytosol. D1

is present in several tissues, such as liver, kidney, thyroid, and pituitary, but it is not present in the central nervous system (CNS). D2 activity is present in the CNS as well as in the peripheral tissues, such as thyroid, heart, skeletal and vascular smooth muscle, kidneys, placenta, and pancreas. D3 is found in the CNS as well as placental and fetal tissues.^{30,31,32} Alterations in deiodinase activities are thought to play an important role in such pathophysiological conditions as the nonthyroidal illness syndrome.

3.5 Thyroid Hormone Regulation

As already noted, although T4 is the main secretory product of the thyroid gland, T3 is responsible for the cellular actions of thyroid hormones. The nuclear thyroid hormone receptors have 10- to 15-fold higher affinity for T3 than T4, and the binding of T3 to the receptor isoform expressed in a particular cell type drives the upregulation or downregulation of the transcription of specific genes.³³ The products of these genes govern the cellular responses to thyroid hormones, as well as the regulation of the synthesis and release of thyroid hormone.

The hypothalamus responds to the ambient thyroid hormone state in a classical negative homeostatic feedback loop by regulating its secretion of thyrotropin-releasing hormone (TRH).

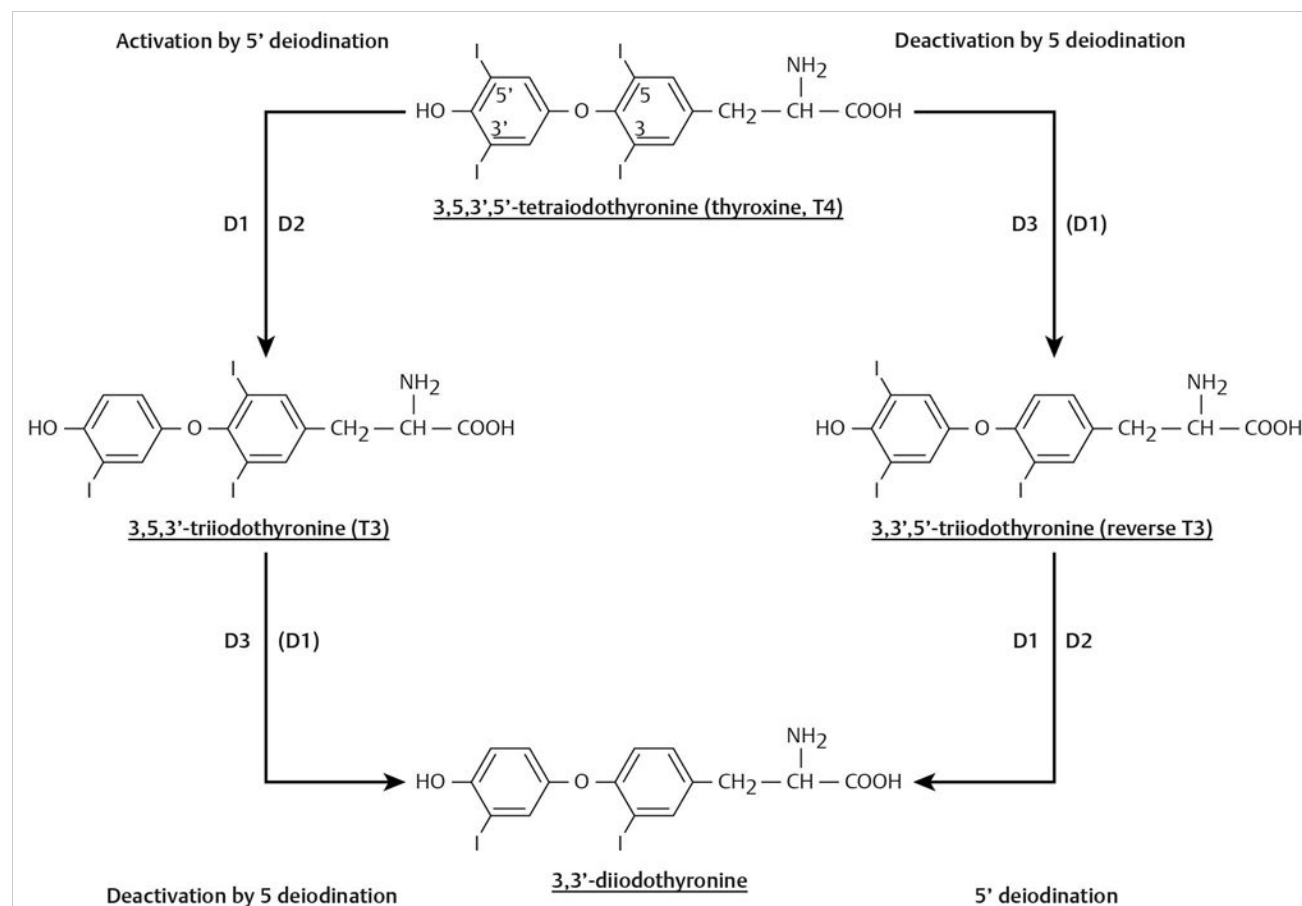


Fig. 3.4 Pathways of thyroid hormone selenodeiodinase-mediated activation and deactivation. Secreted T4 (tetraiodothyronine, l-thyroxine) is converted to the active T3 (triiodothyronine) form by deiodination at the 5' position on its outer phenyl ring. This is accomplished by the selenodeiodinases type 1 (D1) and type 2 (D2). Deiodination at the 5 position on the inner ring is accomplished by type 3 (D3) and D1.

The cell bodies of TRH-secreting neurons are localized in the paraventricular nucleus of the hypothalamus. Their nerve endings secrete TRH into the portal vein in the hypothalamic median eminence for transport to the pituitary gland. This hypothalamic TRH response is regulated by T₃, which is derived more from regional intracellular deiodination of T₄ than from circulating T₃ and is principally mediated by the β 2 T₃ nuclear receptor.³⁴ In this way, the increased level of T₄ in hyperthyroidism potentially downregulate the synthesis and secretion of TRH, whereas the decreased level in hypothyroidism result in enhanced TRH release.

The target for TRH is a cell membrane-based receptor on the TSH-producing cells, the thyrotrophs, located in the anteromedial portion of the pituitary gland—also part of the negative feedback control mechanism. TRH rapidly stimulates TSH synthesis and release. This effect of TRH on the thyrotrophs is modulated by both T₄ and T₃. In hyperthyroidism, the stimulatory effect of TRH on the thyrotrophs is downregulated, and TSH release decreases and may cease. The TSH molecule, a 28 kDa glycoprotein, is composed of a specific β subunit that is unique to TSH, and an α subunit that is common to the other dimeric glycoprotein hormones—luteinizing hormone (LH), follicle-stimulating hormone (FSH), and human chorionic gonadotropin (hCG) (► Fig. 3.5).³⁵

3.6 Laboratory Assessment of Thyroid State

Laboratory testing is used to screen for thyroid gland dysfunction, diagnose or confirm the presence of hypothyroidism or hyperthyroidism, or monitor a patient's response to thyroid disease treatment. Testing strategies are determined by the goal of performing the test and can include serum measurements of thyroid hormones and TSH, nuclear medicine tests, imaging studies, and assessment for the presence of antithyroid autoantibodies.

Although T₃ is the form of thyroid hormone that binds to the thyroid nuclear receptor and is responsible for thyroid biological responses, measuring its serum concentration to determine thyroid function can be misleading. Circulating T₃ has a shorter half-life (1 day) than does T₄ (7 days), and its concentration is frequently transiently lowered by significant intercurrent non-thyroidal illnesses, which may lead to misinterpretation of a patient's thyroid state.³⁶

T₄ is the main secretory product of the thyroid gland and the most commonly prescribed agent for the treatment of hypothyroidism. In addition, because of its longer serum half-life, its concentration is more stable than that of T₃. Similar to T₃, its concentration is affected by the presence of other diseases, but this occurs to a lesser degree. Thyroid hormones are highly bound to their circulating carrier proteins: thyroxine-binding globulin (TBG), human serum albumin (HSA), and transthyretin (TTR). Only 0.02% of serum T₄ and 0.3% of serum T₃ exists in the unbound and therefore metabolically active form. Hence, in addition to the presence of thyroid disease, alterations in the concentration of these thyroid hormone-binding proteins can significantly affect the serum concentration of thyroid hormones.^{37,38} This has led to the development of readily available assays that measure the concentration of free T₄. These assays

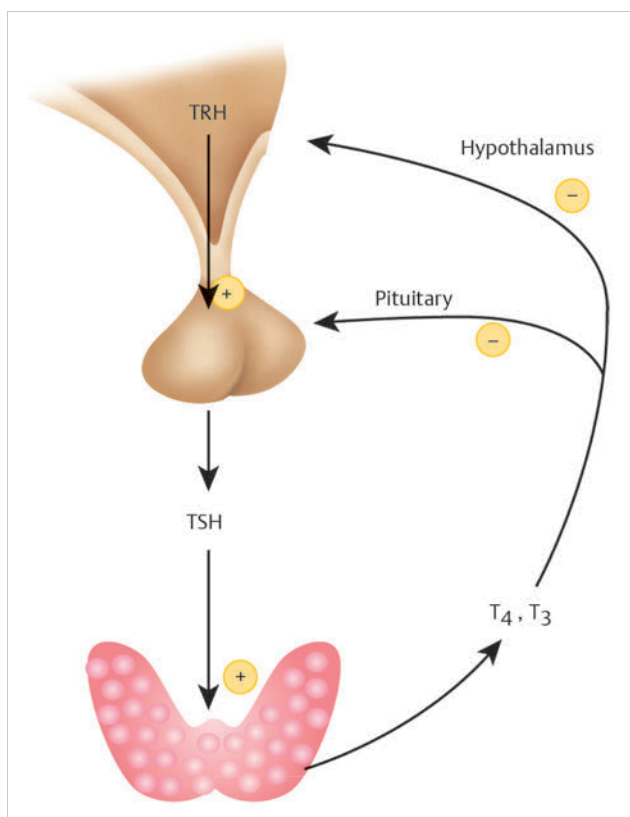


Fig. 3.5 The hypothalamic-pituitary-thyroid negative feedback loop. Hypothalamic thyrotropin-releasing hormone (TRH) stimulates pituitary thyrotrophs to secrete thyrotropin-stimulating hormone (TSH), which stimulates thyroidal hormone synthesis and secretion. The secreted T₄ (tetraiodothyronine, l-thyroxine) and T₃ (triiodothyronine) regulate secretory function at both the hypothalamic and pituitary levels in a classical negative feedback loop: downregulating as T₄ and T₃ levels increase and upregulating as their levels decrease.

have importantly supplemented the measurement of total serum T₄ and T₃ in many clinical circumstances.

While the measurement of free T₄ is often more clinically useful in assessing a patient's thyroid state than employing assays for total T₄, total T₃, or free T₃, there are still important limitations. Many commercially available assays for free T₄ employ specific methods, which perform differently when applied to clinical situations that greatly affect either the concentrations of the thyroid-binding proteins or their binding affinities for thyroid hormones. Examples include increased protein binding due to elevations of TBG occurring in pregnancy, in women treated with oral estrogens or contraceptives, and in chronic liver disease; inherited variations in TBG levels; increased protein-binding affinity for T₄ as in familial dysalbuminemic hyperthyroxinemia; or with critical intercurrent nonthyroidal illness. Even more technically demanding, less widely available assays, which employ equilibrium dialysis to measure free T₄, may not perform reliably in all of these circumstances.^{39,40}

The normal range for serum thyroid hormone concentrations in humans is very large. Typically, the upper limit of normal is 150% higher than the lower limit of the normal range. The set point about which any individual regulates T₄/free T₄ varies

little during a lifetime. It therefore follows that, in an individual in whom the T4/free T4 is usually in the higher part of the normal range, hypothyroidism can result in a lower T4/free T4 that is still in the normal range. In a similar fashion, hyperthyroidism may cause a doubling of an individual's serum T4/free T4 concentration, yet this also may be within the normal range.

TSH and free T4 levels vary inversely in a log-linear relationship,⁴¹ and, consequently, as a single test for thyroid function, TSH is the most reliable. In the presence of hyperthyroidism, TSH serum concentrations are decreased below normal and are often suppressed below the assay's detection limit. Similarly, when primary hypothyroidism is present, even to a mild degree, serum TSH is elevated. However, when secondary hypothyroidism is present and the problem lies in either the hypothalamus or the pituitary, profound hypothyroidism may be present, yet serum TSH is reported as being normal or low. Therefore, care must be exercised in relying on one blood test to diagnose thyroid disease.

There are numerous circumstances in which the serum TSH concentration may not correlate with the clinical state. In critically ill patients treated with dopamine agonists, or when therapy requires the use of high-dose glucocorticoids, pituitary TSH release may be inhibited, even in the face of hypothyroidism.⁴² During severe nonthyroidal illness complex changes occur at all levels of the hypothalamic-pituitary-thyroid (HPT) axis, producing changes in thyroid hormone measurements that make clinical evaluation difficult. Serum levels of T4 and T3 may fall profoundly while those of reverse T3 rise. When patients recover from such illnesses as infection or shock, or they improve after having major surgery, serum TSH may be transiently elevated for several weeks as the serum concentrations of T4 and T3 return to normal.³⁶ Up to one-third of patients with acute psychiatric illness may present with alterations in TSH and thyroid hormone levels. These are usually transient and normalize over several days to a few weeks as the psychiatric illness remits. The pathophysiology is poorly understood, but alterations in the HPT axis have been proposed.⁴³

Recent scholarship has identified that the "normal" range for TSH may vary with age, gender, and ethnicity. In older patients without evidence of thyroid disease, elevations of TSH into the range that has typified mild hypothyroidism may be seen. This has prompted proposals to change the way that TSH is interpreted and alter the threshold for initiating therapy.⁴⁴ In addition, the range of TSH in pregnant women differs from the range in other adults. As previously noted, the structure of hCG is similar to that of TSH, with both sharing a common α subunit. Consequently, when hCG is present in very high concentration, as it is in pregnancy, it binds to the TSH receptor on the thyrotroph cell surface and mimics the action of TSH. As a result, thyroid hormone secretion is stimulated and pituitary TSH secretion is reduced. This results in a lowered "normal" TSH range in pregnancy.^{45,46}

Given the limitations of the clinical laboratory when applied to thyroid assessment, it is reasonable to combine the measurement of TSH with one or more other tests, such as T4 or free T4, when diagnosing thyroid disease or evaluating a patient who requires hospitalization. However, when following a stable patient for the adequacy of thyroid hormone replacement, measurement of serum TSH alone may suffice.

Screening apparently normal adult patients for thyroid disease with blood tests is a controversial practice that has been advocated by some⁴⁷ and determined not to be cost-effective by others.^{48,49} Also controversial is the value of universal or simply targeted screening for thyroid dysfunction of women in early pregnancy to reduce the risk of pregnancy complications and of fetal CNS developmental defects. Studies to date remain inconclusive,^{50,51} and relevant guidelines make no recommendations for or against this practice.⁴⁶ Greater agreement exists in favor of screening populations at increased risk, such as older adults who may not manifest the usual signs and symptoms of thyroid disease.⁵² Screening newborns for the presence of congenital hypothyroidism by measuring TSH is widely accepted. Programs that measure TSH in all neonates are considered to have alleviated significant suffering by preventing the severe cognitive impairment, deafness, and mutism that typify this disease when it is not treated soon after birth.⁵³

3.7 Drugs Affecting Thyroid Functional Status

Many drugs used in clinical practice have significant effects on thyroid functional status. Some, such as proton pump inhibitors, H2 receptor antagonists, and antacids, reduce gastric acidity, thereby reducing absorption of thyroid hormones, whereas others (bile acid sequestrants, calcium, iron, aluminum hydroxide, sucralfate) reduce absorption by increasing hormone binding in the intestine. Activation of the hepatic cytochrome P450 system by phenytoin, rifampin, carbamazepine, and barbiturates results in an increased metabolic clearance rate of thyroid hormone. The cardiac antiarrhythmic amiodarone is an iodine-rich (37% by weight) lipophilic agent with a long half-life of 40 to 60 days, and it has potentially profound and variable thyroidal effects. Its high iodine content can result in an organification block (the Wolff-Chaikoff effect), and it also has antagonistic action at the thyroid hormone receptor (perhaps significant for its antiarrhythmic effect), inhibits D1 activity, and has a follicular cell cytotoxic effect. Consequently, hypothyroidism has been reported in 5 to 15% of patients given amiodarone. Thyrotoxicosis has been identified in up to 12% of treated patients and has been divided into types 1 (introduction of a large iodine load into a patient with preexisting thyroidal autonomy—the Jod-Basedow effect) and 2 (cytotoxic destructive thyroiditis). Lithium can mimic the Wolff-Chaikoff effect because it is concentrated by follicular cells, inhibits the release of thyroidal iodine, and thereby increases intrathyroidal iodine levels. The resulting downregulation of thyroid hormone synthesis and secretion may cause hypothyroidism. Transient thyrotoxicosis due to a cytotoxic destructive thyroiditis has also been described. Tyrosine kinase inhibitors may increase hepatic clearance of thyroid hormone. This may require increased treatment doses in thyroidectomized or previously hypothyroid patients and may lead to hypothyroidism in euthyroid patients as a result of destructive thyroiditis (sometimes with an early thyrotoxic phase) and possibly by decreasing thyroidal blood flow by inhibition of vascular endothelial growth factor receptors (VEGFRs). Immune suppressors, such as alemtuzumab (used in the treatment of multiple sclerosis) and high activity antiretroviral therapy (HAART), have been reported to induce

clinical Graves' disease. Cytokines, such as interferon- α and interleukin-2, have been associated with both autoimmune and cytotoxic destructive thyroid effects resulting in transient or permanent hypothyroidism, transient thyrotoxicosis, or Graves' disease.⁵⁴

3.7.1 Genetic and Molecular Control of Thyrocyte Growth

Recent years have seen major advances in the understanding of the genetic and molecular control of thyrocyte growth, differentiation, proliferation, and survival. A cascade of tyrosine protein kinases has been shown to be central to this regulatory mechanism.^{55,56} The *RET* (rearranged during transfection) proto-oncogene is situated on the long arm of chromosome 10 and contains 21 exons. It codes for the transmembrane receptor

tyrosine kinase *RET*, which is the gateway to the mitogen-activated protein kinase (MAPK) / extracellular signal-regulated kinase (ERK) pathway. Activation of *RET* by binding of one of its growth-stimulating or cytokine ligands to the extracellular domain of the receptor results in phosphorylation of tyrosine residues in the intracellular domain and initiates a cascade of subsequent phosphorylation events, transducing a downstream signal regulating cell growth. The first of these involves the RAS viral oncogene family of 21 kDa protein kinases (H-RAS, N-RAS, and K-RAS). These are activated by phosphorylation of their component guanosine diphosphate (GDP) moieties to guanosine triphosphate (GTP). Subsequent signaling occurs by activating phosphorylations of the downstream RAF family of proto-oncogene serine/threonine tyrosine kinases (A-RAF, B-RAF, and C-RAF), MEK (also known as MAPK kinase or MAPKK), and ERK. Activated ERK then translocates into the nucleus, where it modulates transcription factors, such as PAX8 (paired domain transcription factor 8), and hormone receptors, such as PPAR γ (peroxisome proliferator-activated receptor γ), which are important to thyroid hormone biosynthesis as well as cell growth, survival, and apoptosis.

A second pathway transmitting and modulating the signal for control of cell growth begins with phosphatidylinositol-3 kinase (PI3K). This initiates the PI3K/AKT/mTOR viral oncogene tyrosine kinase cascade.⁵⁷ PI3K is activated both directly by the transmembrane receptor kinase *RET* and indirectly by RAS, whereas it is downregulated by PTEN-mediated dephosphorylation (► Fig. 3.6).

Identifying these pathways and understanding the importance that point mutations and gene fusions (rearrangements) of their components play in cancer development and progression have led to major advances in the diagnosis^{58,59,60,61,62} and targeted treatment^{56,63,64} of thyroid cancer. See Chapter 10 for further detailed discussion of this subject.

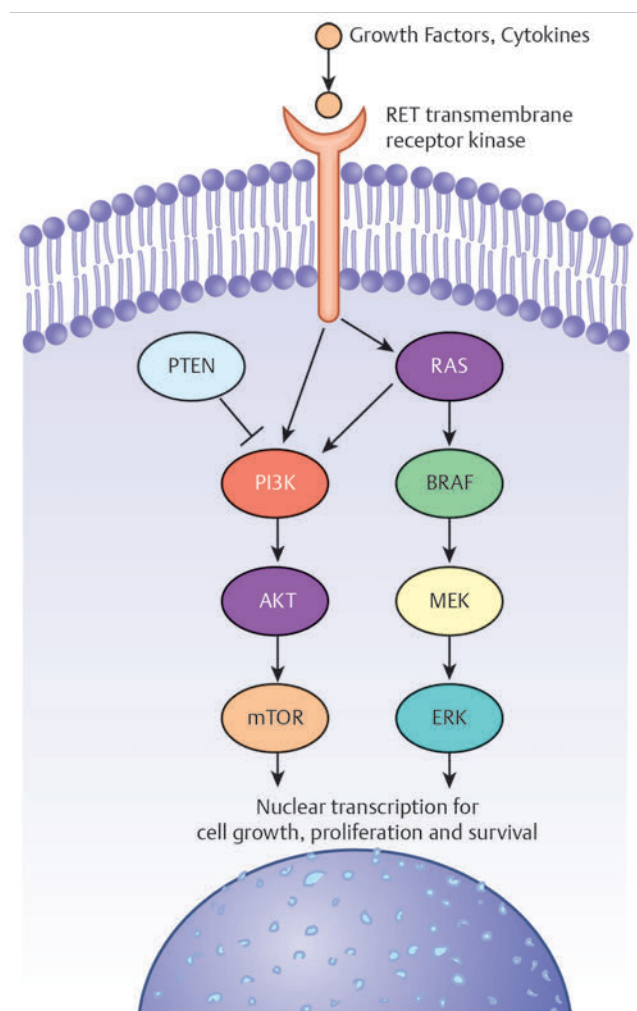


Fig. 3.6 Pathways of intracellular tyrosine kinase signal transduction, modulating cell growth, proliferation, and survival. Ligands of the transmembrane *RET* tyrosine kinase initiate phosphorylation cascades, such as the MAPK (RAS→RAF→MEK→ERK) and the PI3K (PI3K→AKT→mTOR) pathways, modulating nuclear transcription factors for cell growth and survival. PTEN expression inhibits PI3K activity. (Courtesy of Dr. Yuri Nikiforov, Department of Pathology, University of Pittsburgh.)

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4 Physiology of the Parathyroid Glands

Carlos M. Isales and Wendy B. Bollag

4.1 Introduction

Calcium is one of the most tightly regulated ions in the body, highlighting its critical role in everything from intracellular signaling to muscular contraction. Thus, even small deviations in calcium values outside the normal range usually signify some underlying pathology. Disorders involving hypercalcemia are more common than those involving hypocalcemia because of all of the compensatory systems that respond to a drop in serum calcium. In an outpatient setting the most common cause of hypercalcemia is primary hyperparathyroidism. The diagnosis of early primary hyperparathyroidism increased dramatically with the advent of automated multiple sample blood chemistry analysis. The corollary of this fact is that we rarely encounter patients as dramatic as Captain Martell anymore.¹ Therefore, to be able to better diagnose and treat patients with diseases of the parathyroid gland, who often do not have significant clinical signs or symptoms, it is important to have a clear

understanding of the factors involved in the regulation and secretion of parathyroid hormone (PTH) to avoid misdiagnosis.

4.2 History

The comparative anatomical description and naming of parathyroid glands are credited to Sandstroem in 1880,^{2,3} who examined the necks of humans and other mammals (dog, cat, rabbit, horse, and ox) for the glands he eventually named glandulae parathyroidea⁴ (► Fig. 4.1). As a medical student in the Department of Anatomy in the University of Uppsala he examined the necks of human cadavers and identified the same organs he had observed in animals in 43 of 50 cadavers: "Found on both sides of the inferior border of the thyroid an organ of the size of a small pea which judging from its exterior, did not appear to be a lymph gland, or an accessory thyroid gland and which upon histological examination showed a rather peculiar structure."⁴ At that time only two parathyroid glands were

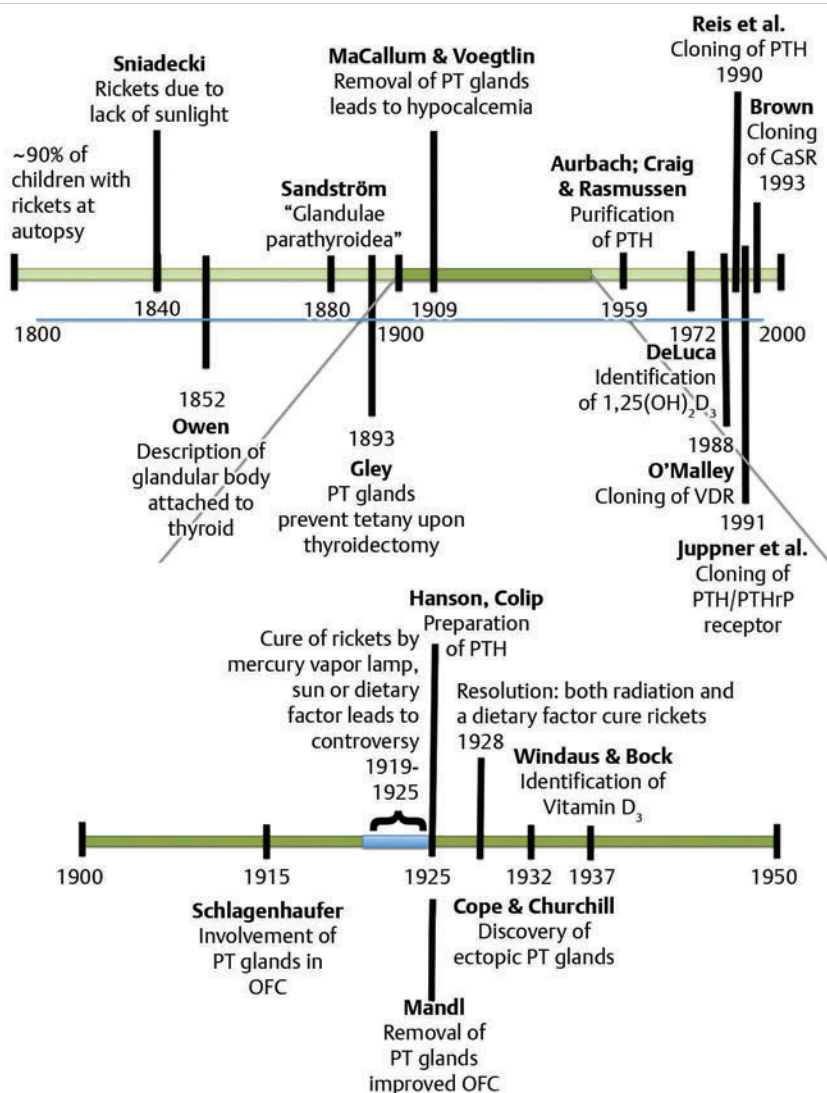


Fig. 4.1 Timeline illustrating the major discoveries related to the parathyroid glands, parathyroid hormone and vitamin D. 1,25(OH)₂D₃, 1,25-dihydroxyvitamin D₃; CaSR, calcium-sensing receptor; OFC, osteitis fibrosa cystica; PT, parathyroid; PTH, parathyroid hormone; PTHrP, parathyroid hormone-related protein; VDR, vitamin D receptor.

recognized to be present in humans. Interestingly, the description of parathyroid glands as distinct organs in animals had been made as far back as 1852 by Owen, who identified “a small compact yellow glandular body attached to the thyroid” in the Indian rhinoceros.^{2,5} A potential role of these organs was not clear until the French physiologist Eugene Gley demonstrated that tetany did not occur after thyroidectomy in experimental animals if the parathyroid glands were excluded.⁴ However, it was felt that the parathyroid gland's role was to remove toxins (such as methyl guanidine) from the body and that it was the accumulation of these toxins that was precipitating the tetany.⁶ It was not until almost 20 years later that MacCallum and Voegtlin demonstrated that removal of the parathyroid glands was associated with hypocalcemia and that infusion of calcium prevented tetany.^{6,7}

A connection between overproduction of PTH and a specific disease was proposed in 1915 when the pathologist Friedrich Schlägenhauser, based on two autopsies he was performing on patients with hyperparathyroidism, speculated that an enlarged parathyroid gland (adenoma) could result in parathyroid bone disease (osteitis fibrosa cystica).^{4,6} Subsequently, in 1925 this hypothesis was put to the test when Dr. Felix Mandl successfully removed an enlarged parathyroid gland in a patient, with marked improvement in the accompanying bone disease.⁶

Around this time, Fuller Albright and colleagues at the Massachusetts General Hospital began careful metabolic studies to characterize calcium and phosphate turnover.^{8,9,10,11,12} A New England sea captain by the name of Charles Martell had developed severe parathyroid bone disease and was operated on by Dr. Edward Richardson, head of the Department of Surgery at the Massachusetts General Hospital. No abnormal parathyroid tissue was located in the neck despite repeated surgeries. Dr. Oliver Cope, then a surgical resident, undertook a study on normal variations in the parathyroid glands. In 1932, Dr. Edward Churchill, together with Dr. Cope, in Captain Martell's seventh surgery, extended the incision to the chest with a sternotomy and successfully removed a parathyroid adenoma from the mediastinum.¹³ Unfortunately, Captain Martell went on to die from renal failure related to kidney stone disease from the many years of severe hyperparathyroidism.

During that time, work was also proceeding on the purification of parathyroid hormone (called “parathyrin” at that time).

Hanson,¹⁴ and later Collip,¹⁵ were able to successfully make a purified extract of PTH from bovine parathyroids. James Collip, who had previously assisted in the preparation of an insulin extract with Drs. Banting and McLeod, demonstrated that administration of his extract successfully prevented the development of tetany in a patient.¹⁶ Further characterization of the PTH molecule required more pure preparations, which was eventually accomplished by Aurbach¹⁷ and Rasmussen and Craig¹⁸ in 1959.

4.3 Parathyroid Physiology

Evolutionarily, parathyroid glands are known to be present in amphibians and mammals but not fish. In view of calcium's multiple essential roles in the body, it has been hypothesized that, as organisms migrated from the ocean (with a high calcium content) to land they required a mechanism for regulating this key ion, and thus those organisms that developed parathyroid glands were at a selective advantage.¹⁹ In humans, the parathyroid glands develop from the endoderm of the third and fourth pharyngeal pouches. A key transcription factor in the development of the parathyroid glands is Gcm-2.²⁰ This transcription factor appears to be exclusively expressed in the parathyroid glands. Phylogenetic studies have also shown it to be expressed in pharyngeal pouches in fish (from which the internal gill buds develop).²¹ Thus Graham et al²² speculate that the evolution of the parathyroid glands was a natural progression from the gills in fish to their present form and thus the reason for the glands' location in the neck.

4.3.1 Calcium Receptors

Calcium is the key regulator of PTH secretion. Until recently, it was not clear how this cation regulated PTH secretion. It is now known that there is a distinct calcium receptor that belongs to the G-protein coupled seven-transmembrane-domain receptor family.²³ In addition to the chief cells in the parathyroid gland, the calcium receptor is expressed in multiple other tissues, including C cells in the thyroid, kidney, bone cells, cartilage, intestine, placenta,²⁴ brain, lung, and keratinocytes,²⁵ where it plays a key role in regulating calcium balance (► Fig. 4.2).

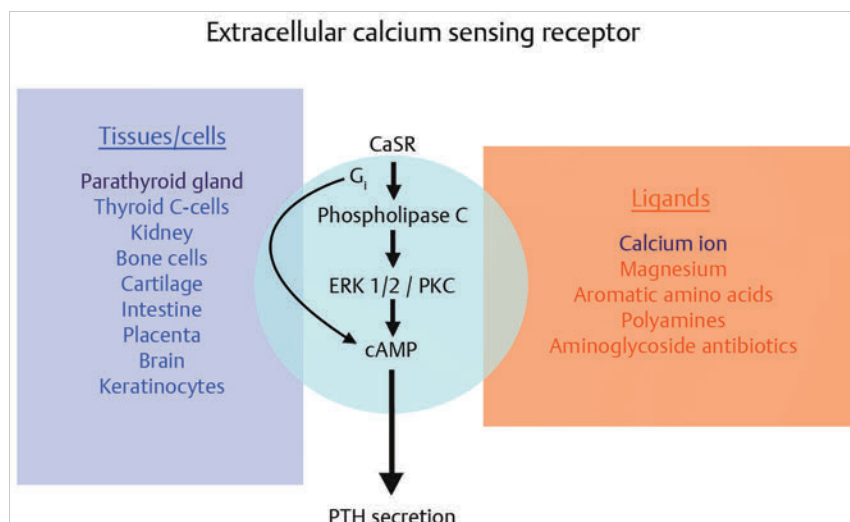


Fig. 4.2 The calcium-sensing receptor is widely expressed and can bind other ligands besides calcium. Parathyroid hormone (PTH) secretion from the parathyroid gland is negatively regulated by ionic calcium concentration. As calcium drops, PTH secretion increases rapidly within a narrow range. cAMP, cyclic adenosine monophosphate; CaSR, calcium-sensing receptor; ERK, extracellular signal-regulated kinase; PKC, protein kinase C; PLC, phospholipase C; PTH, parathyroid hormone.

Although this receptor has the highest affinity for calcium, it will also bind other polyvalent cations, like magnesium, and aromatic amino acids, such as L-phenylalanine and L-tryptophan.²⁶ In fact, the presence of the calcium receptor on antral G cells (which secrete gastrin), gastric parietal cells (which secrete acid), and renal cortical thick ascending limb cells (which regulate urinary calcium) may explain why ingestion of protein or amino acids results in increased gastrin, acid secretion, and urinary calcium excretion, respectively.²⁶

Binding of calcium to the calcium receptor in the parathyroid glands results in suppression of PTH secretion. Stimulation of PTH secretion because of hypocalcemia follows a sigmoidal curve, with large increases in PTH secretion occurring with only small drops in serum calcium. The parathyroid tissue expresses very high levels of the calcium receptor, and calcium binding results in activation of phosphoinositide-specific phospholipase C (PI-PLC) and activation of protein kinase C (PKC). In addition to this signal transduction pathway, calcium binding to its receptor also activates the phospholipase A₂ (PLA₂), phospholipase D (PLD), and mitogen-activated protein kinase (MAPK) pathways. These calcium receptor-regulated proliferative pathways have a major impact on parathyroid cell mitosis. Under normal conditions there is very little proliferative activity in parathyroid tissue; however, hypocalcemia markedly stimulates parathyroid cell division, as seen in patients with renal failure. Calcium receptor binding in parathyroid tissue also activates the inhibitory G protein (G_i) and inhibits adenylate cyclase and lowers cyclic adenosine monophosphate (cAMP) levels. Interestingly, these signal transduction pathways can also be modulated by other cations. It has long been known that hypomagnesemia inhibits PTH secretion. It has recently been shown that this hypomagnesemic-induced inhibition of PTH secretion is secondary to an increased activation of the phosphoinositide pathway and greater inhibition of cAMP.

4.3.2 Parathyroid Hormone Structure and Secretion

PTH is synthesized in the chief cells as a larger peptide that is 115 amino acids long (pre-pro PTH), and is then cleaved in the endoplasmic reticulum to a peptide that is 90 amino acids in length (pro-PTH). Finally, 6 additional amino acid residues are removed in the Golgi complex to result in an 84-amino-acid peptide (PTH1–84) stored in secretory vesicles for immediate release. The amino portion of the molecule (1–34) has been considered to have full biological activity. The first three amino acids of the peptide are essential for activating adenylate cyclase. Amino acids 24 to 32 provide PTH with its amphiphilic alpha helical conformation, which is important in PTH receptor binding and PKC activation.²⁷ Carboxy-terminal fragments distal to amino acids 1 to 34 (i.e., 35–84) were not considered to have any biological activity, even though this portion of the molecule is highly conserved. More recent studies have demonstrated, however, that carboxy-terminal PTH fragments do have specific cellular effects. There is at present no consensus concerning the importance of these effects in terms of either the cell biology or the physiology of PTH action.

PTH secretion is primarily regulated by the calcium concentration via the calcium receptor as already discussed. The

parathyroid gland is primed to secrete PTH tonically, and it is calcium binding that inhibits this PTH secretion. During prolonged hypocalcemia (lasting > 1 h), PTH degradation is markedly reduced. If the hypocalcemia persists, ultimately there is proliferation and hyperplasia of the parathyroid tissue.

The form of PTH secreted can vary according to calcium levels. For example, under normocalcemic conditions PTH is predominantly secreted from the parathyroid glands as the intact molecule (PTH1–84), which is then processed in the liver and kidneys into a number of fragments thought to be biologically inert. Under hypercalcemic conditions the proportion of carboxy-terminal fragments (PTH7–84, PTH24–84; PTH28–84; PTH34–84; PTH37–84, and PTH43–84) secreted by the parathyroid gland increases, and PTH1–84 decreases.

In addition to hypocalcemia, hyperphosphatemia also stimulates PTH secretion in vitro through a decrease in cytosolic PLA₂ activity. Phosphate stimulates PTH gene expression by decreasing the degradation of the PTH transcript. It would also appear that 1,25-dihydroxyvitamin D₃ decreases PTH secretion and inhibits parathyroid gland hyperplasia.

4.3.3 Parathyroid Hormone Receptors

The classic actions of PTH on kidney and bone are mediated by the amino-terminal 1–34 residues of the molecule through a seven-transmembrane-domain G-protein-coupled receptor, PTH1 R. This receptor couples to both adenylate cyclase and PI-PLC.

A second putative receptor for PTH was cloned from a rat cerebral cortex cDNA library.²⁸ The amino acid sequence shares 51% amino acid homology with PTH1 R. This PTH2 R is distributed less widely than PTH1 R and is found predominantly in the brain and pancreas, with lesser expression in the placenta and testis. The PTH2 R binds PTH(1–34) preferentially over parathyroid hormone-related peptide (PTHrP1–36) and appears to activate the adenylate cyclase signal transduction pathway at relatively low concentrations of PTH (between 10⁻¹⁰ and 10⁻⁹ M). However, this receptor does not respond to comparable doses of PTHrP. However, PTH2 R appears to have a higher affinity for the tuberoinfundibular peptide (TIP34) than for PTH. Thus, PTH2 R may be a misnomer because it would appear that this is not a true PTH receptor and may actually be a TIP receptor.

A third putative PTH receptor was identified in zebrafish and has homology to PTH1 R. However, there does not appear to be a human homologue, and this receptor (PTH3R) may have evolved through gene duplication. Thus, even though three putative PTH receptors have been identified (PTH1R–PTH3R), only PTH1 R appears to be a true PTH receptor.

An additional putative carboxy-terminal PTH receptor was characterized by Inomata et al.²⁹ Using radiolabeled C-terminal PTH fragments for binding and cross-linking studies, these investigators characterized two proteins of 90 and 40 kDa in size in a rat osteosarcoma cell line (ROS 17/2.8). These putative receptors demonstrate a higher affinity for C-terminal fragments of PTH (PTH19–84; PTH39–84; PTH53–84) than for N-terminal fragments of PTH or for C-terminal fragments of PTHrP. Carboxy-terminal PTH fragments do not bind to PTH1 R and do not elevate cellular cAMP levels.

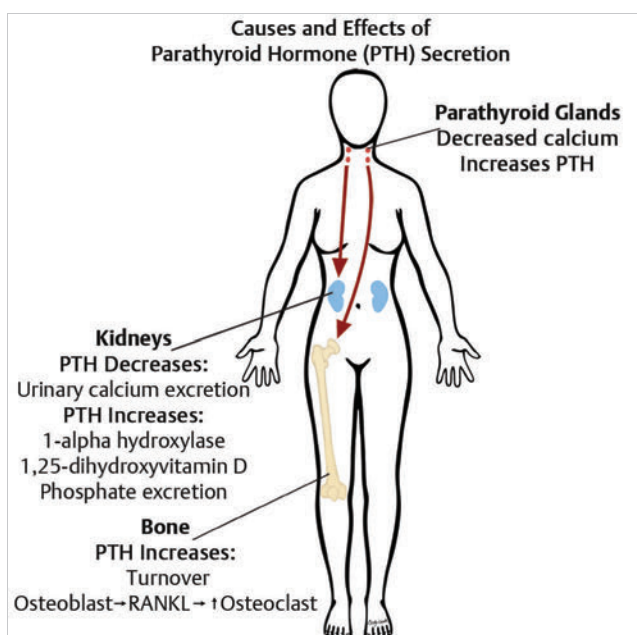


Fig. 4.3 Target tissues for parathyroid hormone (PTH). PTH receptors are present in many tissues, although bone and kidney are the main classical targets. In the kidney, PTH increases 1-alpha hydroxylase activity and synthesis of 1,25-dihydroxyvitamin D₃. It also decreases urinary calcium excretion and increases urinary phosphate excretion. In the bone it predominantly targets the osteoblasts and secondarily the osteoclasts. Ca, calcium; PTH, parathyroid hormone.

4.4 Parathyroid Hormone Target Organs

4.4.1 PTH Actions in the Kidney

PTH has multiple actions in the kidney, including decreasing phosphate and bicarbonate reabsorption in the proximal tubule and increasing calcium reabsorption in the distal tubule (► Fig. 4.3). Because of these PTH actions in the kidney the most common electrolyte abnormalities in primary hyperparathyroidism are hypercalcemia with hypophosphatemia and a hyperchloremic metabolic acidosis. About 50% of patients with primary hyperparathyroidism have a serum phosphorus level < 2.5 mg/dL, and 40% of patients have a chloride level > 107 mEq/L.³⁰

PTH also increases the activity of the 25-hydroxyvitamin D 1-alpha hydroxylase enzyme in the mitochondria of the proximal tubule cells. This enzyme converts circulating 25-hydroxyvitamin D to the active 1,25-dihydroxyvitamin D metabolite, which in turn increases calcium absorption in the small intestine by increasing the levels of an intestinal calcium-binding protein.³¹ Inadequate levels of vitamin D result in poor intestinal calcium absorption from the diet, and even the small amounts of the ion lost in the urine cannot be replaced. PTH secretion remains high in an attempt to compensate, resulting in the progressive draining of calcium from the bone reservoir in an attempt to maintain serum calcium levels. This loss of calcium results in poorly mineralized

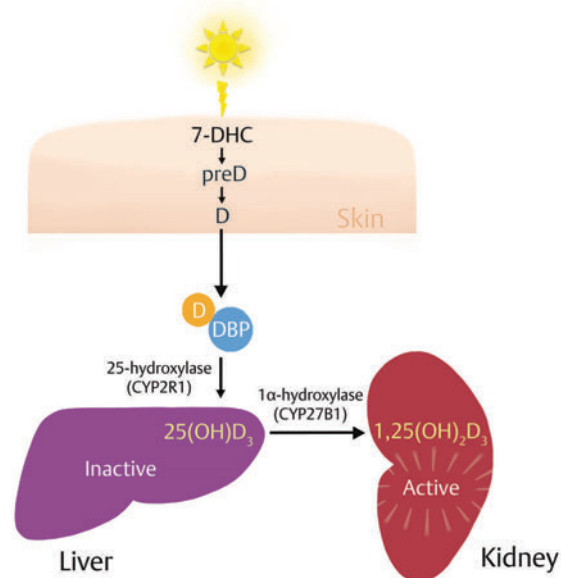


Fig. 4.4 Vitamin D generation and metabolism. Solar irradiation converts 7-dehydrocholesterol (7-DHC) in the skin to previtamin D₃ (preD₃), which then thermally rearranges to vitamin D₃. Vitamin D₃ leaves the skin and is transported throughout the body bound to the serum protein, vitamin D binding protein (DBP). Vitamin D is hydroxylated in the liver to inactive 25-hydroxyvitamin D₃ [25(OH)D₃] by the enzyme 25-hydroxylase (CYP2R1) and then to the active metabolite 1,25-dihydroxyvitamin D₃ [1,25(OH)₂D₃] by the 1-alpha-hydroxylase (CYP27B1) enzyme in the kidney. It should be noted that the skin itself also expresses the 25-hydroxylase and 1-hydroxylase enzymes and so can produce active 1,25-dihydroxyvitamin D₃; however, the skin does not seem to contribute to the systemic levels of 1,25-dihydroxyvitamin D₃, although this sterol hormone does appear to serve a paracrine role to regulate skin cell (keratinocyte) growth and differentiation.

bones and is termed rickets in the young, or osteomalacia in adults.

Vitamin D can be obtained from exposure of the skin to ultraviolet B radiation in sunlight (► Fig. 4.4) or from the diet. Ultraviolet irradiation of 7-dehydrocholesterol (provitamin D) in the skin photolyzes this sterol to previtamin D, a thermodynamically unstable compound that rapidly converts to vitamin D, and is then circulated in the bloodstream bound to vitamin D-binding protein.^{32,33,34} Vitamin D can also be obtained from dietary animal and plant sources. Circulating vitamin D is metabolized in the liver to 25-hydroxyvitamin D, an inactive metabolite that is then converted to active 1,25-dihydroxyvitamin D in the kidney under the control of PTH.

Historically, the ability to obtain vitamin D from two sources (the diet or sun exposure) was a source of confusion and debate among scientists at the time. Between the 1600s and the 1900s, the industrial revolution, with its increased pollution, urbanization, and overall decreased solar exposure, led to an increasing prevalence of rickets in children, such that, at the turn of the 19th century, ~ 90% of children on autopsy presented with the disease.^{32,33} As early as 1822, Sniadecki originally proposed that rickets was due to lack of sunlight,^{32,34} and this idea was

supported almost 7 decades later in the epidemiological studies of Palm.^{32,34} From about 1919 to 1922 various researchers were able to demonstrate that exposure to radiation from a mercury vapor quartz lamp or the sun could cure rickets.^{32,33,34,35} During this same time several investigators also showed that rachitic animal models could be cured by administration of cod liver oil, which is now known to be high in vitamin D. By about 1925 the confusion about whether rickets could be cured by direct exposure to the sun or a dietary factor was resolved by studies of their common mechanism of action, leading to the fortification of milk products with vitamin D and virtually eradicating rickets.^{32,33} Nevertheless, there is an ongoing debate about the exact requirements for this important sterol, with questions about its potential beneficial effects on tissues and organs in addition to bone. The Institute of Medicine (IOM) has recently amended its recommended vitamin D requirement to 600 international units for adults aged 19 to 70, stating that this amount seems to fully protect bone health and indicating that the data for effects on other tissues are equivocal.³⁶ Nevertheless, there are some scientists who feel that the IOM did not properly evaluate all of the data,³⁷ and more research is needed.³⁶

4.4.2 PTH Actions on Bone

PTH has complex effects on the bone (► Fig. 4.3). PTH receptors are present on bone-forming cells, osteoblasts, and in the osteoblast precursors, mesenchymal stem cells. In patients with long-standing hyperparathyroidism there is an increase in the number of cells that break down bone, osteoclasts, but this appears to be an indirect effect mediated by release of soluble factors from the osteoblast in response to PTH. Osteoclast number and activity are regulated by the balance between factors that stimulate osteoclastic maturation, such as receptor activator of nuclear factor- κ B ligand (RANKL), and those factors that inhibit osteoclastic development, such as osteoprotegerin (OPG), which is a soluble decoy receptor for RANKL. Both of these factors are produced by osteoblasts, and PTH favors the production of RANKL over OPG, thus increasing the number and activity of osteoclasts.³¹ On the other hand, PTH increases the number of osteoblasts by decreasing osteoblast apoptosis^{38,39} and increases the production of growth factors, such as insulin-like growth factor 1 (IGF-1), by osteoblasts.^{40,41} The fact that the anabolic effect of PTH predominates is evidenced by the fact that PTH is currently used for the treatment of osteoporosis, although the key difference seems to be that, in primary hyperparathyroidism, PTH levels are elevated in a sustained manner, whereas PTH, when used for treatment of osteoporosis, is administered in an intermittent fashion.

4.4.3 PTH Actions on Nonclassical Target Organs

For many years, the exclusive target cells for PTH action were thought to be those in several segments of the proximal and distal renal tubules and certain bone cells.^{42,43} However, more recent work has led to the discovery that there are effects of PTH on a variety of other cells, including cardiac myocytes,

adrenal glomerulosa cells,⁴⁴ vascular endothelial cells,⁴⁵ and vascular smooth muscle cells.^{44,46,47} It was initially thought that PTH might be a vasoconstrictor because there is a higher incidence of essential hypertension in patients with primary hyperparathyroidism and because parathyroidectomy in spontaneously hypertensive rats (SHR) prevents the development of hypertension. However, investigators found that if PTH was infused in vivo, the hormone caused smooth muscle relaxation,⁴⁸ and if PTH was infused into animals or humans, there was an initial rapid (though transient) fall in blood pressure. The initial hypotensive effect is seen with amino terminal PTH fragments (1–34), is most effective when the muscle is precontracted, and is predominantly a cAMP, and not a nitric oxide cyclic guanosine monophosphate-mediated, relaxation. PTH has also been reported to block L-type calcium channel current in a neural cell line, suggesting an alternate possible mechanism for its ability to induce smooth muscle relaxation.⁴⁹ PTH receptors have been shown to be present in vascular endothelial cells,⁴⁵ and PTH can modulate secretion of the potent vasoconstrictor endothelin-1. Thus some of the discrepancies in the observations of PTH effects on muscle and vasculature may relate to differences in direct PTH effects on smooth muscle versus indirect effects through endothelial cells.

The closely related molecule PTHrP also appears to be a potent vasorelaxant,⁵⁰ and it is possible that the action of PTH on smooth muscle relaxation is mediated through a PTHrP receptor. PTHrP mRNA and the protein itself are known to be present in vascular smooth muscle and endothelial cells. Therefore, it has been proposed that PTHrP may be a vasodilatory paracrine factor secreted to regulate smooth muscle contraction.^{51,52,53,54}

PTH has also been shown to potentiate angiotensin II-stimulated aldosterone secretion in vitro and thus plays a role in the higher incidence of high blood pressure seen in patients with primary hyperparathyroidism, although high PTH concentrations were used in the published studies. It is possible that this PTH effect is seen in vivo only in situations of sustained elevations of PTH, such as in primary hyperparathyroidism.

4.5 Conclusion

Calcium regulation is exquisitely regulated in vivo, with small changes in serum calcium leading to large changes in PTH secretion, and additional changes in calcium handling by the kidney and intestine. Because of the evolutionary transition from a calcium-rich ocean environment to a calcium-poor land environment, the human body contains multiple homeostatic mechanisms to protect against hypocalcemia; thus this is a relatively rare occurrence. Hypercalcemic disorders on the other hand are common and may range from benign to malignant processes involving the parathyroid glands. The present availability of agents that modify calcium binding to its receptor in the parathyroid gland (calcilytic or calcimimetic agents), parathyroid gland growth and proliferation (vitamin D analogues), or parathyroid hormone processing makes it essential for the clinician to have a clear understanding of the normal physiological regulation of PTH secretion to make more rational therapeutic decisions.

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5 Thyroid and Parathyroid Pathology

Paul W. Biddinger and Yuri E. Nikiforov

5.1 Introduction

The thyroid and parathyroid glands are susceptible to a number of pathological processes, including developmental, inflammatory, autoimmune, and neoplastic conditions. A fundamental understanding of thyroid and parathyroid pathology is critical in counseling and managing patients with these diseases.

5.2 Thyroid Pathology

5.2.1 Developmental Lesions of the Thyroid

Ectopic thyroid tissue is usually found medially along the embryological migration track of the medial anlage between the base of tongue and the normal thyroid location. Most cases of ectopia involve the tongue and are asymptomatic. However, lingual ectopia can be symptomatic due to mass effect, and most symptomatic cases lack other functional thyroid tissue.¹ Rare cases of carcinoma arising in lingual thyroids have been reported.²

Thyroglossal duct cysts develop from remnants of the thyroglossal duct, typically in the midline of the neck between the foramen cecum and the thyroid. Cysts usually contain mucoid or gelatinous material, but thyroid tissue is usually not grossly identifiable. The lining of these cysts ranges from ciliated epithelium to simple cuboidal or stratified squamous cells. Colloid-containing follicles are seen in about 50% of cases.³ Fine-needle aspiration (FNA) generally yields sparsely cellular specimens with foamy or hemosiderin-laden macrophages in a background of amorphous material. Ciliated or squamous cells may be seen, but thyroid follicles are uncommon findings in FNAs. Cysts may become infected or may rarely undergo malignant transformation. Most cases of malignancy are papillary thyroid carcinomas (PTCs).²

5.2.2 Thyroiditis

Chronic Lymphocytic Thyroiditis (Hashimoto's or Autoimmune Thyroiditis)

Chronic lymphocytic thyroiditis (CLT), alternatively known as Hashimoto's thyroiditis or autoimmune thyroiditis, is an autoimmune disorder and the most common clinically significant form of thyroiditis. It is characterized by destruction of follicular cells, which, over time, can result in hypothyroidism. The pathogenesis of CLT is incompletely understood, but both cell-mediated and humoral mechanisms appear to be involved, probably induced by the interaction of genetic and environmental factors.⁴

CLT is typically associated with diffuse thyroid enlargement, generally, two to four times normal size. Thyroid tissue is usually paler than its normal red-brown color due to lymphocytic infiltration and loss of follicular tissue. Glands may show accentuated lobulation. Histologically, the most characteristic feature is infiltration by lymphocytes and plasma cells (► Fig. 5.1). The lymphoplasmacytic infiltration is diffuse but variable in its intensity and effacement of the follicles. Lymphoid germinal centers are another characteristic feature.

Variable numbers of follicular epithelial cells exhibit enlargement and abundant, finely granular eosinophilic cytoplasm, known as oncocytic or Hürthle cell metaplasia. This appearance is caused by abundant cytoplasmic mitochondria. Oncocytic follicular cells may also show nuclear enlargement and prominent nucleoli.

Variants of CLT include fibrous, fibrous atrophy, toxic (hashitoxicosis), and juvenile, though most cases of CLT have slight to moderate fibrosis. The fibrous variant usually exhibits some degree of thyroid enlargement associated with marked deposition of dense fibrous tissue and follicular atrophy. Fibrosis is limited to the thyroid, in contrast to the extrathyroidal fibrosis

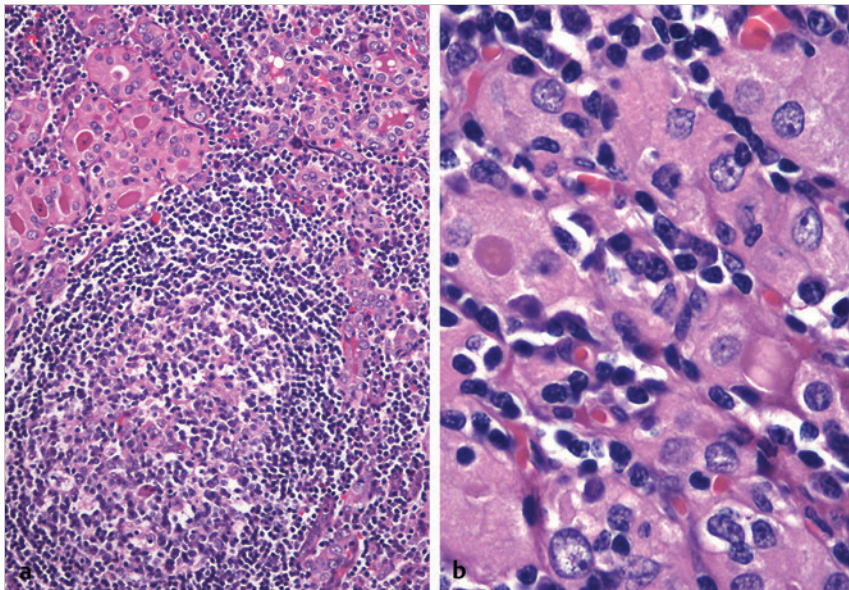


Fig. 5.1 Chronic lymphocytic thyroiditis. (a) Lymphoplasmacytic infiltrate, germinal center, follicular atrophy, and oncocytic metaplasia. (b) High-power view of oncocytic metaplasia. (Hematoxylin-eosin stain)

of invasive fibrous (Riedel's) thyroiditis. Squamous metaplasia is more common and prominent compared to classic CLT. Some cases may represent immunoglobulin G4 (IgG4)-related sclerosing disease involving the thyroid.⁵ The fibrous atrophy variant is histologically similar to the fibrous variant but is distinguished by the small size of the thyroid. Whether the fibrous atrophy variant represents progression of the fibrous variant and/or classic form of CLT or has a distinct pathogenic mechanism is unclear at this time.

CLT may be associated with hyperthyroidism, a condition referred to as hashitoxicosis. Thyroids with this condition generally exhibit classical changes of CLT with variable degrees of follicular epithelial hyperplasia.⁶

Subacute Granulomatous Thyroiditis (Subacute or de Quervain's Thyroiditis)

Subacute granulomatous thyroiditis (SGT) is characterized by the presence of epithelioid macrophages (histiocytes) and variable numbers of multinucleated giant cells. This condition has a variety of alternate names, including de Quervain's, subacute, painful subacute, postviral, and giant cell thyroiditis. SGT appears to be the result of a systemic illness, with viral infection being the leading suspect, although conclusive evidence is lacking at this time.

The thyroid gland is usually enlarged to about twice its normal size. The enlargement may be asymmetric, and a small percentage of cases present as a solitary nodule.⁷ During the early, usually hyperthyroid, stage of disease the thyroid shows follicular damage with loss of epithelium and colloid. Acute and chronic inflammatory cells are present within residual follicles and interfollicular areas. Over time granulomatous and chronic inflammation with variable degrees of fibrosis predominate.⁸ Distinct granulomata or lymphoid follicles are usually not seen; instead giant cells are found around disrupted follicles. The inflammatory and repair process may be heterogeneous with areas of active inflammation coexisting with areas of fibrosis.

Acute Thyroiditis

Acute, or suppurative, thyroiditis is characterized by a predominantly neutrophilic inflammatory infiltrate. This is a rare form of thyroiditis, usually caused by bacterial infection arising elsewhere in the neck and secondarily involving the thyroid. In children, acute thyroiditis is usually associated with a pyriform sinus fistula.⁹

Invasive Fibrous Thyroiditis (Riedel's Thyroiditis)

Invasive fibrous thyroiditis (IFT), also known as Riedel's, fibrosing, or sclerosing thyroiditis, is a rare disease characterized by progressive fibrosis of the thyroid. Affected glands are extremely firm and adherent to perithyroidal tissues due to fibrosis extending beyond the thyroid. The thyroid parenchyma is effaced by chronic inflammation and fibrosis, with absence or marked atrophy of follicles. Lymphocytes and plasma cells are the predominant inflammatory cells. Occlusive vasculitis of small- to medium-sized veins is a distinctive feature. FNA is almost always nondiagnostic due to acellular or paucicellular

specimens. The presence of IgG4-positive plasma cells and association with other fibroinflammatory disorders suggest that IFT may be a manifestation of IgG4-related sclerosing disease.¹⁰

5.2.3 Goiter

Goiter is a nonspecific term meaning enlargement of the thyroid and encompasses multinodular, endemic, dys hormonogenetic, diffuse toxic, and amyloid goiter. These entities, with the exception of amyloid goiter, are associated with hyperplastic changes of the follicles.

Multinodular Goiter (Nodular Hyperplasia)

Multinodular goiter (MNG) is a common condition characterized by enlargement of the thyroid gland with variable amounts of nodularity. MNG is also known as nodular hyperplasia, nodular goiter, colloid goiter or nodule, adenomatoid nodule or hyperplasia, and other combinations of these terms. The term nodular hyperplasia reflects histopathologic changes seen in this condition and is often used in the pathological description and diagnosis.

Sporadic and endemic MNG have comparable pathological features. Endemic goiter is usually due to dietary iodine deficiency.¹¹ Sporadic cases have a number of possible pathogenic mechanisms, including individual dietary iodine deficiency, excessive ingestion of goitrogenic foods, medications, increased thyroid-stimulating hormone (TSH) secretion, and constitutive activation of follicular cells due to somatic mutations of the TSH receptor gene.¹² Identifying a specific cause may be difficult, if not impossible, because most cases of MNG appear to be due to complex interaction between multiple genes and various environmental factors. Congenital defects in the pathways of thyroid hormone synthesis and release can result in dys hormonogenetic goiter and associated hypothyroidism.

MNG is characterized by thyroid enlargement that can range from mild to massive. Most cases have multiple nodules evident grossly, although early cases may lack distinct nodularity or only have a single macroscopic nodule. Thyroid enlargement may be symmetric or asymmetric. The sectioned surfaces typically have a nodular, heterogeneous appearance. Some areas have a semitranslucent appearance due to abundant colloid, whereas other foci exhibit hemorrhage, fibrosis, cystic degeneration, and/or calcification. Nodules may appear partially encapsulated by fibrous tissue.

Microscopically, follicles exhibit variable sizes and shapes, ranging from small with minimal colloid to very large with abundant colloid (► Fig. 5.2). Some pathologists use the term adenomatous nodule to refer to a nodule with high cellularity due to a microfollicular or solid growth pattern, and the term colloid nodule for a nodule with abundant colloid and a low density of follicular cells. The follicular epithelium varies from flattened to cuboidal or columnar and focally may exhibit oncocytic or clear cell features. Follicles may contain papillary-like infolding of epithelium, sometimes raising concern for papillary carcinoma. Foci of hemorrhage and fibrosis are common and may be associated with dystrophic calcification.

FNA typically yields a mixture of colloid and benign-appearing follicular cells. Follicular cells are usually arranged in evenly spaced monolayer sheets. Macrophages are commonly seen and may contain hemosiderin.

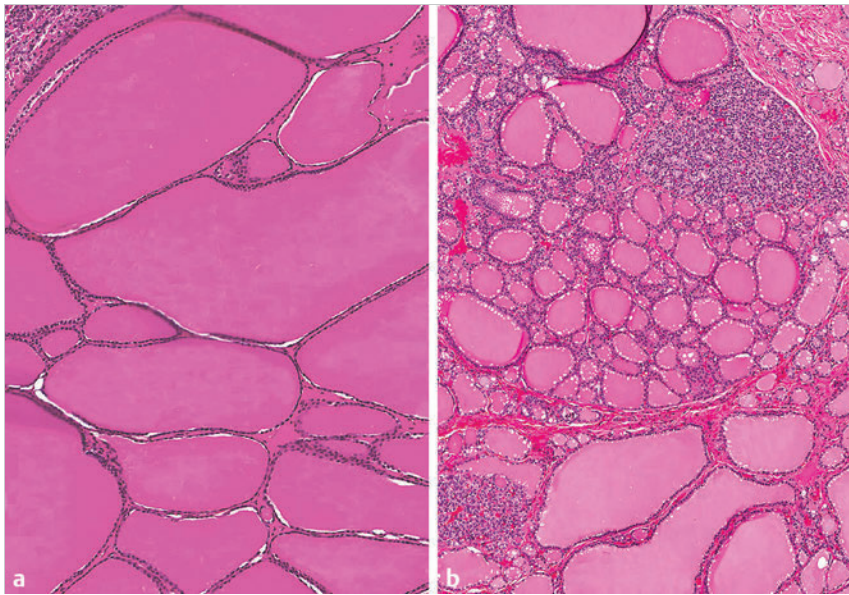


Fig. 5.2 Multinodular goiter (nodular hyperplasia). (a) Macrofollicles with abundant colloid. (b) Area with follicles ranging from macrofollicular to microfollicular with scant colloid. (Hematoxylin-eosin stain)

Endemic Goiter

Endemic goiter refers to thyroid enlargement that occurs in a significant portion of a region or population. A common criterion is 5% or more of children aged 6 to 12 having thyroid enlargement.¹³ The pathological features of endemic goiter are comparable to those of MNG.

Dyshormonogenetic Goiter

Dyshormonogenetic goiter results from a genetic defect that interrupts any one of the steps of thyroid hormone synthesis. Excess TSH, released to try to correct the primary hypothyroidism, leads to enlargement of the thyroid gland. Dyshormonogenetic goiter is grossly indistinguishable from MNG, and their microscopic features overlap. A feature favoring dyshormonogenetic goiter is pronounced hyperplasia with a predominantly solid or microfollicular pattern throughout the entire gland, not just the nodules.¹⁴ Colloid is usually absent or minimal, and follicular cells frequently show marked nuclear atypia. These findings in the thyroid of a child or young adult are suspicious for dyshormonogenetic goiter, but definitive diagnosis will depend on clinicopathologic correlation and confirmatory ancillary studies.

Toxic (Hyperfunctioning) Multinodular Goiter

Toxic MNG is a complication of MNG in which one or more nodular collections of follicular cells secrete an excessive amount of thyroid hormone. Affected glands are grossly comparable to nontoxic MNG. Microscopically, one or more nodules may show features of hyperfunction, including tall follicular cells, papillary-like infoldings, and scant, watery colloid with peripheral scalloping. Definitive diagnosis depends on clinical and laboratory findings of hyperthyroidism.

Diffuse Toxic Hyperplasia (Graves' Disease)

Diffuse toxic hyperplasia (DTH), also known as Graves' disease or diffuse toxic goiter, is an autoimmune disorder characterized

by excessive production of thyroid hormone and diffuse hyperplasia with enlargement of the thyroid. DTH is associated with extrathyroidal lesions, including inflammation of the orbital tissues, known as Graves' ophthalmopathy, and excessive accumulation of glycosaminoglycans in the skin, known as myxedema.

DTH is caused by autoantibodies attaching to the TSH receptor (TSHR) on follicular cells. The autoantibodies activate the receptor and stimulate thyroid hormone synthesis and secretion in addition to proliferation of the follicular epithelium. A combination of genetic susceptibility and one or more environmental triggers appears to result in this autoimmune disorder.⁴

Thyroid glands are mild to moderately enlarged, usually in a symmetrical manner. Untreated cases have a dark red appearance due to high vascularity, whereas treated cases appear lighter and more similar to normal thyroid due to decreased vascularity and the presence of more colloid. The classic microscopic appearance is diffuse hyperplasia, with follicles lined by tall columnar cells that exhibit papillary-like infolding into the central space (► Fig. 5.3). Untreated cases contain very little colloid.

Some form of therapy precedes resection of most cases, resulting in reduction of the hyperplastic changes and an increase in the amount of colloid. The regression of hyperplastic changes is typically incomplete, with scattered areas of follicular hyperplasia still present. Variable numbers of lymphocytes are seen in the interfollicular stroma. Radioiodine may cause nuclear atypia that, in some cases, suggests papillary carcinoma.

A case of treated DTH may be interpreted as MNG or CLT by a pathologist unaware of the clinical diagnosis and prior treatment. Nodular lesions are found in 10 to 25% of thyroids with DTH, and most are benign with features of follicular hyperplasia or colloid nodule. However, about 10 to 20% of nodules are found to have carcinoma, usually papillary carcinoma, and the overall incidence of carcinoma associated with DTH is in the 1 to 9% range.^{15,16}

5.2.4 Thyroid Neoplasia

Thyroid neoplasia is classified into three general categories of primary epithelial, nonepithelial, and secondary (metastatic)

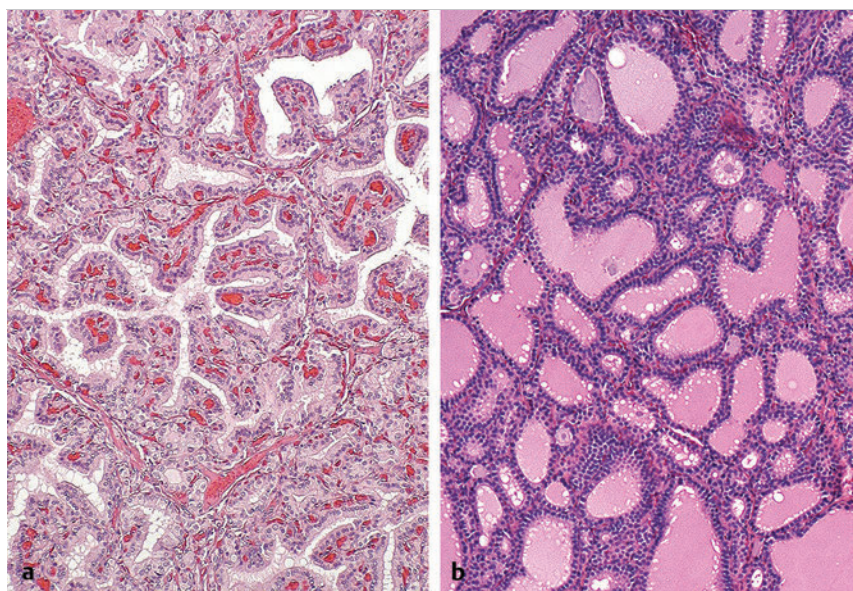


Fig. 5.3 Graves' disease (diffuse toxic hyperplasia). (a) Untreated with high vascularity and scant, watery colloid. (b) Treated with reduced vascularity and accumulation of colloid. (Hematoxylin-eosin stain)

tumors. The World Health Organization classifies thyroid tumors as follows¹⁷:

- Thyroid carcinomas
 - Papillary carcinoma
 - Follicular carcinoma
 - Poorly differentiated carcinoma
 - Undifferentiated (anaplastic) carcinoma
 - Squamous cell carcinoma
 - Mucoepidermoid carcinoma
 - Sclerosing mucoepidermoid carcinoma with eosinophilia
 - Mucinous carcinoma
 - Medullary carcinoma
 - Mixed medullary and follicular cell carcinoma
 - Spindle cell tumor with thymus-like differentiation
 - Carcinoma showing thymus-like differentiation
- Thyroid adenoma and related tumors
 - Follicular adenoma
 - Hyalinizing trabecular tumor
- Other thyroid tumors
 - Teratoma
 - Primary lymphoma and plasmacytoma
 - Ectopic thymoma
 - Angiosarcoma
 - Smooth muscle tumors
 - Peripheral nerve sheath tumors
 - Paraganglioma
 - Solitary fibrous tumor
 - Follicular dendritic cell tumor
 - Langerhans cell histiocytosis
- Secondary (metastatic) tumors

Most thyroid neoplasms are primary epithelial tumors derived from follicular epithelium, with a small fraction originating from C cells. Great strides have been made in understanding the molecular genetics of thyroid neoplasia, and this subject is addressed in Chapter 9.

Papillary Thyroid Carcinoma

PTC is a well-differentiated malignant tumor of thyroid follicular cells defined by characteristic nuclear features. A papillary growth pattern is frequently seen but is not required for the diagnosis. PTC is the most common type of thyroid cancer, accounting for 85 to 90% of cases in the United States.¹⁸

The vast majority of tumors are sporadic cases, with only a small portion being due to germline mutations.¹⁹ Preexisting solitary thyroid nodules and/or adenomas and multinodular goiter are risk factors for PTC, possibly due to an increased cell proliferation rate in adenomas and hyperplastic nodules and *RAS* gene mutations in follicular adenomas that may predispose to malignant transformation.²⁰

Grossly, most PTCs appear as a discrete but ill-defined nodule with irregular borders. A capsule is typically absent, but some tumors may be well demarcated or encapsulated, with the exception of the follicular variant. Tumors range in appearance from tan-brown to gray-white and from firm and solid to more friable with cystic spaces. Irregularly shaped areas of fibrosis are frequent. Spontaneous necrosis and hemorrhage are rare but may be seen after FNA. Multifocal tumors are fairly common.

PTC can exhibit a variety of patterns. Microscopically, most PTCs show a papillary growth pattern characterized by fine, fingerlike strands of fibrovascular stroma covered by neoplastic epithelial cells, usually forming a single layer. This pattern is commonly admixed with a variable proportion of neoplastic follicles. Approximately two-thirds of tumors have this predominantly papillary growth, whereas about one-third exhibit a predominantly follicular architecture (► Fig. 5.4).²¹ Papillary carcinomas can have other growth patterns, including solid and trabecular, but these rarely predominate.

Despite these histological findings, the diagnosis of PTC is dependent on characteristic nuclear features, not growth pattern. These features include nuclear enlargement, overlapping,

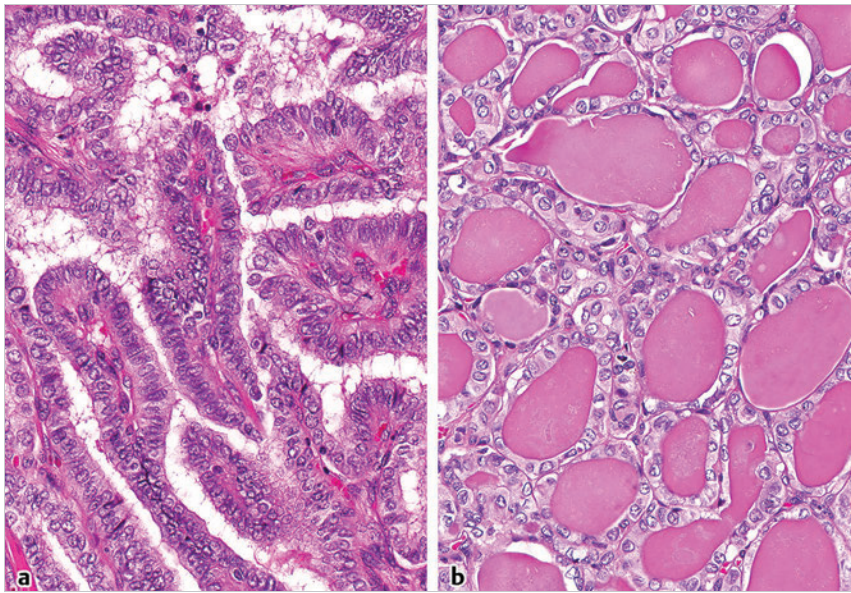


Fig. 5.4 Papillary thyroid carcinoma. (a) Papillary and (b) follicular growth patterns. (Hematoxylin-eosin stain)

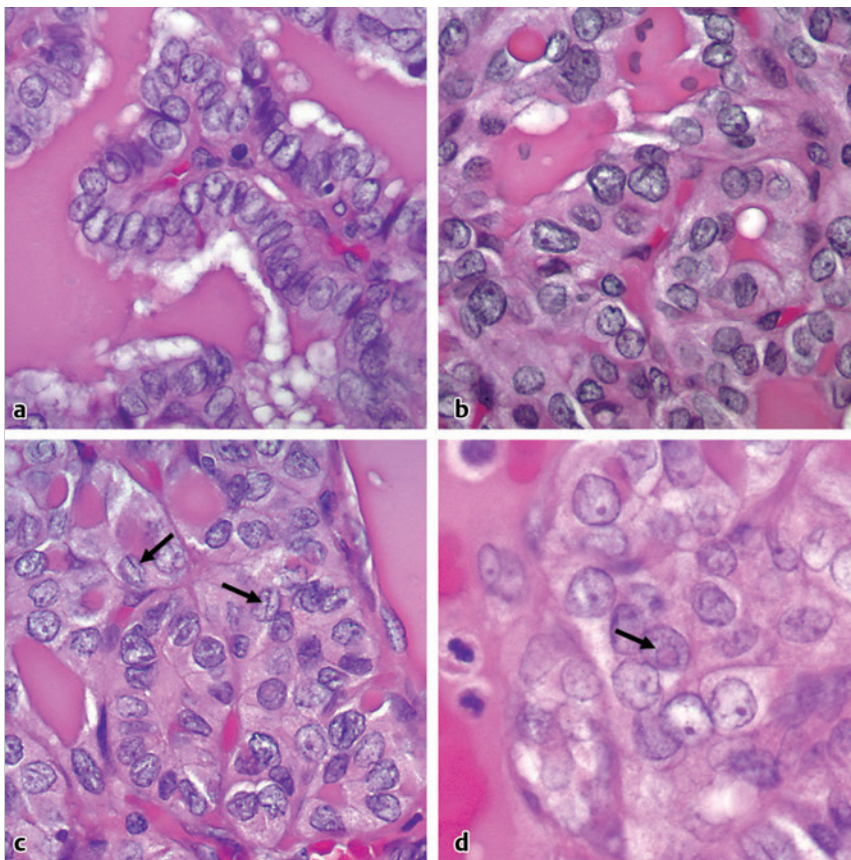


Fig. 5.5 Nuclear features of papillary thyroid carcinoma. (a) Nuclear hypochromasia, enlargement, and overlapping. (b) Irregular nuclear membrane contours. (c) Nuclear grooves (arrows). (d) Nuclear pseudoinclusion (arrow). (Hematoxylin-eosin stain)

hypochromasia, irregular contours, grooves, and pseudoinclusions (► Fig. 5.5). In some PTCs all of the nuclear features are readily identifiable. Others exhibit most, but not all, of these features, or they are found focally. There is no consensus on how many nuclear features are sufficient for the diagnosis and how widespread they should be, but most exhibit at least four. None of these features are pathognomonic for PTC, and a single feature may be seen in a variety of benign lesions. True nuclear pseudoinclusions have a relatively high specificity, but they are

the least common feature and absent in a significant proportion of PTCs.

Psammoma bodies are distinctive laminated calcifications that are found in about half of all PTCs.^{21,22} Psammoma bodies are particularly abundant in the diffuse sclerosing variant of PTC, and true psammoma bodies are exceedingly rare in lesions other than PTC.

PTC FNA specimens contain follicular cells arranged in papillae and/or monolayers. The cells exhibit the characteristic

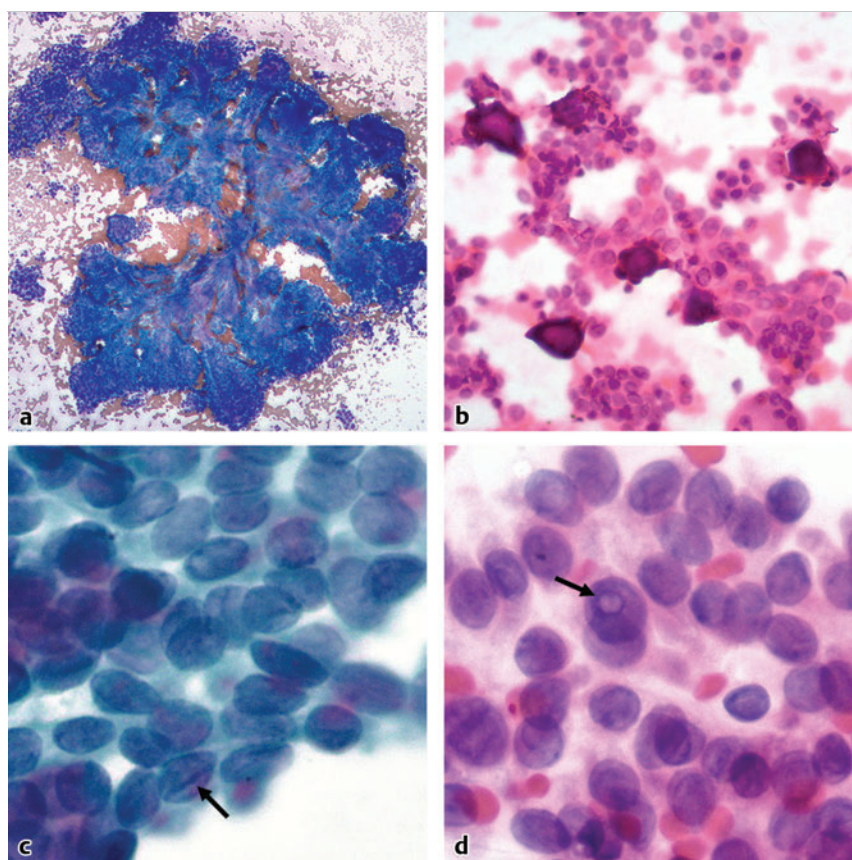


Fig. 5.6 Cytological features of papillary thyroid carcinoma. (a) Papillary tissue fragment (Diff-Quik stain). (b) Psammoma bodies associated with malignant cells (hematoxylin-eosin stain). (c) Nuclear grooves and finely textured chromatin (arrow) (Papanicolaou stain). (d) Nuclear pseudoinclusion (arrow) (hematoxylin-eosin stain).

nuclear features already noted (► Fig. 5.6). The amount of colloid is variable, and sometimes psammoma bodies are seen.

Multifocal disease may represent either multiple independent primary tumors or intraglandular dissemination from a single primary tumor. Lymphatic invasion is frequently seen, whereas blood vessel invasion is very uncommon.

Extrathyroidal extension of tumor may be minimal or extensive. Minimal extrathyroidal extension includes infiltration of perithyroidal skeletal muscle or the areas surrounding sizable vascular structures or nerves.²³ Whether a minimal presence in perithyroidal adipose tissue qualifies as extrathyroidal extension is somewhat controversial. Extensive extrathyroidal extension is defined as involvement of the adjacent viscera (larynx, trachea, and/or esophagus), recurrent laryngeal nerve, carotid artery, mediastinal blood vessels, or subcutaneous soft tissues, and some authors also include involvement of adjacent skeletal muscle in this category. Extensive extrathyroidal invasion may be associated with a poorer prognosis.²⁴

5.3 Variants of Papillary Carcinoma

PTC has more than 10 different histological variants, most of which are rare. The most common is papillary microcarcinoma, defined by the World Health Organization (WHO) classification as PTC, which is both ≤ 1 cm in diameter and found incidentally.¹⁷ Many microcarcinomas are identified only microscopically, and they can exhibit papillary, follicular, or a mixed growth pattern.

Follicular variant PTC (FVPTC) is another common variant characterized by an exclusive or predominantly follicular growth pattern, a lack of well-formed papillae, and the presence of diagnostic nuclear features of PTC. This is a distinct variant of papillary carcinoma with a number of characteristic molecular and biological features, some of which overlap with follicular tumors. FVPTC is frequently well circumscribed and sometimes encapsulated. Most of the characteristic nuclear features of PTC are present, particularly nuclear enlargement, chromatin clearing, and irregularity of nuclear contours. Other nuclear features are typically less abundant than in classic papillary carcinoma. Immunohistochemical staining, particularly for HBME-1, may be helpful when positive to distinguish FVPTC from a follicular adenoma or carcinoma. Encapsulated subtypes of follicular variant are generally indolent tumors with a low rate of distant metastasis.²⁵

The tall cell variant is characterized by a predominance ($>50\%$) of tumor cells with a height at least three times the width (► Fig. 5.7a). The tall cell variant has a poorer prognosis with a significantly higher rate of lymph node and distant metastases and lower 5-year disease-specific survival.^{26,27} Tumors with a tall cell component $<50\%$ are designated as “papillary carcinoma with tall cell features.” The significance of a minor tall cell component is uncertain at this time, but it too may be a marker of more aggressive behavior compared to PTC without tall cell features.

Additional variants include solid, diffuse sclerosing, columnar cell, oncocytic, Warthin-like, clear cell, cribriform-morular, and those with prominent hobnail cells or fasciitis-like stroma. The solid variant has a predominantly ($>50\%$) solid, trabecular, or

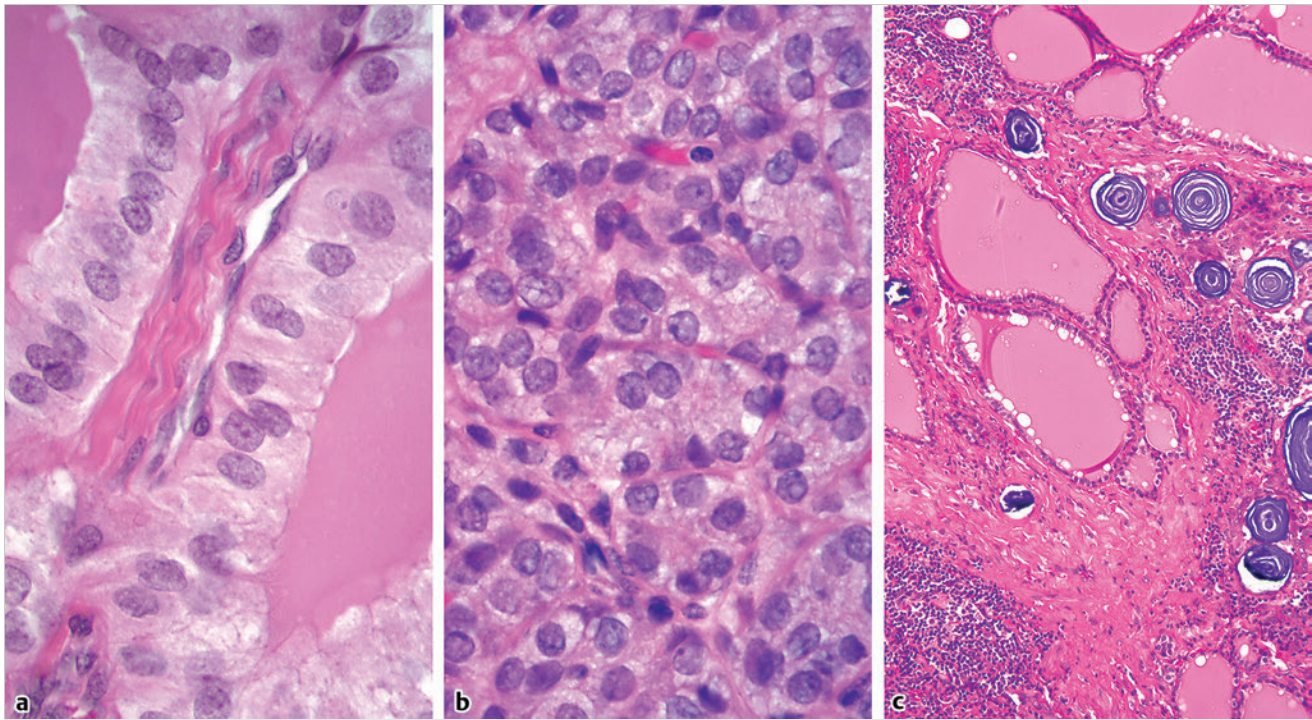


Fig. 5.7 Variants of papillary thyroid carcinoma. (a) Tall cell variant. (b) Solid variant. (c) Diffuse sclerosing variant with marked fibrosis, lymphocytic infiltration, and numerous psammoma bodies. (Hematoxylin-eosin stain)

nested pattern (► Fig. 5.7b). Diffuse sclerosing variant is characterized by diffuse glandular involvement, dense fibrosis, numerous psammoma bodies, extensive lymphocytic infiltration, and frequent squamous metaplasia (► Fig. 5.7c). Columnar cell variant is an aggressive form of PTC characterized by elongated, pseudostratified, and often hyperchromatic nuclei with a variety of growth patterns. The cribriform-morular variant has a frequent association with familial adenomatous polyposis.²⁸

5.3.1 Follicular Adenoma and Carcinoma

Follicular adenoma (FA) is a benign, encapsulated, noninvasive tumor originating from thyroid follicular cells, and follicular carcinoma (FC) is a malignant, well-differentiated tumor of thyroid follicular cells that lacks the diagnostic nuclear features of PTC. Most FAs and FCs are solitary nodules that are clearly demarcated from the surrounding thyroid tissue by a well-formed fibrous capsule. Carcinomas are distinguished from adenomas by invasive growth through the capsule or into blood vessels located in or peripheral to the capsule (► Fig. 5.8). Either is a sufficient criterion for malignancy. Invasive growth is not grossly identifiable in the vast majority of cases. When grossly identifiable, invasion may be focal in an encapsulated tumor or widespread in a tumor that has little or no capsule.

FAs and FCs exhibit architectural and cytological features that are distinct from the surrounding thyroid parenchyma. A variety of microscopic patterns can be seen, including microfollicular, solid/trabecular, normofollicular, and macrofollicular. Microfollicular is the most frequent pattern, but multiple

patterns in a given tumor are common. FCs tend to be more cellular than FAs, but cellularity per se is not a differentiating feature. Nuclei are usually small to medium, round with smooth contours, uniform, and normochromatic or hyperchromatic. Occasionally, cells with large and highly irregular nuclei may be found in either FAs or FCs. Mitotic figures are rarely seen in adenomas, and most carcinomas have low activity (up to 1–2 per 10 high-power fields) with the exception of areas of recent FNA. Necrosis and more frequent mitoses suggest the emergence of poorly differentiated thyroid carcinoma.²⁹

Assessment for capsular and angioinvasion can be challenging due to a number of factors, including infrequent foci and a number of real and artifactual changes that mimic invasion. One example is prior FNA that results in pseudoinvasive alterations of the capsule. The extent of vascular invasion appears to be significant because invasion of four or more blood vessels is associated with an increased rate of tumor recurrence and/or tumor-related mortality.^{30,31}

FAs and FCs have a number of microscopic variants. Oncocytic variants (Hürthle cell) are common and are characterized by cells that are larger than typical neoplastic follicular cells and have granular eosinophilic cytoplasm due to abundant mitochondria (► Fig. 5.9). At least 75% of the cells should be oncocytic to qualify as this variant. The criteria for malignancy are the same as for conventional FC. Whether oncocytic tumors should be considered variants of FAs and FCs or distinct variants is a subject of debate, and future classification may change. The term *oncocytic* is recommended instead of *Hürthle cell*.¹⁷ Other microscopic variants of follicular neoplasia include clear, mucinous, and signet ring cells.

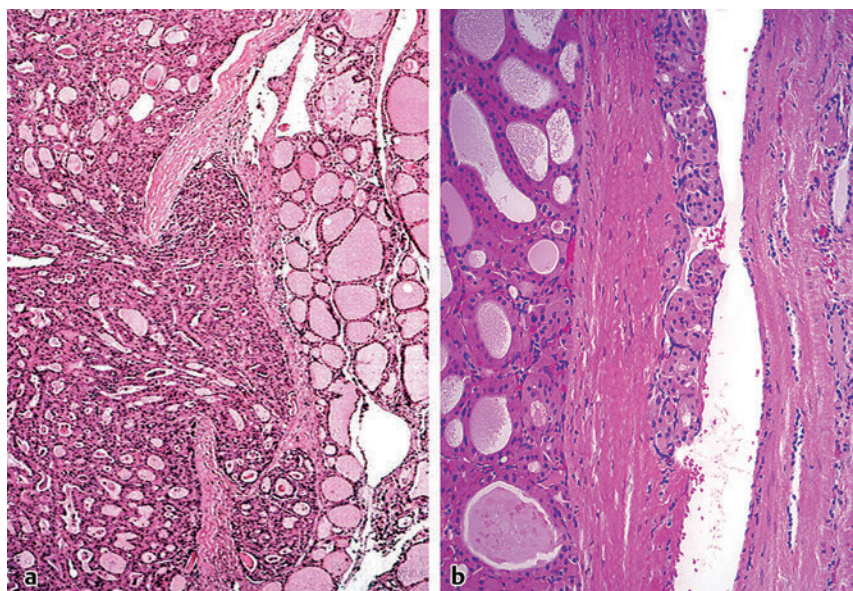


Fig. 5.8 Minimally invasive follicular thyroid carcinoma showing (a) capsular and (b) vascular invasion. (Hematoxylin-eosin stain)

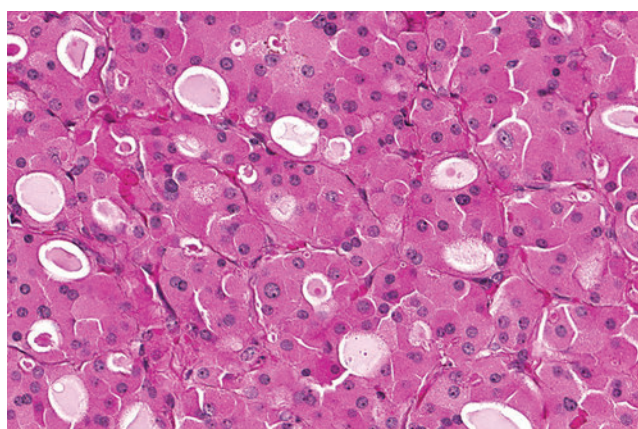


Fig. 5.9 Oncocytic follicular thyroid neoplasm showing abundant granular eosinophilic cytoplasm. (Hematoxylin-eosin stain)

5.3.2 Hyalinizing Trabecular Tumor

Hyalinizing trabecular tumor (HTT) is a rare neoplasm of follicular cell derivation. The tumor is typically well circumscribed, is sometimes encapsulated, and has a solid or vaguely lobulated cut surface. These tumors lack blood vessel or capsular invasion. Microscopically they have a prominent trabecular pattern, and the intratrabecular stroma contains abundant eosinophilic hyaline material.

The cells may have a polygonal, oval, spindled, or fusiform shape. The nuclei are round to oval and often have irregular contours, intranuclear grooves, and pseudoinclusions. Scattered calcifications are frequent, but true psammoma bodies are less common. The tumor cells are strongly positive for thyroglobulin, thyroid transcription factor (TTF-1), and low molecular weight cytokeratins and negative for calcitonin and calcitonin-gene-related peptide.

The malignant potential of HTT is extremely low.³² Surgical excision of a noninvasive HTT should be curative, even if only a lobectomy is performed.

5.3.3 Poorly Differentiated Carcinoma

Poorly differentiated carcinoma (PDC) is a malignant tumor of follicular cell origin that occupies an intermediate position morphologically and behaviorally between well-differentiated thyroid carcinomas and anaplastic carcinoma. The 2004 WHO classification of thyroid tumors recognizes PDC as a specific entity characterized by solid, trabecular, or insular architecture; infiltrative growth; necrosis; and vascular invasion.¹⁷ The Turin consensus criteria, subsequently developed by an international group of thyroid pathologists, are (1) solid/trabecular/insular architectural pattern, (2) lack of well-developed nuclear features of papillary carcinoma, and (3) one of the following: (3a) convoluted nuclei, (3b) tumor necrosis, or (3c) three or more mitoses per 10 high-power fields.²⁹

PDCs typically exhibit grossly overt infiltration, often with extrathyroidal extension. Some tumors show partial encapsulation, but complete and intact capsules are rare. The cut surface is solid, tan to white-tan, and frequently variegated due to foci of hemorrhage and necrosis. Areas of well-differentiated follicular or papillary carcinoma may be seen in continuity with PDC.

PDC has a relatively monotonous cell population, lacking the marked pleomorphism or highly atypical nuclei of anaplastic carcinoma. PDCs also retain diffuse immunoreactivity for cytokeratin and TTF-1, and at least focal positivity for thyroglobulin, in contrast to anaplastic carcinoma. PDC is distinguished from medullary carcinoma by the lack of immunostaining for calcitonin.

5.3.4 Anaplastic (Undifferentiated) Carcinoma

Anaplastic thyroid carcinoma (ATC) is a highly aggressive malignant tumor of follicular cell derivation but is characteristically devoid of morphological and immunophenotypic markers of thyroid origin. An alternate term is *undifferentiated carcinoma*. Most ATCs are thought to develop through dedifferentiation of well-differentiated or poorly differentiated thyroid carcinomas.

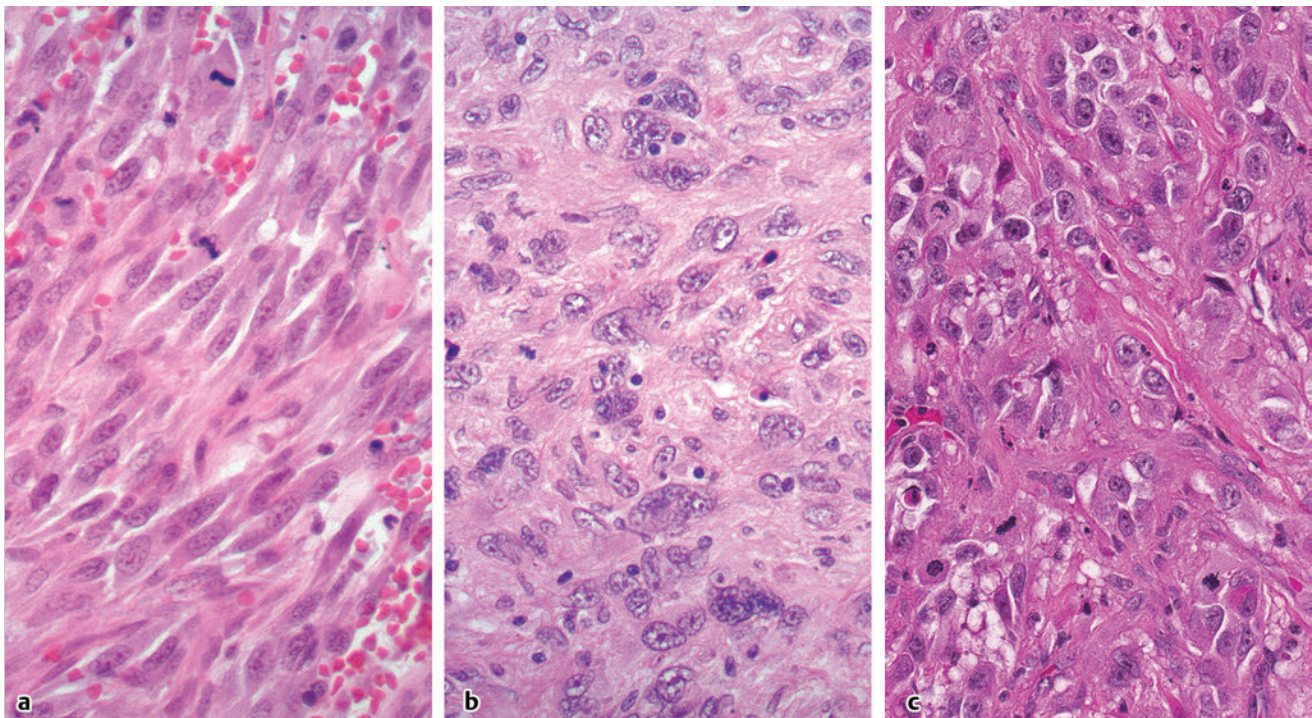


Fig. 5.10 Anaplastic carcinoma. (a) Spindle cell pattern. (b) Pleomorphic giant cell pattern. (c) Squamoid pattern. (Hematoxylin-eosin stain)

ATC is typically a widely infiltrative mass that effaces the thyroid gland and extends into adjacent extrathyroidal tissue. The cut surface usually has a variegated appearance with multiple foci of hemorrhage and necrosis. Common microscopic features include widely invasive growth, tumor necrosis, marked nuclear pleomorphism, and high mitotic activity. ATCs usually exhibit one or a mixture of spindle cell, pleomorphic giant cell, or squamoid cell patterns (► Fig. 5.10).³³

Variably sized areas of well-differentiated or poorly differentiated carcinomas are frequently found in association with ATC. The proportion of ATC in a given tumor may influence prognosis with longer survival in those cases where ATC comprises only a small component of an otherwise well-differentiated papillary or follicular carcinoma.³³

5.3.5 Medullary Carcinoma

Medullary thyroid carcinoma (MTC) is a malignant tumor of the thyroid gland that exhibits C-cell differentiation. In the United States, MTC accounts for ~ 2% of thyroid malignancies.¹⁸ About 75% of cases are sporadic, with the remainder heritable due to a germline mutation of the *RET* (rearranged during transfection) gene.³⁴ The three subtypes of hereditary disease are encompassed by multiple endocrine neoplasia type 2A (MEN2A), multiple endocrine neoplasia type 2B (MEN2B), and familial medullary thyroid carcinoma (FMTC). MEN2A is the most common of the three subtypes, accounting for about 75 to 90% of familial cases, with FMTC and MEN2B accounting for about 15% and 5% of cases, respectively.^{34,35}

MTCs typically have well-defined borders but lack encapsulation and are usually found in the middle regions of the lateral lobes. Tumor is limited to one lobe in most sporadic cases, but

bilateral disease is identifiable in most hereditary cases, particularly if resection was not performed early in life.³⁶

Microscopically, MTCs exhibit a broad range of growth patterns and cytological features (► Fig. 5.11). The most common growth pattern is solid, with sheets and nests of cells separated by fibrovascular stroma. This intervening stroma appears hyalinized in many cases due to amyloid deposition. Cells are usually round to oval but frequently have a polyhedral, angulated, or spindle shape. A number of variants have been reported, including tumors composed predominantly of oncocytic, spindle, squamous, small, giant, mucinous, or melanotic cells. The variety of histopathologic manifestations of MTC can prove challenging, but positive immunostaining for calcitonin facilitates the diagnosis in the vast majority of cases.

A small number of mixed medullary and follicular and mixed medullary and papillary carcinomas have been reported. Diagnosis of the former is problematic in the absence of metastatic lesions with mixed features. The term *mixed medullary and papillary carcinoma* is reserved for tumors that exhibit an intimate admixture of the two types, not for separate coincidental tumors.

5.3.6 Primary Thyroid Lymphoma

Primary thyroid lymphomas (PTLs) are defined by the absence of systemic disease. Almost all PTLs arise in the setting of chronic lymphocytic (Hashimoto's) thyroiditis.³⁷ Almost all PTLs are B-cell lymphomas, the majority being of the diffuse large B-cell lymphoma (DLBCL) subtype, with most of the remainder being extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma).^{37,38} A significant number of MALT lymphomas coexist with DLBCL. Grossly, PTLs vary

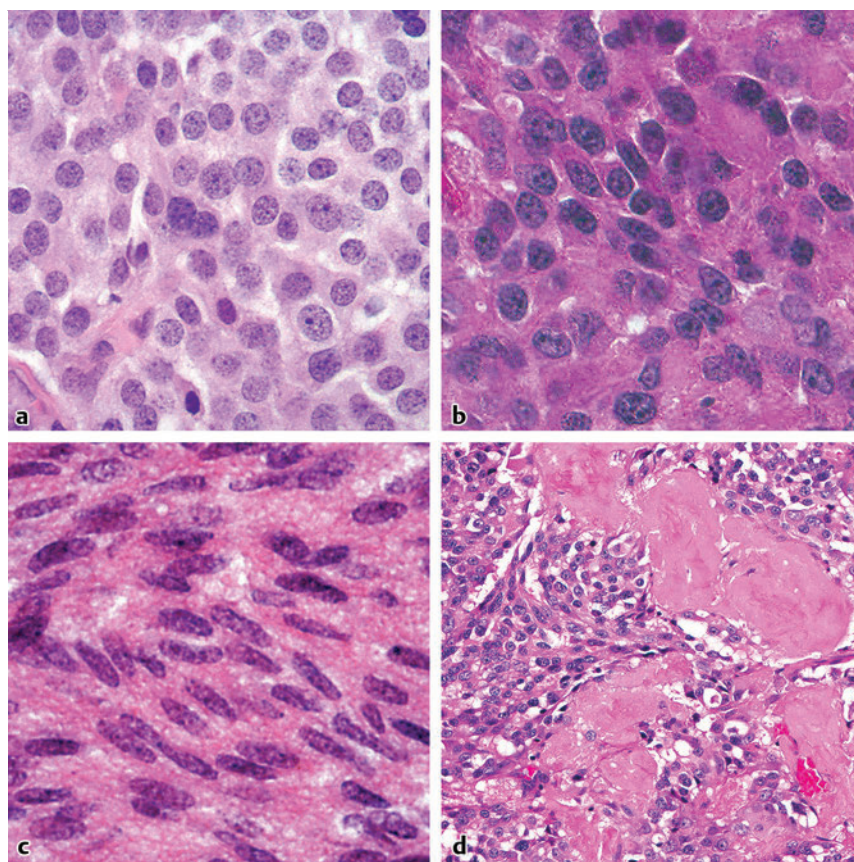


Fig. 5.11 Medullary thyroid carcinoma with (a) round cell, (b) polygonal cell, and (c) spindle cell morphology. (d) Amyloid deposition. (Hematoxylin-eosin stain)

widely in size at the time of diagnosis. They may appear as one or more nodules or as a mass completely effacing one or both lobes. The cut surface typically appears solid and grayish-white to light tan. Foci of hemorrhage, necrosis, and cystic degeneration may be seen. Histological classification uses the same morphological and immunohistochemical criteria as node-based lymphomas.

5.3.7 Rare Primary Thyroid Tumors

The WHO classification of thyroid tumors recognizes a number of rare primary tumors and tumor-like lesions of the thyroid.¹⁷ Rare tumors with epithelial differentiation include squamous cell carcinoma, mucoepidermoid carcinoma, sclerosing mucoepidermoid carcinoma with eosinophilia, mucinous carcinoma, spindle cell tumor with thymus-like differentiation, and carcinoma showing thymus-like differentiation. Other rare primary thyroid tumors and tumor-like conditions include angiosarcoma, teratoma, smooth muscle tumors, peripheral nerve sheath tumors, paraganglioma, solitary fibrous tumor, follicular dendritic cell tumor, Langerhans cell histiocytosis, Rosai–Dorfman's disease, and ectopic thymoma.

5.3.8 Secondary (Metastatic) Thyroid Tumors

Secondary, or metastatic, tumors of the thyroid gland are defined as being the result of lymphatic or hematogenous spread from a distant site, not direct extension from an adjacent

structure. Metastatic tumor can range from microscopic deposits in lymphovascular spaces to grossly apparent masses. The kidney (renal cell carcinoma), lung, breast, and gastrointestinal tract are the most frequent primary sites.³⁹ Diagnosis of metastatic tumor is usually established by basic histological features and panels of immunostains combined with clinical history and/or imaging studies.

5.4 Parathyroid Pathology

5.4.1 Parathyroid Hyperplasia

Parathyroid hyperplasia is an increase in the number of parenchymal cells, manifested by increased size and weight of a gland. Hyperplasia can occur primarily or be secondary to a disorder stimulating parathyroid hormone secretion, most commonly chronic renal failure. The total weight of normal parathyroid glands is usually 80 to 90 mg, and an individual gland weighing more than 40 mg can be considered abnormal.⁴⁰ Hyperplastic glands tend to become more irregular in shape, but the degree of glandular enlargement can vary in a given case. Consequently, gross diagnosis may be problematic.

Microscopic examination reveals an increase in parenchymal cells, with a relative decrease in stromal adipose tissue in most cases. Most normal parathyroid glands contain about 20% stromal adipose tissue,⁴⁰ but the wide variation in the amount and distribution of this stromal adipose tissue in normal glands makes evaluation of borderline enlarged glands challenging. Chief cells usually account for most of the increased parenchymal mass, but increased numbers of oncocytic and clear cells

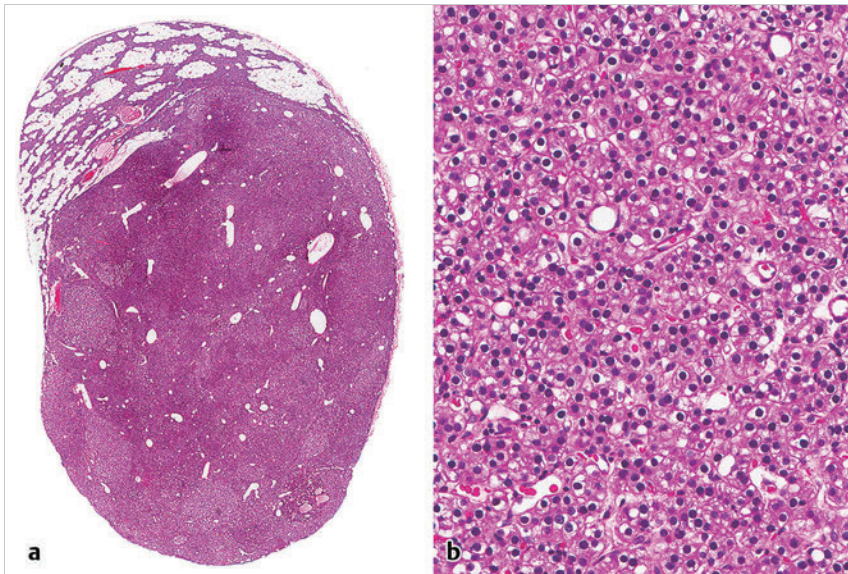


Fig. 5.12 Parathyroid adenoma. **(a)** Low-power photomicrograph showing rim of normal parathyroid (upper region). **(b)** Medium-power photomicrograph showing uniform, cytologically bland cells of adenoma. (Hematoxylin-eosin stain)

may also be seen. Hyperplasia can be diffuse or nodular, and growth patterns include solid, trabecular, and acinar. Hyperplastic cells are usually comparable to normal cells, and mitoses are rare. Occasionally nuclear pleomorphism is seen but it has no clinical significance. The histological features of primary, secondary, and tertiary hyperplasia overlap.

5.4.2 Parathyroid Neoplasia

Parathyroid Adenoma

Parathyroid adenoma is a benign neoplasm predominantly composed of chief cells, though oncocytic cells, transitional oncocytic cells, or a combination of these cell types may be admixed with the chief cells or present in segregated nests.¹⁷ Adipose cells are absent or very sparse. Most adenomas range between 200 and 1,000 mg in weight, have a thin capsule, and vary from tan to reddish-brown in color. A rim of normal parathyroid tissue may be seen at the periphery and serve as a useful diagnostic aid (► Fig. 5.12). The histological growth pattern can vary from solid to nodular with trabecular, follicular, and/or acinar subpatterns. Mitotic activity is absent or very low. Nuclear pleomorphism is seen occasionally, but it is not indicative of malignancy. Histological variants include oncocytic, water-clear, and atypical adenoma. Lipoadenoma is another variant, with abundant adipose tissue and scattered parenchymal cells. Some consider lipoadenoma to be a hamartoma.

The major differential diagnosis of adenoma is parathyroid hyperplasia. Enlargement of two or more glands favors hyperplasia. The presence of an appreciable amount of stromal adipose cells favors hyperplasia, whereas a peripheral remnant of normocellular parathyroid tissue supports adenoma. Histological differentiation of a microadenoma from nodular hyperplasia, particularly on the basis of a small biopsy, may be very difficult if not impossible. Fortunately, intraoperative parathyroid hormone testing has obviated the need for most of these microscopic challenges.

Parathyroid Carcinoma

Parathyroid carcinomas are rare, malignant neoplasms that exhibit overlapping features with parathyroid adenoma. Carcinomas tend to be larger and often adherent to adjacent structures. Diagnosis of carcinoma is dependent on finding metastatic lesions or invasive growth histologically. Invasive growth should be unequivocal and one or more of the following: (1) transcapsular growth into adjacent tissues, (2) vascular invasion of capsular or extracapsular vessels, and (3) perineural space invasion.¹⁷ Other histological findings may include elevated mitotic activity, fibrous trabeculae, and nuclear pleomorphism, but these have not proven to be reliable criteria, and neoplasms with these features are generally called atypical adenomas. A number of proliferative markers and immunohistochemical profiles have been studied, but these too have not proven to be definitive in differentiating carcinomas from adenomas.

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Part 2

Thyroid Diseases

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6 Thyroid Imaging

Bruce Curtiss Gilbert and Ramon E. Figueroa

6.1 Introduction

Imaging of the thyroid is an important complement to the clinical examination and laboratory analysis in the evaluation of thyroid disease. Ultrasound (US) is the primary modality to evaluate thyroid and visceral space pathology.^{1,2} However, cross-sectional modalities, such as computed tomography (CT) and magnetic resonance imaging (MRI), may play an important secondary role. The thyroid gland is often visualized on routine neck, chest, or cervical spine CT and MRI examinations. Knowledge of the normal thyroid appearance as seen with these imaging modalities enables one to recognize incidentally imaged disease processes. Nuclear scintigraphy plays an important role in the thyroid functional evaluation. This chapter discusses the various imaging modalities available for evaluation of thyroid disease, the normal imaging appearance of the thyroid, and the imaging changes in thyroid disease states.

6.2 Imaging Modalities of the Thyroid

6.2.1 Ultrasound

Over the past 4 decades, US has become the preferred diagnostic imaging tool for evaluating thyroid disease. The gland's superficial location in the anterior neck and the high imaging resolution of modern transducers make US an ideal tool for thyroid imaging. US provides an accurate assessment of gland size and parenchymal homogeneity without the adverse effects of ionizing radiation or the high costs of other imaging modalities. The most frequent indications for thyroid US evaluation include a palpable neck mass in the visceral space, an incidental thyroid abnormality detected by other imaging modalities (such as CT and MRI), screening high-risk patients for occult malignancy, evaluating for regional nodal metastases in patients with suspected or proven thyroid carcinoma prior to thyroidectomy, and screening the thyroid bed in postthyroidectomy patients.^{2,3}

US examination employs a linear-array, high-frequency 7.5 to 15 MHz transducer, with the neck in hyperextension. Each lobe of the thyroid is imaged in longitudinal and transverse planes using both B mode and color Doppler US. The average adult thyroid measures 4 to 6 cm in craniocaudal length and 1.3 to 1.8 cm in anteroposterior and transverse dimensions. The normal anteroposterior thickness of the isthmus is up to 3 mm.⁴ The normal thyroid has a homogeneous background of medium-level to high-level echogenicity (uniformly hyperechoic relative to the adjacent strap muscles) surrounded by an echogenic fibrous capsule. The thyroid capsule allows for clear delineation of the thyroid from adjacent structures of the visceral space (► Fig. 6.1a). Color Doppler imaging may be used to evaluate the vascularity of the thyroid as well as thyroid nodules, which may be helpful in determining malignancy. The routine thyroid US also evaluates the normal adjacent anatomical structures of the visceral neck, such as the common carotid arteries, jugular veins, cervical esophagus, parathyroid glands, and

lymph nodes. Familiarity with the normal sonographic appearance of these adjacent structures may prevent misinterpretation of normal anatomical structures as thyroid pathology. Potential limitations of US include the high degree of operator dependence and the inability to adequately evaluate the retrotracheal region and the superior mediastinum.¹

6.2.2 CT and MRI

CT and MRI have limited ability to directly evaluate intrathyroid pathology due to poor capacity to discriminate benign and malignant disease. However, CT and MRI have important adjunctive roles for staging advanced thyroid cancer by identification of extracapsular extension of disease into adjacent structures, such as the esophagus, trachea, larynx, musculature, and vasculature. They are also important for evaluating direct extension of disease into the mediastinum or retrotracheal region, as well as to identify both regional lymph nodes and distal metastases, providing relevant information that can impact surgical management. They may also have specific roles in cases of multinodular goiter to evaluate for retrosternal extension of disease and tracheal deviation or compression.^{5,6} Due to its high iodine content, the normal thyroid has increased attenuation compared to the adjacent musculature, with a density of 80 to 100 Hounsfield units.^{4,5} Contrast-enhanced CT diffusely increases the attenuation of the thyroid due to strong uptake of iodinated contrast, providing additional information about thyroid lesions (► Fig. 6.1b).

However, iodinated contrast should be avoided if functional nuclear imaging is desired or in the workup of differentiated thyroid carcinoma (unless the information obtained from the addition of contrast is expected to significantly alter the patient's management) because a large iodine thyroid gland load may persist for up to 6 weeks and interfere with radioactive iodine uptake. As an alternative, MRI with gadolinium may be performed in conjunction with nuclear scintigraphy because gadolinium does not affect iodine uptake or organification by the thyroid.

The thyroid is imaged by MRI using an anterior neurovascular neck coil centered over the thyroid. Multiple pulse sequences can be obtained through the gland, including sagittal and axial T1 precontrast, axial T2 fast spin-echo with fat saturation, and postgadolinium axial and coronal T1 with fat saturation. The thyroid gland is homogeneous in signal and slightly hyperintense compared to neck musculature on T1 imaging. On T2-weighted imaging, the thyroid is homogeneously hyperintense to neck musculature (► Fig. 6.1c). It demonstrates a diffuse homogeneous pattern of enhancement on postcontrast imaging.

6.2.3 Nuclear Scintigraphy

Nuclear scintigraphy plays an important role in the evaluation of thyroid disease, providing a reflection of the functional state of the thyroid gland as well as the physiological state of any structures within the gland, such as a thyroid nodule. Indications for thyroid scintigraphy include evaluation of the size and

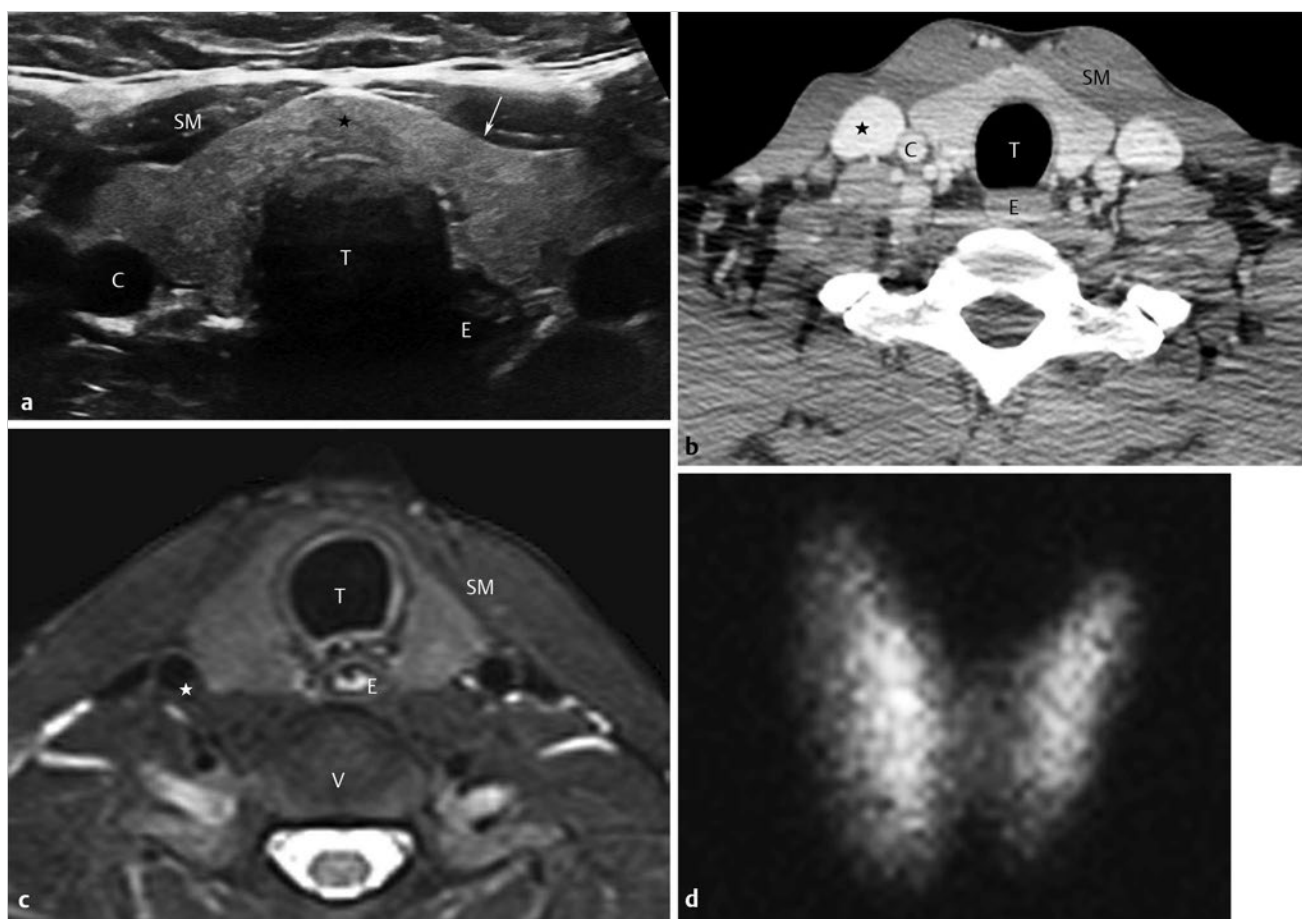


Fig. 6.1 Normal thyroid. (a) Transverse ultrasound image of normal thyroid (black star) shows homogeneously increased echogenicity compared with the overlying strap muscle (SM). The echogenic capsule (white arrow) separates the thyroid from adjacent visceral space structures. T, trachea; E, esophagus; C, common carotid arteries. (b) Axial contrast-enhanced computed tomographic image shows normal homogeneous enhancement throughout the thyroid, slightly less dense than the internal jugular veins (black star). The internal jugular vein is visible (black star). T, trachea; SM, strap muscle; C, common carotid artery; E, esophagus. (c) Axial T2-weighted magnetic resonance imaging shows normal thyroid with homogeneous, slightly hyperintense signal compared to strap muscle (SM). The right common carotid flow void is seen (white star). T, trachea; E, esophagus; V, cervical vertebral body. (d) Normal anteroposterior scintigraphic thyroid image shows diffuse and homogeneous radiotracer uptake.

location of thyroid tissue, thyroid evaluation when clinical laboratory tests suggest abnormal thyroid function, evaluation of patients at risk for thyroid neoplasm, assessment of function of thyroid nodules, and evaluation of congenital thyroid abnormalities.

Thyroid uptake measurements are obtained for differentiation of hyperthyroidism from forms of thyrotoxicosis and for calculating I-131 doses in patients to be treated for hyperthyroidism with thyroid ablative therapy. Whole body imaging is performed to identify the presence and location of residual thyroid tissue after thyroidectomy or ablative therapy for thyroid carcinoma and for identifying iodine avid metastases from thyroid carcinoma.⁶

The two main isotopes for thyroid scintigraphy are technetium-99m (Tc-99m) pertechnetate and iodine 123 (I-123). Tc-99m pertechnetate is trapped by the thyroid, whereas I-123 is trapped and organified. One distinct advantage of I-123 over Tc-99m is in the evaluation of thyroid nodules, in particular when a thyroid nodule appears “warm” by Tc-99m. If “cold” on I-123, this is considered a discordant nodule requiring further

workup and possible thyroid fine-needle aspiration (FNA). I-123 also has an advantage over Tc-99m in identifying and localizing ectopic thyroid tissue because there is significantly less background activity within the head and neck when compared to Tc-99m.^{5,7,8} Whether imaged with Tc-99m pertechnetate or I-123, the normal thyroid shows homogeneous radionuclide uptake throughout the gland (► Fig. 6.1d).

Radioactive iodine uptake may be measured at 4 and 24 hours with normal values of 5 to 15% and 8 to 35%, respectively. The use of iodine-containing supplements or certain medications can potentially affect iodine uptake and incorporation by the thyroid gland. Most centers recommend a low-iodine diet for 7 to 14 days prior to radioiodine administration.

6.3 Congenital Anomalies of the Thyroid Gland

Understanding congenital anomalies of the thyroid gland requires a limited review of thyroid embryology. The median

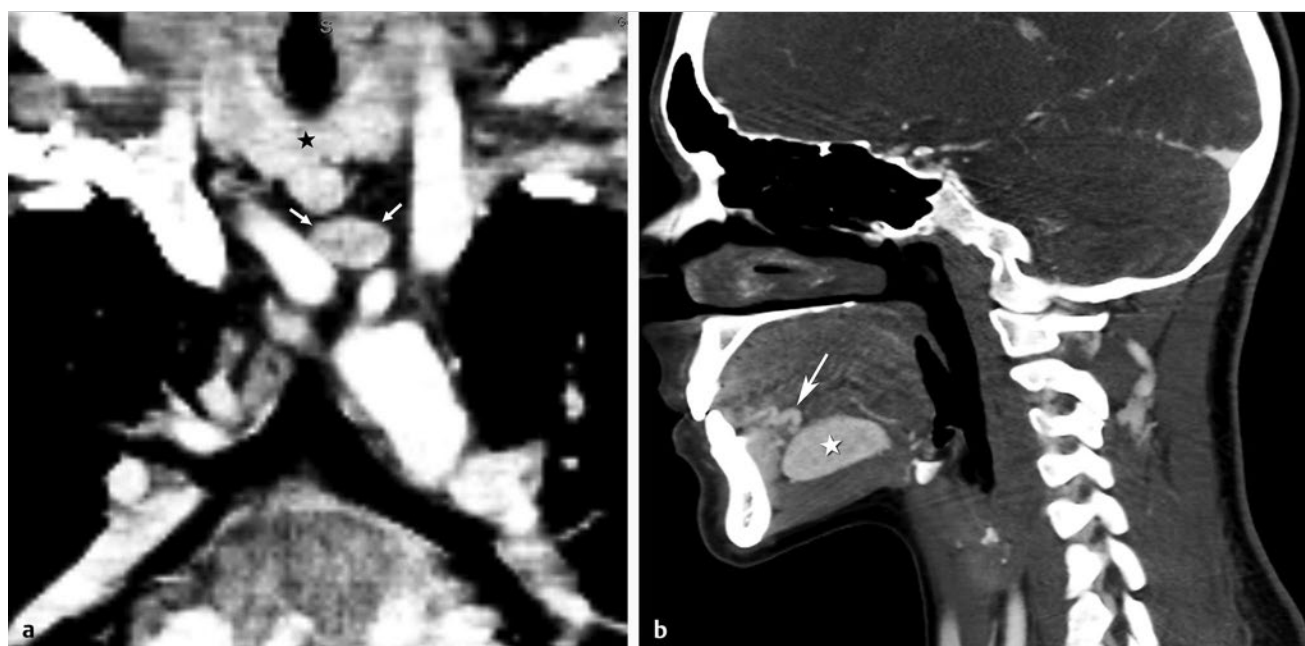


Fig. 6.2 Ectopic thyroid. (a) Coronal computed tomographic image shows nodular ectopic thyroid tissue (white arrows) within the superior mediastinum. Normal thyroid (black star). (b) Lingual thyroid. Nodular hyperdense ectopic thyroid tissue (white star) in the floor of the mouth is consistent with lingual thyroid, supplied by a tortuous lingual artery (white arrow).

anlage of the thyroid gland arises from endodermal cells originating from the third branchial pouch in the floor of the primitive pharynx, at the tongue base. The gland migrates downward from the tongue base, passing anterior to the hyoid bone and thyroid cartilage, to its final destination anterior to the second and third tracheal rings in the lower neck. The thyroid remains attached to the tongue base by the thyroglossal duct, an epithelial-lined tube that elongates during descent and eventually degenerates prior to definitive thyroid formation. The median anlage forms the hormone-secreting follicular cells of the thyroid. The calcitonin-secreting parafollicular C cells are formed by the lateral anlages, which are derived from the fourth and fifth branchial pouches. Within the infrahyoid neck, the lateral anlages fuse with the median anlage to form the bilobed thyroid.^{9,10}

6.3.1 Ectopic Thyroid Tissue

Failure or abnormal descent of the thyroid gland along its normal pathway may occur during the fetal period, resulting in ectopic thyroid tissue at any location along the pathway of descent. Clinically apparent thyroid ectopia is rare, occurring in 1 in 3,000 to 1 in 10,000 people; however, autopsy series suggest a much higher prevalence, ranging from 7 to 10%.^{11,12} Although 90% of ectopic thyroid tissue occurs at the tongue base and arises from the median anlage, ectopic thyroid tissue may also be identified in the lateral neck, larynx, esophagus, mediastinum, pericardium, or heart (► Fig. 6.2a). Rare noncervical and nonmediastinal locations of ectopic thyroid tissue have also been described in the gallbladder, porta hepatis, small bowel, pancreas, and adrenal glands. Ectopic thyroid is vulnerable to any disease process that may occur within the normally located thyroid gland; however,

development of malignancy is considered rare. When tumor does arise within ectopic thyroid tissue, it is reported as papillary carcinoma in >90% of cases.^{12,13}

When thyroid ectopia is identified, patients should undergo further evaluation for the presence of normally located thyroid tissue prior to surgical excision of ectopic thyroid, to avoid an acute thyroid insufficiency. Other than lacking the typical bilobed appearance, ectopic thyroid tissue appears as normal thyroid tissue by all imaging modalities. Nuclear scintigraphy demonstrates uptake of radiotracer in the ectopic thyroid as well as in the orthotopic tissue. The most common US imaging finding is the absence of normal orthotopic thyroid tissue. However, careful evaluation of the neck at the tongue base or along the expected track of thyroid descent may reveal a round, well-circumscribed mass identical to the expected echogenicity of normal thyroid tissue. Ectopic thyroid gland detected by non-contrast CT will present as a hyperdense nodular mass with respect to the adjacent musculature, showing intense enhancement after intravenous administration of iodinated contrast. MRI presents thyroid ectopia as a nodular mass, T1 isointense to mildly hyperintense in signal compared to muscle, mildly T2 hyperintense, and with a variable pattern of enhancement on postgadolinium imaging. Detection of nodules or goitrous enlargement in the ectopic thyroid tissue may also increase the diagnostic confidence.

Lingual thyroid is the most common form of thyroid ectopia.¹⁴ The ectopic tissue at the base of the tongue may range from microscopic to several centimeters (► Fig. 6.2b). Clinical symptoms are often related to growth of the ectopic thyroid tissue, including dysphagia, dysphonia, cough, and foreign body sensation. However, patients may be asymptomatic, with incidental detection by clinical exam or imaging for nonthyroid-related purposes.

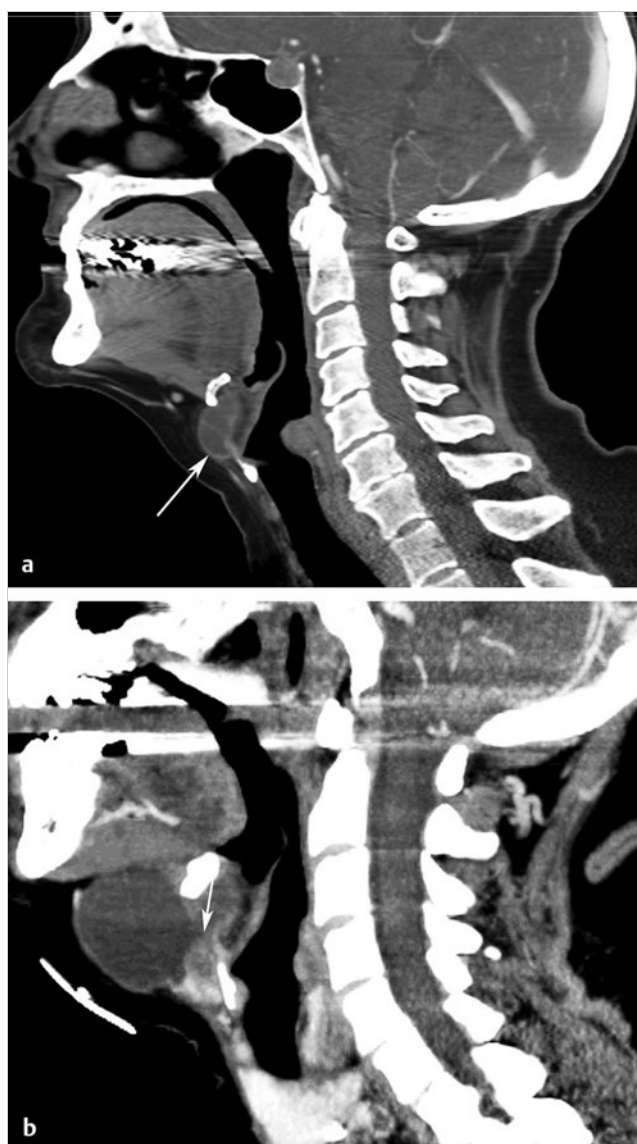


Fig. 6.3 Thyroglossal duct cyst. (a) A midline cystic mass (white arrow) is seen along the inferior margin of the hyoid, proven to be thyroglossal duct (TGD) cyst. (b) A different patient with a TGD cyst with an irregular enhancing nodule of its posterior cyst wall (white arrow), proven to be squamous cell carcinoma.

6.3.2 Thyroglossal Duct Cyst

Thyroglossal duct (TGD) cyst is the most common midline congenital neck mass, arising secondarily to failure of complete regression of the TGD.¹⁵ Similarly to ectopic thyroid tissue, a TGD cyst may arise anywhere along the descent pathway of the median anlage, from the base of the tongue to the suprasternal region. Most lesions present in childhood or in young adults as an enlarging painless mass, with 60 to 80% associated with the hyoid bone. Ectopic thyroid tissue within the cyst wall is seen in up to 5.7% of cases.¹⁶ TGD cysts can be complicated by inflammation and hemorrhage, which may be associated with pain. Carcinoma arising in a TGD cyst is rare, occurring in 0.7 to 1% of TGD cysts, with 90% arising from a thyroid tissue remnant. Papillary carcinoma represents approximately 94% of TGD

cyst carcinomas, with <5% being of squamous cell origin. The average patient age for TGD cyst carcinoma development is 39 years, with the squamous cell type occurring at an average age of 54 years.

US is the modality of choice for initial imaging assessment of a suspected TGD cyst. On US, TGD cysts may have a variable echogenicity pattern based on intrinsic fluid protein content. The most common presentations include a well-circumscribed anechoic cyst or a pseudosolid appearance with a heterogeneous echo pattern (more commonly seen in children). Posterior acoustic enhancement (increased echogenicity deep to the cyst) is a cystic characteristic finding; however, this may be subtle in the setting of a pseudosolid lesion. The presence of thick walls or internal septa often correlates with internal inflammation. CT presents TGD cysts as well-circumscribed, thin-walled midline lesions with mucoid attenuation, usually at or below the level of the hyoid bone (► Fig. 6.3a).

Increased complexity of the lesion, with thickening and enhancement of cyst walls, septations, and increased cyst attenuation, suggests cyst inflammation or infection. TGD cysts may appear on MRI scans as simple cysts, demonstrating low intrinsic T1 and high T2 signal, though intrinsic protein/thyroglobulin content may elicit high T1 and high T2 signal. Identification of a soft tissue nodule within a TGD cyst should raise concern for carcinoma, especially in the presence of calcification (► Fig. 6.3b). The main differential considerations of TGD cysts include a branchial cleft cyst, dermoid, and hemangioma, and an enlarged lymph node.

6.4 Benign Diseases of the Thyroid

Most benign disease processes that affect the thyroid gland are diagnosed by clinical findings and do not require imaging. However, several benign disease processes of the thyroid have a characteristic appearance on imaging.

6.4.1 Graves' Disease

Graves' disease is the most common cause of hyperthyroidism in the United States. It is an autoimmune process in which patients develop autoantibodies against thyroid-stimulating hormone (TSH) receptors, thyroglobulin, and thyroperoxidase. TSH receptor antibodies result in receptor stimulation, leading to glandular growth, increased vascularity, and increased production of thyroid hormone. On gray-scale US, the thyroid is enlarged and diffusely hypoechoic; however, normal echogenicity may be present.^{17,18} On color Doppler imaging, the thyroid shows markedly increased vascularity throughout the thyroid parenchyma, resulting in the "thyroid storm" pattern (► Fig. 6.4a,b).

Peak systolic velocity measurements of the inferior thyroid or intraparenchymal arteries are markedly increased in Graves' disease, which is helpful in distinguishing it from Hashimoto's disease and thyrotoxicosis. CT and MRI have limited usefulness in evaluation of Graves' disease, showing an enlarged thyroid with possible visualization of a pyramidal lobe or prominent intrathyroidal vasculature.¹⁹

Thyroid scintigraphy shows a diffusely enlarged gland with increased thyroid uptake. A pyramidal lobe may also be identified on scintigraphic imaging (► Fig. 6.4c). Radioactive iodine

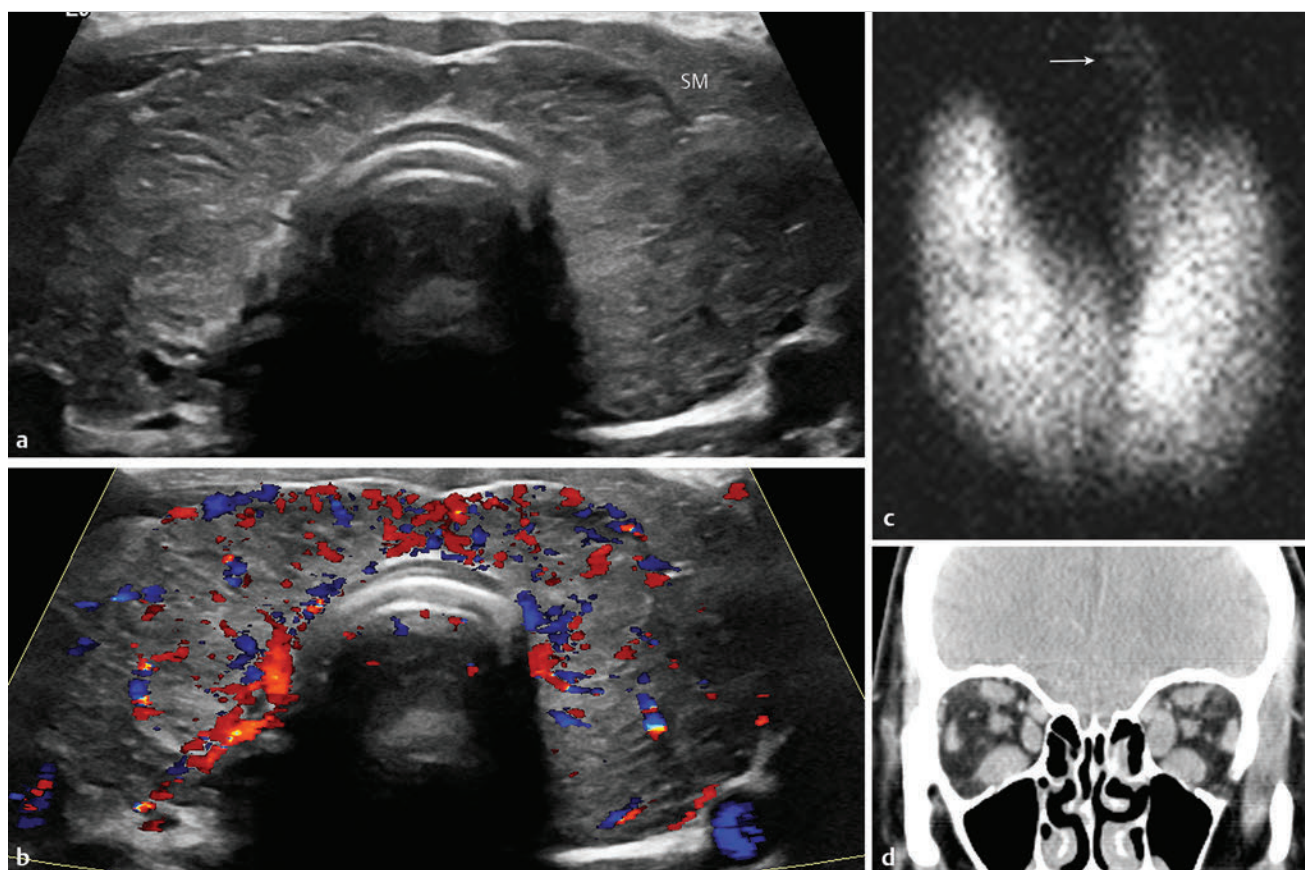


Fig. 6.4 Graves' disease. (a) Transverse gray-scale ultrasound shows a diffusely enlarged thyroid with decreased echogenicity equal to and slightly less than strap muscle (SM). (b) Color Doppler imaging with a "thyroid storm" pattern of diffuse increased vascularity throughout the gland. (c) Anteroposterior scintigraphic image with homogeneously increased tracer uptake with the pyramidal lobe (white arrow) arising from the junction of the isthmus and the left lobe. (d) Coronal computed tomography showing enlargement of the extraocular muscle bellies.

uptake (RAIU) is elevated at 24 hours ($> 35\%$), although a variant form, Graves' disease with rapid iodine turnover, may show normal RAIU at 24 hours but elevated RAIU at 4 to 6 hours ($> 20\%$).⁸

An extrathyroidal manifestation of Graves' disease is thyroid-associated orbitopathy. Its diagnosis is primarily clinical; however, imaging may be performed in uncertain cases.²⁰ CT and MRI are the primary imaging modalities, classically showing proptosis with expansion of the intraorbital fat and enlargement of the extraocular muscle bellies, but not their tendons. The inferior rectus is most commonly affected, followed by the medial rectus and superior muscle complex. Bilateral involvement occurs in approximately 90% of cases (► Fig. 6.4d).

6.4.2 Hashimoto's Disease

Hashimoto's disease is an autoimmune thyroiditis resulting from glandular infiltration by T and B lymphocytes, possibly stimulated by an environmental trigger. Autoantibodies to the TSH receptor, thyroglobulin and thyroid peroxidase, are produced by B cells, whereas T cells contribute to local parenchymal destruction. The net effect is an initial thyrotoxicosis followed by chronic hypothyroidism. Hashimoto's disease is the most common cause of hypothyroidism in the United States, affecting at least 2% of all women.²¹ On US, the thyroid is

enlarged with diffuse heterogeneous hypoechoic pattern outlining echogenic internal septations. A highly diagnostic sonographic feature for Hashimoto's disease is the presence of multiple hypoechoic micronodules, ranging from 1 to 7 mm in size (► Fig. 6.5a).²²

Color Doppler imaging may show mild to markedly increased vascularity as also seen in Graves' disease. On CT, the thyroid may be diffusely enlarged with a heterogeneous, hypodense attenuation pattern. Hashimoto's disease scintigraphic findings are nonspecific, with a heterogeneous, patchy radiotracer activity that may range from uniformly increased activity to severely decreased radiotracer uptake.²³

Hashimoto's thyroiditis has a strong association with lymphoma. The presence of a rapidly growing focal hypodense mass with margins extending beyond the normal thyroid contour should raise suspicion for lymphoma (► Fig. 6.5b). Lymphoma tends to be less invasive than primary thyroid carcinoma and usually lacks calcifications or cystic degeneration, which helps to distinguish it from thyroid carcinoma or goiter.²⁴

6.4.3 Toxic Autonomous Nodule

Toxic autonomous nodule (Plummer's disease) occurs when one or more thyroid nodules produce an excess of thyroid

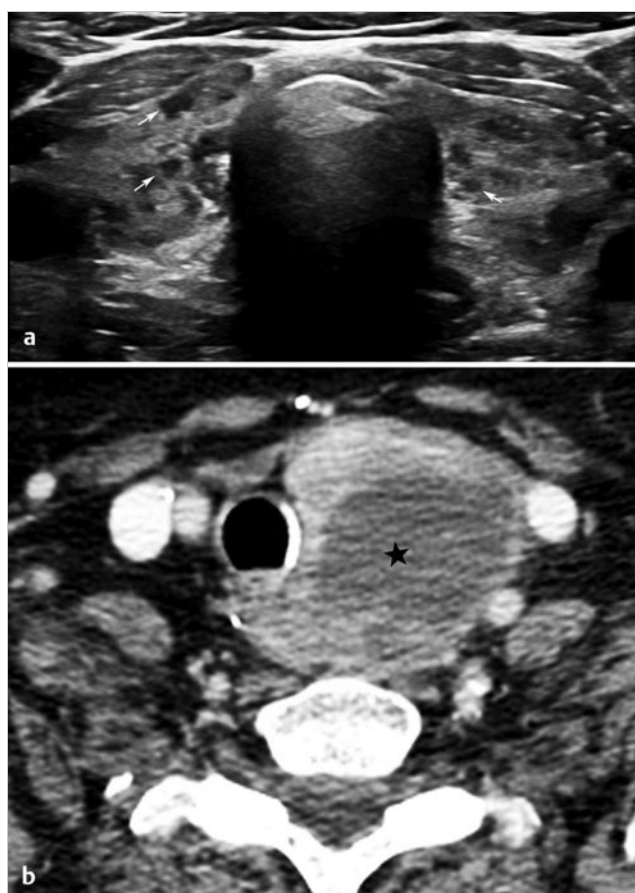


Fig. 6.5 Hashimoto's thyroiditis. (a) Transverse ultrasound image showing multiple bilateral hypoechoic micronodules (white arrows) in the setting of Hashimoto's disease. (b) A patient with a history of Hashimoto's disease and a right hemithyroidectomy presents with a large mass (black star) extending beyond the normal gland margins and displacing adjacent anatomical structures without invasion, which was proved to be primary thyroid lymphoma.

hormone released into the systemic circulation. The proposed etiology is a somatic mutation of the TSH receptor gene of a thyroid adenoma causing the unregulated production and release of thyroid hormone.⁷ Thyroid scintigraphy shows increased activity within the autonomous functioning nodule ("hot nodule") against a background of faint or absent gland activity from the lack of TSH stimulation of normal thyroidal tissue (► Fig. 6.6).

The RAIU is usually mildly elevated or normal. Historically, hot nodules are considered benign; however, some case series have found a prevalence of carcinoma within hot nodules of approximately 3.1%. If suspicious US characteristics are identified or there is growth of a hot nodule over time, then US-guided FNA should be considered.²⁵ The preferred therapy for a toxic nodule is ablation with I-131, which is preferentially concentrated in the hyperfunctioning nodule rather than in the normal thyroid gland.

6.4.4 Multinodular Goiter

A multinodular goiter is an enlarged thyroid containing several nodules, some of which are hyperfunctioning and some of

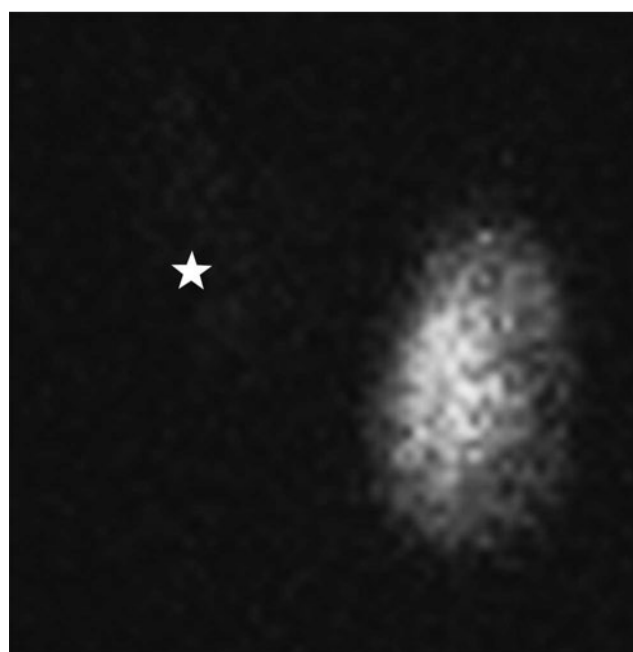


Fig. 6.6 Toxic autonomous nodule. Anteroposterior iodine 123 scintigraphic scan image shows a large, hot nodule in the left thyroid mid to lower lobe with right lobe (white star) and left lobe upper pole photopenia.

which are nonfunctioning, usually providing for a balanced state of thyroid hormone production and thus normal thyroid function (nontoxic goiter). A toxic goiter often occurs when there is an excess of thyroid hormone production resulting in hyperthyroidism. Sporadic goiter occurs in approximately 5% of the U.S. population, with most patients presenting with a neck mass. US shows an enlarged thyroid gland with multiple nodules of various sizes (► Fig. 6.7a). The nodules are often hypoechoic with internal complex/septated cystic areas corresponding to internal degeneration and hemorrhage. Intrinsic comet tail artifact secondary to colloidal degeneration and shadowing secondary to dystrophic calcifications may also be seen. CT and MRI are indicated to assess substernal disease extension and tracheal or esophageal compression (► Fig. 6.7b,c).²⁶ The thyroid may be diffusely or asymmetrically enlarged and nodular, with individual nodules on CT varying from intensely enhancing to hypodense secondary to internal necrosis (► Fig. 6.7d).

Variable fluid composition within the nodules causes a wide range of imaging appearances by MRI. The RAIU in the setting of toxic multinodular goiter is usually normal or slightly elevated. Scintigraphic findings include an enlarged thyroid with global heterogeneous radiotracer uptake, including both hot and cold nodular areas. The presence of a solitary cold nodule in the setting of a multinodular gland should be considered suspicious because the cancer rate in this setting is similar to that of a normal gland. US-guided FNA should be considered in the setting of a solitary cold nodule or dominant/enlarging nodule in a multinodular goiter.^{5,7}

6.4.5 Riedel's Thyroiditis

Riedel's thyroiditis, also known as invasive fibrous thyroiditis, is characterized by thyroid gland destruction with replacement of

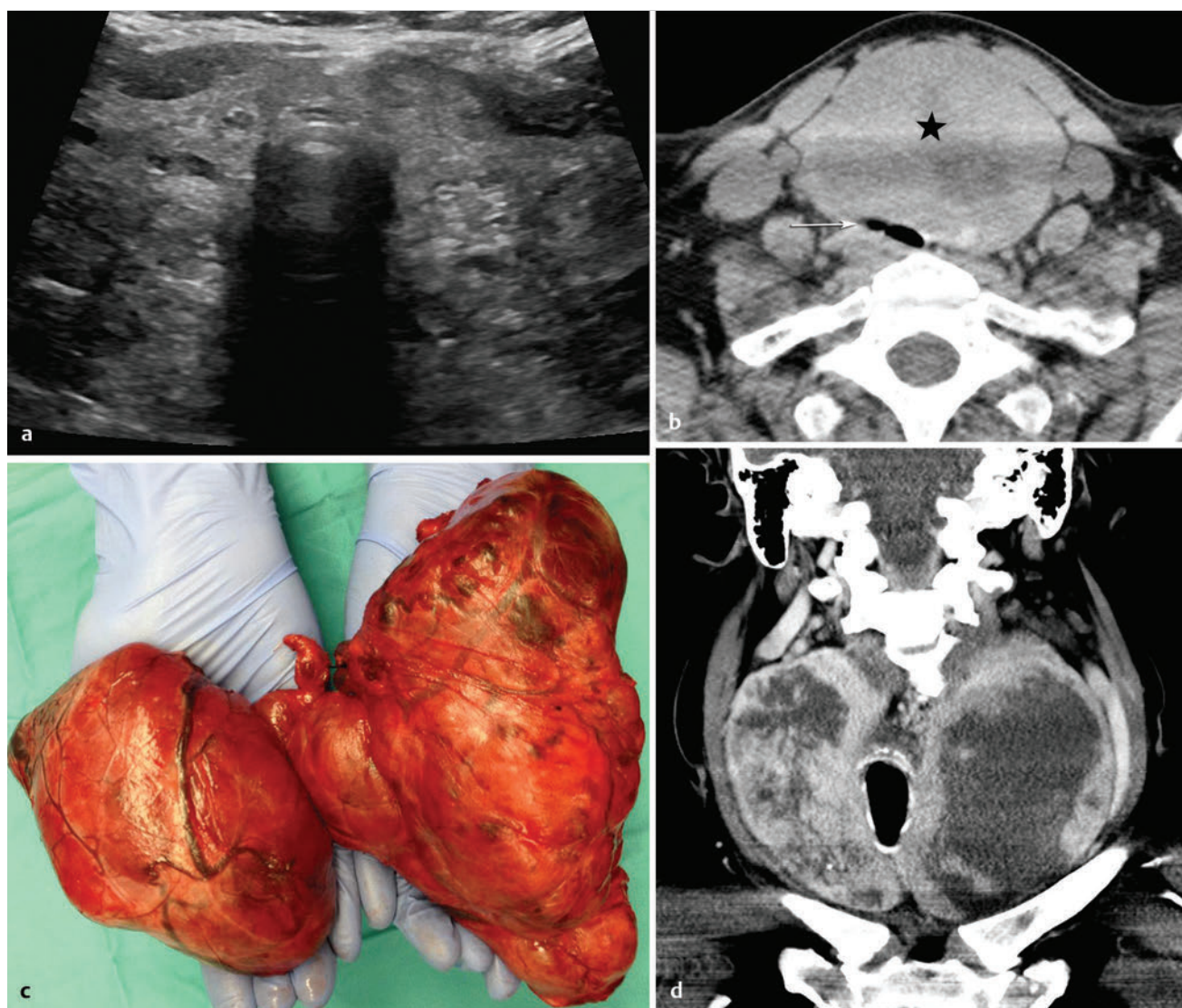


Fig. 6.7 Thyroid goiter. (a) Transverse ultrasound image shows markedly enlarged thyroid with diffuse heterogeneous and nodular echogenicity. (b) Patient with goiter (black star) presenting with marked tracheal compression (arrow) requiring emergent thyroidectomy. (c) Gross surgical specimen from thyroidectomy in (b). (d) Coronal computed tomography shows a markedly enlarged thyroid with heterogeneous attenuation and large cystic bilateral nodules.

the normal parenchyma with dense fibrosis, which may extend beyond the margins of the thyroid capsule into the adjacent soft tissue structures of the neck.²⁷ The clinical presentation may include hypothyroidism, hypoparathyroidism, or symptoms from compression on adjacent structures, such as the recurrent laryngeal nerve. Malignancy may be suspected clinically due to a firm, enlarged thyroid. The thyroid may be enlarged, hypoechoic, and hypovascular on US.²⁸ On CT the thyroid may be diffusely hypodense where there is diffuse gland involvement. However, if there is residual normal tissue on a background of fibrosis, the gland may have a more heterogeneous appearance. Extracapsular infiltration into adjacent neck structures may be present (► Fig. 6.8). MRI shows the gland as T1 iso- to hypointense and T2 hypointense, with decreased enhancement. Both the clinical and the imaging appearance can be suspicious for an aggressive malignant process. If Riedel's thyroiditis is

suspected, an open surgical biopsy should be considered to exclude malignancy.

6.5 Thyroid Nodules

Thyroid nodules are common in the adult population, found in up to 60% of adults in some autopsy series.²⁹ The incidence of thyroid nodules has steadily increased over the last 3 decades, predominantly as a result of imaging. The incidental nodule (incidentaloma) is an asymptomatic thyroid lesion discovered on an imaging examination performed for reasons unrelated to the thyroid gland, reported in up to 9% of carotid US examinations, 16% of CT and MRI examinations, and 3% of positron emission tomographic (PET) scans. The risk of malignancy of the incidental thyroid nodule is not insignificant, with studies showing malignancy rates ranging from 8.6 to 29%.³⁰ Therefore,

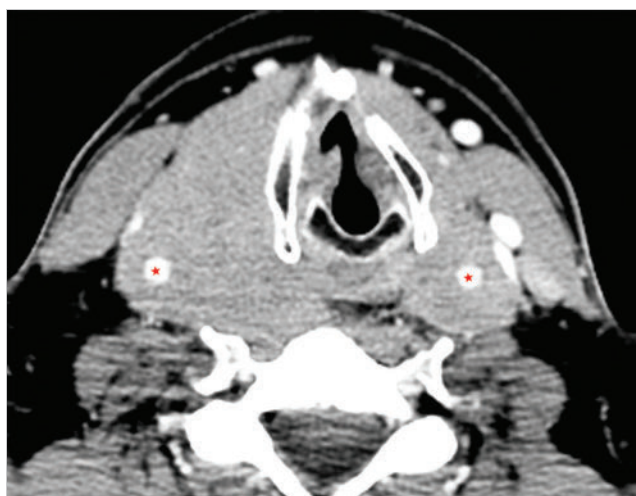


Fig. 6.8 Riedel's thyroiditis. Axial computed tomography with contrast shows diffuse enlargement of the thyroid with markedly decreased attenuation and lack of enhancement. Note infiltration of the adjacent anatomical structures with encasement of the common carotid arteries (red stars).

evaluation of the incidentaloma is an important aspect of patient care.

High-resolution US is the preferred imaging modality for evaluation and characterization of the thyroid incidentaloma. Sonographic features of thyroid nodules that raise suspicion for malignancy include the presence of microcalcifications, evidence of local invasion or nodal metastasis, nodules that are taller than wide in the transverse plane, and marked hypoechoogenicity. Although a single suspicious sonographic feature may be of limited value, two sonographic signs of malignancy correlate with an increased risk of cancer. Patients with decreased TSH levels may undergo I-123 thyroid scintigraphy to evaluate for a hyperfunctional nodule, which is rarely malignant and historically precludes the need for additional testing.³⁰

Microcalcifications most commonly occur in the setting of papillary carcinoma. Nodules with microcalcifications have punctate (< 1 mm) hyperechoic foci on US, with or without posterior acoustic shadowing, representing intranodular psammoma bodies (► Fig. 6.9a).

Macrocalcifications, including rim calcifications, may also be seen associated with thyroid nodules in both benign and malignant processes. The presence of an incomplete rim of

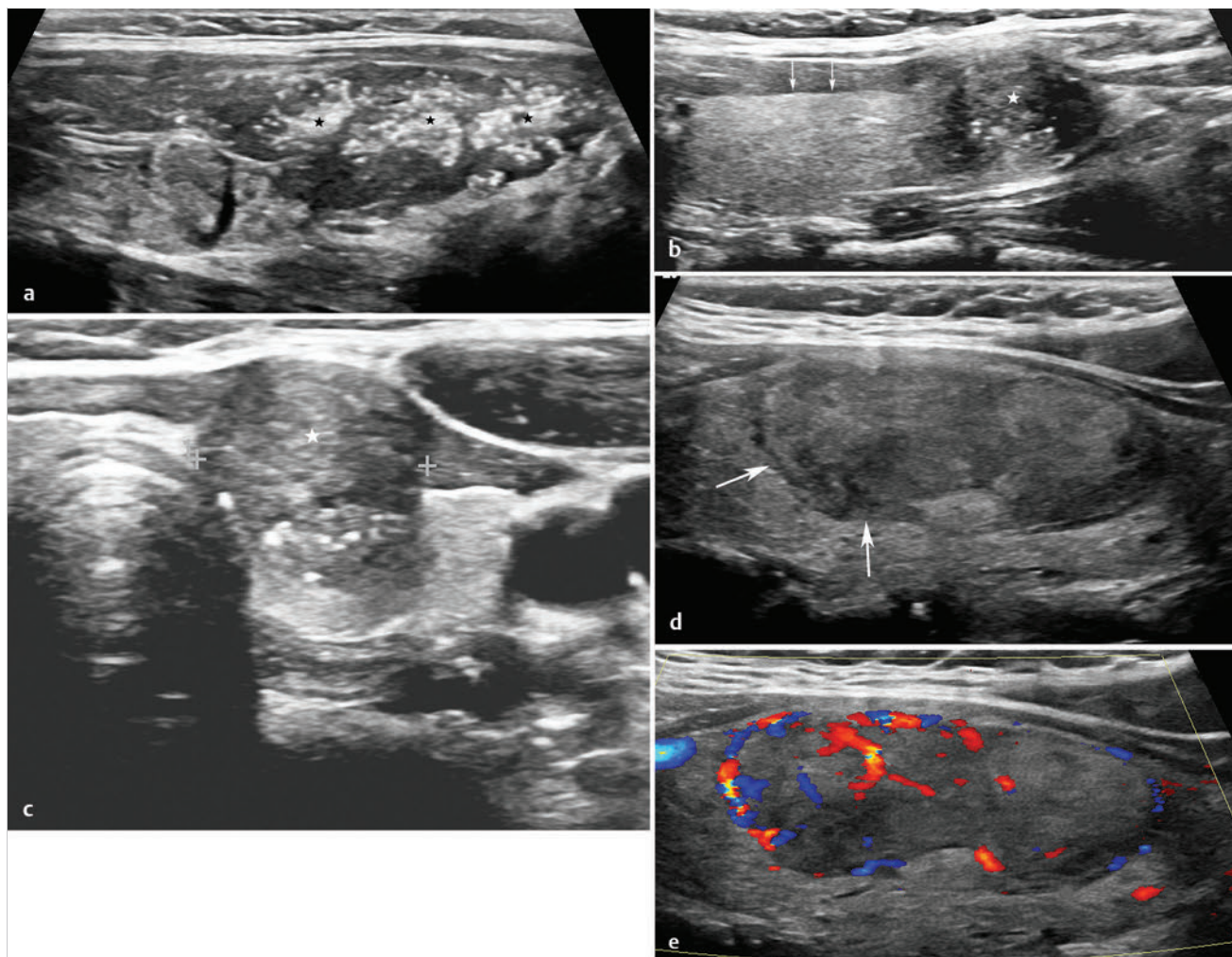


Fig. 6.9 Suspicious thyroid nodules. (a) Longitudinal thyroid ultrasound (US) image shows clusters of hyperechoic microcalcifications (black stars) in the mid to inferior pole of the thyroid in this patient with papillary carcinoma. (b) Longitudinal thyroid US image shows hypoechoic papillary carcinoma (white star) within the inferior pole, extending beyond the normal contour of the thyroid with loss of normal interface between the thyroid and overlying strap muscle. Microcalcifications are present. Normal interface and thyroid capsule are visible (white arrows). (c) Transverse US image of hypoechoic papillary carcinoma (white star) with "taller than wide" nodule dimensions. (d) Longitudinal US image with ovoid solid nodule with incomplete and irregular hypoechoic rim (white arrows). (e) Same solid nodule with central vascularity by color Doppler imaging, proven to be invasive follicular carcinoma at surgery.

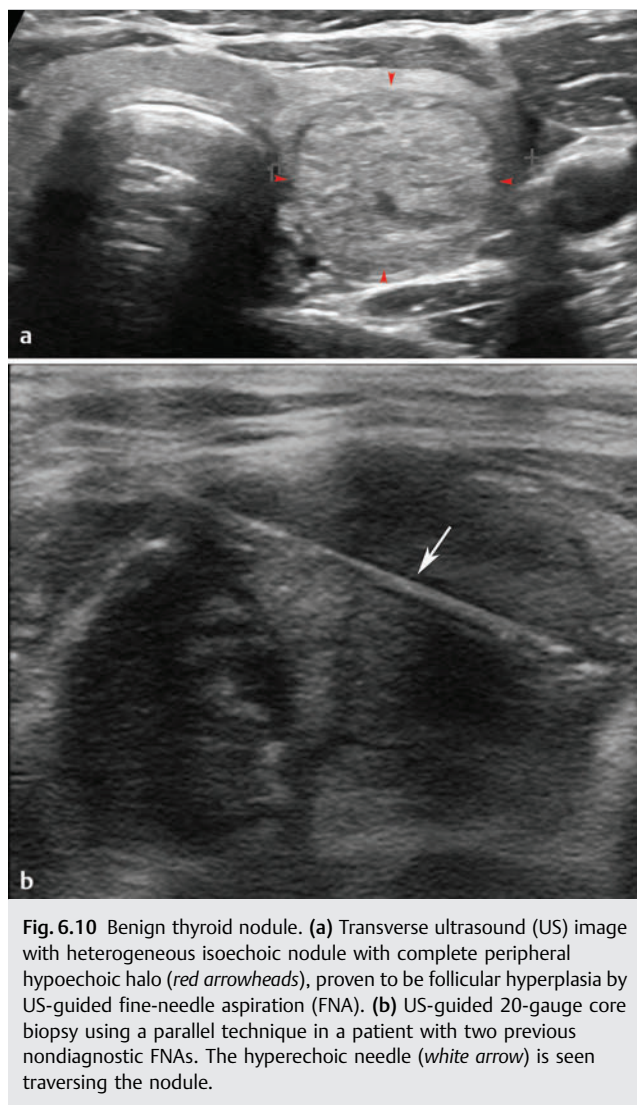


Fig. 6.10 Benign thyroid nodule. (a) Transverse ultrasound (US) image with heterogeneous isoechoic nodule with complete peripheral hypoechoic halo (red arrowheads), proven to be follicular hyperplasia by US-guided fine-needle aspiration (FNA). (b) US-guided 20-gauge core biopsy using a parallel technique in a patient with two previous nondiagnostic FNAs. The hyperechoic needle (white arrow) is seen traversing the nodule.

calcification or hypoechogenicity peripheral to the rim calcification favors a malignant process. Extracapsular extension of a nodular thyroid mass into the adjacent soft tissues is a highly specific sign of malignancy. This may be subtle, with nodule margins extending slightly beyond the thyroid capsule, or it may be overt, with gross invasion of adjacent anatomical structures (► Fig. 6.9b,c).

A cervical lymph node metastasis is also a highly specific sign of thyroid malignancy, commonly identified with papillary and medullary carcinomas. Abnormal lymph nodes may show increased size, loss of fatty hilum, internal cystic change, calcification, and increased vascularity throughout the lymph node, rather than centrally within the hilum. Metastatic lymph nodes associated with papillary carcinoma may appear cystic on US and are easily mistaken for a cystic thyroid nodule.

Less specific ultrasound features of a malignant thyroid nodule include the lack of a complete hypoechoic halo, irregular margins, an intrinsic solid component, or increased central vascularity (► Fig. 6.9d,e).³¹

US features of a benign nodule include a uniform hypoechoic halo around the nodule periphery, a predominantly cystic nodule, an avascular nodule, and an enlarged thyroid with multiple

similar-appearing nodules lacking suspicious imaging characteristics (► Fig. 6.10a).⁴ In a multinodular thyroid, it is essential to evaluate each individual nodule for suspicious sonographic features.

The 2009 American Thyroid Association (ATA) management guidelines for thyroid nodules recommend FNA for nodules > 5 mm in high-risk patients and suspicious sonographic features (► Fig. 6.10b).³² Some studies have shown that adherence to such clinical guidelines achieves the goal of diagnosing clinically significant cancers and avoiding unnecessary procedures in patients with benign nodules.³³

Incidentalomas detected by PET/PET-CT deserve special mention. Approximately 3% of PET scans have incidentally detected focal PET avidity associated with thyroid nodules, with some studies showing up to one-third of these lesions proving to be malignant. At this time no standard uptake value (SUV) cutoff is established that is safe to exclude or suspect malignancy. Therefore all PET avid nodules, regardless of size, should undergo evaluation and fine needle aspiration.³⁴

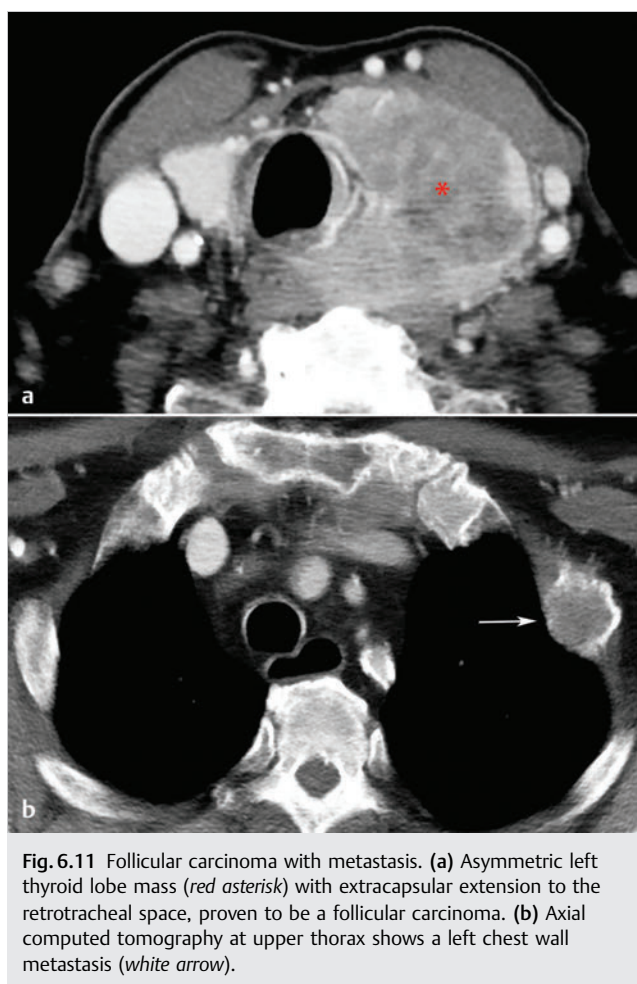
6.6 Malignant Disease of the Thyroid Gland

Thyroid carcinoma is the most rapidly increasing malignancy in the United States. However, despite the significant rise in the number of differentiated thyroid carcinomas over the last decades, the mortality rate has not significantly risen.³⁵ Statistically, most thyroid malignancies are papillary carcinoma, representing approximately 80% of all cases of thyroid carcinoma. Follicular cell and medullary cancers account for approximately 10 to 20% and 6 to 8%, respectively. Aggressive anaplastic carcinoma accounts for only 1 to 2% of thyroid malignancies, yet is responsible for approximately 39% of thyroid cancer-related deaths.³⁶ Although there are no specific imaging findings for the different types of thyroid carcinoma, the initial US imaging helps with staging of thyroid carcinoma by assessing tumor size, extrathyroidal extension of disease, and the presence of lymph node metastasis.

6.6.1 Differentiated Carcinomas

Papillary cancer most commonly presents in young women in the third to fifth decades of life. In papillary carcinoma, careful US examination of the lymph node chains should be performed because regional lymph node metastases at the time of diagnosis occur in 25 to 80% of patients.³⁷ An extensive intrathyroidal lymphatic network allows for tumor spread within the gland. Intraglandular metastases are present in 80% of papillary thyroid carcinoma at histological diagnosis, accounting for the 5 to 20% reported recurrence rates in patients undergoing partial thyroidectomy.³⁸ About 10% of patients show distant metastases, most commonly to the lungs, bones, or central nervous system.

Follicular carcinoma is the second most common thyroid malignancy, usually presenting in the fourth to sixth decades of life as a solitary thyroid mass. In contrast to papillary thyroid carcinoma, multifocal disease and regional lymph node metastases are much less common. Although involvement of regional lymph nodes is not as common as in papillary carcinoma, it is a poor prognostic indicator, implying extrathyroidal extension



of disease. A hematogenous pattern, rather than lymphatic dissemination, is more commonly seen in follicular carcinoma, resulting in distant metastases to the lungs, bones, and central nervous system, which also imply a poor prognosis (► Fig. 6.11).

In patients with differentiated carcinomas, high-resolution US often serves as the only preoperative imaging examination prior to thyroidectomy. Patients with more aggressive forms of differentiated carcinoma, clinical findings suggestive of invasion of local structures, or extensive lymph node disease may benefit from adjunct cross-sectional imaging with CT or MRI to further characterize involvement of adjacent structures and to allow for more accurate preoperative planning (► Fig. 6.12). Lymph node metastases are also better assessed by CT and MRI in areas poorly visualized by US, such as the retropharyngeal and mediastinal spaces.

In the setting of differentiated carcinoma, whole-body radioiodine scanning may be performed several weeks post-thyroidectomy to assess for remnant thyroid tissue, evaluate for functioning metastatic disease, help determine therapeutic radioiodine dose, and reveal altered biodistribution (► Fig. 6.13).

The ATA recommends a whole-body scan prior to ablation when the volume of remnant thyroid is unable to be defined by US or by surgical report, or if the whole-body scan may alter



therapeutic radioiodine dosage or the decision to treat with radioiodine ablation therapy.³⁶ Studies have shown that I-131 therapy reduces the risk of locoregional recurrence, and this therapy has become the standard adjunctive treatment in subsets of patients with differentiated thyroid cancer. The ATA recommends ablation of the thyroid remnant in patients with T3 tumors or lymph node disease and selective ablation in patients with intrathyroidal lesions measuring 1 to 2 cm in size.

Short-term follow-up with physical examination, recombinant TSH-stimulated thyroglobulin measurements, and neck US serve as the initial 6 month follow-up for the majority of post-surgical and postablation patients. After thyroidectomy and

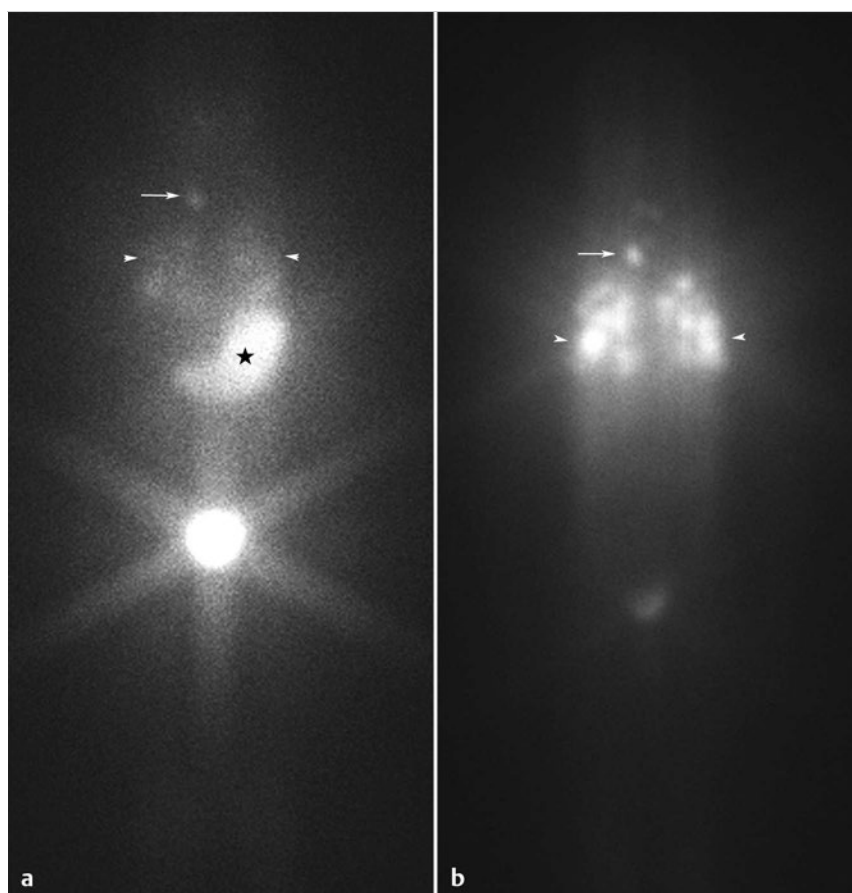


Fig. 6.13 Follicular carcinoma. (a) An 11-year-old child with follicular carcinoma of the right thyroid lobe (white arrow), stomach (black star). Iodine-131 whole-body scan shows diffuse activity in the lungs (white arrowheads) consistent with metastatic disease. (b) Postthyroidectomy scan shows multiple lung metastases (white arrowheads) and cervical adenopathy (arrow).

remnant ablation, only minimal echogenic tissue should be identified within the thyroid bed, likely representing normal connective tissue and scar tissue. The presence of solid or mixed solid and cystic soft tissue in the thyroid bed is concerning for disease recurrence (► Fig. 6.14a).

Recurrent tumor often demonstrates hypervascularity, and use of color Doppler imaging in these cases may be helpful in distinguishing recurrent disease from postoperative abscess, granuloma, or changes in the musculature. In the setting of elevated thyroglobulin levels, US is 96% sensitive in detection of locoregional disease. However, 20% of the population will have a posterosuperior trunk of the thyroid lymphatic pathway that drains into the lateral retropharyngeal nodes, which are poorly evaluated by US (► Fig. 6.14b).³⁹

In the situation of elevated stimulated thyroglobulin and negative neck US, radioactive iodine whole-body imaging may be performed. MRI or CT may also be considered for improved anatomical evaluation for metastatic retropharyngeal, retrotracheal, or mediastinal metastases. Elevated thyroglobulin levels with a negative radioiodine whole-body scan may represent dedifferentiation of thyroid carcinoma cells into a more aggressive form of disease. In this setting, fludeoxyglucose (FDG)-PET/CT is beneficial for disease localization with reported sensitivity for disease detection ranging from 70 to 95% and findings altering patient clinical management in 20 to 40% of cases. FDG-PET/CT findings also provide prognostic information, with a greater number of positive lesions and higher standardized uptake values implying poorer patient prognosis.⁴⁰

6.6.2 Medullary Carcinoma

Medullary carcinoma arises from calcitonin-producing parafollicular C cells. Approximately 25% of medullary carcinomas occur as part of an inherited genetic disorder (familial autosomal dominant medullary thyroid carcinoma or multiple endocrine neoplasia type 2A and 2B [MEN 2A and 2B] syndromes). Medullary carcinoma may be detected early in these patients by following screening calcitonin levels. However, the sporadic form of disease represents the majority of cases, with patients often detected late with a firm palpable thyroid nodule, often with lymph node metastases (35 to 50%).⁴¹

Although there is much overlap with differentiated carcinoma by US, medullary carcinoma may demonstrate a higher propensity for intrinsic cyst formation and more homogeneous echogenicity in solid components of the lesion.⁴² On CT scan, medullary carcinoma usually appears as a well-circumscribed mass with heterogeneous attenuation (► Fig. 6.15a). Radioiodine scintigraphy or therapy is not useful in the setting of medullary carcinoma because these lesions do not concentrate iodine. Surgical resection is the mainstay of treatment. Serum calcitonin levels are monitored after surgery to evaluate for tumor recurrence. Patients with detectable calcitonin levels < 150 pg/mL often have locoregional disease and should undergo high-resolution neck US for detection of local recurrence or lymph node metastases. Calcitonin levels > 150 pg/mL increase the likelihood of distant metastatic disease. In addition to neck US, other diagnostic imaging modalities, such as chest CT with



Fig. 6.14 Postthyroidectomy ultrasound (US). (a) Transverse US image showing no thyroid tissue remnant in the thyroid bed (*white star*). However, a hyperechoic nodule (*white arrow*) along the posterolateral aspect of the common carotid artery is proven to be a lymph node metastasis. (b) Axial computed tomography shows an enlarged hyperenhancing mass (*white arrow*) in the left retropharyngeal space in this patient with papillary carcinoma, consistent with lymph node metastasis.

contrast and liver MRI, may be considered. Reported sensitivity of FDG-PET/CT for medullary carcinoma is 78% (► Fig. 6.15b).⁴³

6.6.3 Hürthle Cell Carcinoma

Hürthle cell carcinoma (HCC), which accounts for 3 to 5% of thyroid cancers, is considered by some to be a variant of follicular carcinoma and by others as a distinct entity. HCC is more aggressive than papillary and follicular carcinoma, with higher

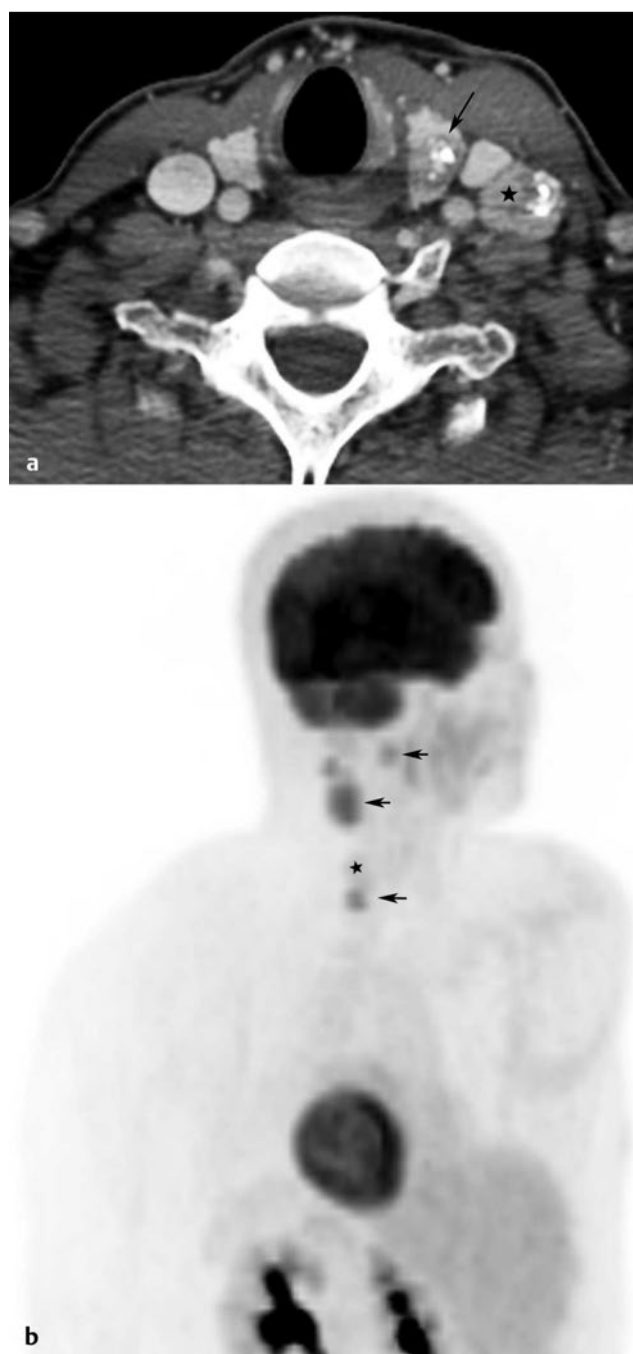


Fig. 6.15 Medullary thyroid carcinoma. (a) Hypodense nodule (*black arrow*) with coarse calcification in the left thyroid lobe. Notice the metastatic level 4 lymph node (*black star*) with an imaging appearance similar to that of the intrathyroid mass. (b) Positron emission tomographic scan of the same patient showing glucose uptake in the thyroid mass (*black star*) as well as in numerous pathological lymph nodes (*black arrows*).

rates of lymph node and distant metastases and a 10-year relative survival rate of approximately 76%.⁴ US imaging features do not differentiate HCC from other thyroid neoplasms. As with follicular neoplasms, US-guided FNA cannot differentiate Hürthle cell adenoma from HCC. This distinction can be made only by tumor capsule evaluations. High-resolution US should

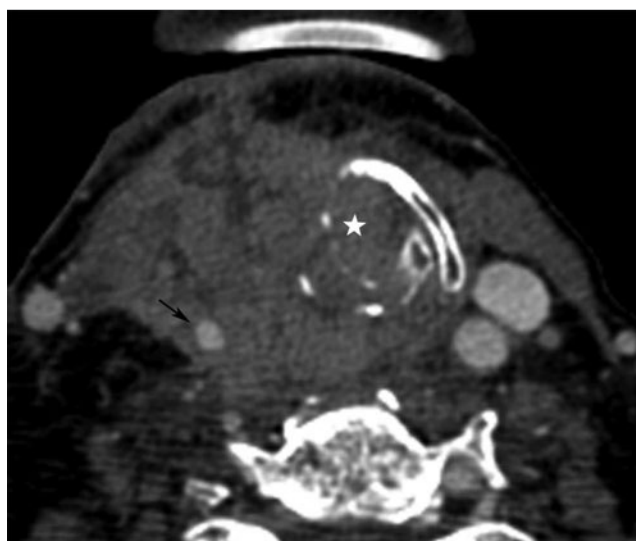


Fig. 6.16 Anaplastic carcinoma. Large heterogeneous mass arising from the right lobe of thyroid with infiltration of the larynx (white star) and common carotid artery encasement (black arrow).

be performed for detection of metastatic cervical nodes. The utility of radioiodine imaging and therapy is limited because HCC often does not concentrate iodine. The mainstay of treatment is aggressive surgical removal, and HCC responds poorly to chemotherapy and radiation.⁴⁴ In the postthyroidectomy patient with elevated thyroglobulin levels, there is a role for FDG-PET/CT, with some studies showing sensitivity and specificity up to 95%.

6.6.4 Poorly Differentiated Thyroid Carcinoma and Anaplastic Thyroid Carcinoma

Poorly differentiated and anaplastic carcinomas have a more aggressive clinical course compared with the previously discussed thyroid cancers. Poorly differentiated carcinoma likely represents an intermediate step in the transition of differentiated carcinoma into anaplastic carcinoma. It often maintains markers of its follicular cell origin, concentrating iodine in 85% of cases, and is prone to radioiodine imaging and ablation treatment. Conversely, anaplastic carcinoma is an extreme undifferentiated form of thyroid carcinoma that is unable to take up iodine or produce thyroglobulin. Although a rare tumor, it accounts for a large percentage of thyroid-related deaths, with median patient survival after diagnosis of approximately 5 months. Patients are usually older and may have a history of thyroid goiter. The tumor may arise de novo or represent a progressive dedifferentiation of a preexisting differentiated thyroid carcinoma. Patients often present with a large, hard thyroid mass with symptoms related to compression or invasion of adjacent structures.

US typically shows a 5 to 10 cm hypoechoic mass, often with intrinsic cystic areas and hyperechoic calcifications. US is also used to evaluate the central and lateral nodal compartments because approximately 40% of patients have lymph node disease at diagnosis. Mass extension beyond the normal margins

of the thyroid capsule is commonly present on US. CT scans show mixed areas of hypodensity and hyperdensity that often represent necrosis and hemorrhage, with about 65% of anaplastic carcinomas showing intrinsic calcifications (► Fig. 6.16). MRI often reveals a heterogeneous T1 and T2 signal with a moderate to marked postgadolinium enhancement pattern. CT and/or MRI examinations should include the entire neck and upper chest to fully evaluate the extent of disease and evaluate for lymph node metastasis. FDG-PET/CT is indicated with anaplastic carcinoma because these lesions do not concentrate iodine and present with distant metastatic disease in approximately 40% of patients. FDG-PET/CT is also recommended every 3 to 6 months posttreatment as a guide to further therapies.^{45,46}

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7 Benign Disease of the Thyroid Gland

Maisie L. Shindo

7.1 Introduction

Benign thyroid diseases comprise both nodular diseases and inflammatory thyroid conditions. Nodular diseases can be categorized as solitary thyroid nodules and multinodular goiters. The term *goiter* is used to describe a pathological enlargement of the thyroid gland. Goiters can be classified as diffuse or nodular, toxic or nontoxic. Toxic conditions of the thyroid are thoroughly reviewed in Chapter 8. Inflammatory thyroid conditions include autoimmune thyroiditis, subacute thyroiditis, and Riedel's thyroiditis.

The prevalence of clinically evident thyroid nodules is approximately 5%, depending on age, sex, and geography.¹ In autopsy series the prevalence of solitary nodules is approximately 10%, and of thyroid nodularity it is as high as 50%.² In recent years imaging modalities have become more ubiquitous and sensitive in medicine, resulting in serendipitous discovery of asymptomatic unexpected thyroid nodules, referred to as incidentalomas. With the routine use of imaging modalities, such as ultrasound (US), computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET), the incidence of thyroid incidentalomas will likely be similar to the prevalence of nodules found on autopsy. US can detect thyroid nodules in 19 to 68% of randomly selected individuals.^{3,4} The incidence of malignancy in a solitary nodule ranges from 10 to 40%, depending on the age, sex, characteristics of the nodule, selective criteria for surgery, and presence of risk factors.^{5,6,7,8} In evaluating a thyroid nodule, a complete history should be elicited regarding factors that may predict the risk of malignancy, such as voice change, hemoptysis, rapid growth, history of childhood head and neck irradiation, total body irradiation for bone marrow transplantation, exposure to ionizing radiation in childhood or adolescence, and thyroid malignancy in first-degree relatives.^{5,7,8,9,10} Radiation exposure can be from prior head and neck irradiation for lymphoma or benign conditions (acne, thymus, enlarged adenoids, tinea capitis),^{11,12} total body irradiation for bone marrow transplantation,^{13,14} and exposure to fallout, such as from the Chernobyl incidents, particularly in those under 15 years of age.^{15,16,17}

A review of the patient's family history is important for assessing the risk factor for thyroid cancer. The probability of a patient with a thyroid nodule having a malignancy is estimated to be approximately 38% when two first-degree family members are affected, and is even higher when three or more are affected.¹⁸ It is also important to be aware that nodular thyroid diseases may be associated with various hereditary syndromes, particularly when present at a younger age. Familial adenomatous polyposis is an autosomal dominant disease caused by mutation of the *APC* gene and is characterized by polyposis of the colon, epidermoid cysts of the skin, desmoid tumors of the abdominal wall, retinal pigmented epithelium, and thyroid carcinoma. A small subset of these patients present with osteomas, referred to as Gardner's syndrome. Thyroid carcinomas occur in 1 to 2% of these patients and are usually papillary carcinoma.^{19,20} Cowden's disease is an autosomal dominant disease characterized by tumors of the thyroid, breast, colon,

endometrium, and brain, and hamartomas and tumors of the skin. The thyroid abnormalities may present in childhood as multinodular goiters, multifocal follicular adenomas, and adenomatous nodules.^{20,21} Carney's complex is an autosomal dominant multiple neoplasia syndrome due to mutation in the *PRKARIA* gene consisting of spotty skin pigmentation, myxomas, endocrine tumors, and schwannomas.²² Multiple endocrine organs are affected, resulting in thyroid tumors; primary pigmented nodular adrenocortical disease, which can result in Cushing's syndrome; prolactin-producing pituitary tumors; testicular tumors causing precocious puberty; and ovarian tumors.²² Up to 75% of patients with Carney's complex have multiple thyroid nodules, and some may also present with thyroid malignancy.²² Skin manifestations include spotty pigmented skin lesions, blue nevi, and café au lait spots. The myxomas can involve the heart, breast, and skin.²² Pendred syndrome is an autosomal recessive disease manifesting as a combination of goiter and congenital deafness. Goiters may be present from childhood to early adolescent years. The genetic defect with this disease has been shown to be a mutation of the *PDS (SLC26A4)* gene on chromosome 7q22–31.1.²³

In the evaluation of nodular thyroid disease, the head and neck examination should include the characteristics of the thyroid gland and an assessment for lymphadenopathy and cranial nerve function, particularly vocal cord mobility. A thyroid nodule associated with ipsilateral vocal cord paralysis is highly suspicious for a malignancy. In the rare patient who may also have hemoptysis, flexible laryngoscopy should be performed to assess laryngeal pathology and to examine the upper trachea for presence of tracheal invasion from a thyroid malignancy.

7.2 Evaluation and Management of Solitary Thyroid Nodules

The natural course of thyroid nodules is not fully understood. One long-term study showed that 23% of thyroid nodules ultimately increased in size.²⁴ The most important goal in the diagnostic evaluation of a thyroid nodule is to exclude malignancy. Because thyroid nodules are quite prevalent, including nonpalpable ones found incidentally, the challenge for the clinician is in deciding which nodules need to be biopsied or surgically excised and which ones can be observed. Serum thyroid-stimulating hormone (TSH) should be the initial first test in the evaluation of nodular thyroid disease.⁵ US is also an important initial test. It is excellent for detection and characterization of thyroid nodules and thus is an adjunct to the physical examination.^{5,25,26,27} Thyroid sonography provides very useful management information that includes accurate measurement of the size of the nodule; whether the nodule is purely cystic, solid, or mixed; whether other nonpalpable nodules are present; and whether there are findings indicating a malignancy, such as microcalcifications and irregular margins, intranodular hypervascularity, and marked hypoechogenicity.^{27,28,29} A thyroid uptake scan for solitary nodules is not particularly useful unless

the TSH level is suppressed (i.e., below normal range). In which case, a thyroid uptake scan can be obtained to see if the nodule is hyperfunctioning, indicative of a toxic single adenomatous nodule. Fine-needle aspiration (FNA) is a very important and useful tool in the diagnostic evaluation of solitary nodules.^{7,30}

In general, a solitary nodule requires histological evaluation, either by FNA or surgical excision, when associated with risk factors for malignancy. These factors include rapid enlargement, associated lymphadenopathy, associated vocal cord paralysis, prior radiation exposure, age over 60 or under 20, and a family history of thyroid cancer in a first-degree relative. The incidence of malignancy in a solitary nodule in childhood is greater than that in adults and has been reported to be as high as 50%.^{11,31,32,33} Therefore, serious consideration should also be given to biopsy or surgical excision of thyroid nodules detected during childhood, particularly if they are > 1.5 cm and solid. Solid thyroid nodules in patients over 65 years of age have a higher risk of being malignant. Furthermore a higher percentage of the malignancies in this age group tend to be of the more aggressive type.^{6,34,35} In a study of 21,748 patients with thyroid nodules who underwent US-guided FNA and surgical pathological correlation in 3,629 patients, 37% of the nodules occurring in those over age 65 were found to be malignant, and up to 36% of the malignancies were diagnosed as anaplastic or metastatic.⁶ Therefore, a cytological or pathological diagnosis is warranted in elderly patients who present with a new thyroid nodule, particularly if it is rapidly growing. Sonographic evaluation of the anterior cervical lymph node (central and bilateral) compartments should be performed whenever thyroid nodules are detected.⁷ If US detects cervical lymph nodes that are sonographically suspicious for thyroid cancer, FNA of the suspicious lymph node should be performed. Incidentalomas pose a management dilemma. Nodules with sonographic findings suspicious for malignancy as discussed earlier should be biopsied.^{28,36} It has been suggested by several authors as well as the American Thyroid Association (ATA) Task Force on Thyroid Nodules and Differentiated Thyroid Cancer that, in the absence of clinical risk factors for malignancy, risk stratification of a thyroid nodule base on a constellation of US findings would help triage which nodules should be biopsied and which should not.^{7,36,37,38,39} The 2014 ATA guidelines recommend characterizing the pattern of US findings and stratifying the nodules into benign or suspicious.⁷ Purely cystic nodules are considered benign and do not require a biopsy. Suspicious findings are risk stratified into high, intermediate, low, and very low suspicion categories based on whether they are solid or cystic, their echogenicity, and the presence of one or more of the following worrisome features: microcalcifications, a taller than wide shape, rim calcifications with a small extrusive soft tissue component, and extrathyroidal extension. Hypoechoic solid nodules with or without a cystic component exhibiting one or more of these worrisome features are considered high risk (70–90% risk of malignancy) and should be biopsied if > 1 cm. Hypoechoic solid nodules without these worrisome features carry a much lower risk of malignancy (10–20%); biopsy of such lesions should be considered if they are > 1 cm. Nodules that are isoechoic, hyperechoic, or partially cystic with eccentric solid areas that do not exhibit any of the worrisome features are considered low risk (5–10% risk of malignancy), and thus biopsy can be considered when the nodules are > 1.5 cm. Mixed cystic solid nodules with

a spongiform appearance strongly correlate with benignity, and FNA can be withheld until they are > 2 cm.

Other laboratory tests considered in the evaluation of a thyroid nodule include serum calcitonin and thyroglobulin levels. A serum calcitonin level should be obtained if there is a family history of medullary thyroid carcinoma, or if the FNA of the nodule reveals atypical small round cells or spindle cells, which are not typical of cells derived from a follicular origin. Serum thyroglobulin is not very helpful as a diagnostic tool. An elevated thyroglobulin level itself is not indicative of a thyroid malignancy because benign conditions, such as an adenomatous nodule or a recent FNA, can cause elevation of serum thyroglobulin. However, should the nodule turn out to be a follicular cell-derived thyroid carcinoma, a normal preoperative level obtained prior to FNA may be indicative of a nonthyroglobulin-secreting tumor, which may guide the methodology of subsequent cancer surveillance.

Thyroid FNA cytological findings are generally reported using the Bethesda System for Reporting Thyroid Cytopathology.^{40,41} The Bethesda System recognizes six diagnostic categories: (I) nondiagnostic/unsatisfactory; (II) benign; (III) atypia of undetermined significance/follicular lesion of undetermined significance (AUS/FLUS); (IV) follicular neoplasm/suspicious for follicular neoplasm (FN), a category that also encompasses the diagnosis of Hürthle cell neoplasm/suspicious for Hürthle cell neoplasm; (V) suspicious for malignancy (SUSP), and (VI) malignant.

A nondiagnostic FNA results from poor preservation of the specimen or low cellularity obtained from the aspiration, which can occur for several reasons, including small nodules, densely fibrotic or calcified nodules, cystic nodules, and operator inexperience. The diagnostic yield of FNA can be improved when performed under US guidance.^{42,43} Furthermore, with US guidance, small, nonpalpable nodules can be biopsied with high yield. The rate of nondiagnostic aspiration can be further reduced to <2% when the biopsy is performed under US guidance with on-site cytological preparation where cytotechnologists or cytopathologists can provide immediate feedback on whether or not the aspirate is sufficiently cellular.^{6,44,45}

Thyroidectomy should be recommended if the FNA cytology is consistent with or suspicious for a malignancy. The risk of malignancy in an indeterminate nodule (Bethesda classifications III and IV) ranges from 20 to 30%.^{46,47,48} With indeterminate cytology, the options are surgical excision for definitive diagnosis, or testing the FNA with the Afirma Gene Expression Classifier (GEC), which evaluates mRNA expression of 167 genes.⁴⁹ The GEC has been shown in a multi-institutional study to have a negative predictive value of 95%, and a 37% positive predictive value. This means that if the GEC is nonsuspicious, the risk of malignancy is 5%; however, if it is suspicious, the risk of malignancy is only 37%; thus it is considered a rule-out test.

The decision is not as straightforward when the FNA cytology is nondiagnostic. Repeat FNA or surgery should be recommended if the cytologically nondiagnostic nodule is solid, depending on the clinical and US suspicious features. The patient's age and underlying medical condition also need to be factored into the decision making. In young patients with large nodules, particularly if they are solid or demonstrate some atypia, surgical excision for definitive diagnosis and long-term treatment is preferred over observation. In elderly patients with

this scenario, if the patient has little or no anesthetic risks, surgical excision should be considered. However, in those with significant comorbidities, it would be appropriate to repeat the FNA and closely observe the nodule.⁵⁰

Cystic nodules are diagnostically challenging because aspiration of the fluid usually yields a hypocellular specimen. The risk of malignancy in cystic thyroid nodules among adults ranges from approximately 15 to 30%, similar to that of solid nodules, and the risk of a false-negative aspirate is high.^{51,52,53} The recommendation formulated by the ATA is that cystic nodules which repeatedly yield nondiagnostic aspirates need surgical excision or close observation with fastidious follow-up and repeat FNA.⁷ A cystic nodule containing a large solid component, particularly with microcalcifications, or with an irregular and fingerlike pedunculated mass extending into the lumen, is suspicious for a cystic papillary carcinoma.^{54,55} If the initial FNA of a cystic nodule with these US characteristics is nondiagnostic, either the FNA should be repeated with US guidance and on-site cytologic evaluation, or surgery should be recommended. When performing FNA on a cystic nodule, the diagnostic yield can be improved by first aspirating the fluid content and then reaspirating under US guidance the remaining cyst wall or solid component.^{55,56,57} A cystic thyroid nodule associated with cystic lymphadenopathy in the paratracheal region is strongly suggestive of cystic papillary thyroid carcinoma and should be treated as such until proven otherwise. FNA of the thyroid nodule and cystic node, particularly if performed under US and cytological guidance, should confirm the diagnosis. A cystic thyroid nodule associated with cystic lymphadenopathy in the lateral neck is more challenging in terms of establishing a cytological diagnosis because the aspirate from the lymph node can be hypocellular or can mimic lesions of nonthyroid origin, such as a branchial cleft cyst.^{52,58} In that setting, the fluid from the lymph node aspiration can be sent for a thyroglobulin level; if elevated, it would be diagnostic of cystic papillary carcinoma; however, a normal level does not exclude malignancy. Measuring the thyroglobulin level in the fluid obtained from FNA of a cystic thyroid nodule is generally not helpful because it can also be elevated in a benign nodule. If FNA of a thyroid nodule associated with cystic cervical lymphadenopathy cannot establish a diagnosis, surgery with frozen section is warranted.

7.3 Nodular Goiters

Nodular goiters encompass several different pathological conditions, including hyperthyroidism, hypothyroidism, autoimmune thyroiditis, and malignancy. In the absence of such conditions, it constitutes an entity described as simple nodular goiter, often interchangeably termed multinodular goiter. Multinodular goiter is the most common endocrine disorder worldwide. Goiters can occur endemically and sporadically. An endemic goiter is one that occurs in a region, such as the Andes and Pyrenees, where its prevalence in children 6 to 12 years of age is > 5%.⁵⁹ Sporadic goiter is one that occurs in a nonendemic region in a euthyroid individual.

7.3.1 Pathogenesis

The etiology of nodular goitrous enlargement is multifactorial and can be categorized into environmental and genetic.^{59,60} Iodine deficiency is the most common environmental factor contributing to formation of endemic goiters.⁶¹ Iodine deficiency affects the organification step in thyroxine synthesis, resulting in inadequate thyroid hormone production, which leads to increased TSH production by the pituitary. TSH stimulation ultimately causes growth of thyroid follicles and glandular enlargement. Once iodine was supplemented in the diet as iodized salt, the prevalence of goiters decreased significantly in many parts of the world. Although iodine deficiency may also be a cause of goiters in nonendemic regions, the etiology in most cases of sporadic goiters is unclear. Various natural substances that interfere with the iodine-trapping mechanism have been implicated in the development of goiters.⁶² Some of these natural goitrogens, such as cyanogenic glycosides and thiocyanates, are found in vegetables; others are found in grass and weeds, which are then transmitted through cows and animals that consume them. Female sex is also associated with increased risk of nodular goiter formation. Other etiologies that have been implicated in development of goiters are smoking,^{59,63,64} medications,⁶⁵ and low selenium level.⁶⁶ Rarely, iodine excess has also been advocated as a cause of goiter.

Genetics has also been implicated in the formation of nodular goiters.^{67,68,69,70,71} Immunogenic stimulation has also been speculated to be a potential cause of goiter formation. Immunoglobulins that can stimulate growth of thyroid follicles in vitro have been detected in patients with both toxic and nontoxic nodular goiters^{72,73}; however, their role in development of these goiters has yet to be clearly established. Regardless of the thyrotrophic stimulating agent, be it TSH or immunoglobulin, the initial response in the thyroid is diffuse enlargement. With chronic stimulation, various areas of the gland continue to proliferate at different rates. Some areas will become hypofunctional, whereas others may become hyperfunctional. The increased tissue mass is also modulated by apoptosis, resulting in death of thyrocytes and involution in some areas. The apoptosis is thought to be mediated by the Fas antigen.⁷⁴

7.3.2 Patterns of Growth

The natural history of untreated euthyroid multinodular goiters can be somewhat variable.^{75,76} Some will continue to grow in volume, up to 20% in a year, while remaining euthyroid.⁷⁶ As growth continues, the enlarging thyroid gland can extend outside of the thyroid bed and spread inferiorly to the mediastinum or posteriorly along the sides or behind the pharynx. Chin and colleagues studied the patterns of growth on CT scans in 190 patients with goiters.⁷⁷ They reported that in 44% of the patients the goiters spread outside of the thyroid bed. Thirty-seven percent of the goiters demonstrated extension into the mediastinum, and 7 percent extended along or behind the pharynx. Of those that extended into the mediastinum, all extended into the anterior compartment, and 7% extended into the posterior compartment.

7.3.3 Evaluation and Management of Nontoxic Goiters

Approaches to the management of nontoxic goiters differ considerably among physicians of the same specialty and different specialties, between different continents, and for young versus old patients. North American clinicians use serum TSH (100%), followed by FNA and thyroid US, with the majority employing US guidance for FNA. Thyroid uptake scintigraphy and serum calcitonin levels are used less frequently by North American clinicians compared to European clinicians. There is also considerable disagreement among clinicians on the management of nontoxic goiters. In the same survey reported by Bonnema et al⁷⁸ one-third preferred observation, whereas approximately half used levothyroxine, despite a lack of evidence from prospective clinical trials demonstrating the value of levothyroxine therapy. Seventy-eight percent recommended surgery if rapid growth is observed, and 69% recommended surgery for compressive symptoms. Surgery was also preferred by approximately two-thirds of the clinicians if there is a history of prior head and neck radiation or a family history of thyroid malignancy. Without a uniform consensus in approaches to the management of nontoxic goiters, a logical approach would be to base the decision on the presence or absence of dominant nodules, and whether or not the goiter is increasing in size or causing compression. The patient's age and sex, history of rapid growth, prior head and neck irradiation exposure, and family history of thyroid malignancy also need to be factored into the decision.

Noncompressive Goiters

In the absence of any associated risk factors for malignancy, small, nontoxic goiters with small nodules can generally be observed with periodic thyroid sonograms. Nodules should be biopsied when growth is observed. Dominant nodules in a multinodular goiter, particularly if they are hypofunctional, should undergo FNA. Guidelines on when to biopsy a thyroid nodule have been discussed in the previous section on solitary nodules. In the presence of two or more thyroid nodules >1 cm, those with a suspicious sonographic appearance should be aspirated preferentially. If none of the nodules has a suspicious sonographic appearance and multiple sonographically similar nodules are present, the largest nodule (>2 cm) should be biopsied.⁷

In recent years the use of ethanol injection for long-term management of cystic nodular goiters has been advocated by some as an alternative to surgical excision. With this technique, the cyst is decompressed under US guidance and highly concentrated (i.e., 95%) ethanol is injected. Several studies have shown that volume reduction by as much as 95% can be achieved, with low recurrence rates.^{79,80,81,82,83} Some have even advocated that cysts up to 40 mL can be successfully treated.⁸¹ When comparing the techniques of simply injecting ethanol into the cyst, versus aspirating the cyst first then injecting the ethanol, the cure and complication rates are similar with both techniques; in fact, the patients prefer only one needle puncture, and the time of procedure is shorter without aspiration of the cyst.⁸⁰ Cysts with

high viscosity tend to be difficult to treat. For these types of cysts, Zielesnik and colleagues advocate a two-stage ethanol injection technique where ethanol is injected into the cyst under US during the first procedure and left for 2 weeks, which helps reduce the viscosity. In the second stage, the thinner fluid is aspirated and 95% ethanol is reinjected under US.⁸⁴ The authors reported a 92% reduction in volume and no recurrence. The therapeutic use of ethanol injection for thyroid nodules remains controversial. Opinions range from those who believe that this is still an investigative technique to others who use it selectively in patients who cannot undergo surgery to those who use it routinely.^{59,80,85,86} Although this has become a popular primary treatment modality for thyroid cysts and toxic adenomatous nodules in Europe and Asia, this procedure is generally not favored as the primary treatment of choice in the United States.

Compressive and Substernal Goiters

When nodular goiters become sufficiently large, they can cause deviation or compression of the aerodigestive tract. With further extension inferiorly, they can advance into the mediastinum and become substernal goiters. Lahey and Swinton defined a substernal goiter as a "gland in which the greatest diameter of the intrathoracic mass by roentgenogram is well below the upper aperture of the thoracic cage made by the sternum, first rib, and vertebral bodies."⁸⁷ The incidence of substernal goiter in the general population based on screening chest X-ray is 0.02% to 0.5%.^{88,89} Several classification systems have been proposed for substernal goiters. Higgins originally described a classification system based on the percentage of the goiter in the neck versus the thorax.⁹⁰ He classified a goiter as intrathoracic if at least four-fifths of the gland lies in the thorax. In addition, he described substernal (part or all of the gland extending below the sternum) and/or subclavicular (part or all of the gland extending below the clavicle) components. Another classification was developed by Cohen and Cho based on the percentage of the mediastinal component of the substernal goiter. Grade I is defined as up to 25% of the goiter in the chest, grade II is defined as 26 to 50%, grade III is defined as 51 to 75%, and grade IV is defined as >75%.⁹¹

Compressive cervical and substernal goiters can grow considerably for years before causing any symptoms. When sufficiently large, they can impinge on the trachea and cause deviation or narrowing of the tracheal lumen. Many patients with tracheal narrowing are asymptomatic, but some may experience dyspnea. Patients with tracheal deviation are usually asymptomatic. Large goiters can also impinge on the esophagus and cause dysphagia. Substernal goiters can occasionally impinge on the intrathoracic great vessels and cause venous obstruction. When venous compression is severe, it can impede venous outflow from the head and neck, resulting in facial erythema when arms are raised above the head, known as Pemberton's sign. In those who are symptomatic from a substernal goiter the most common compressive manifestation is dyspnea (48–67%), followed by dysphagia (26–53%), and stridor (11–17%).^{92,93,94,95,96}



Fig. 7.1 Substernal goiter with mild tracheal narrowing and compression.

Levothyroxine therapy is recommended in a patient with nontoxic multinodular goiter with hypothyroidism, and in this setting, radioactive iodine ablation has been associated with a 40 to 60% reduction in volume within 2 years of therapy.^{97,98} Recombinant human TSH has also been shown to enhance radioactive iodine uptake in euthyroid goiters.^{99,100,101} It has also been shown to reduce the dose of radioactive iodine needed for effective ablation and improve its long-term effectiveness.^{99,100,102} Despite the fact that radioactive iodine has been shown to be effective in reducing the volume of goiters,^{97,98,99,100,101} thyroidectomy is the preferred definitive treatment modality for young patients with cervical and substernal goiters, especially when compressive.

The decision for thyroidectomy is not as straightforward in the elderly with such goiters because of associated comorbidities. Rapid enlargement of a goiter in an elderly patient is worrisome for a thyroid malignancy and therefore requires at least FNA, if not thyroidectomy. Observation is a reasonable approach for the asymptomatic elderly patient with a cervical or substernal compressive goiter that is known to have been present for years with very little change in size and degree of compression. Compressive goiters that are incidentally discovered on imaging studies performed for some other reason, however, pose a management dilemma in elderly patients. In this situation, if the patient is asymptomatic and radiographs demonstrate only mild to moderate tracheal deviation or narrowing (► Fig. 7.1), observation with FNA of the dominant nodule(s) is a reasonable approach. If the patient is experiencing dysphagia or shortness of breath, it is important to differentiate if their symptoms are actually due to compression by the goiter or due to some other conditions that frequently coexist in this age group, such as congestive heart failure, cricopharyngeal spasm, or esophageal dysmotility. Pulmonary functions tests with flow loops may occasionally be helpful if extrathoracic obstruction is seen, but a normal flow loop does not necessarily exclude symptomatic tracheal compression. An esophagram, if it demonstrates extrinsic compression, may also provide supportive evidence that the goiter is causing dysphagia. However, a normal study does not necessarily mean that the goiter is not the cause of the dysphagia. Noncontrast CT of the neck and chest is helpful in assessing the extent of substernal extension

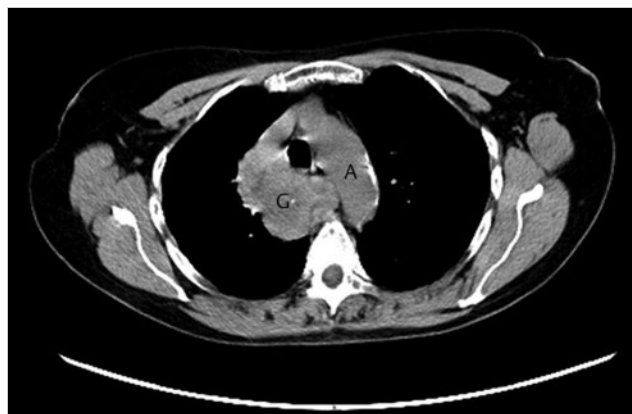


Fig. 7.2 Substernal goiter with significant extension below the aortic arch and into the posterior mediastinum. A, aortic arch; G, substernal goiter.

(► Fig. 7.2), the degree of tracheal compression, or if the goiter is actually compressing on the esophagus to help determine if the patient would truly benefit from thyroidectomy. For routine imaging of the thyroid, intravenous contrast is unnecessary and should be avoided because the gland is often well visualized on CT. Thus, in an elderly patient with a large compressive goiter (intrathoracic or cervical) and symptoms of compression, such as dysphagia, dyspnea, and facial venous congestion, in the absence of other concurrent conditions that can explain these compressive symptoms, subtotal or near-total thyroidectomy should be recommended, provided the patient's anesthetic risks are low. Otherwise, radioactive iodine can be used, which has been shown to decrease up to 50% of the goiter size.^{97,98,99}

7.4 Inflammatory Thyroid Conditions

Thyroiditis can be classified as (1) chronic, which encompasses Hashimoto's thyroiditis (HT) and Riedel's struma; (2) subacute, which includes granulomatous and lymphocytic painless thyroiditis; and (3) acute suppurative, which is exceedingly rare.

7.4.1 Hashimoto's Thyroiditis

By far, the most common of all inflammatory thyroid disorders, HT affects approximately 2% of the general population. It is characterized by lymphocytic infiltration of the thyroid gland, followed by a gradual destruction and fibrous replacement of the thyroid parenchyma. Patients may or may not develop a goiter. The principal biochemical characteristic of the disease is the presence of thyroid autoantibodies in the patients' sera against two major thyroid antigens, thyroid peroxidase (TPO) and thyroglobulin (Tg). TPO antibodies are present in more than 90% of patients with HT, whereas approximately 80% will have positive Tg antibodies.¹⁰³ Although both antibodies are markers for this disease, they are likely not the primary pathogenesis. It is likely that T-cell-mediated cytotoxicity and activation of apoptotic pathways influence the disease. Unlike Tg antibodies, TPO antibodies can activate complement and are able to cause damage to thyroid cells due to antibody-dependent cell

cytotoxicity.¹⁰⁴ A complex interaction between genetic and nongenetic factors presumably results in enhanced thyroid antigen presentation and reduced immune tolerance leading to thyroid destruction and clinical disease. Multiple susceptibility genes may be involved in the disease development, some of which are also common for other autoimmune diseases, whereas others are specific for thyroid autoimmunity. The gene for Tg, located on chromosome 8q24, as well as various immune-regulatory genes, such as *HLA*, *CTLA-4*, and *PTPN22*, have all been shown to be associated with development of HT, along with Graves' disease and other autoimmune diseases. The *VDR* gene, also associated with various autoimmune diseases, such as type 1 diabetes or Addison's disease, is also another HT predisposing gene. Cytokine genes, such as *IFN-γ*, *IL-4*, or *TGF-β*, indicate the association with the development and severity of HT.¹⁰⁵

Histologically, the gland is infiltrated with a polymorphous population of lymphocytes, and destruction of thyroid follicles and formation of lymphoid follicles is seen. Unlike painless lymphocytic thyroiditis (see Subacute Painless Lymphocytic Thyroiditis), oxyphilic (Hürthle cell) changes and areas of glandular fibrosis are also seen. The clinical presentation varies, depending on the stage at the time of presentation. The patient may be completely asymptomatic or present with symptoms of hypothyroidism. The gland is generally enlarged, symmetric, and finely nodular without any discrete palpable nodules. Rarely, the patient may present with pain, and the gland may be tender to palpation, mimicking the clinical features of subacute thyroiditis.^{106,107} Thyroid hormone levels will also vary at the time of presentation. They may be normal with a normal TSH (euthyroid), low with an elevated TSH (hypothyroid), or normal with an elevated TSH (subclinically hypothyroid). The clinical course of HT is variable. Up to 50% of the patients can become subclinically hypothyroid and 5 to 40% can become clinically hypothyroid, emphasizing the importance of following thyroid function tests in these patients.^{108,109,110} Treatment for chronic autoimmune thyroiditis depends on the results of the thyroid function tests. Patients with overt hypothyroidism are treated with levothyroxine. The dose is age dependent. TSH levels should be monitored, and the dose should be adjusted to maintain levels within the reference range. Patients with HT have a higher frequency of other autoimmune disorders, such as adrenal insufficiency, diabetes mellitus, Sjögren's syndrome, celiac disease, rheumatoid arthritis, and lupus erythematosus. They also have an increased risk of developing B-cell lymphoma of the thyroid.^{111,112,113} Rapid growth in the setting of HT should alert the clinician to the possibility of thyroid lymphoma.

7.4.2 Subacute Painless Lymphocytic Thyroiditis

There are two forms of painless thyroiditis, sporadic and postpartum, both sharing very similar features. It is characterized by destruction of the thyroid gland by lymphocytes, absence of pain, and temporary thyroid dysfunction. It is much more common in women. The etiology is uncertain, but it is clear that the immune system is involved because it has been found in patients with a wide variety of autoimmune diseases. *HLA-DR3* is present in increased frequency in both sporadic and postpartum forms.¹¹⁴ In addition to *HLA-DR3*, *HLA-DR5* is also

increased in frequency in postpartum thyroiditis.¹¹⁴ Histologically, the gland is prominently infiltrated with lymphocytes, and areas of follicle destruction are prominent.¹¹⁵ Clinically, the patient typically passes through four phases: thyrotoxic, euthyroid, hypothyroid, and euthyroid. The initial thyrotoxicosis is caused by a release of preformed hormone and not because of sustained overproduction of the hormone, and therefore is not true hyperthyroidism. It typically lasts 3 to 6 months but may persist for 1 year.¹⁰⁹ Symptoms are generally mild, although in some cases they may be severe enough to require hospitalization. The initial thyrotoxic phase of postpartum thyroiditis is usually milder than sporadic thyroiditis. The gland is usually symmetrical and may be slightly to moderately enlarged. It is completely painless to palpation. Thyroid function tests will reflect the degree of hypo- or hyperthyroidism at the time of testing. The thyroglobulin levels are elevated, as are antimicrosomal antibodies. Unlike subacute granulomatous thyroiditis, the erythrocyte sedimentation rate is generally normal. Iodine-131 uptake is low, usually below 5%. Because the hyperthyroid phase of the disease is usually transient and mild in nature, most patients do not require treatment. If the cardiac symptoms are prominent, they can be controlled with beta-blockers.

7.4.3 Subacute Granulomatous Thyroiditis

Also known as painful thyroiditis and granulomatous thyroiditis, this disorder is characterized by sudden onset of anterior neck pain, localized over the thyroid gland, which may radiate to one or both ears or jaws. It may be associated with antecedent viral illness. There is a female preponderance. The patients frequently report malaise, weakness, and fatigue as well as symptoms of thyrotoxicosis, such as palpitations, nervousness, tremor, heat intolerance, and weight loss. The most prominent physical finding is an enlarged thyroid gland that is exquisitely tender to palpation. Frequently, patients present with tachycardia and hyperpyrexia, with the temperature elevated up to 102° F. The erythrocyte sedimentation rate is consistently high, and the white blood cell count may be elevated. Thyroid function tests may be normal, elevated, or low, depending on the stage of the disease at the time of presentation. Similar to painless thyroiditis, patients will go through the initial phases of thyrotoxicosis for 1 to 3 months, which is a result of release of stored thyroid hormones from acute destruction of the thyroid parenchyma. Subsequent to that they become euthyroid. In severe cases, after returning to a euthyroid state the patient can then develop hypothyroidism, which usually lasts 2 to 6 months. This phase is usually transient, with approximately 90% of the patients recovering and returning to a euthyroid state. Pathologically, the thyroid is infiltrated with neutrophils, lymphocytes, and large monocytes. Multinuclear giant cells with granuloma formation are also seen. Thyroid follicles become hyperplastic, and areas of follicular disruption are seen. In the late stage of the disease, follicular regeneration is evident with only minimal fibrosis.

7.4.4 Acute Suppurative Thyroiditis

This rare entity usually occurs from a bacterial infection, and rarely from a nonbacterial infection, of the thyroid. It tends to

affect a younger age group in the 30 to 40 range, and not infrequently affects children. The infection may reach the gland via blood, lymphatics, or directly through a persistent thyroglossal duct or a nearby internal fistula, such as a pyriform sinus fistula. History of an antecedent infection, such as pharyngitis, can frequently be elicited. Patients typically present with symptoms very similar to subacute thyroiditis, in that there is usually anterior neck pain and fever. The patient may experience dysphagia, and left untreated may progress to dyspnea. Physical findings include tenderness over the thyroid with localized erythema and warmth. Pyriform sinus fistula should be included in the differential diagnosis in children.¹¹⁶ The white blood cell count is usually elevated. The bacterial pathogens include *Staphylococcus*, *Streptococcus*, and a variety of gram-negative organisms, particularly oral pathogens.^{117,118,119} Nonbacterial infection of the thyroid gland is very rare but can result from *Aspergillus*, *Coccidioides*, and *Candida*.¹¹⁷ Treatment consists of appropriate antimicrobial therapy and analgesics.

7.4.5 Riedel's Struma

Also known as invasive fibrous thyroiditis or Riedel's thyroiditis, this exceedingly rare disorder is characterized by intense infiltration of the thyroid parenchyma by inflammatory cells and subsequent replacement by dense fibrosis and collagen.¹²⁰ It is not a primary disorder of the thyroid but involves the thyroid and represents part of a systemic disease. It may affect only the thyroid gland or may also involve other sites, such as the mediastinum, retroperitoneum, orbit, and biliary tract. It generally affects women in the fourth to fifth decade of life. Patients typically present with a painless thyroid mass that feels hard and fixed. With time the fibrosis will extend beyond the thyroid capsule and infiltrate into the surrounding structures, including the strap muscles. Vasculitis and phlebitis may also be seen. Thyroid function tests will reflect euthyroidism in approximately two-thirds of patients; however, they may also reveal hypothyroidism when the gland is sufficiently replaced by the fibroid tissue. The clinical presentation may be confused with an aggressive thyroid malignancy, such as anaplastic carcinoma. Imaging studies and FNA can help differentiate the two. Unlike the CT findings of most thyroid malignancies, the thyroid gland with Riedel's appears as an infiltrative mass that is isodense with the neck muscles, hypodense with the normal thyroid tissue, and nonenhancing with contrast.¹²¹ Recently immunoglobulin G4 (IgG4) is thought to play a role in development of Riedel's thyroiditis based on findings of infiltration by IgG4 containing lymphoplasmacytic cells, leading to fibrosis.¹²² This condition is benign and usually self-limiting. However, as it progresses and encases the trachea, the patient may develop dyspnea. If symptomatic, a wedge resection of the isthmus and insertion of tracheotomy can be performed. High-dose glucocorticoid and levothyroxine treatment has been reported to be effective for reducing the symptoms from Riedel's.¹²³ Tamoxifen, mycophenolate mofetil, and rituximab have also been shown to be effective in reducing the mass effect on the airway.^{123,124,125}

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8 Medical Management of Benign Thyroid Disease

Jacqueline Jonklaas

8.1 Hypothyroidism

Hypothyroidism is a condition characterized by decreased thyroid hormone production. The particular biochemical profile is determined by the endocrine gland initially responsible for the failure to maintain adequate thyroid hormone levels, with a raised serum thyroid-stimulating hormone (TSH) level indicating primary hypothyroidism and a low or inappropriately normal serum TSH level characterizing secondary hypothyroidism. The clinical syndrome is notable for wide-ranging symptoms associated with thyroid hormone deficiency at the level of all tissues and organ systems (► Fig. 8.1). Secondary hypothyroidism is also likely to be accompanied by signs and symptoms of pituitary dysfunction. Myxedema coma can result from organ system decompensation, generally after long-standing hypothyroidism.

8.1.1 Primary Hypothyroidism

Failure of the thyroid gland itself causes primary hypothyroidism. The most common cause in the United States is lymphocytic infiltration of the thyroid gland associated with autoimmune thyroid disease (Hashimoto's thyroiditis), which had a prevalence of 5.13% in one population-based study.¹ Other causes of primary hypothyroidism are destruction of thyroid tissue by surgery, radioiodine therapy, external beam radiation, or infiltrative diseases. Subclinical hypothyroidism, in which thyroid hormone levels are still maintained in the normal range, is the more common abnormality (4–8% of the U.S. population), compared with overt hypothyroidism, which occurs in 0.3 to 0.4% of the population.^{2,3}

Iodine deficiency, while common as a cause of hypothyroidism in inland regions of Africa (e.g., Ethiopia, Algeria, and Sudan), and mountainous areas (e.g., the Andes and the

Himalayas), is an uncommon cause of hypothyroidism in the United States. Other uncommon causes of primary hypothyroidism include goitrogens, enzyme deficiencies, and thyroid agenesis.

Diagnosis

An elevated serum TSH indicates reduced thyroid hormone feedback on the pituitary thyrotropes, which secrete TSH, and is the cardinal feature of primary hypothyroidism. Many patients will have a free thyroxine (T₄) level within the normal range and few symptoms of hypothyroidism. With progression of hypothyroidism, the free T₄ concentration will drop below the normal level. Thyroidal hormone production will shift toward greater amounts of tri-iodothyronine (T₃); thus T₃ concentrations will often be maintained in the normal range in spite of a low T₄.⁴ If the disease is not recognized, serum T₃ levels will also progressively fall below the normal range. Symptoms of hypothyroidism include fatigue, weight gain, depression, exercise intolerance, cold intolerance, dry skin, coarse hair, constipation, and impaired mentation. Clinical features of myxedema coma include hypothermia, bradycardia, and altered sensorium ranging from diminished consciousness to coma.

Treatment

The goal of therapy for hypothyroidism is to reverse the myriad symptoms of thyroid hormone deficiency and the accompanying biochemical abnormalities. Levothyroxine (LT₄) is the mainstay of therapy and is easily administered, efficacious, and inexpensive, and it ameliorates the symptoms of hypothyroidism in the vast majority of cases.⁵ Approximately 75% of an oral dose of LT₄ is absorbed, with impaired absorption being associated with close proximity to meals, medications that adsorb the LT₄, and medications that decrease gastric acidity, to name but a few culprits.⁵ Serum TSH can be checked approximately 6 weeks after initiating or changing an LT₄ dose, when a steady state has been reached, and the LT₄ can be titrated up or down if the TSH is above or below the reference interval, respectively. Although many practitioners will attempt to achieve a serum TSH within the range of 1 to 2 mIU/L in order to replicate the values seen in a population free of thyroid disease,² there is currently little evidence to support that this approach improves patients' symptoms or well-being.^{6,7} However, most experts agree on very specific TSH goals when hypothyroidism is being treated in the pregnant population. TSH reference intervals are 0.1 to 2.5 mIU/L during the first trimester, 0.2 to 3 mIU/L during the second trimester, and 0.3 to 3 mIU/L during the third trimester, and treatment to keep the serum TSH within these values is generally endorsed.⁸ Modified, higher TSH targets may also be appropriate for older age groups.

Iatrogenic thyroid disease should be avoided due to the attendant risks, but several studies suggest that this goal may not be achieved in as many as 40% of patients.^{2,3,9} There has been a trend to initiate hypothyroidism therapy for milder disease in recent years, thus placing more individuals at risk for

Organ systems affected by thyroid hormone

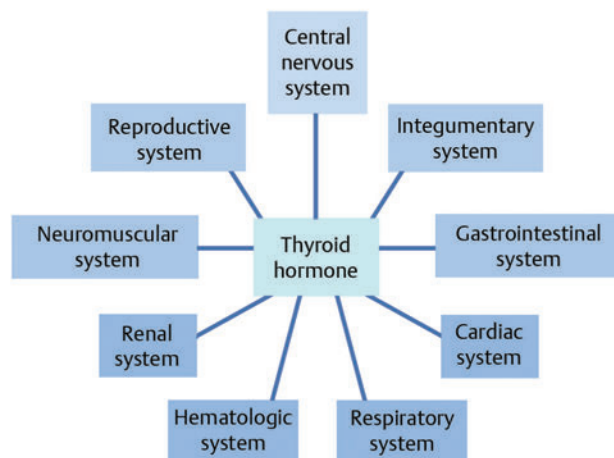


Fig. 8.1 Organ systems affected by thyroid hormone dysfunction.

iatrogenic thyroid disease.¹⁰ In addition, there is a high rate of LT4 initiation in older age groups, potentially exposing these individuals who may have additional medical problems to risks of overtreatment.¹¹

A subset of those treated with LT4 therapy will continue to have residual symptoms, such as fatigue, weight gain, and impaired well-being, despite full resolution of their biochemical abnormalities.⁵ The thyroid gland usually contributes about 20% of circulating serum T3 levels.¹² Animal studies have demonstrated closer replication of normal T4 and T3 levels in serum and tissues during intravenous LT4 and liothyronine (LT3) infusion compared with LT4 alone.^{13,14} Based on these findings, it has been hypothesized that combination therapy with both LT4 and LT3 may provide greater patient satisfaction. Obtaining proof of this concept, however, has been an elusive goal. Despite 13 trials with various regimens of combination therapy, superiority of combination therapy has not been consistently shown.^{5,15,16,17} The preference for T3 therapy noted in some of these trials could potentially indicate an unrecognized parameter or end point affected by the T3-containing combination. However, it should be emphasized that most trials have been of short duration (~ 8–16 weeks) and have targeted middle-aged women. Therefore, long-term risk and benefits have not been assessed, especially in older age groups. Other shortcomings of this body of evidence include heterogeneity of study design and results and varying and nonvalidated end points⁵ (► Table 8.1). A single randomized trial of desiccated thyroid extract compared with LT4 showed an average weight loss of 3 lb with the extract and preference for the extract in 49% of studied patients.¹⁸ A small, randomized cross-over trial of three times daily LT4 compared with LT3 illustrated the difficulties in adhering to a thrice daily regimen, and demonstrated a modest weight loss and improved LDL cholesterol with the T3 regimen.¹⁹

Myxedema coma should be treated with intravenous LT4 to ensure adequate absorption in the setting of impaired gastrointestinal functioning.⁵ A loading dose of LT4, adjusted for the weight of the patient, is indicated to ensure both reoccupation of depleted protein-binding sites and an incremental increase in serum free T4 levels. Concomitant use of intravenous LT3 is recommended by some experts.

8.1.2 Secondary Hypothyroidism

Adequate TSH stimulation is required for normal thyroid function. Thyrotrope insufficiency due to pituitary tumors, pituitary surgery, pituitary irradiation, or pituitary hemorrhage is associated with thyroid atrophy and secondary hypothyroidism. Secondary hypothyroidism is considerably less common than primary hypothyroidism, with a prevalence of 1:80,000 to 1:120,000.²⁰

Diagnosis

Hypothyroidism in patients with pituitary disease is characterized by low or normal serum TSH concentrations. A serum TSH concentration in the normal range is clearly inappropriate if the patient also has a low free T4.

Table 8.1 Issues affecting the assessment of combination therapy trials for hypothyroidism treatment

Heterogeneity of study design
Diverse causes of hypothyroidism
Different dosing regimens used
Different outcomes measures
Different duration of treatment
Other design problems
Non-validated outcome measures
Carryover effects in some studies
Overtreatment not explored
Men and the elderly not studied
Heterogeneity of study results
End of study TSH differences between groups <i>Values the same versus higher versus lower in T3 group</i>
T3 and FT3 differences between groups <i>Values the same versus higher in T3 group</i>
Health related quality of life or mood <i>Superiority of combination therapy on multiple measures in two trials versus superiority of combination therapy on a minority of measures in two trials versus no superiority of combination therapy in eight trials</i>
Neurocognitive functioning <i>Superiority of combination therapy on multiple measures in one trial versus superiority of combination therapy on a minority of measures in one trial versus no superiority of combination therapy in eight trials</i>
Treatment preference in five blinded, cross-over design trials <i>Combination therapy preferred in four trials (128 patients) versus no treatment preference between groups in one trial (101 patients)</i>
Examined in two blinded, parallel design trials <i>Combination therapy preferred in one trial (130 patients) versus no preference in other trial (573 patients)</i>
Abbreviations: TSH, thyroid-stimulating hormone; T3, tri-iodothyronine; FT3, free T3.
Source: Adapted from Jonklaas J, Bianco AC, Bauer AJ, et al. 2014 Guidelines for the Treatment of Hypothyroidism: Prepared by the American Association Taskforce on Thyroid Hormone Replacement. <i>Thyroid</i> 2014; 24: 1670-1751.

Treatment

As is the case with primary hypothyroidism, LT4 is the recommended treatment for secondary hypothyroidism. Because the serum TSH concentration cannot be used to make therapeutic adjustments, the serum free T4, combined with nonthyroid analytes, such as serum lipids and patient symptoms, must suffice.⁵ Several studies have attempted to determine the optimum serum free T4 in treated patients, and based on these studies it seems reasonable to keep the free T4 in the upper half of the reference interval based on successful reversal of the symptoms of hypothyroidism and favorable effects on the lipid profile and body composition.²¹

8.2 Hyperthyroidism

Thyrotoxicosis results when tissues are exposed to excessive levels of thyroid hormones, either T4, T3, or both. With appropriate negative feedback on the pituitary thyrotropes, thyroid autonomy is accompanied by lowering of the serum TSH concentration. In contradistinction, thyrotrope autonomy is characterized by both elevated serum TSH and elevated thyroid hormone concentrations. As is the case with hypothyroidism, the symptoms are due to the effects of thyroid hormone on multiple organ systems and tissues (► Fig. 8.1). Thyroid storm occurs when there is failure to compensate for these systemic derangements. The prevalence of hyperthyroidism in the U.S. population was 1.3% in the third National Health and Nutrition Examination Survey (NHANES III), with 0.75% being subclinical disease and 0.55% overt hyperthyroidism.²

8.2.1 Diffuse Goiter

A diffuse goiter can be responsible for excessive production of thyroid hormones either due to stimulation of the gland by thyroid autoantibodies, such as thyroid-stimulating antibodies (TSABs), as occurs in Graves' disease, or to stimulation by TSH, as occurs with development of a TSH-secreting adenoma (► Fig. 8.2).

8.3 Graves' Disease

Graves' disease is an autoimmune condition that typically includes hyperthyroidism and diffuse thyroid enlargement. There is also accompanying ophthalmopathy (orbitopathy) in some patients, with at least 50% having some mild symptoms of eye disease and approximately 5% having severe ophthalmopathy.^{22,23} Less commonly there may also be Graves' dermopathy (pretibial myxedema) and thyroid acropachy. Graves' dermopathy is noted on physical examination in about 13% of those with severe ophthalmopathy.²²

Graves' disease is the most common cause of hyperthyroidism in iodine-sufficient countries, in which it accounts for about 80% of cases. When countries with iodine sufficiency are compared to those with iodine deficiency, the incidence of Graves' disease is greater in the former and the incidence of toxic multinodular goiter is greater in the latter.²⁴ Graves' hyperthyroidism results from the action of TSABs, which are directed against the thyrotropin receptor on the surface of the thyroid cell. Having bound to the receptor, they induce thyrocyte proliferation and hyperfunction by activating the adenyl cyclase signaling pathway in the same manner as TSH.²⁵ Autoantibodies that react with orbital muscle and fibroblast tissue in the skin are responsible for the extrathyroidal manifestations of Graves' disease.²² Interestingly, the extrathyroidal disorders may not appear at the same time as the hyperthyroidism but may precede or follow the hyperthyroidism.

8.3.1 Diagnosis

Laboratory testing in Graves' disease is characterized by suppressed or undetectable TSH due to negative feedback by elevated levels of thyroid hormone acting on the pituitary. In mild Graves' disease that has resulted only in subclinical hyperthyroidism, the thyroid hormone levels will remain within the normal range. Overt hyperthyroidism will be characterized by frankly elevated thyroid hormone concentrations due to an increase in the overall hormone production rate. Symptoms include tachycardia, hyperdefecation, proximal muscle weakness, tremors, and heat intolerance. There is often a disproportionate increase in serum T3 relative to serum T4 due to the stimulation of the type 2 deiodinase by TSAB.²⁶ The disproportionate production of T3 can result in a T3 thyrotoxicosis in which only the serum T3 concentration is increased. If the patient is not pregnant or lactating, a 24-hour radioactive iodine uptake (RAIU) should be obtained if there is any diagnostic uncertainty. An increased RAIU documents that the thyroid gland is inappropriately using the iodine to produce more

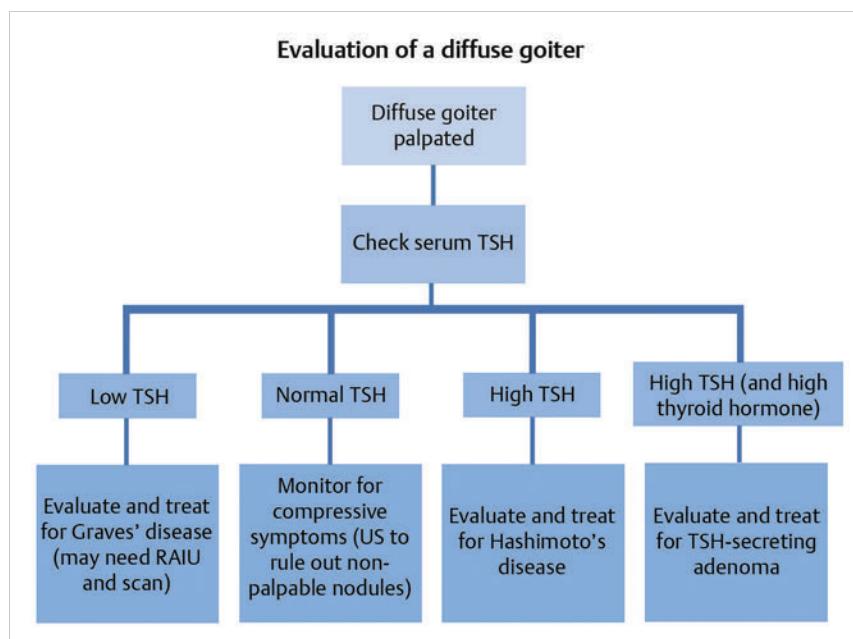


Fig. 8.2 Evaluation algorithm for a diffuse goiter. TSH, thyroid-stimulating hormone; RAIU, radioactive iodine uptake; US, ultrasound.

Table 8.2 Comparison of thionamides

Characteristic	Methimazole	Propylthiouracil ^a
Serum half-life	4–6 h	75 min
Dosing	Daily	Two to three times a day
Compliance	Easier	More difficult
Response time (for patient to become euthyroid)	Faster	Slower
Inhibition of T4 to T3 conversion	No	Yes
Side effects	Dose related	Less dose related
Nature of hepatotoxicity	Cholestatic injury	Hepatocellular injury
Recommended use in pregnancy	Second, third trimester	First trimester
Incidence of teratogenicity	Probably higher	Probably lower
Spectrum of teratogenic effects	“MMI-embryopathy” (choanal atresia, omphalocele, esophageal atresia, omphalomesenteric duct anomalies)	Face and neck malformations
Effect on subsequent RAI	May reduce efficacy	Reduces efficacy

Abbreviation: MMI, methimazole; RAI, radioactive iodine; T3, tri-iodothyronine; T4, thyroxine.

^aPropylthiouracil is no longer considered a first-line agent.

thyroid hormone at a time when the patient is thyrotoxic. In contrast, a low RAIU is suggestive of damaged thyroid tissue that is not able to transport iodine. A homogeneous pattern of uptake is consistent with the generalized glandular stimulation characteristic of Graves' disease.

Thyroid storm ensues when the patient is no longer able to compensate for the effects of the persistent increases in thyroid hormone levels and is characterized by hyperthermia and altered sensorium, with resultant features such as severe tachycardia, heart failure, agitation, disorientation, mania, coma, nausea, vomiting, volume depletion, diarrhea, jaundice, and fever.

8.3.2 Treatment

To treat Graves' disease, dual therapy to reduce the tissue effects of the excessive thyroid hormone and also to lower the thyroid hormone levels is needed. Beta-blockers serve to reduce the tachycardia and tremulousness and to decrease the patient's symptoms. A thionamide is concurrently used to reduce further thyroid hormone synthesis. The thionamides approved for use in the United States are methimazole (MMI) and propylthiouracil (PTU) (► Table 8.2).

Both of these agents prevent the incorporation of iodine into tyrosine residues and inhibit the coupling of iodotyrosine residues. They are both well absorbed from the gastrointestinal tract and are actively concentrated within the thyroid gland.²⁷ This latter feature accounts for the fact that, despite their short plasma half-lives, MMI, and sometimes even PTU, can effectively be given as a single daily dose. Initial doses for therapy with MMI are 10 to 30 mg/d, sometimes given in two divided doses. Initial doses for therapy with PTU range from 150 to 300 mg/d, often given in three divided doses. Patients with severe hyperthyroidism may require larger initial doses,²⁸ and may also respond better if the dose is divided. The maximal blocking doses of PTU and MMI are 1,200 mg and 120 mg daily,

respectively. Once the intrathyroidal pool of thyroid hormone is reduced and new hormone synthesis is sufficiently blocked, clinical improvement should ensue. MMI may be associated with a more rapid achievement of euthyroidism than PTU.²⁹ Usually within 4 to 8 weeks of initiating therapy, symptoms will diminish, and circulating thyroid hormone levels will return toward normal. At this time a tapering regimen can be started. Changes in dose for each drug should be made on a monthly basis, because the endogenously produced T4 will reach a new steady-state concentration in this interval. Effective daily maintenance doses for PTU and MMI vary widely, but typical ranges are 100 to 150 mg and 5 to 15 mg, respectively.

Side effects can occur in approximately 5 to 25% of those treated with thionamides, depending on the thoroughness of the documentation and the doses used. With MMI, the side effects generally appear to be dose related, whereas they tend to be more idiosyncratic with PTU (► Table 8.2). Minor adverse reactions, which occurred in about 5% of patients in one literature review,³⁰ included rashes, arthralgias, fevers, and gastrointestinal symptoms. Rashes may sometimes regress spontaneously. Leukopenia may also occur. The leukopenia is often transient, may be confused with the mild leukopenia seen in Graves' disease itself,³¹ and is not usually a predictor of subsequent agranulocytosis. Agranulocytosis is seen more frequently at higher doses of thionamides and may be a direct toxic effect following concentration of the drug within granulocytes or an immune-mediated process, or it may have a dual pathogenesis. Agranulocytosis often occurs within the first 3 months of therapy, but its onset is sudden and may not be detected with monitoring of complete blood counts.³² The development of agranulocytosis is heralded by fever, malaise, oropharyngeal infection, and a granulocyte count of <500/mm³; hence the recommendation that patients discontinue therapy and contact their physician when flulike symptoms, such as fever, malaise, or sore throat, develop. Supportive care

with antibiotic therapy is critical for the recovery of affected patients. Use of colony-stimulating factors has not been shown to speed recovery or shorten hospital stay in a randomized trial.³³ Nevertheless, these agents are generally recommended, particularly in patients with poor prognostic factors.³⁴ Patients who have suffered this side effect should not be reexposed to either thionamide because the agranulocytosis may be immunologically mediated and thus could recur with either drug.

Hyperthyroidism may be associated with abnormal liver tests, with 14 to 23% of hyperthyroid patients having transaminase elevations in one small study.³⁵ Use of MMI and PTU may also be associated with transaminase elevations,^{28,36} as can be seen in 6 to 9% of MMI-treated patients and 26% of patients treated with PTU. A study of PTU therapy reported in 1993 suggested that initial enzyme elevations eventually normalize in most patients with continued therapy.³⁷ The authors suggested that subclinical liver injury is common and that PTU therapy could be continued with caution in the absence of symptoms and hyperbilirubinemia.³⁷ However, more substantial hepatotoxicity may also occur, and PTU is no longer considered a first-line drug (► Table 8.2). The liver injury seen with PTU seems to be hepatocellular in nature.^{30,38,39} A literature review performed in 1997 documented 49 cases of serious hepatotoxicity: 28 cases associated with PTU use and 21 cases associated with MMI use.⁴⁰ Accompanying the hepatotoxicity were seven deaths in the PTU-treated group and three deaths in the MMI-treated group. The dose or duration of thionamide treatment did not appear to predict the outcome.⁴⁰ A more recent analysis of 20 years of PTU use in the United States revealed that 22 adults had developed severe hepatotoxicity leading to nine deaths and five liver transplants.⁴¹ The risk of this complication was greater in children (1:2,000) than in adults (1:10,000). Finally, an analysis of data reported to the Food and Drug Administration (FDA) from 1982 to 2008 found that toxicity in children was generally related to higher doses of PTU and that toxicity in both children and adults was associated with therapy lasting more than 4 months in duration.⁴² In light of such evidence for hepatotoxicity, PTU carries a black box warning. It has been recommended that PTU not be considered as first-line therapy in either adults or children. One exception includes the first trimester of pregnancy, when the risk of MMI-induced embryopathy may exceed that of PTU-induced hepatotoxicity. Other exceptions include intolerance to MMI and thyroid storm.

MMI use can also be associated with severe hepatotoxicity. Based on animal studies the toxicity of MMI to the liver may be due to the formation of N-methylthiourea.⁴³ From a review of cases of MMI-induced hepatotoxicity, it appears that the nature of the liver injury was cholestatic in many of these cases.⁴⁴ Older patient age and higher drug doses appeared to be risk factors for hepatotoxicity.

There are some special considerations regarding medical treatment of hyperthyroidism during pregnancy (► Table 8.2). Although historically both thionamides were thought to be safe during pregnancy, MMI has now been clearly linked to embryopathy, including tracheoesophageal fistulas and choanal atresia.⁴⁵ PTU was then considered the preferred antithyroidal agent during pregnancy until the incidence of its hepatotoxicity was fully appreciated. At this juncture most clinicians recommend use of PTU during the first trimester of pregnancy when organogenesis is occurring, with subsequent consideration of

transition to MMI for the remainder of pregnancy based on the avoidance of the greater hepatotoxicity risk of PTU.⁸ This approach may minimize the congenital malformations associated with MMI and the length of exposure to PTU. Supporting this approach, a recent Japanese study⁴⁶ reported that the incidence of major anomalies associated with first trimester MMI use was 4.1%, compared with 1.9% in the PTU-treated group. The anomalies associated with MMI included aplasia cutis, omphalocele, omphalomesenteric duct anomaly, and esophageal atresia. However, worryingly, an analysis of data from a Danish registry showed similar rates of anomalies when MMI or carbimazole (9.1%) versus PTU (8%) were used during early pregnancy.⁴⁷ The main difference between the two drug classes was the spectrum of anomalies, which consisted of malformations in the face and neck region with PTU and choanal atresia, esophageal atresia, omphalocele, omphalomesenteric duct anomalies, and aplasia cutis with MMI.

Mild hyperthyroidism is well tolerated by both mother and fetus, so the concerns about thionamide use during pregnancy, and the unresolved issues about their safety, underscore the need to use the lowest effective dose that will maintain the thyroid hormone levels in the upper part of the normal range. As was discussed previously for serum TSH values, total and free thyroid hormones have reference intervals that are specific for pregnancy.⁸ Total thyroid hormone values are increased by approximately 50%.⁴⁸ Free T4 values are usually lower than nonpregnant values but differ greatly between various immunoassays^{48,49} and mass spectrometry assays.⁵⁰ These caveats should be considered when adjustments are being made in thionamide dose. As is the case for pregnancy, the lowest effective thionamide dose should also be used during lactation. Both MMI and PTU are excreted in the breast milk of thionamide-treated nursing mothers, and using the thionamide in divided doses administered after each feeding is recommended.⁸

Nonmedical management options for the treatment of Graves' hyperthyroidism include radioiodine therapy and surgery. If pretreatment with thionamides is used prior to radioactive iodine therapy, there can be a decrease in the efficacy of the radioiodine therapy.⁵¹ However, some individual studies have not shown that MMI was associated with treatment failures after radioiodine therapy. Prior surveys of practicing physicians in North America have shown a preference for using radioiodine therapy to treat patients with uncomplicated Graves' disease. However, a survey conducted in 2011 showed a trend for increasing use of thionamide therapy. In fact, 40.5% of physicians indicated their choice of thionamide therapy for an index patient, compared with 30% in 1990.⁵² A study of prescriptions written for MMI and PTU during the period 1991 to 2008 revealed a ninefold increase in annual MMI prescriptions, compared with a 19% increase in annual PTU prescriptions.⁵³ The number of MMI prescriptions exceeded the number of PTU prescriptions from 1996 onward. Study of future trends will shed light on whether this apparent trend to favor pharmacological therapy for Graves' disease will be mitigated by concern for the adverse effects of these drugs.

The cornerstone of treating thyroid storm is multimodality therapy with a thionamide, beta-blockers, inorganic iodide, and glucocorticoids, along with appropriate supportive care and treatment of precipitating conditions in an intensive care unit setting.³⁸

8.4 TSH-Secreting Pituitary Adenoma

Pituitary tumors that overproduce functional TSH are quite rare, representing 0.5 to 3% of all pituitary adenomas.⁵⁴ These tumors can be diagnosed at any age but are typically diagnosed in the 30- to 60-year age group, and are slightly more frequent in women (female to male ratio of 1.35:1).⁵⁵ Hyperthyroidism ensues when these sporadically occurring tumors produce TSH that is unresponsive to normal feedback control. Thus the obvious presentation is that of a goiter and thyrotoxicosis. In addition, there may be compromise of other pituitary function and visual field defects. The clinical picture may be further complicated if there is cosecretion of prolactin or growth hormone by the tumor.

8.4.1 Diagnosis

Criteria for the diagnosis of TSH-induced hyperthyroidism include (1) evidence of peripheral hypermetabolism, (2) diffuse thyroid gland enlargement, (3) elevated free thyroid hormone levels, and (4) elevated or inappropriately “normal” serum TSH concentrations.^{54,55} Because the pituitary gland is extremely sensitive to even minimal elevations of circulating thyroid hormones, a “normal” or elevated TSH level in any thyrotoxic patient indicates the inappropriate production of TSH. The distinction between Graves’ disease and a TSH-secreting pituitary adenoma is easily made, as long as the serum TSH concentration is considered. Failure to note that a hallmark of Graves’ disease is a low or undetectable TSH can lead to inappropriate therapy, in the form of radioiodine therapy or thyroidectomy, being employed. Because TSH-secreting adenomas retain a minor degree of responsiveness to the negative feedback from elevated thyroid hormone levels, this therapy can result in uninhibited growth of the pituitary adenoma.⁵⁵ However, the differential diagnosis for a thyrotoxic patient with a goiter and a normal or mildly elevated serum TSH concentration also includes pituitary resistance to thyroid hormone

(PRTH). This condition can be distinguished from a TSH-secreting adenoma based on several features, which need to be interpreted together.⁵⁴ Lack of TSH response to TRH injection (now not usually used due to lack of availability of TRH) favors a TSH-secreting adenoma. A pituitary adenoma identified on MRI scan favors a TSH-secreting adenoma. An elevated alpha subunit or alpha-subunit:TSH ratio favors a TSH-secreting tumor (TSHoma).⁵⁴

8.4.2 Treatment

The treatment of choice for a TSH-secreting pituitary adenoma is transsphenoidal (or subfrontal) resection of the tumor. If a cure is not achieved by surgery, other options include targeted radiotherapy and medical management with somatostatin analogues and dopamine agonist therapy.⁵⁴ Temporizing treatment with beta-blockers and thionamides will help reduce thyrotoxic symptoms and is thus useful to restore euthyroidism before surgical removal of the adenoma.

8.5 Toxic Nodular Disease

Toxic nodular disease includes both toxic adenoma and toxic multinodular goiter (MNG) (► Fig. 8.3). The pathogenesis of these entities is thought to be similar: diffuse hyperplasia caused by goitrogenic stimuli, leading to mutations and clonal expansion of benign neoplasms.⁵⁶ The functional status of the nodule(s) depends on the nature of the underlying mutations, whether activating (such as TSH receptor mutations) or inhibitory. Thyrotoxicosis occurs when a sufficient mass of autonomous follicles generates enough thyroid hormone to exceed the needs of the patient.

8.6 Toxic Adenoma

An autonomous thyroid nodule is a discrete thyroid mass whose function is independent of pituitary and TSH control. The prevalence of toxic adenoma ranges from about 2 to 9% of

Evaluation of a multinodular goiter or thyroid nodule

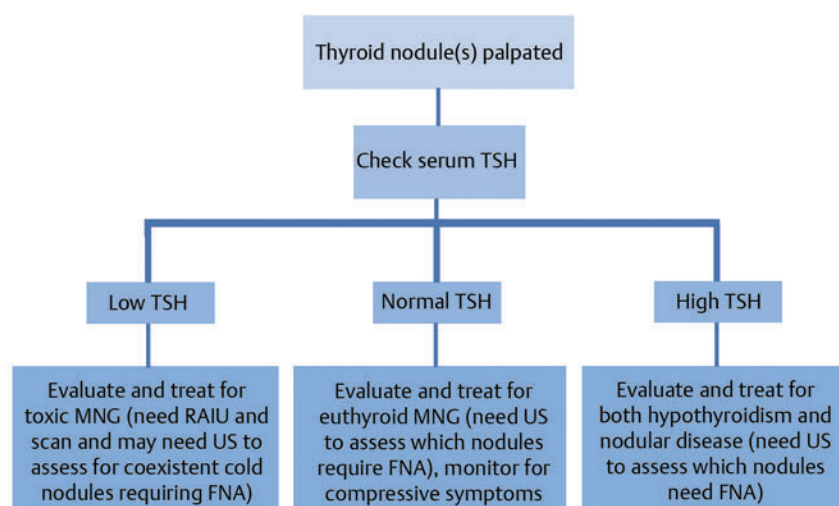


Fig. 8.3 Evaluation algorithm for a thyroid nodule or multinodular goiter. FNA, fine-needle aspiration; MNG, multinodular goiter; RAIU, radioactive iodine uptake; TSH, thyroid-stimulating hormone; US, ultrasound.

thyrotoxic patients, and depends on iodine availability and geographic location. Toxic adenomas are benign tumors that produce thyroid hormone. They arise from gain-of-function somatic mutations of the TSH receptor or, less commonly, the $G\alpha$ protein, such that the cyclic adenosine monophosphate (cAMP) cascade is activated and there is increased growth and function of the follicular cells.⁵⁶ More than a dozen TSH receptor mutations have been described.⁵⁷ This is in contrast to the situation with Graves' disease where the hyperthyroidism is mediated by an activating antibody. These nodules are referred to as toxic adenomas, or hot nodules, because of their elevated uptake on a radioiodine thyroid scan, with decreased uptake in the surrounding thyroid tissue due to suppression by the autonomously functioning area. The amount of thyroid hormone produced by an autonomous nodule is mass related. Therefore, hyperthyroidism usually occurs with larger nodules (i.e., > 3 cm in diameter). Patients older than 60 years are up to 60% more likely to be thyrotoxic from autonomous nodules than are younger patients (12%).⁵⁸

8.6.1 Diagnosis

Laboratory data showing hyperthyroidism combined with physical examination findings suggestive of a thyroid nodule support the diagnosis of a toxic adenoma. A radioiodine uptake and scan will show the discrete area of iodine uptake representing the autonomously functioning thyroid tissue. Laboratory findings range from subclinical hyperthyroidism through to overt hyperthyroidism, generally proportional to the size of the toxic adenoma. There are many reports of isolated elevation of serum T3 in patients with autonomously functioning nodules. Therefore, if the FT4 level is normal, a T3 level must be measured to rule out T3 toxicosis. Autonomous function can even be present when the TSH is normal due to compensatory suppression of the remainder of the thyroid. If desired, the diagnosis can be confirmed by a failure of the autonomous nodule to decrease its iodine uptake during exogenous T3 administration sufficient to suppress TSH.

8.6.2 Treatment

Surgical resection, radioactive iodine ablation, thionamides, and percutaneous ethanol injection are treatment options for toxic adenoma,⁵⁹ but, because thionamides do not halt the proliferative process in the nodule, definitive therapies are recommended.³⁸ It has been hypothesized that sublethal radiation doses received by the surrounding non-nodular thyroid tissue during radioactive iodine therapy of toxic nodules may lead to induction of thyroid cancer, but gastric cancer appears to be the malignancy most associated with radioactive iodine therapy of toxic nodular disease.⁶⁰ An autonomously functioning nodule, if not large enough to cause thyrotoxicosis, can often be observed conservatively without therapy. Ethanol ablation may be associated with pain and damage to surrounding extrathyroidal tissues, limiting its acceptance in institutions without expertise in its use.

8.7 Toxic Multinodular Goiter

In toxic MNGs, follicles with autonomous function coexist with normal or even nonfunctioning follicles. The pathogenesis

of MNG is thought to be similar to that of toxic adenoma.⁵⁶ Thyrotoxicosis in an MNG occurs when a sufficient mass of autonomous follicles generates enough thyroid hormone to exert negative feedback on the pituitary and lower the serum TSH. This type of hyperthyroidism develops insidiously over a period of several years and predominantly affects older individuals with long-standing goiters.⁵⁸ The patient's complaints of weight loss, depression, anxiety, and insomnia may be attributed to old age,⁶¹ and their presentation in an elderly patient with an MNG calls for the exclusion of unrecognized thyrotoxicosis.

8.7.1 Diagnosis

Physical examination is usually notable for an enlarged gland with an irregular contour due to the underlying nodules. Nodules larger than 1 to 1.5 cm may be palpable depending on the contours of the gland and the patient's habitus. Laboratory evaluation of thyroid function shows thyrotoxicosis that may be subclinical or overt. The thyrotoxicosis may incorporate a pattern of predominant elevation of serum T3. Thyroid autoantibodies are generally negative. A thyroid scan and uptake will show discrete areas of autonomously functioning thyroid tissue intermixed with hypofunctioning areas representing the suppressed extranodular tissue.⁶² If discrete cold nodules are documented, these should be characterized by ultrasonography and biopsied based on their features and size (discussed in the section addressing euthyroid MNG).

8.7.2 Treatment

The preferred treatment for toxic MNG is radioiodine therapy or surgery because these selections usually provide definitive therapy.³⁸ Surgery is usually selected for younger patients and patients in whom large goiters impinge on vital structures. Thionamide therapy can be used, but, again, this choice does not address the underlying proliferative process with its natural history of progression over time. Alternatively, percutaneous injection of 95% ethanol has also been used to destroy single or multinodular adenomas, with a 5-year success rate approaching 80%.

8.8 Euthyroid Goiter

Patients who are euthyroid may also have diffuse thyroid enlargement or single or multiple nodules. Management of diffuse goiter is directed at monitoring growth, tracking the proximity of thyroid tissue to vital structures in the neck and chest, and limiting any compressive symptoms. Management of nodules is directed at selecting nodules that require biopsy to rule out malignancy (► Fig. 8.2 and ► Fig. 8.3).

8.9 Diffuse Goiter

An enlarged thyroid gland is generally thought of as one that is estimated to have a weight > 20 g, or documented to have dimensions > 4 to 5 cm in length and 2 to 3 cm in width. When such a gland does not, in fact, harbor any nodules, or only subcentimeter nodules are noted, a diffuse goiter is present.

Physical examination is disappointingly inaccurate for the assessment of whether an apparently diffuse thyroid gland enlargement is in fact an MNG harboring nonpalpable nodules. The ability to palpate nodules depends on their size, their location within the thyroid gland, the anatomy of the patient's neck, and the training of the examiner. Ultrasonography is critical in this regard and will document whether nodules are actually present in a gland that appears diffusely enlarged (► Fig. 8.2).

8.9.1 Diagnosis

A diffuse goiter exists when the thyroid is enlarged in the absence of discrete nodules. If a serum TSH level indicates hypothyroidism or hyperthyroidism, evaluation for Hashimoto's thyroiditis or Graves' disease, respectively, is indicated. In a euthyroid patient, Hashimoto's thyroiditis may nevertheless be present and can be recognized by the altered thyroid gland echotexture seen on ultrasonography and the presence of circulating thyroid peroxidase antibodies. Rapid enlargement of a goiter, particularly in the setting of Hashimoto's thyroiditis, may herald the development of lymphoma.

8.9.2 Treatment

Many diffuse goiters may need no treatment at all, once hypothyroidism, hyperthyroidism, and malignancy have been ruled out. When the patient is euthyroid, therapy is based on the need to reduce the goiter size due to mass-related symptoms such as dysphagia. If there are compressive symptoms or compromise of vital structures, surgical intervention is indicated. TSH-suppressive LT4 therapy can be given to patients with nodular thyroid disease and diffuse goiter. The rationale for suppression therapy is to reduce TSH secretion because TSH stimulation promotes growth and function of the abnormal thyroid tissue. However, such management, other than for patients with elevated TSH levels, is quite controversial. Doses of thyroid hormone sufficient to suppress TSH levels may slow goiter growth or cause some degree of shrinkage, and overall diffuse goiters may respond better to such therapy than nodular goiters.⁶³ However, in general, suppression therapy for diffuse goiter is inadequate to address mass effect, does not persist beyond the period of LT4 treatment, and exposes the patient to the risks of iatrogenic hyperthyroidism.^{63,64,65}

8.10 Multinodular Goiter

As described for toxic MNGs, the autonomous areas within a euthyroid MNG may be compensated for by suppression of surrounding tissue, such that the patient retains normal overall thyroid function and has a normal serum TSH. Alternatively nodular areas may be hypofunctioning and, again, the patient may remain euthyroid. Ultrasonography is critical when nodules are present to document the number of nodules, their size, their location, and their characteristics (► Fig. 8.3).

8.10.1 Diagnosis

In a euthyroid (or hypothyroid) patient, diagnostic studies would focus on ultrasonography to document the size and

characteristics of the nodules present within the goiter. Fine-needle aspiration of the nodules is pursued based on the size of the nodule and the ultrasound characteristics. Ultrasound characteristics that have been used, and that have varying degrees of sensitivity and specificity for predicting malignancy, include microcalcifications, absence of halo, irregular margins, hypoechogenicity, and increased vascularity.⁶⁶ Nodules with worrisome characteristics merit biopsy at smaller dimensions than nodules with a more benign appearance.⁶⁷ To illustrate this concept, the suggested size criterion for biopsy of nodules with moderately and highly suspicious features is 1 cm or greater, whereas nodules with ultrasound characteristics that are of a low degree of suspicion are not recommended for biopsy unless they are 1.5 cm or larger, and spongiform nodules do not merit biopsy unless they are at least 2 cm.⁶⁷ Some studies,⁶⁸ but not all studies,⁶⁹ suggest that patients with MNG have the same risk of malignancy as those with solitary thyroid nodules. Thus biopsy of only the "dominant" nodule may not detect an existing thyroid cancer, and targeting the most suspicious nodules is critical. When some nodules within an MNG are autonomous, a thyroid scan can be correlated with the ultrasonographic findings in order to focus biopsy efforts on isofunctioning or hypofunctioning areas. Management of thyroid nodules shown to be malignant is usually surgical. Nodules with benign cytology can be monitored, with the follow-up schedule being determined by the degree of suspicion suggested by the ultrasound features.⁶⁷ As discussed elsewhere in this volume, nodules with Bethesda categories of follicular neoplasm, atypia of undetermined significance, and follicular lesions of undetermined significance may, after appropriate discussion with the patient, be subject to molecular testing in order to facilitate management decisions.

8.10.2 Treatment

Management of thyroid nodules shown to be malignant is usually surgical. Once malignancy has been ruled out in a euthyroid patient with an MNG or a single nodule, the nodules are monitored. Nodules that increase in size by 20% in two dimensions or by 50% in volume during follow-up warrant a repeat biopsy. A nodule "calculator" is available on the American Thyroid Association website (<http://www.thyroid.org/thyroid-physicians-professionals/calculators/>). Even if the absence of malignancy has been convincingly demonstrated, surgery may be needed to reduce the goiter size due to mass-related symptoms such as dysphagia. Doses of thyroid hormone sufficient to suppress TSH levels may slow goiter growth or cause some degree of shrinkage, but in general, suppression therapy for nodular disease is quite controversial, as it is for diffuse goiter. Some clinicians rarely recommend or use such therapy; others will recommend a trial of LT4 as suppressive therapy in selected patients.

The conclusions of three meta-analyses were that suppressive therapy for nodules was associated with a small decrease in nodule growth,⁷⁰ a statistically nonsignificant reduction in nodule growth,⁷¹ and a significant reduction in nodule growth that was reduced with longer-term treatment.⁷² Radioactive iodine therapy, often assisted by recombinant human TSH, has been used to reduce the size of large goiters, including those with substernal extension.⁷³ This therapy has been favored for patients who are older or have medical conditions that make

surgery a less attractive option. A 35 to 50% reduction in nodule size is generally achieved over a 1- to 2-year time frame. Temporary swelling of the thyroid tissue and thyroiditis with hyperthyroidism can occur within a few days and a few weeks after radioiodine administration, respectively, but usually these side effects are not of a magnitude that precludes use of this therapy.

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9 Malignant Disease of the Thyroid Gland

Jaime L. Wiebel and Megan R. Haymart

9.1 Introduction

Thyroid malignancies are generally classified as differentiated thyroid cancer (including papillary and follicular histology), medullary thyroid cancer, or anaplastic thyroid cancer. Each category varies drastically in overall prognosis as well as in therapeutic options. Although localized differentiated thyroid cancer has a 10-year disease-specific survival that exceeds 90%, anaplastic thyroid cancer has a life expectancy on the order of months.^{1,2} Thyroid cancer is becoming increasingly common. Over the past 3 decades, the incidence of thyroid cancer in the United States has nearly tripled.³ This chapter reviews the evaluation of thyroid nodules, clinical characteristics of thyroid malignancies, the initial evaluation of patients with thyroid cancer, clinical staging, and postoperative management.

9.2 Thyroid Nodules

A thyroid nodule is a distinct area on radiological imaging that is different from the surrounding thyroid parenchyma. Most cases of differentiated thyroid cancer present as a thyroid nodule that may have been discovered by the patient, during a physical exam, or incidentally on imaging. All patients with thyroid nodules should be assessed for risk factors for thyroid cancer, such as prior radiation exposure or a family history of thyroid cancer or thyroid cancer syndrome in a first-degree relative.⁴

The evaluation of a thyroid nodule begins with measurement of the thyroid-stimulating hormone (TSH). If the TSH level is normal or elevated, additional evaluation should be undertaken. A diagnostic ultrasound should be performed on all patients suspected of having a thyroid nodule. As shown in ► Table 9.1, sonographic characteristics concerning for malignancy include increasing size of the nodule, solid nodules, hypoechoic echogenicity, increased internal vascularity, irregular borders,

presence of microcalcifications, and presence of abnormal lymph nodes.^{5,6}

Pathological evaluation for malignancy begins with fine-needle aspiration (FNA) of the nodule. Indications for FNA are largely based on the size of the nodule. In patients with a high-risk history (radiation exposure, previous thyroid cancer, family history of thyroid cancer), nodules as small as 5 mm can be considered for biopsy. In patients with general risk, nodules ≥ 1 cm should be biopsied if there are any concerning ultrasound features, and benign-appearing nodules > 1.5 to 2 cm should undergo biopsy.⁷ Studies have found lower rates of nondiagnostic and false-negative biopsies when FNA is performed under ultrasound guidance.^{8,9} The cytopathology results from the FNA should be classified under the Bethesda system into one of the following pathological categories: benign, follicular lesion of undetermined significance/atypia of undetermined significance (FLUS/AUS), follicular neoplasm, suspicious for malignancy, or malignant with corresponding reported risks of malignancy of $< 1\%$, 5 to 10%, 20 to 30%, 50 to 75%, and 100%, respectively.¹⁰ Inadequate specimens are categorized as nondiagnostic; the rate of malignancy in these nodules is more varied, but one series found a 5% malignancy rate.¹¹

FNA samples with benign cytology do not require any further immediate action. Follow-up ultrasound can be obtained 6 to 18 months after the biopsy to ensure stability of the nodule.¹² FNA samples that are nondiagnostic should be repeated because up to 76% of solid nodules will yield a diagnostic cytology specimen on ultrasound-guided FNA.¹¹ Lesions with cytology suspicious for malignancy or malignant should generally undergo surgical excision with hemithyroidectomy or thyroidectomy. Lesions with cytology positive for follicular neoplasm or Hürthle cell neoplasm generally undergo surgical resection.¹³ Nodules with FLUS/AUS present a clinical challenge. The reported rate of malignancy in this group is low at 5 to 10%, but some studies have suggested that it varies from center to center, with malignancy rates as high as 25% at comprehensive cancer centers.¹⁴ Repeat FNA should be considered because benign or higher-acuity cytology will be obtained about 50% of the time on second biopsy.¹⁵ A large portion of patients with indeterminate lesions (FLUS/AUS and follicular neoplasm) will have benign pathology, so universal excision results in a large number of unnecessary surgeries. Determining which patients are most likely to have malignancy is a growing area of research. The presence of genetic mutations commonly associated with thyroid cancer, such as *RET/PTC* and *BRAF*, is indicative of malignancy.^{16,17,18} Additionally, a gene expression classifier was recently introduced to identify benign thyroid nodules, but its use in clinic practice is not yet routine.¹⁹

9.3 Differentiated Thyroid Cancer

Differentiated thyroid cancer (DTC) originates from follicular epithelial cells within the thyroid. It is, by far, the most prevalent form of thyroid cancer and carries the best prognosis.²⁰ Cancers are typically classified by their histological appearance

Table 9.1 Ultrasound characteristics of thyroid nodules

Ultrasound characteristic	Suggests benign	Suggests malignant
Density	Cystic	Solid
Echogenicity	Iso- or hyperechoic	Hypoechoic
Vascularity	None or peripheral	Central
Calcifications	None or rim	Micro or coarse
Size	< 1 cm	> 2 cm
Shape	Flat (width $>$ height)	Round (height $>$ width)
Borders	Well circumscribed	Irregular
Lymphadenopathy	None or flat with intact fatty hilum	Round, loss of fatty hilum, intranodal cystic components, microcalcifications

Sources: Smith-Bindman et al,⁵ Papini et al,⁶ Leboulleux et al.⁵⁸

Table 9.2 Poor prognostic indicators in differentiated thyroid cancer

Increasing patient age
Distant metastasis
Extrathyroidal extension (macroscopic > microscopic)
Cervical lymph node metastasis (lateral > central)
Capsular invasion
Lymphovascular invasion
Increasing tumor size
Aggressive histologic subtype (i.e., tall cell, diffuse sclerosing)
Sources: Lundgren et al, ²⁵ Banerjee et al, ²² Kim et al. ⁶⁹

into papillary, follicular, or Hürthle cell carcinomas. Papillary thyroid carcinomas (PTCs) account for approximately 85% of this group, follicular cancers make up 12%, and about 3% have Hürthle cell histology.²¹

Prognostic indicators in DTC are summarized in ► Table 9.2. Thyroid cancer is unique in that patient age is a highly important prognostic indicator for risk of death.^{22,23} Tumor characteristics with poor prognostic features include increasing size of the tumor, capsular invasion, extrathyroidal extension into surrounding tissues, and the presence of lymph node or distant metastasis.^{24,25} PTC has a tendency to spread by lymph node metastasis; in fact, more than 50% of patients with PTC and clinically uninvolved lymph nodes will have micrometastases at the time of initial surgery.²⁶ In addition, specific histological findings, such as lymphovascular invasion, abundant mitosis, and extensive tumor necrosis have been associated with an increased risk of recurrent and metastatic disease and poor clinical outcomes.^{27,28}

PTC is categorized into several histologic subtypes; some commonly encountered subtypes include follicular variant, tall cell variant, and diffuse sclerosing.²⁹ The follicular variant of PTC carries a similar prognosis to conventional PTC. However, it can be difficult to differentiate from follicular adenomas and follicular carcinomas, so it can present a diagnostic challenge.²⁹ The tall cell and diffuse sclerosing variants are associated with a worse prognosis.³⁰ Patients with tall cell variant have been described to experience higher rates of recurrence and metastatic disease, especially in those over the age of 50 years.^{31,32} The diffuse sclerosing variant of PTC is often encountered in pediatric patients (41.2% of PTC in one series), and is associated with a lower recurrence-free survival.³³ The previously discussed high-risk histopathologic findings are often present in these aggressive subtypes.

Although it appears patients with follicular cancer are more likely to present with metastatic disease, the prognosis for follicular thyroid cancer is similar to that for PTC when controlling for stage at diagnosis.^{23,34} In contrast to PTC, which tends to metastasize to cervical lymph nodes, follicular cancers are more likely to spread hematogenously.³⁵ Histological specimens are often classified by the degree of invasion: minimally invasive invades only into the capsule, and widely invasive invades through the capsule. Patients with minimally invasive follicular cancers have an excellent prognosis.³⁶ Some authors have suggested adding a moderately invasive category that includes

tumors with angioinvasion, because these patients have a slightly worse prognosis compared to those with minimally invasive disease.³⁷ Outcomes for patients with follicular carcinoma are dependent on the degree of invasion seen on histology, as well as age and initial tumor stage. Patients with highly invasive tumors tend to have other poor prognostic factors, such as older age, distant metastasis, and incomplete resection, so the degree of invasiveness has not been shown to be an independent risk factor.³⁸

Hürthle cell carcinoma is a rare tumor that is classified as a variant of follicular cancer. Classically thought to be a more aggressive tumor than PTC and follicular cancer, more recent data suggest that the outcomes for Hürthle cell carcinoma are similar to those for follicular cancers.^{39,40} When compared to a population of mostly PTC, however, the overall and disease-specific survival are lower for patients with Hürthle cell carcinoma.⁴¹ Like other well differentiated cancers, outcomes are very dependent on initial stage and invasiveness of the tumor.³⁹ Additionally, Hürthle cell tumors are often less iodine avid compared to other differentiated tumors.⁴²

9.3.1 Genetics of Differentiated Thyroid Cancer

Several genetic mutations have been associated with tumor development in differentiated thyroid cancer. The most extensively studied are the *RET/PTC*, *BRAF* V600E, *RAS*, and *PAX8/PPARG* mutations. *RET/PTC* rearrangements result in activation of the *RET* proto-oncogene and have been described in up to 43% of papillary thyroid cancers.⁴³ Activation of the *RET* proto-oncogene has been associated with prior radiation exposure. Recently, *RET/PTC* mutations have been described in follicular adenomas and other benign thyroid pathologies, and when present are associated with an increased rate of growth.⁴⁴

Mutation in the *BRAF* gene, resulting in constitutive activation of BRAF kinase, has been linked to development of PTC and poorly differentiated thyroid cancers.⁴⁵ The *BRAF* mutation, which has been described in 50 to 90% of conventional PTC, is associated with older age, lymph node metastasis, distant metastasis, recurrence, and persistent disease.^{46,47} However, because of its high prevalence, use of *BRAF* positivity has been difficult to integrate into clinical practice. Coexistent mutations in *BRAF* and *RET/PTC* have been described in up to 13% of PTC and were more common in advanced stages of disease.⁴⁸

Mutations in the four *RAS* proto-oncogenes, *HRAS*, *KRAS*, *KRASB*, and *NRAS*, result in a conformational change to their active form and promote downstream growth effects. *RAS* mutations have been found to have a high prevalence in follicular adenomas and follicular variants of PTC.^{49,50} They are associated with worse outcomes in papillary thyroid cancer and poorly differentiated thyroid cancers.^{51,52}

PAX8/PPARG is a fusion gene, often the result of a t(2;3)(q13;p25) chromosomal translocation. Constitutive activation in thyroid cells leads to the overexpression of PPARG and consequent loss of the normal inhibition of cell proliferation and induction of apoptosis. The loss of these functions results in uncontrolled cell growth.⁵³ The *PAX8/PPARG* fusion gene is a common genetic abnormality seen in approximately 50% of follicular adenomas and 35% of follicular carcinomas.^{54,55}

9.3.2 Preoperative Evaluation

If malignancy has been confirmed by FNA, or is highly suspected, then an ultrasound of the thyroid and lateral neck should be obtained prior to any surgical intervention. Cervical lymph node involvement is estimated to occur in 20 to 50% of cases of differentiated thyroid cancer.²⁴ Patient outcomes are highly affected by the completeness of the resection, including cervical lymph nodes, so it is important to identify patients with evidence of lymph node metastasis for optimal surgical planning.^{56,57}

On ultrasound imaging, involved lymph nodes tend to have loss of the fatty hilum, a rounded shape, hypoechogenicity, cystic change, increased peripheral vascularity, and microcalcifications.⁵⁸ The location of the lymph node is also important; lymph nodes located in the lower portion of the neck are more likely to be affected than lymph nodes in the upper portion of the neck, where they are more likely to be reactive.⁵⁹ However, none of these criteria are sufficiently sensitive or specific to definitively identify cervical metastasis. Therefore, all abnormal-appearing lymph nodes should undergo FNA biopsy if it will change surgical management. The lymph node aspirates may also be sent for thyroglobulin to increase the diagnostic accuracy of detecting metastatic DTC.⁶⁰ The sensitivity of other imaging modalities, such as computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET), for abnormal neck lymph nodes is lower than neck ultrasound and, therefore, not routinely recommended in the preoperative evaluation.⁶¹

9.3.3 Staging

Staging for differentiated thyroid cancer is generally performed using the American Joint Committee on Cancer's (AJCC) TNM staging system.⁶² This is the most universally accepted staging system and is required for cancer registries. Stage is based first on patient age because older patients have a higher risk of death from thyroid cancer than younger patients.²³ Patients under the age of 45 have stage I disease if there is no evidence of distant metastasis and stage II disease if there is evidence of distant metastasis. For patients over the age of 45, stage I disease is defined as tumor <2 cm without lymph node or distant metastasis. Stage II disease is a tumor 2 to 4 cm without lymph node or distant metastasis. Stage III disease is a tumor that is >4 cm or has minimal extrathyroidal extension, or the presence of metastasis to the central lymph node compartment. Stage IV is divided into three substages: IVa is a tumor that invades through the thyroid capsule or tumor with lateral compartment lymph node metastasis; IVb is a tumor that invades into the prevertebral fascia or encases the carotid artery or mediastinal vessels; IVc is a tumor with evidence of distant metastasis.

The AJCC staging system addresses a patient's risk of death due to differentiated thyroid cancer but was not developed to determine the patient's risk of recurrence, which causes significant morbidity in patients. Thus it is suggested that risk of recurrence be classified into high, intermediate, and low risk of recurrence.⁷ High-risk patients have macroscopic tumor invasion through the capsule, incomplete tumor resection, or distant metastatic disease. Intermediate-risk patients demonstrate microscopic tumor invasion through the capsule, cervical

lymph node metastasis, aggressive histology (i.e., tall cell, insular, columnar cell), or vascular invasion. Low-risk patients have no regional or distant metastatic disease, and complete tumor resection without evidence of capsular or vascular invasion.⁷

9.3.4 Postoperative Management

Under the influence of TSH, radioactive iodine (RAI) is taken up into thyroid cells and induces cell apoptosis. RAI has increasingly been administered in the treatment of papillary thyroid cancer, though there is variation in its use, and the indications for therapy remain a topic of debate.⁶³ The most universally accepted indication for RAI is for the treatment of distant metastatic thyroid cancer, especially to the lungs.^{64,65,66} In addition, RAI has been used in an adjunctive role to treat cancer cells that are suspected to be present after operative treatment but are not clinically apparent. There have been studies that show reductions in the rate of recurrence, as well as all-cause mortality.^{23,67,68} However, other studies have not confirmed this benefit, especially in low-risk patients.^{69,70,71,72} Finally, radioiodine has been used to ablate the normal remnant thyroid tissue, which facilitates postoperative surveillance of thyroglobulin levels and allows the physician to diagnose recurrence at an earlier stage.⁷³ Radioiodine is not without side effects, most commonly salivary gland damage and obstruction of the nasolacrimal duct.^{74,75} Additionally, after RAI, there appears to be a small risk of increased malignancy, especially leukemia, which is dose dependent.^{76,77}

Recommendations for RAI are largely dependent on the risk of death and/or recurrence due to thyroid cancer, balanced with the increased cost and morbidity associated with treatment. For PTC, RAI is recommended for all patients with evidence of distant metastasis, gross extrathyroidal extension of the tumor, and tumors >4 cm in size. RAI may be indicated in tumors 1 to 4 cm in size with lymph node metastasis, lymphovascular invasion, or aggressive histology, and should be considered on a case-by-case basis. RAI is not recommended in unifocal or multifocal PTC if all foci are <1 cm and there are no other high-risk features. In contrast to PTC, follicular and Hürthle cell cancers are considered higher risk for recurrence; therefore, almost all patients with these tumors are treated with RAI (if iodine avid), with the exception of minimally invasive follicular carcinoma.^{7,78}

If a patient is determined to be a candidate for RAI, there appear to be similar results using thyroid hormone withdrawal to increase the TSH versus using recombinant human TSH (rhTSH).^{79,80} The treatment dose of RAI should be minimized to the greatest extent possible to prevent side effects. For thyroid remnant ablation, use of 30 mCi was found to be as effective as a higher dose of 100 mCi.⁸¹ Treatment doses for suspected microscopic or macroscopic disease are generally higher. No randomized studies on this topic have been performed, however, so the treatment dose is largely based on physician preference.

Levothyroxine must be used to replace physiological thyroid hormone levels after total thyroidectomy, but it is also often employed as a therapeutic agent. TSH receptor proteins are present on the membranes of DTC, and these cells respond with accelerated cell growth in the presence of TSH. For that reason, larger doses of levothyroxine have been used following primary

treatment for DTC to suppress the TSH, preventing growth of tumor cells. This practice, which has been shown to reduce both mortality and recurrence, is supported by most studies in the literature, including a previous meta-analysis.⁸² Like RAI, these benefits are not as clear in low-risk patients.⁷² TSH suppression is also not without side effects; it may contribute to increased cardiovascular mortality in elderly patients and fractures in postmenopausal women.^{83,84,85}

The physician must balance the risks and benefits of TSH suppression therapy in each patient. With the increasing incidence of low-risk DTC, controversy remains over the degree and duration of TSH suppression. Patients at intermediate and high risk for recurrence should generally undergo TSH suppression to < 0.1 mU/L, whereas those at low risk for recurrence should have a TSH in the 0.1 to 0.5 mU/L range.⁷ Long-term TSH goals may be more relaxed, with a target of 0.5 to 2 mU/L in those at low risk for recurrence. However, those at high risk should continue to have a TSH suppressed below 0.1 mU/L in the absence of significant risk of side effects.^{86,87}

Although the risk of death from thyroid cancer is low, persistent and recurrent disease remains a significant source of morbidity. Several techniques are employed to detect recurrent disease in patients after treatment of DTC. Thyroglobulin (Tg) is a protein produced only by thyroid cells, so its presence in blood suggests that there are residual thyroid cells (either normal thyroid or DTC). It can be measured while the patient has a suppressed TSH on levothyroxine therapy (suppressed Tg) or under levothyroxine withdrawal (stimulated Tg). Alternatively, rhTSH has also been employed to obtain stimulated Tg levels.⁸⁸ In a patient who has undergone thyroid remnant ablation, Tg should be undetectable. Stimulated Tg < 1 ng/mL is indicative of remission, whereas a suppressed Tg > 1 ng/mL suggests the presence of disease.⁸⁹ Tg levels are more difficult to interpret in a patient who has not undergone remnant ablation. Additionally, some patients develop Tg antibodies, which can result in a falsely low level in a patient with recurrent disease.

The most common area for DTC recurrence is in the neck.⁶⁸ Therefore, an ultrasound is generally obtained 6 to 12 months after therapy to determine if there are any suspicious-appearing lymph nodes. Concerning lymph nodes should undergo FNA biopsy. An iodine-131 (I-131) diagnostic scan can also be performed, especially in patients with mildly elevated Tg levels (suppressed Tg > 1 ng/mL or stimulated Tg > 2 ng/mL) and a normal neck ultrasound; however, it is of little utility in patients with undetectable thyroglobulin levels.⁹⁰ In patients with a negative I-131 scan and significantly elevated stimulated Tg (> 5–10 ng/mL), a PET scan may be useful to detect noniodine avid disease.^{91,92}

Tumor characteristics can be used to estimate the risk of recurrence, discussed earlier in this chapter. Additionally, patient response to initial therapy is predictive of the likelihood of recurrence and can therefore be used to “restage” patients.⁹³ In one study, patients at low risk for recurrence had a 3% rate of recurrent disease in the 2 years after treatment, whereas those at intermediate risk had a 21% rate and those at high risk had a 68% rate. In the cohort who demonstrated an excellent response to therapy (stimulated Tg < 1 ng/mL, negative neck ultrasound), the risk of recurrence was 2% in the low-risk group, 2% in the intermediate-risk group, and 14% in the high-risk group. Alternatively, the cohort who had an incomplete response to

therapy (suppressed Tg > 1 ng/mL, stimulated Tg > 10 ng/mL, rising Tg level or evidence of structural disease on imaging) had a 13% recurrence rate in the low-risk group, 41% in the intermediate group, and 79% in the high-risk group.

9.4 Medullary Thyroid Cancer

Medullary thyroid cancer (MTC) arises from the calcitonin-secreting parafollicular C cells of the thyroid gland, which are derived from the neural crest during development. Medullary thyroid cancer accounts for <4% of all cases of thyroid cancer diagnosed in the United States.²¹ Overall survival rates in MTC are 80 to 85% at 5 years and 70 to 75% at 10 years.⁹⁴ Fewer than 50% of patients with MTC are cured after surgical resection; however, even in the presence of residual disease, the 10-year survival is approximately 70%.⁹⁵ The strongest predictors of decreased survival are older age at diagnosis, extent of the primary tumor, nodal disease, and distant metastasis.^{94,96,97}

9.4.1 Genetics of Medullary Thyroid Cancer

MTC is often associated with a genetic abnormality in the *RET* proto-oncogene; an estimated 20 to 25% of MTC is associated with the autosomal dominant genetic syndromes of multiple endocrine neoplasia (MEN) 2A, MEN 2B, and familial MTC.^{98,99} ▶ Table 9.3 discusses clinical characteristics of MTC syndromes. *RET* germline mutations associated with inherited cancer syndromes lead to overexpression of the Ret protein in all tissues and are, therefore, associated with other tumors, such as pheochromocytoma and parathyroid adenomas.¹⁰⁰ Alternatively, somatic *RET* mutations are present in 40 to 50% of sporadic cases of MTC and are associated with an advanced stage at diagnosis and lower long-term survival.¹⁰¹

The most common genetic syndrome associated with MTC is MEN 2A. MEN 2A is associated with development of pheochromocytoma in up to 68% of patients and primary hyperparathyroidism in 15 to 30%.^{95,102} Penetrance in MEN 2A is not 100%, but an estimated 90% of MEN 2A gene carriers will develop biochemical evidence of MTC by age 31, and 60% of patients will develop clinical disease by age 70.¹⁰³ Familial MTC is considered a clinical variant of MEN 2A, where multiple family members have been diagnosed with MTC, but there is no history of pheochromocytoma or primary hyperparathyroidism.¹⁰⁴ It can be difficult at times to differentiate MEN 2A from familial MTC; misdiagnosis of familial MTC risks failure to appropriately screen for pheochromocytoma.

MEN 2B is not as common as MEN 2A but is associated with more aggressive disease. Patients universally develop MTC, often at a more advanced stage and earlier in life.^{105,106} Pheochromocytoma is described in up to 28% of patients affected by MEN 2B.¹⁰⁷ Patients with MEN 2B have extraendocrine manifestations, such as marfanoid habitus, ganglioneuromatosis of the gut and oral mucosa, and medullated corneal nerve fibers. Up to 90% of patients have a colonic disturbance; most present with chronic constipation, but a significant number will also develop megacolon requiring surgical intervention.¹⁰⁸

All patients diagnosed with MTC should undergo germline screening for a *RET* mutation. The presence of specific *RET*

Table 9.3 Genetic syndromes in medullary thyroid cancer

	MEN 2A	MEN 2B	Familial MTC
Associated disorders	Pheochromocytoma and primary hyperparathyroidism	Pheochromocytoma, marfanoid habitus, neurogangliomas, megacolon, medullated corneal nerve fibers	None
MTC characteristics	Most common, 80% of genetic MTC	Youngest age at diagnosis, most aggressive	Variant of MEN 2A
Prophylactic thyroidectomy	Before 5 years old	Before 1 year old	Before 5 years old
Need to test family members	Yes, at age 3–5 years	Yes, preferably at birth	Yes, at age 3–5 years

Abbreviations: MEN, multiple endocrine neoplasia; MTC, medullary thyroid cancer.

Source: American Thyroid Association Guidelines Task Force, Thyroid, 2009.

mutations may require surveillance and treatment for pheochromocytoma or primary hyperparathyroidism. Additionally, the presence of a germline mutation in the *RET* proto-oncogene necessitates screening of first-degree relatives.¹⁰⁹ It is recommended that children of patients with MEN 2A and familial MTC undergo *RET* testing at 3 to 5 years of age, and those that test positive should have a prophylactic thyroidectomy by the age of 5.^{110,111} For children of parents with MEN 2B, testing should be done as soon as possible and thyroidectomy should be performed by 1 year of age, though MTC has been reported in children as young as 2 months old.^{112,113}

9.4.2 Preoperative Evaluation

For patients suspected of having MTC, the preoperative evaluation begins with a neck ultrasound to evaluate for evidence of lymph node metastasis; this should include the central and lateral lymph node compartments.¹¹⁴ Ultrasound has the highest sensitivity to detect metastatic lymph nodes in the neck.¹¹⁵ All patients should also undergo serum testing for calcium, calcitonin, carcino-embryonic antigen (CEA), and *RET* mutation, if not already done. Patients with elevated plasma calcitonin levels above 400 pg/mL should undergo evaluation for metastatic disease with CT scan of the neck and chest, as well as triple-phase liver CT scan or MRI of the liver, to evaluate for evidence of metastatic disease prior to surgical intervention.¹¹⁶

Patients with hereditary tumor syndromes should also undergo evaluation for primary hyperparathyroidism and pheochromocytoma. If there is elevated calcium on preoperative testing, consistent with primary hyperparathyroidism, a subtotal parathyroidectomy or four-gland resection with autograft should be performed at the same time.^{117,118} Any patient with suspected or confirmed MEN should also have evaluation for pheochromocytoma prior to any surgical intervention. This can be done with measurement of plasma metanephrines or 24-hour urinary metanephrines.¹¹⁹ Although biochemical screening is the standard approach, imaging of the abdomen without evidence of an adrenal nodule rules out pheochromocytoma.¹²⁰ If there is evidence of pheochromocytoma, this should be treated prior to resection of MTC because hypertensive crisis associated with untreated pheochromocytoma during surgical procedures is associated with a high mortality.¹²¹

9.4.3 Staging

Like differentiated thyroid cancer, staging for MTC is also based on the AJCC TNM staging system.⁶² Stage I disease is defined as a tumor <2 cm without evidence of lymph node metastasis or distant metastatic disease; this group is further subcategorized into stage IA for tumors <1 cm and stage IB for tumors 1 to 1.9 cm. Stage II disease is defined by a tumor 2 to 4 cm without evidence of lymph node metastasis or metastatic disease. Stage III disease is any tumor over 4 cm, microscopic evidence of capsule invasion, or the presence of central compartment lymph node metastasis. Stage IV disease is subcategorized into three groups: stage IVA disease is tumor with macroscopic invasion through the capsule, or cervical or mediastinal lymph node metastasis; stage IVB is tumor that invades into prevertebral fascia or encases the carotid artery or mediastinal vessels; stage IVC disease is defined as distant metastasis.

9.5 Anaplastic Thyroid Cancer

Anaplastic thyroid cancer (ATC) is considered the most aggressive form of the primary thyroid malignancies. It accounts for <2% of all thyroid cancers in the United States, but has the worst prognosis, with a median survival of 3 to 5 months and a 1-year survival of 20%.¹²² ATC has been associated with iodine deficiency. The incidence of ATC has fallen in several countries, which has been attributed in part to the institution of dietary iodine supplementation.^{123,124,125} In contrast to the differentiated thyroid cancers, ATC tumors are rapidly growing and often present with symptoms due to local invasion, such as dysphagia, dyspnea, and hoarseness.¹²⁶

ATC often arises from a preexisting differentiated thyroid cancer, and the two often coexist in the pathological specimen.^{127,128} Common types of differentiated cancers found with ATC are tall cell variant of papillary carcinoma, followed by follicular carcinoma and Hürthle cell carcinoma.¹²⁹ Some studies have suggested there is improved survival when only a small portion of the tumor has anaplastic features in a background of differentiated thyroid cancer, termed incidental ATC.^{130,131,132} Other important prognostic features in ATC include extent of disease, size of the primary tumor, and patient age.^{1,133} Additionally, patients who undergo complete surgical resection appear to have improved survival.^{134,135}

Table 9.4 Preoperative evaluation in patients with suspected anaplastic thyroid cancer

Test	Indication
Basic metabolic panel (including calcium)	Hypercalcemia due to PTHrP production, or hypocalcemia due to destruction of parathyroid glands
Complete blood count	Leukocytosis due to chemokine production or infection; poor prognostic indicator
Thyroid function tests	Thyrotoxicosis or hypothyroidism due to gland destruction
Ultrasound of neck	Extrathyroidal extension of tumor, presence of abnormal lymph nodes
Cross-sectional imaging of neck (usually CT)	Evaluate resectability of lesion
PET scan	Evaluate for distant metastasis

Abbreviations: CT, computed tomography; PET, positron emission tomography; PTHrP, parathyroid hormone–related peptide.
Source: Smallridge et al.⁵⁵

9.5.1 Genetics of Anaplastic Thyroid Cancer

ATC tumors are often aneuploid and associated with complex chromosomal deletions and rearrangements.^{136,137} Additionally, loss of heterozygosity has been demonstrated at the site of several tumor suppressor genes, which supports the hypothesis that ATC arises from preexisting differentiated thyroid cancer.¹³⁸ Mutations associated with differentiated thyroid cancer, such as *BRAF* and *RAS*, are thought to occur early in the thyroid cancer development and predispose to dedifferentiation.¹³⁹ Mutations in genes such as *p53* and *β-catenin*, thought to be the “second hit” causing dedifferentiation, are commonly encountered in anaplastic thyroid cancer.^{140,141} Mutations in *p53* and *β-catenin* are not specific to thyroid tissues and are seen in many other malignancies.^{142,143,144} *BRAF* and *RAS* mutations are more commonly associated with thyroid malignancies but can be seen in other malignancies, such as melanoma and hematologic cancers.^{145,146} *RET/PTC* and *PAX8/PPARG* mutations are fairly specific for thyroid tissues but are uncommonly encountered in ATC.^{147,148} Although these mutations provide potential targets for future molecular therapies, they are not currently required for diagnosis of ATC.

9.5.2 Preoperative Evaluation

As summarized in ► Table 9.4, patients confirmed or suspected to have ATC should have a basic laboratory evaluation, including a complete metabolic panel (including calcium and phosphorus), complete blood count, and thyroid function tests prior to any surgical intervention. Leukocytosis may suggest an underlying infection, or severe leukocytosis may be due to production of cytokines by the tumor itself.^{149,150} The presence of leukocytosis is a poor prognostic indicator.¹³¹ Preoperative thyroid function testing is important because large tumors may replace normal thyroid tissue, causing hypothyroidism. Alternatively, ATC has also been associated with thyrotoxicosis secondary to thyroiditis.¹⁵¹ Hypercalcemia due to production of parathyroid hormone–related peptide has been described.¹⁵²

As in other thyroid malignancies, ultrasound of the neck is useful to characterize the thyroid tumor, as well as the presence of any abnormal lymph nodes. The extent of tumor invasion and resectability of the lesion should be assessed with cross-sectional imaging, most commonly CT scan. It is critical to

determine extension of the tumor into adjacent tissues of the neck, as well as the presence of lymph nodes in areas not well visualized by ultrasound, such as the parapharyngeal space.¹⁵³ CT scan can also be used to evaluate for distant metastases, most commonly in the chest and abdomen. PET scan may have higher sensitivity for distant metastases than other imaging modalities.¹⁵⁴ Due to the rapid growth of these tumors, surgical intervention should not be significantly delayed to obtain additional preoperative imaging.

9.5.3 Staging

Like other thyroid malignancies, staging for ATC is also based on the AJCC TNM staging system.⁶² Due to its poor prognosis, ATC is universally defined as stage IV at the time of diagnosis. Tumors that are confined to the thyroid gland, with or without lymph node metastasis, are stage IVA. Stage IVB tumors invade into the adjacent tissues and may have lymph node metastases but no distant metastases. Stage IVC is distant metastatic disease. Additionally, because the extent of surgical resection is a significant prognostic factor, the AJCC also developed a residual tumor classification. R0 is no residual tumor, R1 is microscopic residual tumor, and R2 is macroscopic residual tumor.

Patients with R0/R1 disease after surgical resection have significantly longer survival, especially in studies that have evaluated adjunctive chemotherapy and radiation.^{134,135} However, it is difficult to assess the efficacy of chemotherapy or radiation because these trials are not randomized. Patients who undergo chemotherapy or radiation are likely to have improved functional status at baseline, and lack of randomization fails to control for this significant confounder. To date, there are no randomized, controlled trials for treatment of ATC.¹⁵⁵ The overall poor prognosis for ATC, and the marginal treatment benefit of current therapies should be discussed with the patient; palliative care is an option that should be considered for all patients.^{133,156}

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10 Molecular Advances in the Diagnosis and Treatment of Thyroid Cancer

Susan J. Hsiao and Yuri E. Nikiforov

10.1 Introduction

Significant work has been done over the last few decades to illuminate the genetic basis of thyroid neoplasia. These efforts, accelerated in recent years by the availability of increasing amounts of data generated through next-generation sequencing technologies, have led to the elucidation of the cancer genes underlying the pathogenesis of the majority (>90%) of thyroid tumors. Indeed, thyroid tumors are among the few tumors in which this level of understanding has been achieved to date. This knowledge (1) allows the accurate diagnosis of tumor, (2) aids in tumor classification, (3) provides guidance in the clinical management of patients with thyroid tumors, (4) offers potential targets for therapy, and (5) forms a framework for future discoveries of new cancer genes or biomarkers.

This chapter reviews the molecular mechanisms underlying thyroid cancer, which primarily involve the mitogen-activated protein kinase (MAPK) and phosphatidylinositol 3-kinase (PI3K) pathways. Recent data from studies examining multiple genes mutated in thyroid cancer as well as data from more than 400 thyroid carcinomas sequenced by The Cancer Genome Atlas initiative suggest that, for most well-differentiated follicular cell-derived thyroid tumors, a single mutation in a driver gene is sufficient for tumor development. Aggressive or poorly differentiated tumors, on the other hand, are more likely to have multiple mutations. These additional acquired mutations are likely late events that promote tumor progression and aggressiveness. Other molecular alterations are found typically only in benign nodules, and can be helpful in differentiating tumor from benign disease.

In addition to playing a role in thyroid cancer diagnosis, molecular findings are increasingly being used to determine surgical management of thyroid nodules, or, in the case of

familial medullary thyroid cancer, to determine the need for prophylactic surgery. Examples of how molecular findings can be used to guide medical and surgical management of patients as well as potential targeted therapies will also be discussed in this chapter.

10.2 Gene Alterations in Thyroid Disease

The genetic landscape of different types of thyroid tumors includes genetic alterations that occur in different tumor types and alterations that are specific for certain types of thyroid tumors (► Fig. 10.1).

10.2.1 Papillary Thyroid Cancer

Papillary thyroid cancer (PTC) is the most common type of thyroid cancer, accounting for approximately 80% of all thyroid malignancies and 90% of thyroid cancers in children. Most papillary thyroid cancers are associated with a low mortality rate, with a survival rate of >98%.¹ However, approximately 10% of patients will have recurrent disease.²

A common molecular alteration, seen in approximately 45% of papillary thyroid cancers, is mutation of the *BRAF* gene.^{1,3} *BRAF* is a serine-threonine kinase that functions in the MAPK pathway. *BRAF* is activated by *RAS*. Activated *BRAF* then activates *MEK*, leading to downstream activation of effectors in the MAPK pathway. *BRAF* is typically activated by point mutation, with the *BRAF* V600E mutation seen in more than 98% of cases. The *BRAF* K601E mutation can be seen in 1 to 2% of cases, and other *BRAF* mutations, such as small in-frame insertions or deletions, account for the remainder.^{4,5,6,7} In addition to point

Papillary thyroid carcinoma	Follicular variant of papillary thyroid carcinoma	Follicular adenoma	Follicular carcinoma	Poorly differentiated carcinoma	Anaplastic carcinoma	Medullary carcinoma
<i>BRAF</i> (V600E)	<i>RAS</i>	<i>RAS</i>	<i>RAS</i>	<i>RAS</i>	<i>TP53</i>	<i>RET</i>
<i>RET/PTC</i>	<i>PAX8/PPARG</i>	<i>PAX8/PPARG</i>	<i>PAX8/PPARG</i>	<i>TP53</i>	<i>CTNNB1</i>	<i>RAS</i>
<i>RAS</i>	<i>BRAF</i> (K601E)	<i>PTEN</i>	<i>PIK3CA</i>	<i>CTNNB1</i>	<i>RAS</i>	
<i>NTRK</i>	<i>RET/PTC</i>	<i>TSHR</i>	<i>PTEN</i>	<i>BRAF</i>	<i>BRAF</i>	
<i>TERT</i>		<i>GNAS</i>	<i>TERT</i>	<i>AKT1</i>	<i>PIK3CA</i>	
				<i>PIK3CA</i>	<i>PTEN</i>	
				<i>TERT</i>	<i>AKT1</i>	
					<i>TERT</i>	

Fig. 10.1 Common gene mutations and gene fusions in different thyroid tumors. (Data from Nikiforova MN, Nikiforov YE. Molecular diagnostics and predictors in thyroid cancer. *Thyroid*. 2009;19[12]:1351–1361, and references described in text.)

mutations and insertion or deletion mutations, *BRAF* may be activated as a result of chromosomal rearrangement, such as one leading to a fusion of *BRAF* to *AKAP9* (A kinase protein anchor 9).⁸ The *AKAP9-BRAF* fusion is seen in up to 11% of cases associated with radiation exposure but is uncommon in sporadic papillary cancers.⁸ Specific types of PTC are associated with different *BRAF* mutations. The *BRAF* V600E mutation is seen most frequently in classical and tall-cell variants of PTC and the *BRAF* K601E mutation is frequently seen in the follicular variant of PTC.^{9,10,11}

Another important alteration in PTC involves fusion of the *RET* (rearranged during transfection) gene with other partner genes. The *RET* gene is a receptor tyrosine kinase, and typically the 3' portion of *RET* encoding the tyrosine kinase domain is involved in oncogenic fusions with the 5' portion of partner genes.^{12,13} Several types of *RET* rearrangements, termed *RET/PTC*, have been described.^{14,15,16,17,18,19,20,21,22} Of these *RET/PTC* rearrangements, the most common types are *RET/PTC1* (which is formed by the fusion of *RET* with *CCDC6*) and *RET/PTC3* (which is formed by the fusion of *RET* with *NCOA4*).^{14,15} *RET/PTC* rearrangements are found in approximately 10 to 20% of PTC cases.^{23,24} Tumors carrying *RET/PTC* rearrangement are usually classic PTC, although these rearrangements have been observed in other variants of PTC.^{25,26,27} *RET/PTC* rearrangements are typically found more commonly in children and young adults, and in association with radiation exposure.^{28,29,30}

The *RAS* genes (*HRAS*, *NRAS*, and *KRAS*) also play a role in PTC. *RAS* proteins are G proteins that function in signaling to the MAPK and PI3K pathways. *RAS* mutations are more typically associated with follicular cancers and will be discussed in further detail later in the chapter, but *RAS* mutations also account for 10 to 20% of PTCs.^{31,32,33} *RAS* mutations are seen almost exclusively in the follicular variant of PTC, in contrast to other mutations, such as *BRAF* V600E, which are rarely found in this variant of PTC.³⁴

Rearrangements involving the *NTRK* genes account for up to 5% of PTCs. *NTRK1* and *NTRK3* are members of the neurotrophic receptor tyrosine kinase family of genes, and their fusions also activate the MAPK signaling pathway. To date, three fusion partners, *TPM3*, *TPR*, and *TFG*, have been identified for *NTRK1*, and one fusion partner, *ETV6*, has been identified for *NTRK3*.^{35,36,37,38,39} These rearrangements may occur in higher frequencies in patients with radiation exposure.^{8,39,40} Rearrangements involving the *ALK* gene, particularly *STRN-ALK*, occur in approximately 1% of PTCs.⁴¹

10.2.2 Follicular Thyroid Tumors

Follicular thyroid carcinomas, including the conventional and oncocytic (Hürthle cell) types, account for 10 to 15% of thyroid cancers. Follicular thyroid adenoma is a benign tumor belonging to this group. Point mutations in *RAS* genes (*HRAS*, *NRAS*, and *KRAS*), which typically occur in codons 12, 13, and 61, are found in 40 to 50% of follicular carcinomas and in 20 to 40% of follicular adenomas.^{31,32,33} Of the *RAS* genes, the most commonly mutated is *NRAS* codon 61, followed by *HRAS* codon 61, and then *KRAS* codons 61 and 12/13. A recent study of 204 thyroid nodules found that nodules with *KRAS* codon 12/13 mutation had a lower risk of carcinoma (41.7%) than nodules with *NRAS* codon 61 mutation (86.8% risk) or *HRAS* codon 61

mutation (95.5% risk), and furthermore that *KRAS* codon 12/13 mutation was associated with oncocytic change.⁴²

Another important alteration in follicular thyroid tumors involves rearrangement of the *PAX8* and *PPARG* genes. *PAX8* is a paired domain transcription factor and *PPARG* is a nuclear hormone receptor. The *PAX8/PPARG* rearrangement has been reported in 30 to 40% of follicular carcinomas.^{43,44,45} This rearrangement is also present at lower frequencies in oncocytic (Hürthle) cell carcinomas, in the follicular variant of PTC, and in follicular adenomas.^{43,44,45,46,47}

Genes involved in the PI3K/AKT signaling pathway have also been implicated in follicular tumors. Aberrant signaling of the PI3K/AKT pathway may be due to activation of upstream regulators, may result from activating mutations in *PIK3CA* and *AKT1*, or may result from inactivation of *PTEN*, which negatively regulates this pathway. *PIK3CA* is a catalytic subunit of PI3Ks and is typically activated by mutations in exon 9 and exon 20. Mutation of *PIK3CA* has been reported in 6 to 13% of follicular carcinomas.^{48,49,50} *PTEN* mutation may occur as germline or somatic events; germline *PTEN* mutations can cause follicular tumors in patients with *PTEN* hamartoma syndrome, and somatic *PTEN* mutations can be seen in both follicular thyroid tumors and follicular adenomas.^{49,50,51,52,53}

10.2.3 Poorly Differentiated and Anaplastic Thyroid Cancer

Poorly differentiated thyroid carcinomas are partially dedifferentiated cancers, whereas anaplastic (undifferentiated) carcinomas lose entirely the phenotypical features of thyroid and even epithelial differentiation. It is thought that most poorly differentiated and anaplastic carcinomas arise via dedifferentiation of a well-differentiated cancer. Both well-differentiated and poorly/undifferentiated components are often seen in these tumors, and both components often share mutations in *RAS* or *BRAF*.

RAS mutations have been reported in 25 to 30% of poorly differentiated carcinomas and 40 to 50% of anaplastic carcinomas, whereas *BRAF* mutation has been reported in 10 to 15% of poorly differentiated carcinomas and 20 to 30% of anaplastic carcinomas. Poorly differentiated or anaplastic tumors with *RAS* or *BRAF* mutation often harbor other mutations as well, which contribute toward tumor dedifferentiation. The most common additional mutations involve the *TP53* and *CTNNB1* genes. *TP53* is a tumor suppressor with roles in DNA repair, cell cycle regulation, and apoptosis. Most mutations in *TP53* are point mutations within the DNA binding domain. *TP53* mutations have been seen in 20 to 30% of poorly differentiated carcinomas and 70 to 80% of anaplastic carcinomas.^{54,55,56,57,58} *CTNNB1* (beta-catenin) is a gene involved in the Wnt signaling pathway. Typically, mutations in *CTNNB1* occur at phosphorylation sites, resulting in stabilization of the protein and increased signaling. Mutations in *CTNNB1* have been reported in 25% of poorly differentiated carcinomas and 60 to 70% of anaplastic carcinomas.^{59,60} *ALK* fusions are found in 5 to 10% of these tumors and result in constitutive activation of *ALK* kinase.⁴¹

The PI3K pathway also plays a role in these tumors. Mutations in *PIK3CA* have been observed in 10 to 20% of anaplastic carcinomas.^{48,49} In addition, one study reported the presence of *AKT1* mutation in metastatic poorly differentiated carcinoma.⁶¹

Recently, two mutations in the promoter region of telomerase (*TERT*) have been described in thyroid cancer. Telomerase is a reverse transcriptase that functions to maintain telomere length and is frequently expressed in tumor cells.⁶² These *TERT* promoter mutations, c.-124C>T (C228T) and c.-146C>T (C250T), were first described in melanoma and were found to increase promoter activity.^{63,64} In thyroid cancer, these mutations were detected in follicular cell-derived thyroid cancers (but not in medullary carcinoma), and were present at the highest frequency in poorly differentiated and anaplastic carcinomas.^{65,66,67,68}

10.2.4 Medullary Thyroid Cancer

Medullary thyroid carcinoma arises from C (parafollicular) cells and accounts for approximately 3 to 4% of thyroid cancers.¹ The majority of medullary carcinomas are sporadic, but medullary carcinoma may also arise in multiple endocrine neoplasia type 2A or 2B (MEN2A or MEN2B) syndrome, or in familial medullary thyroid carcinoma (FMTC). Medullary carcinomas that develop in the context of familial syndromes typically are multicentric and occur in younger patients.

RET gene mutation is commonly found in both familial and sporadic medullary thyroid carcinoma. In contrast to papillary thyroid cancer, where the 3' portion of the *RET* gene is activated via chromosomal rearrangement, in medullary thyroid carcinomas, *RET* is activated by point mutation. In sporadic medullary carcinomas, the most common mutation is *RET* M918T.^{69,70} The M918T mutation is located within the tyrosine kinase domain and results in altered substrate specificity.⁷¹ The M918T mutation is also seen in >90% of medullary carcinomas arising in MEN2B syndrome.^{70,72,73,74} In MEN2A and FMTC, *RET* mutations usually occur at cysteine residues in the cysteine-rich extracellular domain. In MEN2A, this commonly involves codon 634, whereas in FMTC, other cysteine residues can be involved.^{75,76} Mutation of a cysteine residue in the extracellular domain confers the mutant *RET* protein the ability to undergo ligand-independent dimerization with another mutant *RET* protein.

More recent studies have shown that *RAS* mutations also occur in sporadic medullary thyroid carcinomas, and are mutually exclusive with *RET* mutations.^{77,78,79} *HRAS* and *KRAS* mutations occur in approximately 8% of these tumors, which tend to behave less aggressively.⁷⁸

10.2.5 Genetic Alterations in Hyperfunctioning Thyroid Nodules

Hyperfunctioning (hot) thyroid nodules, which on histopathologic examination may be diagnosed as follicular adenomas, hyperplastic nodules, or, rarely, follicular carcinomas, often carry mutations in thyroid-stimulating hormone receptor (*TSHR*) or *GNAS*. *TSHR* encodes a membrane receptor whose activity is mediated by G proteins. Activating mutations in *TSHR* have been reported in 50 to 80% of nodules.^{80,81} These mutations are typically located in the extracellular and transmembrane domains of *TSHR*. *GNAS* encodes an alpha subunit of heterotrimeric G protein complexes, and thus functions downstream of *TSHR*. Activating mutations of *GNAS*, which mostly occur in codons 201 and 227, have been seen in 3 to 6% of

hyperfunctioning nodules.^{82,83,84} Although *TSHR* mutations at specific hotspots may also be seen in thyroid carcinomas, in a limited series of cases, all nodules with *GNAS* mutation were benign.⁵³ Thus *GNAS* mutation may be a unique marker of benign nodules.

10.2.6 Additional Molecular Alterations in Thyroid Cancer

miRNA Expression in Thyroid Carcinomas

A micro RNA (miRNA) is a small, noncoding RNA that functions in regulating gene expression. miRNAs bind to the 3' untranslated region of target mRNAs and cause degradation or translation inhibition. Several miRNAs have been identified in miRNA microarray studies and found to be recurrently up- or downregulated in thyroid carcinoma.

In PTC, many miRNAs have been identified, but some of the best characterized include miR-187, -221, -222, and -146b, which have been found to be significantly overexpressed in tumor tissue in several studies.^{85,86,87,88} miR-146b upregulation has been associated with advanced tumors, extrathyroidal extension, and poor prognosis.^{89,90} In follicular carcinomas, miR-221, -222, and -146b as well as miR-182, -183, -96, -874, and -449a were reported to be upregulated, and miR-542-5p, -574-3p, -455-3p, -455-5p, -199a-5p, -199a-3p, and 125a-3p were downregulated.^{86,91,92,93} Interestingly, differential expression of miR-885-5p was observed between conventional and oncocytic follicular carcinomas.⁹³ A number of miRNAs were found to be altered in poorly differentiated and anaplastic thyroid carcinomas.^{86,94,95}

Methylation in Thyroid Carcinomas

DNA methylation typically occurs on cytosine residues in CpG islands (regions with a high occurrence of CpG dinucleotides), which typically are located in gene promoters. Hypermethylation of promoters may result in silencing of tumor suppressor genes, and, conversely, hypomethylation can result in increased transcription of oncogenes. In addition, hypomethylation is thought to lead to chromosome instability.

In PTC, hypermethylation of several genes has been observed, including tissue inhibitor of metalloproteinases 3 (*TIMP3*), *SLC5A8*, death-associated protein kinase 1 (*DAPK1*), and *TSHR*.^{96,97,98,99} Methylation of these genes was observed in association with the *BRAF* V600E mutation.⁹⁹ These genes function in several cellular pathways: *DAPK1* is a calmodulin-dependent serine threonine kinase with roles in apoptosis; *SLC5A8* is an iodide, monocarboxylate, and short-chain fatty acid transporter; and *TSHR* is thyroid-stimulating hormone receptor. *TIMP3* functions by binding to the metalloproteinase zinc cofactor, thereby inactivating metalloproteinase. Studies have suggested that silencing of the *TIMP3* gene and the subsequent loss of metalloproteinase inhibition are associated with extrathyroidal invasion and lymph node metastasis.⁹⁹

In follicular thyroid tumors, hypermethylation of genes, including *PTEN* and *RASSF1*, have been reported.^{98,100,101,102} Alterations of the PI3K-AKT pathway, in which *PTEN* functions, are common in follicular tumors. *RASSF1* is a gene related to the *RAS* genes and has roles in cell cycle regulation and apoptosis.

PTEN and *RASSF1* hypermethylation have been seen in both follicular thyroid tumors and benign lesions, such as follicular adenomas and hyperplastic nodules.^{98,100,101,103}

Altered DNA methylation patterns have been seen in poorly differentiated and anaplastic thyroid carcinomas as well. Some evidence exists that, compared to well-differentiated thyroid carcinomas, anaplastic thyroid carcinomas tend to have aberrant gene promoter hypomethylation rather than hypermethylation.¹⁰⁴

10.3 Utility of Molecular Testing in Diagnosis, Management, and Therapy

10.3.1 Molecular Diagnostics in Indeterminate Cytology Thyroid Nodules

The diagnosis of thyroid cancer through the use of ultrasound examination and cytological examination of cells obtained by fine-needle aspiration (FNA) typically diagnoses the majority of thyroid nodules as benign or malignant.^{105,106} However, in approximately 20 to 30% of nodules, cytological analysis of the cells results in an indeterminate classification.^{107,108} These indeterminate categories include atypia of undetermined significance or follicular lesion of undetermined significance (AUS/FLUS) (Bethesda category III), follicular neoplasm or suspicious for a follicular neoplasm (FN/SFN) (Bethesda category IV), and suspicious for malignancy (SUSP) (Bethesda category V).^{107,109} The risk of malignancy is 5 to 15% in the AUS/FLUS category; 15 to 30% in the FN/SFN category, and 60 to 75% in the SUSP category.¹⁰⁹ However, on surgical resection, only 10 to 40% of indeterminate nodules are malignant.^{105,110,111}

Molecular testing of indeterminate cytology thyroid nodules offers the ability to correctly identify and diagnose malignancies, including low-grade malignancies, and to classify malignancies based on likelihood of progression or aggressive behavior. In evaluating the utility of any test, comparisons of sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) are important. A test that is useful to rule out malignancy should have a high sensitivity (percentage of correctly identified positives) and a high NPV (percentage of patients with a negative test result who do not have the disease). To rule in malignancy, a test with high specificity (percentage of correctly identified negatives) and high PPV (percentage of patients with a positive test result who have the disease) should be used. It is important to note that, while sensitivity and specificity of a test reflect test performance, NPV and PPV can vary based on the prevalence (or pretest probability) of malignancy. In clinical practice, prevalence of malignancy may change not only based on the patient population but also by institutional variations in malignancy rates conferred by each cytological diagnosis.

Approaches to Molecular Testing

Many different diagnostic tools have been used in indeterminate cytology thyroid nodules in an attempt to better classify these nodules. These diagnostic tools were developed based on

knowledge accumulated about mechanisms underlying thyroid tumorigenesis and include immunohistochemical markers, miRNAs, gene mutations/rearrangements, and gene expression markers.^{105,106,111,112} Although all of these tools have been shown to have utility as diagnostic markers, the two types of molecular markers currently being used in clinical practice are gene mutations/rearrangements and gene expression markers, and will be discussed in further detail. Gene mutation/rearrangement testing is being offered in institutions and commercial laboratories as single-gene testing or panel testing, and a gene expression panel is currently offered commercially.

Gene Mutation/Rearrangement Testing

The molecular genetics of thyroid tumors are very well characterized, with many mutations and rearrangements that are specific for malignancy. The single gene mutation *BRAF* V600E is specific and has a high PPV for malignancy, and testing for this mutation has been shown to increase the sensitivity of FNA biopsies.^{111,113,114} Mutations in the *RAS* genes have a lower PPV for malignancy of 74 to 87%.^{110,115,116} This is due to the occurrence of *RAS* mutations in benign follicular adenomas. However, although follicular adenomas are benign, some studies have found evidence that *RAS* mutations in follicular adenomas are precancerous changes that may progress to malignancy.^{117,118,119,120}

Increased sensitivity and specificity from single-gene testing can be achieved by using multigene panels. A multigene panel consisting of the seven (or eight) most commonly altered genes (*BRAF*, *KRAS*, *HRAS*, *NRAS*, *PAX8/PPARG*, *RET/PTC1*, *RET/PTC3* [and *TRK* rearrangement]) has been demonstrated to provide high specificity and PPV for cancer detection in three prospective studies.^{114,118,119} With the seven gene panel for molecular testing, high NPV (94%) was achieved for AUS/FLUS cytology nodules; though lower NPV was seen in FN/SFN and SUSP nodules.¹¹⁰

Advances in technology have made it possible to test for more gene mutations using the limited amount of DNA available in FNA biopsy specimens. Next-generation sequencing (NGS) platforms allow high-throughput, massively parallel nucleic acid sequencing, and highly sensitive and quantitative assessment of the mutant allele (► Fig. 10.2). NGS has been increasingly integrated into clinical use for molecular testing as an efficient and cost-effective way of analyzing multiple genes in one reaction (► Fig. 10.3). Expanded diagnostic panels are expected to further increase sensitivity and NPV, as was shown in a recent report of an NGS thyroid gene mutation panel that included > 60 genes and gene fusions.¹²¹ This panel expanded from the previously described seven-gene panel to also test for mutations in hotspots of *RET*, *GNAS*, *TSHR*, *CTNNB1*, *TP53*, *AKT1*, *PTEN*, *PIK3CA*, and *TERT*, and 42 types of rearrangements involving *RET*, *BRAF*, *PPARG*, *NTRK1*, *NTRK3*, *ALK*, and *THADA*. In FN/SFN cytology thyroid nodules, the 60-gene panel showed high sensitivity (90%), specificity (93%), PPV (83%), and NPV (96%) for cancer detection.¹²¹

An additional advantage of NGS-based mutational analysis is the ability to detect the presence of multiple mutations. Although the majority of thyroid nodules with mutations have only a single molecular alteration, in a small number of cases, multiple mutations may be present.^{121,122} Thus identification of

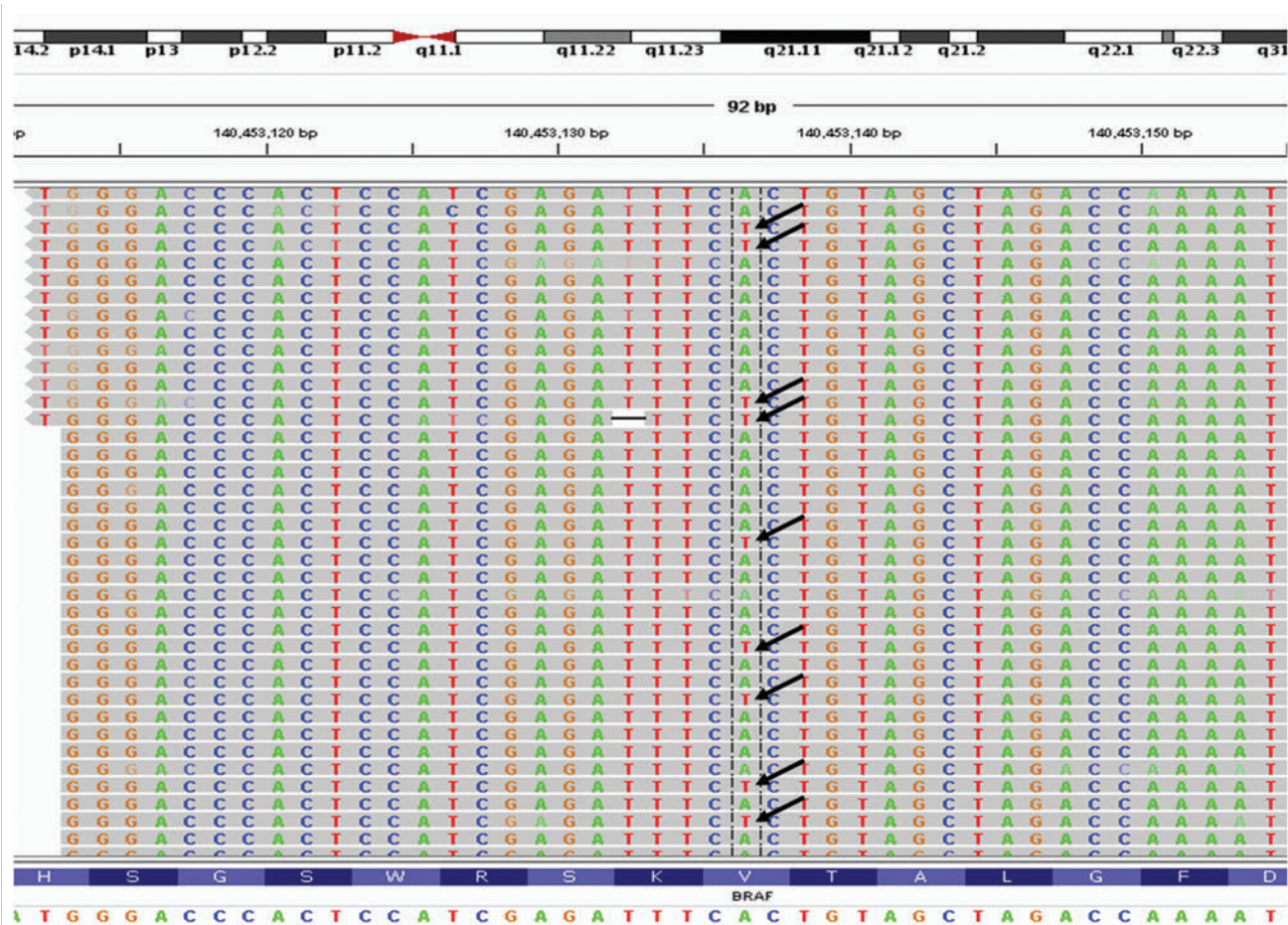


Fig. 10.2 Quantitative detection of a *BRAF* V600E mutation by next-generation sequencing. View of sequence alignments in the Integrative Genomics Viewer (IGV) (Broad Institute) showing mutant sequencing reads (arrows) in a sample obtained by thyroid fine-needle aspiration.

molecular alterations can be useful diagnostically, but finding multiple mutations in a thyroid nodule may have prognostic implications as well and will be discussed in further detail.

Gene Expression Markers

A gene expression panel is currently being commercially offered as Afirma (Veracyte). Using mRNA expression profiles of a proprietary set of 142 genes, indeterminate thyroid nodules are classified into either a benign or a suspicious category.¹²³ In an industry-sponsored, multi-institutional, prospective, double-blind study, this gene expression classifier was found to demonstrate a high NPV in AUS/FLUS (95%), FN/SFN (94%), and SUSP (85%) cytology nodules.¹⁰⁵ However, the PPV in all indeterminate cytology categories was lower, reported as 38% in AUS/FLUS nodules, 37% in FN/SFN nodules, and 76% in SUSP nodules.¹⁰⁵ A recent smaller, independent study using the Afirma gene expression classifier in AUS/FLUS and FN nodules found a significantly lower PPV of 16%.¹²⁴

As with all tests, the NPV of the gene expression classifier will vary with disease prevalence. In the original validation study, the disease prevalence was 24% in AUS/FLUS nodules, 25% in FN/SFN nodules, and 62% in SUSP nodules.¹⁰⁵ In a separate study in which the disease prevalence in indeterminate nodules

(AUS/FLUS and FN/SFN) was 33%, the NPV was found to be 89.6%.¹²⁵

10.3.2 Molecular Diagnostics and Management of Thyroid Nodules and Tumors

Typically, patients with AUS/FLUS nodules undergo a repeat FNA, whereas surgical lobectomy is recommended for patients with FN/SFN nodules, and total thyroidectomy is recommended for patients with SUSP nodules.^{109,126} According to American Thyroid Association guidelines, molecular markers may be considered for patients with indeterminate nodules to help guide management.¹²⁶ A negative result in molecular tests with a high NPV, for example, the 60-gene panel or Afirma gene expression classifier, reduces the risk of malignancy to levels similar to the risk of a nodule with benign cytology.^{105,121} Thus these patients may be able to avoid unnecessary surgery.

Although most diagnostic lobectomies are performed for benign thyroid nodules, in 10 to 40% of cases, the nodule is found to be malignant.^{105,127,128} If a patient who has undergone surgical lobectomy has a tumor > 1 cm in size, a completion thyroidectomy is usually performed. In these cases, preoperative

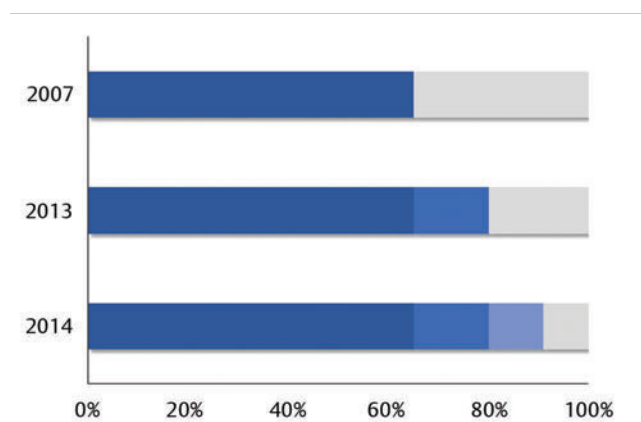


Fig. 10.3 Progress in composition of multigene mutational panels. A seven-gene panel developed in 2007 covered mutations and rearrangements accounting for 65% of thyroid tumors; by 2013 with new genes identified and the availability of next-generation sequencing technologies, a 15-gene panel was developed to encompass mutations in approximately 80% of thyroid tumors. By 2014, further advances in knowledge and technology allowed the molecular testing of 60 gene mutations and rearrangements, involved in 91% of thyroid tumors.

molecular testing using a molecular test with high PPV could be beneficial in reducing the need for a two-step surgery. Gene mutation panels have been consistently shown to have high specificity and high PPV.^{110,115,116,121} A positive result in a gene mutation panel (with the possible exception of genes that may be mutated in benign lesions, such as *RAS* or *TSHR*), would be an indication for a total thyroidectomy rather than an initial lobectomy followed by a completion lobectomy. Use of a seven gene mutation panel was recently reported to be effective in reducing the number of two-step surgeries.¹²⁹ In this study of a series of 471 indeterminate nodules, the authors found that patients who did not undergo gene mutation marker testing were 2.5-fold more likely to need a two-step surgery.¹²⁹ In pediatric patients, where indeterminate cytology nodules may account for up to 38% of nodules, similar results were seen.¹³⁰ In a small series of cases, gene mutation panel testing was used to guide surgical management and prevent two-step surgeries in 60% of cases.¹²⁷

Molecular markers can also provide valuable prognostic information. Patients with molecular alterations characteristic of aggressive tumors could potentially benefit from a more extensive initial resection that includes central compartment lymph node dissection, as well as close clinical follow-up postsurgery.

The *BRAF* V600E mutation was one of the first mutations studied as a molecular marker for aggressive tumors, and testing of FNA biopsies for the *BRAF* V600E mutation has been shown to have utility in preoperative risk stratification.¹²⁸ Many studies have examined the association of the *BRAF* V600E mutation with aggressive tumor features, such as extrathyroidal invasion, lymph node metastasis, and tumor recurrence. A meta-analysis of these studies found that the presence of the *BRAF* V600E mutation was significantly associated with tumor recurrence or persistent disease (25% of *BRAF* V600E-positive tumors vs. 13% of *BRAF* V600E-negative tumors).¹³¹ The presence of the *BRAF* V600E mutation in papillary thyroid carcinomas has also been shown to be associated with a small but

significantly increased risk of mortality (5% of *BRAF* V600E-positive tumors vs. 1% of *BRAF* V600E-negative tumors).¹³² Thus *BRAF* V600E-positive tumors tend to show more aggressive features and have increased risk of recurrence and mortality. However, most *BRAF* V600E tumors will not recur, and overall survival remains high in patients regardless of *BRAF* mutational status. These findings suggest that use of the *BRAF* V600E mutation alone is not specific as a marker of aggressive tumor behavior.

TP53 is an important tumor suppressor with roles in cell cycle regulation and apoptosis. Mutation of *TP53* frequently occurs in poorly differentiated and anaplastic thyroid cancer and is an important event in thyroid tumor dedifferentiation.^{54,55} Thus the presence of *TP53* mutation suggests an aggressive tumor. However, *TP53* mutations have also been reported in some well-differentiated carcinomas; thus the specificity of *TP53* mutation for aggressive tumors should be characterized further.⁵³

More recent studies have suggested that, rather than the presence of a single genetic alteration, the presence of multiple driver mutations may be a more specific marker of aggressive tumor behavior. Coexisting mutations in early driver genes, such as *BRAF* or *RAS*, along with mutation in genes such as *PIK3CA*, *AKT1*, or *TP53*, whose mutation is thought to be a late event, have been reported in poorly differentiated and anaplastic carcinomas.^{48,49,133} Newer genetic panels, run on NGS platforms, are ideally suited to interrogate tumors for the presence of multiple mutations. In one reported NGS-based analysis, 4% of thyroid carcinomas had more than one mutation, and these tumors with multiple mutations tended to display aggressive features.⁵³

Another promising prognostic molecular marker is mutation of the *TERT* promoter region at c.-124C>T (C228T) or c.-146C>T (C250T). These mutations have been reported in 7 to 22% of well-differentiated papillary and follicular carcinomas, but they occur at a higher frequency (29–52%) in poorly differentiated and anaplastic thyroid carcinomas.^{65,66,67,68} *TERT* promoter mutations were found to be associated with persistent disease, metastatic disease, and increased mortality.⁶⁸ An association of *TERT* promoter mutations with the presence of the *BRAF* V600E mutation has also been observed in some studies, suggesting an interplay between both genes that may contribute toward aggressive tumor behavior.^{65,67}

Finally, mutations in *RET* detected in a thyroid nodule may be useful as an indication for germline testing. Specific mutations in *RET* are characteristic of patients with familial forms of medullary thyroid carcinoma; for example, in MEN2A, 90% of mutations occur at codon 634.^{70,74,75} Knowledge of germline *RET* mutations has implications for intraoperative management of parathyroid glands, for surveillance and management of other tumors, and for screening and prophylactic thyroidectomy of family members.⁶⁹ For *PTEN*, mutations may be seen in both benign and malignant nodules, and many different mutations in *PTEN* have been reported for *PTEN* hamartoma syndrome.^{49,50,51,52,53} Thus detection of *PTEN* mutation in a nodule would not necessarily be an indication for germline testing unless there was an appropriate clinical context.

10.3.3 Molecular Diagnostics and Targeted Therapy

For most well-differentiated thyroid tumors, surgical resection is the primary therapy. However, in advanced disease thyroid

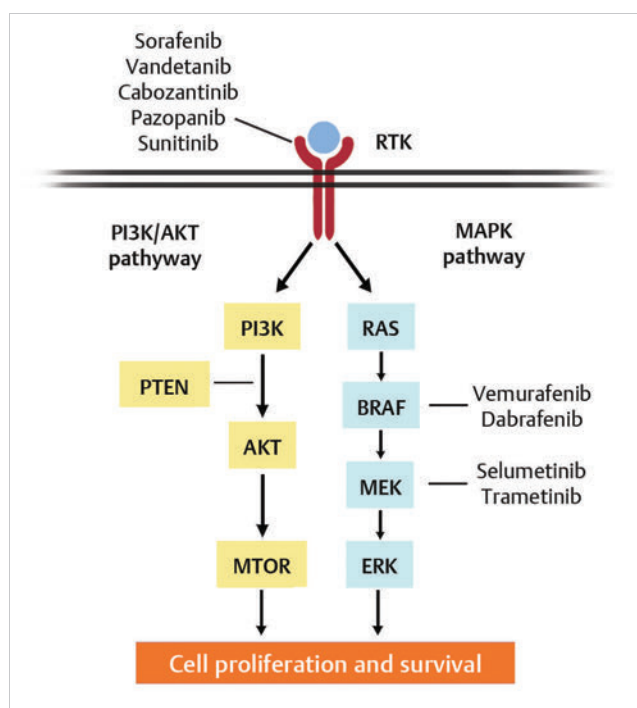


Fig. 10.4 Thyroid tumor therapies target components of the MAPK and PI3K/AKT pathway. Therapeutics acting on receptor tyrosine kinases include vandetanib and cabozantinib, which are multi-tyrosine kinase inhibitors with activity against *RET* that are FDA approved in the treatment of advanced medullary thyroid cancer, sorafenib (a multi-tyrosine kinase inhibitor), which is FDA approved for the treatment of progressive differentiated thyroid carcinoma refractory to radioactive iodine treatment, as well as other tyrosine kinase inhibitors currently under investigation, including pazopanib and sunitinib. Other targeted therapeutics that have shown promising results in clinical trials target *BRAF* (vemurafenib and dabrafenib), or inhibit MEK (trametinib and selumetinib).

tumors may have distant metastases, may be inoperable, or may be refractory to radioactive iodine therapy. For these patients, limited therapeutic options are available. Advances in our understanding of the genetic changes underlying most thyroid cancers has identified potential targets for therapy. Therapies currently available as well as those under investigation target components of the MAPK and PI3K/AKT pathways, which are activated in most thyroid tumors (► Fig. 10.4).

The FDA recently approved sorafenib (a multi-tyrosine kinase inhibitor) for the treatment of locally recurrent or metastatic, progressive differentiated thyroid carcinoma refractory to radioactive iodine treatment. In a randomized, double-blind, multicenter, phase 3 trial, sorafenib was shown to significantly increase progression-free survival over placebo.¹³⁴ Several other potential therapies are currently being investigated for differentiated thyroid cancers. Vemurafenib and dabrafenib are *BRAF* inhibitors that are FDA approved for the treatment of metastatic melanoma. A phase 1 trial of vemurafenib in patients with metastatic papillary thyroid cancer has shown promising results.¹³⁵ Current phase 2 trials are under way examining the effect of vemurafenib and dabrafenib (with or without the MEK inhibitor trametinib). Other therapies that have shown promising results in phase 2 trials of differentiated thyroid cancers include selumetinib (a MEK inhibitor), pazopanib (a tyrosine

kinase inhibitor), and sunitinib (a multi-tyrosine kinase inhibitor).^{136,137,138} Crizotinib and other ALK inhibitors may be explored in patients with advanced thyroid cancer positive for *STRN-ALK* or other *ALK* fusions.^{41,139,140}

In advanced medullary cancer, two FDA-approved targeted therapies are available: vandetanib and cabozantinib. These are multi-tyrosine kinase inhibitors with activity against *RET*. Both vandetanib and cabozantinib therapy were shown in phase 3 trials to significantly improve progression-free survival over placebo-treated patients.^{141,142}

10.4 Conclusion

Most of the genetic alterations underlying thyroid cancer involve dysregulation of the MAPK or PI3K/AKT pathways. As of today, genetic changes in >90% of thyroid cancers have been identified. Elucidation of the genetic mechanisms of cancer development has led to many practical applications. Molecular diagnostics are increasingly being incorporated into routine clinical care to guide diagnosis, surgical management, and therapy. Future advances will be through improved sequencing technology. NGS-based testing of expanded panels of genes has been shown to significantly improve the sensitivity and specificity in the diagnosis of thyroid cancer from the limited samples obtained by FNA biopsy. As the technology improves and costs of testing decrease, routine use of these tools will allow more detailed characterization of the molecular profiles of thyroid tumors. Each molecular profile will likely be associated with different risks of tumor progression, recurrence, or mortality, and will likely require specific surgical management or therapy. Thus incorporation of molecular findings will be essential in offering the patient with a thyroid nodule truly personalized medical care.

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11 Medical Management of Aggressive Differentiated Thyroid Cancer

Sara Ahmadi and R. Michael Tuttle

11.1 Introduction

Although patients with thyroid cancer present with either intermediate- or low-risk disease that is very effectively treated with thyroid surgery (with or without the addition of radioactive iodine [RAI]), as many as 10 to 15% of patients have advanced disease that is manifest either by distant metastases or locally aggressive disease. Distant metastases can occur during follow-up in 6 to 20% of patients with thyroid cancer and can be seen in 3 to 15% of patients at their presentation.^{1,2,3,4,5,6,7,8,9} In locally advanced disease, the primary clinical management issues relate to invasion of major cervical structures (vessels, esophagus, trachea, larynx, recurrent laryngeal nerves). In distant metastases, the management issues are often related to local compressive symptoms if metastatic foci are located near (or in) major neurovascular structures or the aerodigestive tract, or as an impending (or actual) pathological bone fracture.

Although advanced disease can manifest either at the time of initial presentation or during follow-up, the basic management principles remain the same. Management of advanced disease is ideally undertaken in the context of a functional, integrated team, because the care of these patients usually requires complex decision making and a wide array of potential therapies.

Treatment options for advanced disease can be divided into localized therapies directed toward one or more individual tumor foci or systemic therapies designed to treat more widespread disease. A wide variety of localized therapies are currently available and include options such as extensive surgery or focused surgical metastasectomy, external beam radiation therapy (EBRT), embolization, and radiofrequency ablation.¹⁰ In most clinical situations, a biopsy of the suspected metastatic foci is needed to confirm the diagnosis prior to proceeding with localized therapies. Although thyroid-stimulating hormone (TSH) suppression and RAI therapy have been the mainstays of systemic therapy for more than 50 years, recent studies have demonstrated clinical efficacy of several oral kinase inhibitors in the treatment of RAI refractory thyroid cancer.

11.2 Localized Therapies in Advanced Thyroid Cancer

In patients with advanced thyroid cancer, localized therapies are valuable tools to address malignant foci that arise in critical locations and are at high risk of causing significant morbidity or mortality secondary to tumor infiltration or compression of vital structures if not treated expeditiously.¹¹ In fact, treatment of disease at these critical locations takes precedence over thyroidectomy and RAI therapy. Examples of critical locations include the brain, neurovascular structures (e.g., spine metastases; major disease in the neck, upper mediastinum, or base of the skull; or metastases causing superior vena cava syndrome), major airways (e.g., trachea, larynx, major bronchi), or bone

with impending (or previous) pathological fracture. In addition to averting local symptoms that could develop from tumor progression, directly treating these lesions before using RAI therapy may prevent morbidity related to swelling that can occur in some of these metastatic foci with an increase in TSH (either endogenous or exogenous TSH). The choice of a specific localized therapy is dependent on tumor size, tumor location, and preferences of the patient and disease management team.

11.2.1 Localized Therapy for Distant Metastases

Localized therapies are very frequently used in the management of bone metastases from thyroid cancer. Bone metastases occur in 2 to 13% of all patients with differentiated thyroid cancer and are associated with poor clinical outcome and significant morbidities, including pathological fracture, severe pain, and immobility.¹² Surgical metastasectomy is the preferred treatment option for bone metastases that are associated with structural instability or are in critical locations that may cause neurovascular compromise.

A retrospective study of 109 patients with bone metastases from thyroid cancer reported that complete resection of bone metastases in young patients is associated with a significant improvement in survival.¹³ EBRT is the preferred treatment option for bone metastases that are structurally stable but are causing pain, increasing in size, or located where progressive growth could cause local compressive symptoms or structural instability. Although embolization of tumor vasculature can be used for pain control, it is more often used prior to surgical resection of bone lesions because these metastatic foci tend to be very vascular and prone to intraoperative bleeding. Radiofrequency ablation has been predominantly used to treat liver metastasis from thyroid cancer, but it has also been reported to reduce the pain from thyroid cancer skeletal metastases.^{14,15,16}

Brain metastases originating from differentiated thyroid carcinoma are uncommon. They are usually found in the setting of widespread distant metastases and associated with a very poor prognosis.^{17,18,19} Once identified, high-dose glucocorticoids are usually recommended to decrease the surrounding edema. Then the preferred treatment option is surgical resection of the metastatic lesion unless the lesions are very small and/or multifocal.^{20,21} Stereotactic radiation can be an effective treatment if fewer than 3 to 5 small lesions are present, whereas whole brain radiation is required for more numerous lesions.¹⁷

Localized therapies can also be effective treatment options for disease involving the airways. Bronchoscopy with laser therapy can be effectively used to treat intraluminal disease. Endobronchial stents are occasionally used to maintain patent airways. Because postobstructive pneumonia is a common cause of death in advanced thyroid cancer, localized therapies to prevent or alleviate compression of major bronchi can decrease morbidity. Depending on the size of the lesion,

location of lesions, and clinical condition of the patient, additional options include surgical resection of metastatic lesions or focused EBRT.

Although not commonly performed, resection of individual dominant metastatic lesions in the lung or liver can be considered in patients in whom the remainder of the disease is relatively stable. Even though metastasectomy is not curative, resection of a dominant progressive metastatic lesion may obviate the need for systemic therapies for months to years.

11.2.2 Localized Therapy for Advanced Disease in the Neck

In patients presenting with locally advanced thyroid cancer, the treatment options may extend beyond total thyroidectomy and RAI ablation. Consideration should be given to EBRT in all patients with clinically evident gross extrathyroidal extension.^{22,23,24} It is important to balance the potential for locoregional control with the well-described long-term complications of EBRT (particularly when used in conjunction with RAI) of dental decay, tracheal stenosis, esophageal stricture, osteonecrosis, fibrosis, and xerostomia.²

There is consensus that EBRT can provide effective locoregional control for gross residual disease that cannot be surgically removed. Current available radiotherapy techniques such as intensity-modulated radiation therapy (IMRT) has made it possible to give a higher dose of EBRT safely without exceeding the tolerance of surrounding critical structures.^{25,26,27}

However, the role of EBRT as adjuvant therapy in patients that had all clinical evidence of locally invasive disease surgically removed is much more controversial.^{26,27,28,29,30} In the absence of gross residual disease, we usually reserve EBRT for use in older patients (>50 y) with tumors that are likely to be RAI refractory (e.g., Hürthle cell carcinoma, poorly differentiated thyroid cancer, tall cell variants) who we feel are at high risk of early locoregional disease recurrence that may not be amenable to additional surgery in the future. In younger patients, especially those with tumors that are likely to be RAI responsive (classic papillary thyroid cancer, follicular thyroid cancer), we seldom use EBRT as adjuvant therapy but rather follow with close cross-sectional imaging, reserving EBRT for the very few younger patients that develop rapid structural disease recurrence that cannot be adequately treated with additional surgery or RAI.

EBRT is also considered in the recurrent disease setting if the gross recurrent disease cannot be surgically resected or if the extent of resection required would result in removal of structures that is unacceptable to the patient (e.g., laryngectomy). However, surgical resection remains the primary treatment modality for recurrent thyroid cancer in the neck and is associated with the best locoregional control in most settings.

11.3 Systemic Therapies in Advanced Thyroid Cancer

Although localized therapies are frequently effective at managing individual metastatic lesions, systemic therapies are often required in patients with more widespread disease. Over time, these systemic therapy options have become more diverse and more effective.

11.3.1 TSH Suppressive Therapy with Levothyroxine

Differentiated thyroid cancer cells express the TSH receptor and respond to TSH stimulation by increasing the expression of several thyroid-specific proteins and the rates of cell growth. TSH suppression by using supraphysiological doses of levothyroxine is usually used in patients with thyroid cancer to decrease the risk of recurrence.¹¹

Both the 2009 and the 2015 American Thyroid Association (ATA) management guidelines recommended initial TSH suppression to <0.1 mIU/L in high- and intermediate-risk thyroid cancer patients and a TSH between 0.1 and 0.5 mIU/L in low-risk patients. In long-term follow-up, the TSH goals are based on an integration of the patient's response to therapy classification with the patient's comorbid conditions that could be associated with an increased risk of prolonged aggressive TSH suppression. In the absence of comorbid conditions, a TSH goal of 0.5 to 2 mIU/L is recommended in patients without evidence of disease (excellent response). However, in patients with structurally or biochemically incomplete responses to therapy, a TSH goal of <0.1 mIU/L is recommended unless comorbidities that increase the risk of complications from TSH suppression (e.g., postmenopausal women, underlying heart disease, osteopenia/osteoporosis, atrial fibrillation) are present, in which cases TSH levels as high as 0.1 to 0.5 mIU/L are considered appropriate.^{11,31}

11.3.2 Radioactive Iodine Therapy

RAI treatment is one of the main treatments in patients with metastatic differentiated thyroid cancer. Avidity to RAI is directly related to the degree of differentiation of thyroid cancer, and this is directly related to the age of the patients. Loss of RAI avidity occurs when thyroid cancer undergoes dedifferentiation and is associated with poor outcome.

Many studies have shown both a higher rate of RAI avidity in younger patients (<45 y) and a better prognosis in younger patients with small-volume RAI avid distant metastases.^{2,9,32,33} Furthermore, tumors harboring *RAS* driver mutations are more likely to be RAI avid than tumors with *BRAF* mutations.^{34,35,36} Conversely, extrapulmonary metastases (e.g., brain and bone metastases) are associated with a poor prognosis and are less responsive to RAI treatment.^{2,5,6,7,9,32,33} Unfortunately, many of the aggressive thyroid cancers have poorly differentiated or tall cell variant histology that usually do not concentrate RAI well. Tumors with remaining functional differentiation for thyroglobulin synthesis and iodine uptake have low glucose metabolism and are 18-fluorodeoxyglucose positron emission tomography (FDG-PET) negative. Tumors that dedifferentiate and lose the ability to uptake iodine-131 (¹³¹I) and synthesize thyroid hormone show high glucose metabolism and are FDG-PET positive.³⁷ High rates of FDG uptake and a high volume of FDG-avid disease are poor prognostic factors. These patients are less likely to respond to RAI and have a higher mortality.^{38,39}

Although RAI is usually ineffective in aggressive thyroid cancer, there are well-described cases of aggressive tumors responding to RAI. Therefore, it is critical that the determination of whether or not RAI is likely to be beneficial be carefully made. Over the years, several definitions for RAI refractory

disease have been developed for use in this critical management decision. We consider patients to be definitively RAI refractory (more than 95% probability that RAI will produce no clinically meaningful effect) in the following cases:

- Direct lesional dosimetry measurements of the metastatic foci indicate that therapeutic doses of RAI cannot be achieved using either collimated uptake in the selected regions of interest or iodine-124 PET scanning.⁴⁰
- A negative posttherapy RAI scan is obtained after an appropriately performed administration of > 30 mCi ¹³¹I following either thyroid hormone withdrawal or recombinant human TSH preparation.
- Cumulative RAI administered activities of > 600 mCi are required.³²
- Structural disease progression occurs within 1 year of a properly administered therapeutic dose of RAI.

Furthermore, we consider patients to be very likely to be RAI refractory (> 75–80% probability that RAI will produce no clinically meaningful effect) in the following cases:

- The diagnostic RAI scan is negative in the setting of structurally identifiable disease.⁴¹
- Markedly positive FDG-PET lesions are present.³⁹
- Serum thyroglobulin levels rise within 6 months of previous RAI therapy.

When evaluating the effectiveness of previous RAI therapies, it is important to ensure that the prior treatments were done correctly. If there is significant concern that the prior evaluations could have been associated with accidental iodine contamination or inadequate TSH stimulation, then repeat RAI scanning (or possibly even additional empirical RAI therapy) should be strongly considered.

One of the most exciting areas of research in thyroid cancer is the discovery that inhibition of the *BRAF/RAS/ERK* mitogen-activated protein (MAP) kinase pathway can lead to redifferentiation of thyroid cancer cells and restore RAI avidity in both preclinical and animal studies.^{40,42} Short-term (~ 4 wk) administration of *BRAF* or MEK inhibitors appear to significantly upregulate both the sodium iodine symporter and the TSH receptor, which dramatically enhances the ability of thyroid cancer cells to concentrate RAI. Multiple clinical trials are under way exploring the impact of this type of redifferentiation therapy in the application of RAI therapies.

11.3.3 Antiresorptive Therapies for Bone Metastases

In addition to the localized therapy options already described, antiresorptive therapies have been demonstrated to be clinically effective in patients with bone involvement in a variety of solid and liquid tumors.⁴³ The data with regard to efficacy of these agents in thyroid cancer are still incomplete; however, two small studies do suggest a benefit in thyroid cancer.^{44,45} Nonetheless, antiresorptive therapies with either a bisphosphonate (usually intravenous zoledronic acid) or a receptor activator of nuclear factor κ B (RANK) ligand inhibitor (usually denosumab) are recommended for thyroid cancer patients with clinically significant, multiple bone metastases and in patients that have experienced a skeletal-related event. *Skeletal-related*

event (SRE) is a term used to quantify the morbidity associated with skeletal metastases and includes (1) spinal cord compression, (2) pathological fracture, (3) external beam radiation or surgery to control pain or to prevent fracture, and (4) hypercalcemia of malignancy. Small bone metastases that are not associated with cortical bone involvement, especially if RAI avid, do not require antiresorptive therapy.⁴⁶ The optimal dosing and duration of treatment with antiresorptive therapies are not known.

11.3.4 Novel Systemic Therapies

In the past, traditional chemotherapies were seldom used in advanced thyroid cancer because of the low response rate and relatively high incidence of side effects.¹¹ The last decade has seen a dramatic expansion in the availability of novel systemic therapy options for RAI refractory thyroid cancer.⁴⁷ The initial promising result from thyroid cancer patients enrolled in phase 1 trials of multitargeted oral kinase inhibitors was verified in multiple phase 2 trials. More recently, both sorafenib and lenvatinib have been demonstrated to improve progression-free survival in prospective, randomized clinical trials.⁴⁸

Currently sorafenib is the only Food and Drug Administration (FDA)-approved multi-kinase inhibitor for thyroid cancer. However, the National Comprehensive Cancer Network guidelines note that axitinib, pazopanib, sunitinib, or vandetanib can be considered if clinical trials are not available or appropriate.⁴⁹ Furthermore, based on the results of the phase 3 trial, it is anticipated that lenvatinib will be FDA approved for RAI refractory thyroid cancer in 2015. In general, these kinase inhibitors often provide progression-free survival (usually stable structural disease, sometimes with shrinkage of metastatic lesions) but have not yet been shown to improve either disease-specific survival or overall survival. Nonetheless, remarkable treatment responses with these agents have been seen, with numerous patients experiencing prolonged progression-free survival (at least 12–18 mo) with a side-effect profile that is tolerable in properly selected patients.

Because many patients with RAI refractory thyroid cancer can survive many years with only minimal disease progression that is asymptomatic, it is important to identify which patients may or may not benefit from an improvement in progression-free survival. These are complex management decisions that need to incorporate a variety of factors related to the tumor, the patient's associated comorbidities, the patient's tolerance of side effects and impact on quality of life, and the patient preferences. Critical factors that should be considered include the following:

- Size of the metastatic lesions: It is unusual to initiate a novel systemic therapy for lesions < 1 cm; however, not all metastatic lesions > 1 cm require systemic therapy.
- Location of the metastatic lesions: Systemic therapy may be initiated sooner if metastatic lesions are in locations where continued growth would result in compromise of critical surrounding structures.
- Symptoms: These could include symptoms attributed to a significant disease burden and may include weight loss, muscle wasting, fatigue, or other constitutional symptoms.
- Rate of structural disease progression: Tumors that are very slowly growing are better candidates for observation rather

than intervention. However, when the rate of progression is rapid enough that the disease is likely to cause morbidity or mortality, systemic therapy should be considered.

- Additional metastatic foci identified: Even if the foci are small, the identification of additional metastatic foci will lead to consideration of systemic therapy.
- Patient preference: Because none of the currently available drugs have been definitively demonstrated to improve disease-specific survival, patient preference is always an important consideration. Factors such as how aggressive the patient wants the treatment to be, the patient's willingness to accept and tolerate the side effects of these therapies, and the patient's understanding of both the risks and the benefits (and costs) of these treatments and the potential impact on quality of life are critical issues to be carefully discussed.

In addition to the novel systemic therapy options that are currently available, a wide range of clinical trials are available for patients with RAI refractory thyroid cancer. A list of available clinical trials can be found on the Web sites of the International Thyroid Oncology Group (<http://www.itog.org/>) and the National Institute of Health (<https://clinicaltrials.gov/>).

11.4 Conclusion

The medical management of aggressive differentiated thyroid cancer requires complex decision making with input from a wide variety of clinical specialists. Fortunately, very effective localized therapies are available to provide disease control both in the neck and at distant sites. Even more importantly, the development of a novel approach to redifferentiation therapy holds promise that RAI may become an even more important tool in the management of aggressive thyroid cancer. Finally, the FDA approval of novel agents for RAI refractory thyroid cancer has provided the first meaningful systemic therapy options beyond RAI for patients with structurally progressive disease that is not amenable to localized therapies.

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12 Medical Management of Medullary and Anaplastic Thyroid Cancer

Victor J. Bernet and Robert C. Smallridge

12.1 Introduction

Although the vast majority of patients with thyroid cancer, particularly differentiated thyroid cancer (DTC), do extremely well, patients with medullary thyroid cancer (MTC) and anaplastic thyroid cancer (ATC) have a significant risk for morbidity and mortality related to their disease. ATC originates from follicular cells and many times arises from preexisting DTC, particularly foci of papillary thyroid cancer, whereas MTC originates from C cells, which are of neural crest origin and typically reside in the posterolateral aspect of the thyroid gland.^{1,2} C cells have a distinct function separate from thyroid follicles, producing calcitonin (Ct) and carcinoembryonic antigen (CEA) instead of thyroid hormone and thyroglobulin. MTC was first described in 1906 as “malignant goiter with amyloid.”³ ATC is an aggressive form of undifferentiated thyroid cancer that tends to grow rapidly, invade local tissues, and metastasize early, and it lacks the ability to concentrate iodine. ATC cells do not secrete thyroglobulin and most commonly present as a giant cell tumor with biphasic spindle cells, although several morphological variations can be encountered.

The treatment of patients with MTC and ATC varies significantly from regimens used to treat DTC. So much so, that the American Thyroid Association provides independent guidelines for the management of both MTC and ATC. Although surgery plays a significant role in MTC and is sometimes indicated in ATC, unlike DTC, radioiodine therapy and TSH suppression have no role. Instead, therapies such as external beam radiotherapy and systemic chemotherapy are standard in cases of ATC and frequently used in cases of MTC, depending on the disease course. Recent advances, particularly in the area of systemic therapy, provide hope for continued improvement in outcomes for patients with both MTC and ATC, though the latter is still associated with a sobering mortality risk.

12.2 Epidemiology

MTC accounts for approximately 4% of all thyroid cancers in the United States.⁴ MTC primarily occurs as sporadic disease (75%), with the remainder representing one of the autosomal dominant inherited forms.^{4,5} Inherited forms of MTC include multiple endocrine neoplasia (MEN) types 2A (80%) and 2B (5%) as well as familial MTC (FMTC) (15%). MEN2A is associated with MTC (~ 100%), pheochromocytoma (50%), and hyperparathyroidism (30%), whereas MEN2B consists of MTC (~ 100%), pheochromocytoma (50%), and cutaneous neuromas, with <5% exhibiting hyperparathyroidism. Requirements for FMTC, an apparent variant of MEN2A, include the presence of MTC without evidence for pheochromocytoma and primary hyperparathyroidism. Reports do exist of families initially categorized as having FMTC later being found to have MEN2A upon clinical expression of pheochromocytoma or hyperparathyroidism.^{6,7} Recommendations vary in regard to the number of individuals

and generations that must be affected with MTC alone in order to meet the criteria for FMTC.^{8,9}

The prevalence of ATC varies geographically, ranging between 1.3 to 9.8% of all thyroid cancers, and accounts for 1.7% of thyroid cancers in the United States.¹⁰ It tends to occur later in life, at a median age of 69 years, and more so in women (65.8%).¹¹ Data from the Surveillance, Epidemiology and End Results (SEER) database indicates ATC may occur somewhat more frequently in non-Hispanic Caucasians, but this finding requires additional confirmation.¹² Patients with ATC may present with such findings as an enlarging neck mass, voice changes (e.g., hoarseness or dysphonia), dysphagia, dyspnea, hemoptysis, neck pain, superior vena cava syndrome, and distant metastasis.¹² ATC frequently (>80%) arises from an abnormal thyroid, such as a goiter, and can arise within the context of a preexisting DTC, although the reported frequency of this occurrence varies widely (7–89%).^{1,2,4,13,14,15,16}

12.3 Diagnosis

12.3.1 Cytology

MTC cytology consists of polygonal-shaped cells, eccentric nuclei, granular chromatin, amyloid, and azurophilic cytoplasmic granules.¹⁷ Studies report a sensitivity range between 63 and 89% for identifying MTC by FNA cytology, and there are reports of cytological misdiagnosis.¹⁸ In many of these instances, cellular atypia was noted or another form of malignancy suspected, with the diagnosis of MTC being appreciated only on surgical histology.¹⁹

The presence of ATC can many times be surmised by the classic clinical presentation of a rapidly enlarging neck mass that is fixed and hard in texture. Prompt tissue confirmation is essential. Although fine-needle aspiration (FNA) is typically helpful in the evaluation of thyroid nodules/masses, in the case of ATC, extensive fibrosis and cellular necrosis limit the ability to obtain an adequate sample for confirmatory diagnosis.^{20,21} Use of a core biopsy should be pursued when FNA yields inadequate cellularity, and progression to open biopsy should be considered if the core biopsy is nondiagnostic.

12.3.2 Histology

Confirmation of ATC by histology can be challenging because the differential diagnosis includes poorly differentiated thyroid cancer, lymphoma, metastases to the thyroid, sarcoma, squamous cell carcinoma of the thyroid or head/neck, and Riedel's thyroiditis.²² Additionally, variations in presenting ATC histology include spindle cell, giant cell, squamoid, and paucicellular forms.^{13,23} Detailed pathological examination may reveal the presence of areas of DTC or poorly differentiated thyroid cancer in concert with ATC in 20 to 90% of cases.^{2,4,24} Whereas immunostaining for thyroglobulin and Ct tend to be positive in differentiated and medullary thyroid cancer, respectively, such

staining is negative in ATC. Testing for P53 and pancytokeratin is usually positive in ATC tissue. Furthermore, positive immunostaining for E-cadherin is common, whereas positivity for PAX8 and TTF-1 is considered uncommon.²⁵

12.3.3 Biochemical

Although no blood test exists to diagnose ATC, measurement of serum calcitonin can be used to identify cases of MTC, with basal serum Ct levels > 20 to 100 pg/mL being suspicious for MTC.²⁶ Serum Ct screening yielded an MTC prevalence of 0.40% in a European-based study of 10,864 patients with thyroid nodules. Ct elevation was associated with a better sensitivity and specificity for MTC than cytology as well as earlier diagnosis with improved remission rates (59% vs. 2.7%; $p = 0.0001$).²⁷ In the United States, Ct measurement has traditionally been targeted toward at-risk individuals with thyroid nodules, such as those with a family history of MTC or type of thyroid cancer unconfirmed, suspicious cervical lymphadenopathy, a history of parathyroid-related hypercalcemia, or suspicion for pheochromocytoma. However, a U.S.-based study found that Ct screening of thyroid nodules could be cost effective at \$11,793 per life-years saved while yielding 113,000 life-years at a cost increase of only 5.3%.²⁸

Prior to the clinical availability of *RET* (rearranged during transfection) mutation testing, stimulated Ct levels were used to identify C cell hyperplasia and/or MTC in at-risk individuals. Infusion of calcium and/or pentagastrin stimulates Ct release, with stimulated Ct levels > 100 to 500 pg/mL being suspicious for the presence of C-cell hyperplasia and/or MTC.²⁹ The sensitivity and specificity of this testing is impacted by the specific Ct cutoff levels applied.³⁰ However, pentagastrin is no longer available in the United States, and *RET* oncogene mutation testing is now preferred for identification of at-risk individuals. Preoperative calcitonin levels do provide helpful information to guide the extent of preoperative staging as the probability of extracervical disease rises with calcitonin levels > 400 pg/mL.⁸

12.3.4 Mutational Testing

RET oncogene mutation testing allows for identification of individuals with inherited forms of MTC. Initial *RET* oncogene testing typically involves screening of the more commonly affected exons: 8, 9, 10, 11, 13, 14, and 16. It must be realized that lack of a *RET* oncogene mutation does not exclude inherited forms of MTC because previously unidentified mutations continue to be discovered.¹⁶ Therefore, full *RET* oncogene sequencing is recommended when an inherited form of MTC is suspected but initial screening is negative. Identification of *RET* mutations also holds prognostic value because patients with certain mutations (634, 804, 883, 918) display a more aggressive disease course, whereas those with other mutations (609, 620, 630, 635) display a much more indolent course.⁴ In addition to *RET* mutations, *HRAS* and *KRAS* gene mutations have been shown to be present in cases of sporadic MTC and impact tumor behavior, including possibly the response to targeted therapy, such as multikinase inhibitors.^{31,32}

Cutaneous lichen amyloidosis (CLA) is seen with MEN2 and tends to involve the T2 to T6 scapular area dermatomes. Pruritus related to CLA can precede development of MTC and, if

recognized, allow for early diagnosis. Hirschsprung's disease (HD) can also occur and is secondary to a *RET* gene loss-of-function altered migration of neural crest to enteric submucosa.³³ HD occurs in only about 7% of patients with MEN2A and FMTC, and only 2 to 5% of patients with HD are found to have MTC.^{34,35}

MEN2B occurs as a de novo mutation in > 50% of cases, with the M918T *RET* mutation (exon 16) being found in > 95% and another 2 to 3% exhibiting the A883F (exon 15) mutation.³⁶ MEN2B-associated MTC tends to exhibit more aggressive behavior and present about a decade earlier than that associated with MEN2A. MEN2B is associated with several phenotypic findings, including Marfanoid habitus; pectus excavatum; pes cavus; neuromas of the lips, tongue, and cornea; and gastrointestinal disorders, such as constipation (sometimes complicated by megacolon), vomiting with dehydration, intestinal ganglioneuromatosis, and obstruction.³⁷ Additional findings in young children include an inability to generate tears when crying, severe constipation, and feeding-related issues.³⁸

RET oncogene testing allows for potential early recognition of at-risk family members prior to the development of MTC, even prior to evidence of Ct elevation. With the natural course of MTC associated with various *RET* mutations being better understood, the timing for prophylactic thyroidectomy can be individualized based on the mutation present. The American Thyroid Association (ATA) MTC guidelines divide *RET* oncogene mutations into groups that represent severity of disease and expected time of onset.¹⁶ With MEN2B mutations exhibiting a trend for an aggressive disease pattern with early onset, surgical intervention should be considered within the first year of life.³⁹ Those with MEN2A-related mutations with higher-risk MTC are recommended to undergo thyroidectomy with evidence of Ct elevation or prior to 5 years of age, whereas those with less concerning mutations can potentially be followed with serial neck ultrasound (US) imaging and Ct levels.⁴⁰ Thyroidectomy should be considered for development of Ct elevations or in childhood when lengthy serial follow-up is not preferred by the patient and/or parents.¹⁶

Pheochromocytoma screening should begin by age 16 years. Because primary hyperparathyroidism (HPT) frequently occurs in association with MEN2A kindreds, screening for this entity should occur prior to thyroid surgery. Laboratory testing consistent with primary HPT should precipitate additional evaluation for confirmation of the diagnosis. Localization testing should be interpreted with caution because multigland disease is common, but not all involved parathyroid glands may be noted on sestamibi parathyroid scanning or neck US.

Microscopic evaluation reveals most ATC samples to be aneuploid in nature and contain significant abnormalities in chromosomal numbers and structure.^{41,42} The evident mutational progression and evolution of chromosomal changes progressing from PTC to poorly differentiated thyroid cancer and then to ATC supports the concept of multistep mutation-driven dedifferentiation.^{43,44,45} Mutations commonly found in both well-differentiated DTC and ATC include *BRAF*, *RAS*, phosphoinositide-3-kinase (PIK3- α), as well as *RET/PTC3* rearrangement.^{46,47} In a report of 652 ATC cases, the following prevalence of genetic mutations was noted: *RAS* 60%, *TP53* 48%, *PI3KCA* 24%, *BRAF* 23%, *PTEN* 16%, and *RET/PTC* 4%.⁴⁸ Other mutations noted in ATC include axin, *TP53* and β -catenin, anaplastic lymphoma kinase (ALK), and adenomatous polyposis coli (APC).^{26,49,50} A

Table 12.1 Notable cellular pathway changes evident in anaplastic thyroid cancer

Function	↑ Expression	↓ Expression
Transcription	<i>PPAR-γ</i> , <i>C-myc</i> , <i>fra1</i> , <i>HNF-1α</i> , <i>Id1</i> , <i>HMG1(y)</i> , <i>YPX1</i>	<i>FOXE1</i> , <i>Pax8</i> , <i>NKX2-1</i> , <i>CBX5</i>
Signaling	<i>EGFR</i> , <i>pERK</i> , <i>pAKT1</i> , <i>CXCR4</i> , <i>JAK/STAT</i> ,	<i>SOCS 1,3,5</i>
Mitosis	Aurora kinases, <i>k-α1 tubulin</i> , <i>topoisomerase-11</i>	<i>TACC3</i>
Proliferation	<i>SPAG9</i> , <i>OEATC-1</i> , <i>RBBP4</i> , <i>MKI67</i> , <i>epCAM</i> , <i>CD44v6</i> , <i>Claudin-7</i> , <i>ALDH1</i> , <i>FoxO3a</i> , <i>MIR-25</i> , <i>MIR-30d</i>	
Cell cycle	<i>Cyclin D1</i> , <i>Cyclin D3</i> , <i>Cyclin E</i>	<i>p21</i> , <i>p27</i>
Apoptosis	<i>NF-κB</i> <i>IAPS</i> , <i>DJ-1</i> , <i>LCN2</i>	<i>Bcl2</i> , <i>αβ-crytallin</i>
Adhesion	<i>β-catenin</i> , <i>FAK</i> , <i>ILK1</i>	<i>E-cadherin</i>
Tumor suppression	<i>p53</i> , <i>MIR-20a</i>	<i>p16</i> , <i>Rb</i> , <i>PTEN</i>

Abbreviations: Abbreviations: *PPAR-γ*, Peroxisome proliferator-activated receptor gamma; *C-myc*, Myc proto-oncogene protein; *fra1*, FOS-like antigen 1; *HNF-1α*, Hepatic Nuclear Factor 1 Alpha; *Id1*, DNA-binding protein inhibitor; *HMG1(y)*, high mobility group 1(y); *EGFR*, epidermal growth factor receptor; *pERK*, phosphorylation of ERK; *pAKT1*, protein kinase B; *CXCR4*, receptor for the stromal cell-derived factor-1 (SDF-1)/CXCL12; *JAK/STAT*, Janus kinase/signal transducers and activators of transcription; Aurora kinases, family of serine-threonine kinases; *Ka1 tubulin*, α-tubulin isotype (Ka1); *SPAG9*, sperm associated antigen 9; *OEATC-1*, overexpressed in anaplastic thyroid carcinoma-1; *RBBP4*, Histone-binding protein RBP; *MKI67*, marker of proliferation Ki-67; *epCAM*, Epithelial cell adhesion molecule; *ALDH1*, Aldehyde dehydrogenase 1; *Fox-O3a*, Forkhead box protein O3; *MIR-25*, microRNA-25; *MIR-30d*, microRNA-30d; *NF-κB*: nuclear factor κB; *IAPS*, inhibitors of apoptosis proteins; *LCN2*, Lipocalin-2; *FAK*, focal adhesion kinase; *ILK1*, integrity-linked kinase; *p53*, cyclin-dependent kinase inhibitor; *MIR-20a*, MicroRNA-20a; *FOXE1*, forehead box E1; *Pax8*, paired box 8; *NKX2-1*, NK2 homeobox 1; *CBX5*, chromosome protein homolog 5; *SOCS*, Suppressor of cytokines signaling 1, 2, 3; *TACC3*, transforming acid coiled-coil 3; *p21*, cyclin-dependent kinase inhibitor; *p27*, cyclin-dependent kinase inhibitor; *Bcl2*, B cell lymphoma 2; *E-Cadherin*, Cadherins cell-cell (calcium-dependent) adhesion molecule; *Rb*, Retinoblastoma; *PTEN*, Phosphatase and tensin homolog (PTEN)

significant amount of gene mutations and microRNA alterations leads to protein expression changes impacting critical cellular roles. These changes are summarized in ► Table 12.1.

12.3.5 Staging

Staging for MTC is based on the American Joint Committee on Cancer (AJCC).⁵¹ Stage I consists of tumors <2 cm and stage II includes tumors between 2 and 4 cm, both without evidence of extraglandular disease. Stage III encompasses any tumors >4 cm, level VI nodal metastases or microscopic extrathyroidal invasion irrespective of tumor size. The presence of any distant metastases, lymph node involvement beyond level VI, or gross soft tissue extension qualifies as stage IV. The reported associated mortality by stage is stage I, 0%; stage II, 13%; stage III, 56%; and stage IV, 100%.⁵²

Correct initial staging of patients with ATC provides information that plays an important role for both assessment of prognosis and therapeutic decision planning. All cases of ATC are considered stage IV and are subdivided as follows: IVA, primary tumor limited to thyroid; IVB, extrathyroidal extension; and IVC, distant metastases. The preponderance of data indicates that patients with ATC tend to present with more advanced disease burden: stage IVC (~45%), IVB (~40%), and IVA (~10%).^{2,53,54,55,56} The reported median survival in months by stage are IVA, 7.3; IVB, 3.9; and IVC, 1.7, with respective 1-year survival rates of 72.7%, 24.8%, and 8.2%.^{2,10}

12.4 Preoperative Assessment

The surgical management of MTC and ATC is thoroughly reviewed in Chapters 17 and 18, respectively, and the reader is

referred to these sections for detailed discussion of this area. This section is limited to surgical issues pertinent to the discussion of medical management.

Optimal surgical management is essential in patients with MTC. MTC tumors are known to often invade perithyroidal soft tissue structures and also frequently spread to central and lateral cervical lymph nodes. Therefore, preoperative anatomical imaging is essential and includes detailed cervical lymph node mapping with neck US or computed tomographic (CT) scanning, the latter allowing detailed central node assessment despite an intact thyroid.⁵⁷ Aerodigestive tract involvement can occur, and the presence of hoarseness, dysphagia, or other upper respiratory complaints should precipitate upper respiratory tract and vocal cord visualization. Additionally, contrast CT of the chest is useful for identification of metastases to the mediastinum and lungs, whereas CT of the abdomen and pelvis should be pursued when calcitonin levels are >400 pg/mL.¹⁶ Contrast-enhanced three-phase liver CT and magnetic resonance imaging (MRI) are more sensitive than conventional CT for detection of liver metastases. Preoperative laparoscopic liver screening for micrometastases was advocated but now is rarely performed, because extensive cervical microdissections are no longer recommended given that sustained clinical benefit was infrequent.⁵⁸

Preoperative identification of MEN is important because pheochromocytoma occurs in 50% of MEN2A and MEN2B cases. Identification and treatment of pheochromocytoma is essential to avoid perioperative morbidity and mortality related to this entity.⁵⁹ MEN-related pheochromocytomas are typically benign, multicentric, intraglandular, and bilateral.⁶⁰ Preoperative screening for pheochromocytoma may include plasma metanephrines, 24-hour urine catecholamines, and metanephrines with creatinine or CT of the adrenal glands.

Patients with ATC frequently present with signs or symptoms indicating upper airway involvement (hoarseness, stridor, dysphagia, hemoptysis, etc.). Mirror or fiberoptic visualization allows assessment of the larynx and vocal cords for evidence of invasion or vocal cord dysfunction. Follow-up bronchoscopy for further tracheal inspection is recommended in cases with evidence of any upper airway involvement, which necessitates prompt intervention to secure it.

Initial laboratory testing upon diagnosis of ATC includes a complete blood count and metabolic profile. Hypocalcemia secondary to tumor-related hypoparathyroidism may be encountered and, rarely, humoral-induced hypercalcemia may occur.^{61,62,63} Thyroid function status should be assessed with TSH and free T4 levels because hypothyroidism or thyrotoxicosis may be present.⁶⁴

Imaging to assess the primary tumor and metastatic burden is integral in treatment planning, including determining the potential for tumor resection. The preferred imaging modality is 18-fluorodeoxyglucose positron emission tomography (18-FDG-PET) CT scanning is the preferred imaging modality for ATC cases, allowing for both anatomical assessment of the neck and chest and screening for extracervical 18-FDG avid metastases. If PET-CT is unavailable then cross-sectional imaging of the neck, chest, and abdomen should be obtained.^{44,65} Metastases from ATC may occur in the lungs, mediastinum, liver, kidneys, heart, adrenal glands, brain, and bones.²² Additional targeted imaging with neck US and MRI or bone scan may be clinically useful.²² Radioactive iodine scanning does not have a role because ATC tumors do not concentrate iodine.

12.5 Treatment

In the context of inherited forms of MTC, prophylactic thyroidectomy should occur prior to the expected onset of cancer based on the *RET* oncogene mutation present. Total thyroidectomy with central lymph node dissection is recommended in patients >8 years old with MEN2A or FMTC, and at any age for patients with MEN2B. However, total thyroidectomy alone is considered appropriate in children <5 years old with MEN2A or FMTC without cervical lymphadenopathy.¹⁶ Patients with local cervical metastases (≥ 10 lymph nodes) tend not to achieve biochemical cure, with only approximately 10% cured despite extensive surgical interventions.⁶⁶ However, patients with persistent postoperative Ct elevations exhibit reasonable survival rates of 80.2% at 5 years and 70.3% at 10 years.⁶⁷

When MTC is diagnosed following hemithyroidectomy, completion thyroidectomy and cervical lymph node dissection should be considered. Potential indications for additional surgery include the presence of multifocal MTC, cervical lymphadenopathy, and postsurgical Ct levels. Multifocal MTC is more common in familial forms (~75% in MEN2A) in comparison to sporadic MTC (0–22%).⁶⁸ Although Ct elevations indicate persistent MTC, there is no definitive cutoff for pursuing additional surgery.¹³ If serial follow-up is elected, Ct levels should be closely monitored, with any rise prompting reevaluation.

When feasible, complete excision of the thyroid/anaplastic tumor should occur because survival is significantly impacted by extent of resection. The extent of invasion, the specific cervical structures involved, and the presence of distant metastases

are the main factors that impact tumor resectability. If surgery is deemed appropriate, then surgical goals include total thyroidectomy with central and lateral lymph node resection. The degree of tumor resection is divided into four levels: R0, no residual tumor; R1, microscopic residual tumor; R2, macroscopic residual tumor; and RX, presence of residual tumor cannot be assessed.⁵¹

Available data indicate improvement in survival with complete resection, whether or not additional chemotherapy and/or radiotherapy are being considered. Additionally, incomplete tumor resection is preferred over lesser resection or no surgery at all.^{10,44,69,70,71,72,73} In an effort to achieve disease-free margins, en bloc resection of tumor may be appropriate, but tumor debulking has not been associated with an improvement in outcomes.²² Of interest, neoadjuvant therapy with combination chemotherapy and radiotherapy can result in originally unresectable tumors meeting criteria for potential resection.⁷⁴

Management of airway issues is particularly challenging in patients with ATC. Although avoidance of tracheostomy placement is preferred, if necessary, it is best to perform the procedure in an operating room under controlled circumstances and avoid emergent placement.⁷⁵ To successfully place the tracheostomy, an isthmusectomy or debulking of tumor anterior to the trachea may be required when thyroidectomy is not feasible.

12.5.1 Radiation Therapy

Because C cells do not concentrate iodine, postoperative radioactive iodine (RAI) ablation is not used except possibly in rare occasions when coincident DTC is diagnosed. The role of external beam radiation therapy (EBRT) in the treatment of MTC remains controversial because prospective data for a survival benefit are lacking. EBRT may improve local disease control, but Ct levels rarely become undetectable. EBRT has not uniformly been shown to affect locoregional recurrence rates, although cases with persistent microscopic disease, extrathyroidal extension, or positive lymphadenopathy displayed a better 10-year local relapse-free rate with EBRT than without (86 vs. 52%; $p=0.049$). Similar results were noted in another, much smaller study.⁷⁶ No consensus exists in regard to the use of EBRT for persistent Ct elevation following successful resection of macroscopic disease. A study of 207 patients with persistent Ct elevation without distant metastases revealed a reduced recurrence rate.⁷⁷ However, measurable postoperative Ct levels may represent either persistent local microscopic disease or unidentified distant metastases, with EBRT therapy holding no significant benefit in the latter scenario.

Because surgical resection of recurrent MTC is an effective alternative for local control and because radiation changes make future surgery much more challenging, EBRT is best reserved for cases where only incomplete resection is feasible and gross residual disease remains. The ATA MTC guidelines suggest the potential use of postoperative adjuvant EBRT of the neck or mediastinum following surgery in cases of high-volume disease, particularly with microscopically positive margins.¹⁷ Evidence of extranodal extension and persistently measurable Ct postoperatively are other possible indications for EBRT. Of note, the latter two indications are only supported by a grade C rating and reflect expert opinion rather than conclusive data.

EBRT plays an integral role in the management of patients with ATC. Radiotherapy can slow the growth of locoregional disease, and in combination with prior successful surgical resection (R0 and R1) and chemotherapy is associated with the best local control and survival rates.^{1,54,78,79} A multivariate analysis of 516 ATC cases noted that only patient age and combined surgery with radiotherapy were reliable survival predictors.¹³

Because ATC tumors display very rapid growth, hyperfractionated or accelerated treatment protocols are preferred over conventional techniques, although these protocols are associated with a rise in adverse effects.⁸⁰ Intensity-modulated radiation therapy (IMRT), which enables concentration of treatment to tumor tissue while minimizing exposure to adjacent normal tissue, is most commonly used.^{81,82,83} Outcomes appear to improve when at least 40 Gy is delivered, as observed in two studies with extension in survival from 3.2 to 11.1 months and 1.7 to 5.4 months.^{1,56} Another report noted improved median survival at 1 year (54% vs. 17%) with a treatment dose > 45 Gy.⁷⁴ There has been some debate as to whether radiotherapy should be delivered pre- or postoperatively.^{84,85,86} The ATA ATC guidelines advise that, for patients with resectable disease, radiotherapy after surgery is appropriate, and that treatment should begin about 2 to 3 weeks postoperatively to allow for resolution of swelling and adequate healing.²²

Available data indicate that better results occur with a combination of surgery and radiation than radiotherapy alone.^{53,54,85,87,88} However, in cases where tumors are unresectable, radiotherapy, particularly combined with systemic therapy, should be considered in patients who prefer aggressive treatment, have been educated on potential risks and benefits, and are deemed fit to undergo such treatment. Palliative radiation therapeutic regimens can be considered in patients with poor performance status who are unfit for more aggressive intervention but have local symptoms and are interested in receiving at least some therapy. Radiation therapy may also be considered beyond the region of the neck and mediastinum for distant metastases to locations such as the brain or bone.²² Complications from EBRT can be clinically significant and include odynophagia, dysphagia, anorexia with weight loss, radiation burns, fatigue, and poor nutritional state.

12.5.2 Metastases

Approximately 50% of patients with MTC present with metastases, most commonly involving cervical lymph nodes, although lung, liver, or bone metastases can also be present. The risk for metastases correlates with increasing Ct levels, ranging from approximately 50% with Ct levels > 5,000 pg/mL to nearly 100% in patients with Ct levels > 20,000 pg/mL.⁶⁶

Brain metastases can occur with either MTC or ATC and carry a significant risk for associated morbidity. The use of steroids to reduce brain edema and antiseizure medication should be individualized and include input from neurology and neurosurgery consultants. When feasible, surgical removal of brain metastases is preferred but is not always possible. EBRT, to include stereotactic radiosurgery, should be considered for treatment of brain metastases when resection is not possible.⁸⁹

Distant metastases occur in approximately 65% of ATC patients and can impact the lungs, liver, bones, brain, and skin, particularly the scalp.⁹⁰ Solitary pulmonary nodules are

candidates for resection or radiotherapy, whereas multiple lung lesions do not lend themselves to such intervention. Palliative radiation is useful for treatment of painful chest wall or pleural-based metastases. Liver metastases are usually numerous and not amenable to resection, but stereotactic radiosurgery or radiofrequency ablation can be considered selectively.

Osseous metastases, seen with both MTC and ATC, may present as bone pain or be found incidentally on imaging.⁹¹ Metastases impacting weight-bearing bones require orthopedic intervention to prevent fracture or to provide stabilization following a fracture. EBRT is an appropriate treatment consideration, especially for bone metastases that are partially resectable, unresectable, threaten nearby structures, or are associated with pain. Palliative radiotherapy is appropriate in certain circumstances and typically consists of a total of 2,000 to 3,000 cGy delivered over 1 to 2 weeks.²² Additional treatment options include radiofrequency ablation, arterial embolization, or cryosurgery, which may be followed by surgery, EBRT, or cementation in certain instances.⁹² Spine metastases can threaten the spinal cord and are an urgent matter. Glucocorticoid therapy to reduce inflammation may be used until more definitive therapy with surgery or EBRT can occur.⁹³ Intravenous bisphosphonates or denosumab has shown effectiveness in treating thyroid cancer-related bone metastases, though data are limited in relation to their use in ATC and MTC.^{94,95} Metastases to the skin occur in patients with ATC and require pathological confirmation when suspected. Although FNA or core biopsy is a reasonable first step, complete excision is both diagnostic and therapeutic.

12.5.3 Systemic Therapy

For many years, only traditional chemotherapeutic agents, which yielded disappointing clinical results, were available for treatment of MTC and ATC. However, the discovery of protein kinases that regulate cellular communication and processes led to the identification of more than 500 kinases, some of which play an integral role in cellular function, including pathogenesis of thyroid cancer.⁹⁶ More recently, substances impacting kinase activity have shown therapeutic promise in a growing amount of malignancies to include both MTC and ATC (► Table 12.2).⁹⁷

Research has revealed that the vascular endothelial growth factor receptor (VEGFR) and epidermal growth factor receptor (EGFR) pathways play an important role in the pathogenesis of MTC. This led to the development of tyrosine kinase/multikinase inhibitors that modulate dysfunctional kinase pathways. Vandetanib and cabozantinib were approved by the Food and Drug Administration (FDA) in April 2011 and November 2012, respectively, for use in patients with advanced MTC. Their use has been associated with improved progression-free survival (PFS) but not improved overall survival.³²

A large study assessing cabozantinib therapy (140 mg daily) in patients with advanced, primarily sporadic, MTC found a median PFS of 11.2 months in comparison to 4 months for placebo. The improvement in PFS at 1 year was 47.2% in comparison to 7.2% in the placebo group. An objective response rate (RR) of 28% and a partial response (PR) duration of 14.6 months were noted, as well as 45% and 24% decreases in calcitonin and CEA, respectively.⁹⁸ The phase 3 evaluation of vandetanib was performed primarily in cases of sporadic and metastatic MTC. Vandetanib therapy (300 mg daily) achieved a disease control

Table 12.2 Potential systemic agents for treatments of medullary thyroid cancer and/or anaplastic thyroid cancer

Agent	Mechanism of action	MTC	ATC
Axitinib	Inhibitor of VEGFR	X	
Cabozantinib	Inhibitor of <i>c-MET</i> and VEGFR inhibitor	X	
Dacarbazine	Alkylating agent	X	
Everolimus	Inhibitor of mTOR	X	
Fluorouracil	Irreversible inhibition of thymidylate synthase	X	
Motesanib	Inhibitor of VEGFR	X	
Sunitinib	Inhibitor of VEGFR, PDGFR, KIT, RET	X	
Vandetanib	Inhibitor of VEGFR, EGFR and RET-tyrosine	X	
Doxorubicin	Anthracycline antibiotic	X	X
Pazopanib	Inhibitor of VEGFRs:1,2 &3; PDGFR, KIT	X	X
Sorafenib	Inhibitor of Raf-1,PDGFR,RET,KIT and VEGFR2	X	X
Carboplatin	Alkylating agent		X
Efatutazone	PPAR- γ agonist		X
Fosbretabulin	Microtubule disrupting agent		X
Imatinib	Inhibitor of <i>Bcr-Abl</i> , PDGFRs: α & β ; KIT, RET		X
Paclitaxel	Disruption of microtubule function, mitotic inhibitor		X
Vorinostat	Inhibitor of histone deacetylase (HDAC)		X

Abbreviations: ATC, anaplastic thyroid cancer; MTC, medullary thyroid cancer; VEGFR, vascular endothelial growth factor receptor, *c-MET*, hepatocyte growth factor receptor; Inhibitor of mTOR, mammalian target of rapamycin; PDGFR, platelet-derived growth factor receptors; KIT, tyrosine kinase; *RET*, ret proto-oncogene; *Bcr-Abl*, Philadelphia translocation; HDAC, histone deacetylase.

rate of 87%, with a relative RR of 45%, an improved PFS with a median hazard ratio of 0.46 ($p < 0.001$), and a decline in calcitonin and CEA of 69% and 52%, respectively.³² Studies of sorafenib (400 mg twice daily) therapy in patients with advanced MTC found an improvement in median PFS of between 10.5 and 17.9 months.

Everolimus has been studied in nine patients with advanced MTC.⁹⁹ Preliminary results revealed an improved PFS of 47 weeks for all thyroid cancer types. Motesanib achieved stable disease in 81% of patients with a durable response ≥ 24 weeks in 48%. PFS was 48 weeks, and calcitonin and CEA were reduced by 83% and 75%, respectively.¹⁰⁰ Imatinib yielded stable disease (SD) in 27% of advanced MTC cases, but no objective responses were noted.¹⁰¹ Treatment with axitinib achieved an RR of 30%, an SD in 40%, and progressive disease (PD) in 30% with first-line treatment, with the response decreasing with second- and third-line treatments.¹⁰² Pazopanib therapy was associated with a median PFS of 9.4 months and overall survival of 19.9 months.¹⁰³ A small study of sunitinib in MTC also yielded positive responses, whereas therapy with suberanilohydroxamic acid (vorinostat), a histone deacetylase (HDAC) inhibitor, did not yield any objective response in three MTC patients.¹⁰⁴

Systemic therapy is associated with risk for significant adverse effects, which not infrequently precipitate either a reduction in dose or discontinuation of therapy altogether. More common adverse side effects related to systemic therapy include fatigue, weight loss, hypertension, hand-foot syndrome, rash, nausea, vomiting, diarrhea, and stomatitis. Vandetanib has

been also associated with significant QTc interval prolongation; thus special training is required to prescribe this medication.

Some positive therapeutic effect has been reported with treatment using radiolabeled molecules, such as [^{90}Y trium-DOTA]-TOC, and radioimmunotherapy using pretargeted radioimmunotherapy (PRAIT) with a bispecific monoclonal antibody (CEA/anti diethylenetriamine pentaacetic acid [DPTA]-indium BsMAb) and iodine-131 (^{131}I)-labeled bivalent hapten, as well as ^{131}I -metaiodobenzylguanidine (MIBG) therapy to a lesser extent.^{105,106} However, adverse effects were also noted, and these therapies remain more investigational in nature.

Chemotherapy, typically with radiotherapy, has been traditionally used in treatment of ATC but with relatively modest success until the development of new multimodal regimens. Data from Mayo Clinic for patients with ATC treated between 1949 and 1999 revealed no chemotherapy-related improvement in median survival.² The radiosensitizing agents doxorubicin and cisplatin have been associated with variable success in treatment of ATC.^{56,63,107} More recently, studies have shown a benefit from taxane therapy, with one study noting a 53% RR to paclitaxel and another reporting a 33% RR and 1-year survival of 44%.^{108,109} Docetaxel, another taxane, achieved only a 14% RR alone, but administered with IMRT a median survival > 21 months was achieved in five out of six patients.^{110,111} Foote et al reported a notable response in 10 ATC patients receiving combination IMRT and systemic therapy, with stage IVA/IVB patients displaying an overall survival of 70% at the 1-year and 60% at the 2-year time points (► Fig. 12.1).¹¹²

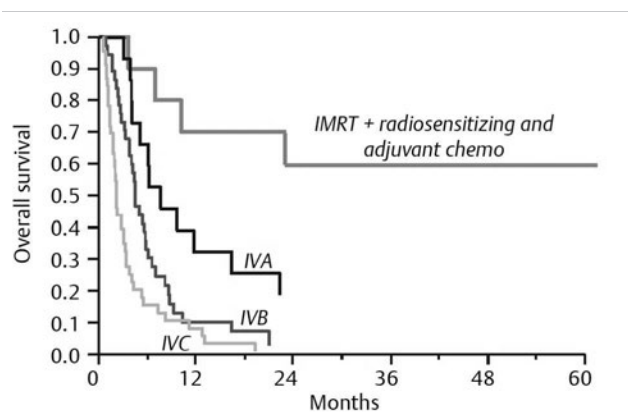


Fig. 12.1 Survival improvement in anaplastic thyroid cancer with multimodal therapy. IMRT, intensity-modulated radiation therapy. (Used with permission from Foote RL, Molina JR, Kasperbauer JL, et al. Enhanced survival in locoregionally confined anaplastic thyroid carcinoma: a single institution experience using aggressive multimodal therapy. *Thyroid* 2011;21:25–30.)

There is a growing body of evidence for other potential agents in the treatment of ATC. Imatinib, a tyrosine kinase inhibitor (TKI), achieved a PR in 25% of cases and SD in 50% with a PFS of 6 months in 36%.¹¹³ Another study found that imatinib appears to enhance the antitumor effect of docetaxel in ATC cell cultures.¹¹⁴ Sorafenib therapy attained a median PFS of 4.4 months, whereas another trial yielded SD in 25% and PR in 10% with a median PFS of 1.9 months.^{115,116} The response to fosbretabulin, a microtubule disrupting agent, has been mixed, achieving a 27% SD rate in one study but no change in median survival in combination with carboplatin/paclitaxel in another.^{117,118} Testing of efatutazone, a PPAR- γ agonist, dosed orally twice daily with paclitaxel every 3 weeks, achieved a median survival of 98 and 138 days with 0.15 mg and 0.3 mg treatment doses, respectively.¹¹⁹

Preclinical studies testing Aurora-A and Aurora-B inhibition have revealed tumor inhibition in both cell culture and xenograft models, whereas a combination of afatinib and sorafenib revealed a synergistic apoptotic effect on the ATC cell line (SW1736).^{120,121,122} Studies in the area of systemic therapy for thyroid cancer have been increasing over the first decade of this century.¹²³ At the time of writing, the National Cancer Institute (NCI) Clinical Trials Web site includes three treatment studies recruiting ATC patients. These protocols include a phase 1/2 trial comparing the following regimens: crolibulin (EPC2407), a microtubulin inhibitor, plus cisplatin; IMRT and paclitaxel with and without pazopanib; and efatutazone with paclitaxel in comparison to paclitaxel alone.¹²⁴ At present, ATA ATC guidelines recommend a chemotherapeutic regimen that includes a taxane and/or anthracycline, such as doxorubicin, and/or a platin, such as cisplatin or carboplatin.²²

Although diarrhea is a potential adverse effect of certain systemic therapies, it is also encountered in MTC patients, related to significant calcitonin elevations. The diarrhea can be relatively problematic and challenging to control in some patients. Although reduction of calcitonin levels by means of reducing tumor burden is desirable, it is not always attainable. Many patients respond to treatment with antimotility agents, and

some success has also been achieved with somatostatin analogue therapy.¹²⁵ Additionally, although diarrhea is a potential adverse effect of some TKI agents, reduction in calcitonin levels secondary to kinase therapy can be associated with decreased diarrhea as well. Data on use of clay-derived binders also show promise.¹²⁶

12.6 Surveillance Testing

The presenting stage of disease, residual tumor burden following surgery, presence of postoperative complications, and individual patient needs all impact the schedule of surveillance testing. In MTC cases, Ct and CEA levels should initially be obtained at 6-month intervals. Testing should occur more frequently with evidence of rising tumor markers, occurring at approximately one-fourth the shortest doubling rate period. Although the finding of an undetectable Ct level along with negative surveillance imaging is consistent with lack of evidence for disease, continued surveillance is required. The interval between surveillance testing can be broadened over time if patients remain free of evidence for disease.

Measurable basal Ct levels leave open the possibility of recurrence, and levels > 150 pg/mL are suggestive of the presence of metastatic disease. CEA levels can also be monitored. The rate in rise of Ct and CEA, also known as the Ct and/or CEA doubling times, has been shown to be useful in predicting both the progression and aggressiveness of MTC. Ten-year survival correlates with MTC tumor marker doubling time: < 6 months 8%, 6 to 24 months 37%, and > 2 years 100%.^{66,127} The ATA provides free access to an online doubling rate calculator.¹²⁸

Ct elevation > 400 pg/mL or the presence of cervical lymph node metastases indicates the need for additional localization imaging. The ATA MTC guidelines suggest use of cross-sectional imaging, such as neck and chest CT plus three-phase contrast-enhanced liver CT or MRI.^{16,129} A bone scan and/or MRI of the spine and pelvis is recommended for identifying bone metastases.¹³⁰

There are conflicting data on the usefulness of FDG-PET for the detection of MTC metastases. A meta-analysis revealed a 59% metastasis detection rate (DR) by FDG-PET or PET/CT in patients with recurrent MTC (95% confidence interval: 54–63%), with lack of localization in approximately 40% of recurrent MTC.¹³¹ Results were more promising for patients with serum Ct $\geq$ 1,000 ng/L, CEA $\geq$ 5 ng/mL, calcitonin-doubling time < 12 months, or CEA doubling-time < 24 months, which exhibited respective DRs of 75%, 69%, 76%, and 91%.⁴⁴ Due to their relatively low sensitivity, imaging with radionuclides, such as iridium 111 (¹¹¹In)-octreotide, technetium-99m (^{99m}Tc)-dimercaptosuccinic acid (^{99m}Tc-DMSA), or ¹³¹I-labeled anti-CEA antibodies are not recommended for initial localization efforts, although these modalities can be considered in the face of elevated Ct or CEA levels and persistently negative conventional imaging.¹³² In cases where local recurrence or metastatic disease is found, tumor or metastases resection is preferred when feasible. Otherwise, additional therapeutic options include EBRT, targeted therapy with radiofrequency ablation, arterial embolization, cryosurgery, or systemic therapy.

Because patients with ATC typically exhibit progression within only a few months' time, initial monitoring should occur in 1- to 3-month intervals. In cases without evidence of

progression at 1 year, this can occur less frequently. 18-FDG-PET scanning is superior to CT alone for detection of metastases and alters treatment decision making in 25 to 50% of cases.⁴⁴ Additional targeted use of US and cross-sectional imaging with CT and MRI can be employed as well. Because osseous ATC metastases tend to be osteolytic, bone scan is of limited utility. ATC tumors do not produce or secrete thyroglobulin, so its measurement does not play a role in follow-up. In cases of progressive ATC, the patient and treatment team need to continually discuss and update treatment goals and the therapeutic plan accordingly. Also, the need for involvement of palliative and/or hospice care services should be regularly reconsidered in such cases as well.

Ethical concerns can arise when caring for patients with ATC and MTC. Inherited forms of MTC are particularly complicated. It is recommended that patients with MTC or MEN who are found to have a *RET* mutation notify relevant family members so that counseling and potential screening can occur in a prompt manner. Should a patient refuse to provide such notification to potentially affected family members, consultation with the supporting medical facility's ethics committee should occur. Such consultation, along with medical-legal input, will help determine the most appropriate course of action to address such challenging situations.

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Part 3

Surgical Management of Thyroid Diseases

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13 Conventional Thyroidectomy

Gerard Doherty

13.1 Introduction

Conventional thyroidectomy is the standard and most commonly employed approach to thyroid surgery. This open operative approach (► Table 13.1) is universally applicable, whereas other approaches may have specific requirements or exclusions based on patient or thyroid gland characteristics. Thyroidectomy is considered a delicate procedure based on significant technical complications that can create permanent changes to patient function. The most common of these are hypoparathyroidism and nerve injury. A clear understanding of the anatomy and safe approaches to the procedure are critical to minimizing the occurrence of these complications.

13.2 Operative Steps

13.2.1 Beach Chair Position and Curvilinear Skin Crease Incision

General anesthesia is preferred, with the patient semisupine in a partially sitting position (beach chair position), hands in the lap, and the neck gently extended by a support placed transversely beneath the shoulders. Local anesthetic techniques, with or without concomitant sedation, can be used in selected patient circumstances. Neck extension should be limited to minimize postoperative discomfort and to keep the overlying strap muscles relaxed. A transverse cervical incision of 4 to 5 cm in length is typical, though this may be longer or shorter depending upon the patient's habitus and the size of the gland to be removed. For larger thyroid glands, the skin incision is rarely the limiting factor in exposure; rather, the strap muscles may impede delivery of the gland from the wound. An incision over the thyroid isthmus, which is consistently positioned one fingerbreadth below the cricoid cartilage, gives good exposure to the upper and lower poles. The incision should generally be gently curved, symmetrical, and placed in a natural skin crease for good cosmesis.

13.2.2 Strap Muscle Separation and Thyroid Exposure

The incision is carried through the subcutaneous fat and platysma muscle. Subplatysmal flaps can improve the mobility of the

underlying muscles and thyroid gland. The anterior jugular veins may be used to define the deep limit of the plane of dissection when the platysma muscle cannot be easily identified. The strap muscles are separated in the midline. The paired sternohyoid and sternothyroid muscles are elevated and dissected away from the thyroid capsule. The strap muscles can be transected transversely if necessary to gain additional exposure.

13.2.3 Upper Pole Mobilization

With the strap muscles and carotid artery retracted with a small Richardson retractor, inferolateral tension is placed on the upper pole of the thyroid lobe. The space between the cricothyroid muscle and the medial aspect of the upper pole of the thyroid gland is opened. The upper pole is separated from the larynx by dissecting from inferior to superior, isolating the superior thyroid vessels away from the external branch of the superior laryngeal nerve (EBSLN).

13.2.4 Division of the Superior Vascular Pedicle

The superior pedicle may be divided with a powered dissection instrument (e.g., the harmonic scalpel or an electrosurgical device), or between clips or ties. The vessels must be carefully divided adjacent to their site of penetration of the thyroid capsule to avoid injury to the EBSLN and devascularization of a superior parathyroid gland, which can be supplied in part by the superior thyroid artery.

13.2.5 Lateral Dissection and Middle Thyroid Vein Division

With the superior pole of the thyroid free of fascial attachments, the thyroid lobe is retracted medially, rotating the larynx to expose the tracheoesophageal groove, and dissection commences on the lateral aspect of the lobe. One or more middle thyroid veins may be encountered and divided along the lateral aspect of the thyroid.

13.2.6 Recurrent Laryngeal Nerve and Parathyroid Gland Identification

The thyroid lobe is reflected anteriorly to expose the tracheoesophageal groove. The dissection is carried down along the medial surface of the carotid artery to the prevertebral fascia. The inferior thyroid artery (ITA) can be identified passing deep to the carotid in its course toward the lower pole of the thyroid. Careful dissection is necessary around the ITA to identify the recurrent laryngeal nerve (RLN) as it passes underneath, or less commonly, anterior to the artery (► Fig. 13.1). If the RLN is not visible, it can usually be identified caudally (in previously undissected areas) as it ascends in the tracheoesophageal groove. The cephalad course of the nerve is defined, taking care

Table 13.1 Sequential steps of thyroidectomy

1	Beach chair position and curvilinear skin crease incision
2	Strap muscle separation and thyroid exposure
3	Upper pole mobilization
4	Division of superior vascular pedicle
5	Lateral dissection and middle thyroid vein division
6	Recurrent laryngeal nerve and parathyroid gland identification
7	Inferior vessel division and ligament of Berry dissection

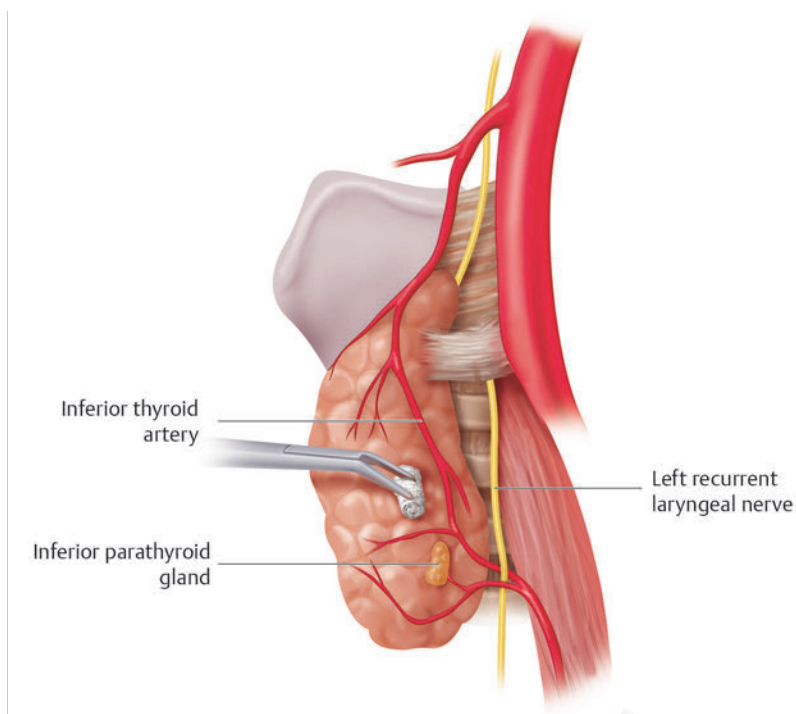


Fig. 13.1 Reflection of the left lobe of the thyroid gland reveals the relationship of the inferior parathyroid gland, inferior thyroid artery, and left recurrent laryngeal nerve.

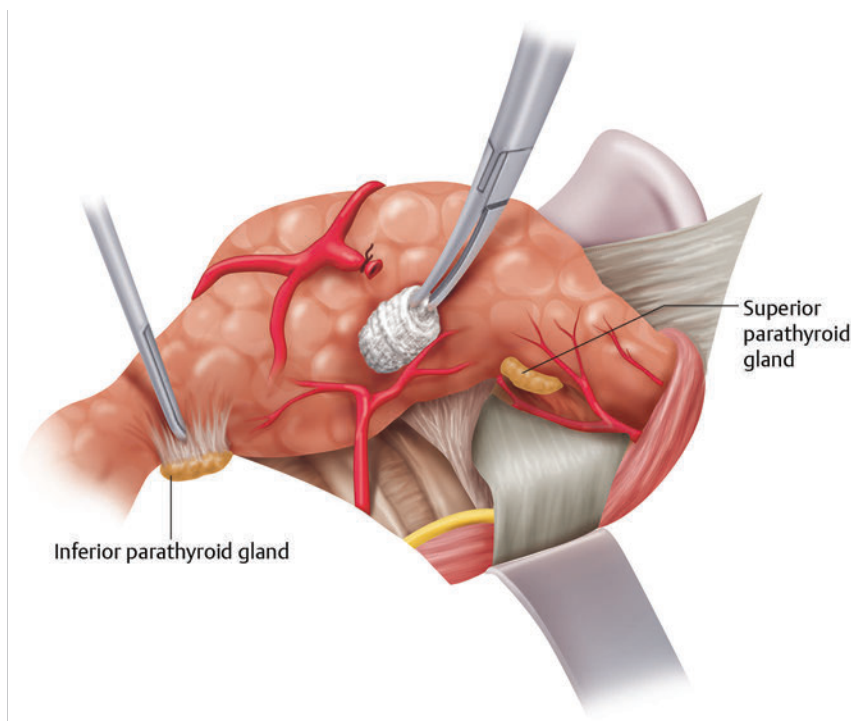


Fig. 13.2 The superior parathyroid gland is often tucked posterior to the upper pole, typically superior to the inferior thyroid artery, and posterior to the recurrent laryngeal nerve.

to preserve branches that arise proximal to its disappearance under the caudal border of the inferior constrictor muscle. The right RLN arises more laterally in the chest than the left, leading to a more oblique course. The right RLN can also branch directly from the vagus nerve to the larynx (a “nonrecurrent” nerve). This variant nerve always passes posterior to the carotid artery en route to the larynx.

The superior and inferior parathyroid glands can be preserved by dissecting them away from the posterior capsule of the thyroid gland with their vascular pedicles. The superior

glands are most commonly located on the dorsal surface of the thyroid lobe at the level of the upper two-thirds of the gland (► Fig. 13.2). Although their location is more variable, the lower glands usually lie caudal to the ITA.

13.2.7 Inferior Vessel Division and Ligament of Berry Dissection

With the course of the RLN directly identified, the branches of the ITA are divided adjacent to their entrance into the thyroid

gland to preserve the parathyroid blood supply. The inferior pole is then dissected. The small arteries and veins in this area are divided. The RLN is vulnerable to injury in this area if its course is not clear. With its upper and lower poles free, the thyroid lobe remains fixed to the trachea by the ligament of Berry. The thyroid gland is rolled medially, and with the RLN separated from the thyroid gland and in clear view, the ligament is encircled, ligated, and divided (► Fig. 13.3). The thyroid gland can then be dissected from the anterior surface of the trachea.

13.3 Principles of Thyroid Dissection

Though the steps of dissection already detailed are applicable in most circumstances, they may require modification in certain patients. Cancer or very large thyroid glands, in particular, can prevent the performance of the operation in the usual

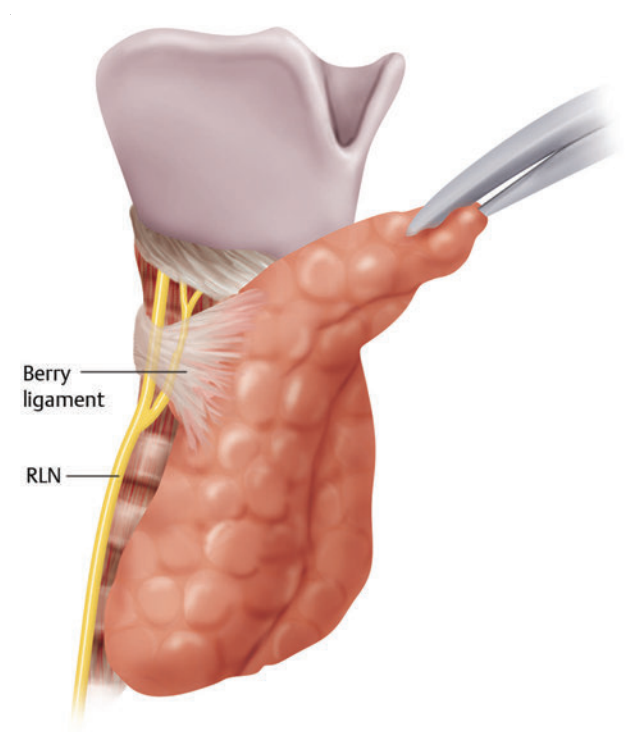


Fig. 13.3 Once the superior and inferior pole vessels have been divided, the parathyroid glands have been dropped away from the posterior surface of the thyroid gland, and the recurrent laryngeal nerve (RLN) has been exposed up to the insertion into the larynx, the ligament of Berry can be safely divided as shown in this depiction of the dissection of the right thyroid lobe.

sequence. However, although the steps of the operation may change, the principles of safe dissection to minimize the risk of damage to adjacent structures should not change (► Table 13.2).

13.3.1 Five Key Principles of Dissection

1. Avoid dividing any structures in the tracheoesophageal groove until the nerve is definitively identified. Small branches of the ITA may seem like they can clearly be safely transected; however, the distortion of tumor, retraction, or previous scar may lead the surgeon to mistakenly divide a branch of the RLN. The identifying feature of the RLN is that, the more it is dissected, the more it looks like the correct structure, based on both the morphological appearance and the anatomical course. The nerve can tolerate manipulation but not cutting. Once cut, repair of the nerve is of unproven benefit.
2. Identify the nerve low in the neck, well below the ITA, at the level of the lower pole of the thyroid gland, or below. This allows dissection of the nerve at a site where it is not tethered by its attachments to the larynx or its proximity to the ITA. Traction injuries to the nerve can occur when the nerve is manipulated near a site of fixation.
3. Keep the nerve in view during the subsequent dissection of the thyroid away from the larynx. Once the nerve is identified, the dissection can generally proceed from inferior to superior along the nerve, dividing the ITA branches and preserving the parathyroid glands. This allows careful dissection of the tissues with minimal manipulation of the RLN.
4. Minimize the use of powered dissection posterior to the thyroid. Although the electrocautery and high-frequency ultrasonic scalpel are useful tools in dissection, they have some risk of lateral thermal spread, which can damage adjacent tissues. Careful cold dissection and hemostasis with ligatures or clips will avoid this risk. This is particularly important at the entry of the RLN to the larynx, immediately adjacent to the ligament of Berry and its vessels.
5. Treat every parathyroid gland as though it were the last; use parathyroid autografting liberally when the parathyroid gland appearance is changed. It can be challenging to identify damaged parathyroid glands. Given the very high success rate of fresh parathyroid autografting, this should be routinely used for any glands that have been compromised by dissection.

13.4 Thyroidectomy Complications

Safe performance of conventional thyroidectomy requires knowledge of the potential complications of the procedure

Table 13.2 Key principles of thyroid dissection

1	Avoid dividing any structures in the tracheoesophageal groove until the nerve is definitively identified
2	Identify the nerve low in the neck, well below the inferior thyroid artery, at the level of the lower pole of the thyroid gland, or below
3	Keep the nerve in view during the subsequent dissection of the thyroid away from the larynx
4	Minimize the use of powered dissection posterior to the thyroid
5	Treat every parathyroid gland as though it were the last; use parathyroid autograft liberally when parathyroid gland appearance is changed

Table 13.3 Incidence of complications after total thyroidectomy

Authors, year	Number of patients	Transient nerve paresis, N (%)	Permanent nerve paresis, N (%)	Transient hypoparathyroidism, N (%)	Permanent hypoparathyroidism, N (%)
Thompson et al, 1978 ⁷	165	NR	0	NR	<2%
Farrar et al, 1980 ⁶	29	NR	1 (3%)	2 (7%)	4 (14%)
Schroder et al, 1986 ⁸	56	1 (2%)	0	9 (17%)	3 (6%)
Clark et al, 1988 ⁹	160	4 (2.5%)	3 (2%)	NR	1 (0.6%)
Ley et al, 1993 ¹⁰	124	1 (0.8%)	1 (0.8%)	13 (10%)	2 (1.6%)
Tartaglia et al, 2003 ¹¹	1,636	31 (1.9%)	15 (0.9%)	NR	14 (0.9%)
Rosato et al, 2004 ¹²	9,599	195 (2%)	94 (1%)	797 (8.3%)	163 (1.7%)
Grant et al, 2010 ¹³	420	NR	6 (1.4%)	NR	5 (1.2%)
Laird et al, 2012 ¹⁴	119	2 (1.7%)	0	NR	2 (1.7%)

Abbreviation: NR, not reported.

because anticipation of these issues is what informs the sequence and principles of dissection. The potential complications of thyroid operations include the immediate danger of cervical hematoma, as well as the more chronic complications of hypoparathyroidism and nerve injury (► Table 13.3).

13.4.1 Neck Hematoma

A postoperative neck hematoma requiring reoperation develops in about 1 of every 150 thyroidectomies.^{1,2,3,4,5} Hematomas usually appear within the initial 6 hours after the completion of the procedure, though they may appear even later if a patient is on anticoagulation. The hematoma can collect either between the platysma muscle and the sternohyoid muscles (superficial), or deep to the strap muscles along the larynx (deep). The deep hematomas are the more dangerous because they can lead to laryngeal edema and airway obstruction.

The risk of cervical hematoma has led some to question the safety of outpatient thyroidectomy because there is the possibility of a hematoma developing after discharge.^{1,2,3,4,5} The current experience by experts in the field has demonstrated that outpatient thyroid surgery can be done safely, though postoperative observation for several hours may be considered in order to detect this complication prior to discharge.

13.4.2 Hypoparathyroidism

The parathyroid glands are small, delicate structures that share a blood supply with the thyroid gland. Their diminutive size (normal 30–60 mg) and fragile nature make them particularly prone to damage during thyroidectomy. Patients who have markedly diminished or absent parathyroid function after thyroidectomy have severe hypocalcemia that requires replacement to normalize. If permanent, this complication can be palliated by calcium supplements, but this requires multiple doses each day, and uncomfortable symptoms occur if doses are late or missed. In addition, there is cumulative bone damage over time.

Temporary hypocalcemia occurs in about 10% of patients after total thyroidectomy, and permanent hypocalcemia in about 1% (see ► Table 13.3).^{6,7,8,9,10,11,12,13,14} Temporary hypocalcemia can be severe and may require intravenous or oral supplementation for the duration of the effect. Permanent hypoparathyroidism requires lifelong support with calcium supplements and vitamin D analogues. Missing doses of the supplements will usually produce symptoms of varying severity, which, while manageable, are often quite bothersome for patients. In addition to the discomfort and inconvenience of the supplements, patients develop low-turnover bone disease, which resembles osteomalacia.¹⁵

Avoidance of permanent hypoparathyroidism is far more desirable than treatment of it. This can be accomplished by preservation of the parathyroid glands on their native blood supply, or autografting of parathyroid tissue to a muscular bed.¹⁶ During thyroidectomy, the blood supply to each parathyroid gland should be identified and specifically considered during dissection. As stated earlier, every parathyroid gland should be treated as though it were the only remaining gland. During dissection of the thyroid, the ITA branches should be divided distal to the branching of the parathyroid end-arteries. The parathyroid glands can then be moved posteriorly in the neck away from the thyroid, to allow safe dissection of the RLN and thyroid attachments to the trachea.

If the parathyroid glands cannot be preserved on their native blood supply, then transfer of the gland to a convenient grafting site can maintain function.^{16,17} For normal parathyroid glands, transfer to the sternocleidomastoid muscle provides a convenient vascular bed for transplant. The parathyroid gland must be reduced to pieces that can survive on the diffusion of nutrients temporarily while neovascular ingrowth occurs over several weeks.

13.4.3 Nerve Injuries

There are several nerves adjacent to the thyroid gland that can be deliberately or inadvertently affected during thyroidectomy. These include the RLN immediately adjacent to the thyroid, and

the vagus nerve, which is slightly more removed, but causes the same symptoms if damaged. The external branch of the superior laryngeal nerve can be injured during dissection of the upper pole of the thyroid gland, and the sympathetic chain and stellate ganglion can be injured near the posterior aspect of the upper pole of the gland as well. The RLN and the external branch of the superior laryngeal nerve are directly involved in every thyroidectomy.

The RLN fibers are a part of the vagus nerve on each side until they branch off in the upper chest, course around the ligamentum arteriosum (left RLN) or the subclavian artery (right RLN), and back along the tracheoesophageal groove on each side. They pass between the thyroid and the larynx and insert in the larynx at the inferior border of the cricopharyngeal muscle. The nerve often branches at about the level of the lower pole of the thyroid and inserts to the larynx as two or more adjacent fibers; there is also an esophageal branch that extends posteriorly from about the level of the thyroid lower pole.

Damage to the RLN causes unilateral paralysis of the muscles that control ipsilateral vocal cord mobility. Unilateral RLN injury changes the voice substantially in most patients, and also significantly affects the swallowing mechanism. Bilateral RLN injury causes paralysis of both cords and usually results in a very limited airway lumen at the glottis. Patients with this injury may require reintubation to maintain ventilation.

RLN paresis is usually temporary and resolves over days to months.^{6,7,8,9,10,11,12,13,14} There is no known method of aiding or speeding recovery. Avoidance of RLN injury is far superior to palliation. Great care must be taken during the dissection of the nerve in order to protect it. In some clinical situations, the RLN is sacrificed in order to allow adequate tumor resection, but, absent this unusual circumstance, careful dissection can generally preserve cord function.

The use of nerve stimulators and laryngeal muscle potential monitors has recently been investigated as a tool to try to limit or avoid nerve injuries.^{18,19} However, the risk of nerve injury is related to several factors, and the data do not currently support the use of these devices as standard of care.^{20,21,22,23} This may be because they merely help to identify the nerve, whereas the portion of the operation most likely to produce damage in experienced hands is the dissection of the RLN at the fixed point of the cricopharyngeus. However, many experienced surgeons now routinely use a nerve-monitoring system for a variety of reasons, including the opportunity to alter a planned bilateral thyroidectomy if there is nerve dysfunction on the side dissected initially.²³

The external branch of the superior laryngeal nerve courses adjacent to the superior pole vessels of the thyroid gland, then separates from the thyroid to penetrate the cricopharyngeus muscle fascia at its superoposterior aspect. The nerve supplies motor innervation to the cricothyroid muscle. Damage to this nerve changes the ability of the larynx to control high-pressure phonation, such as high-pitched singing (soprano/falsetto) or yelling.^{12,23,24}

To avoid damaging the EBSLN, the dissection of the upper pole vessels should proceed from a space where the nerve is sequestered under the cricopharyngeal fascia, to the superior vessels themselves, thus safely separating the nerve from the tissue to be divided.

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14 Minimally Invasive Thyroid Surgery

Paolo Miccoli and Gabriele Materazzi

14.1 Introduction

Minimally invasive thyroid surgery offers several advantages over the traditional thyroidectomy procedure in carefully selected patients. Shorter incision lengths reduce the cosmetic impact of the operation. A smaller extent of dissection, the omission of postoperative drains, and outpatient management strategies decrease postoperative pain, speed the recovery process, and improve the patient's postoperative experience.^{1,2,3} Two minimally invasive thyroidectomy procedures are currently performed: minimally invasive nonendoscopic thyroidectomy (MINET) and minimally invasive video-assisted thyroidectomy (MIVAT). MINET is typically performed through a 4 cm incision, whereas MIVAT can be performed through incisions as small as 1.5 cm.⁴ MIVAT uses endoscopic assistance to visualize the operative field under the soft tissue envelope; otherwise the procedures are identical. Although this chapter focuses on the MIVAT technique, the principles discussed are easily adapted for the MINET procedure.

14.2 Patient Selection

Strict selection criteria have been described to improve the chance of operative success and minimize complications in MIVAT (► Table 14.1).⁵ Patients should have benign or indeterminate nodules <3 to 3.5 cm or low-risk papillary thyroid carcinomas <2 cm, with an overall thyroid volume <25 mL. Contraindications include recurrent disease, locally advanced or metastatic carcinoma, and thyroiditis.

14.3 Operative Steps

The MIVAT technique has been previously described in detail⁶ and is summarized here. The procedure consists of both open and endoscopic portions. Extending the incision slightly allows the procedure to be performed without endoscopic assistance. In these cases (the MINET procedure), the endoscopic steps are performed under direct visualization.

Table 14.1 Indications and contraindications for minimally invasive video-assisted thyroidectomy

Indication	Contraindication
Benign disease ^a	Recurrent disease (previous cervicotomy)
Graves' disease ^a	Locally advanced and/or metastatic carcinoma
Indeterminate nodule	Short neck in obese patient
"Low-risk" papillary carcinoma	Thyroiditis

^aThyroid volume <25 mL and nodule diameter <3 cm.

14.3.1 Step 1: Preparation of the Operative Space

The patient, under general endotracheal anesthesia, is placed in a supine position. Neck hyperextension has to be avoided in order not to reduce the operative space, which is maintained only by an external retraction and not by means of any insufflation. Furthermore, this position is strongly suggested to minimize cervical trauma, which is one of the most important contributors to postoperative pain, particularly in elderly patients, who often suffer from cervical ailments.

The skin is protected by means of a sterile film (Bioclusive, Johnson & Johnson). A 1.5 cm horizontal skin incision is performed in a skin crease approximately 2 cm above the sternal notch in the central cervical area (► Fig. 14.1). The monopolar electrocautery blade is protected, leaving just the tip able to coagulate, in order to avoid any possible burning of the skin or the superficial planes. The subcutaneous fat and platysma are carefully dissected while the midline is opened for no more than 2 cm, just enough to allow the endoscope and needle-scope instruments to enter the operative space. Because the absence of positive pressure provided by insufflation cannot limit the bleeding as in the majority of laparoscopic procedures, particular caution is necessary when dividing the strap muscles along the linea alba so as to avoid any bleeding during this

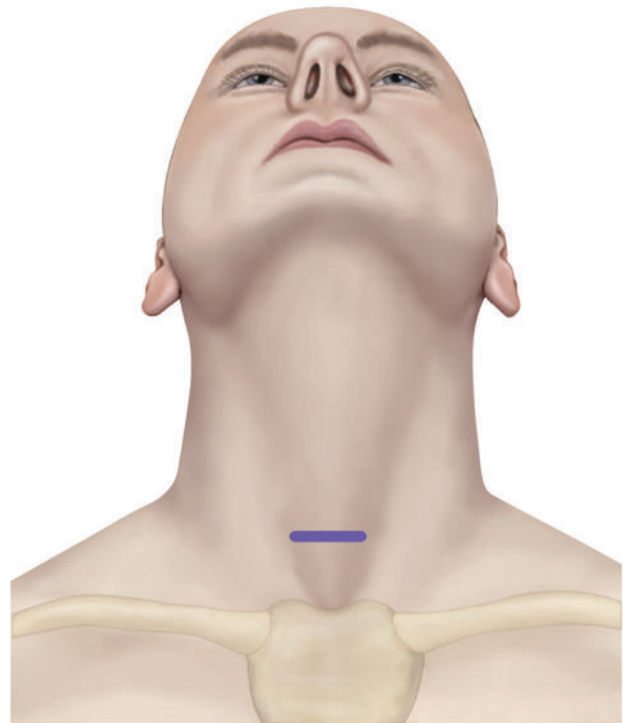


Fig. 14.1 Minimally invasive video-assisted thyroidectomy is performed through a 1.5 cm horizontal skin incision placed in a skin crease ~ 2 cm above the sternal notch in the central cervical area.

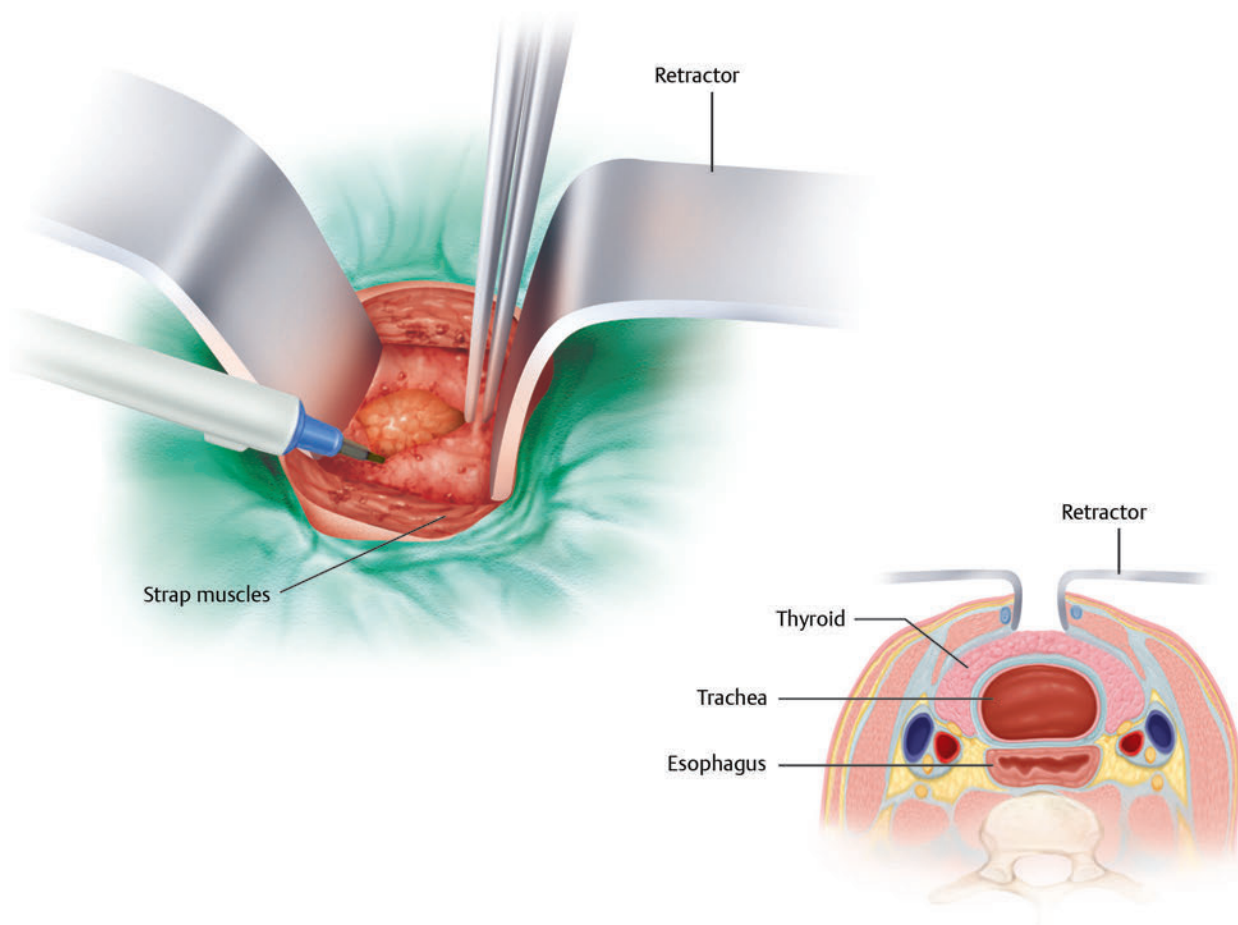


Fig. 14.2 (a) The strap muscles are divided in the midline along the linea alba to avoid any bleeding. (b) Two small, modified, miniaturized Farabeuf retractors give optimal access to the thyroid compartment.

phase. Two small, modified, miniaturized Farabeuf retractors give optimal access to the midline (► Fig. 14.2).

Blunt dissection of the strap muscles off the thyroid lobe is performed through the skin incision by gentle retraction and using tiny spatulas. When the thyroid lobe is almost completely dissected from the strap muscles, larger and deeper retractors (standard Farabeuf retractors) are placed, one retracting the thyroid lobe, and the other retracting the neck bundle, in particular the carotid artery, which has to be well visualized before being gently retracted (► Fig. 14.3a). The medial retractor should almost completely load the thyroid lobe; when the correct position is achieved, thyroid parenchyma should not be visible through the endoscope, except a minimal portion of the posterior part of the lobe (► Fig. 14.3b). The medial retractor basically plays the role of the hand of the assistant during a conventional thyroidectomy. Then the operative space will be correctly established and will provide an excellent access to all the critical structures during the endoscopic part of the procedure. Then a 5 mm, 30° endoscope is introduced through this cervical access. From this moment on the operation is performed endoscopically until the extraction of the lobe of the gland. Preparation of the thyrotracheal groove is completed using small (2 mm in

diameter) instruments, such as spatulas, forceps, a suction spatula, and scissors, under endoscopic visualization (► Fig. 14.4).

14.3.2 Step 2: Division of the Main Thyroid Vessels

A Harmonic device (Ethicon Endo-Surgery, Inc., Blue Ash, Cincinnati, OH, USA) is used for almost all the vascular structures, but, if the vessel to be coagulated is running particularly close to the recurrent laryngeal nerve (RLN), then hemostasis is achieved by means of small vascular clips applied by a disposable or reusable clip applier.

The first vessel to be ligated is the middle vein, when present, or the small veins between the jugular vein and thyroid capsule. This provides a larger operative space and a better retraction between the carotid artery and the thyroid lobe, further exposing the thyrotracheal groove. During this step the endoscope has to be held with the 30° tip looking downward and in an orthogonal axis with the thyroid lobe and trachea.

The next step is exposure of the upper pedicle, which must be carefully prepared, until optimal visualization of the different branches is achieved. At this point the endoscope must be

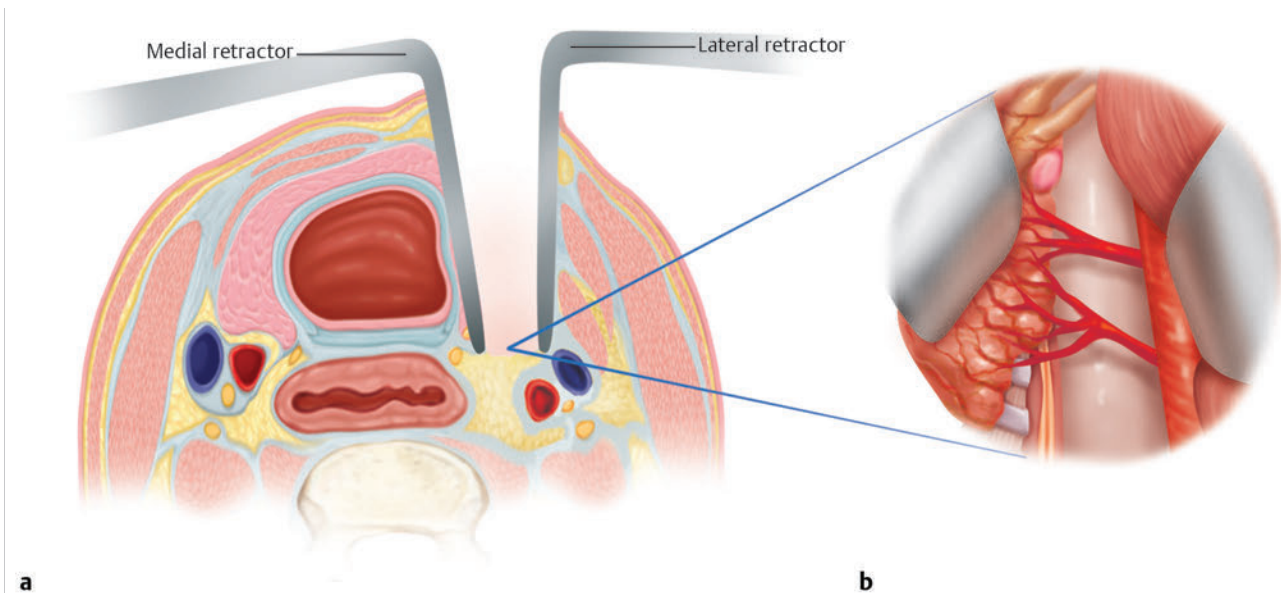


Fig. 14.3 (a) Standard Farabeuf retractors are used to maintain the operative space. One retractor is placed on the thyroid lobe and the other on the lateral neck structures. (b) When the medial retractor is correctly placed only a minimal portion of the thyroid lobe should be visible.

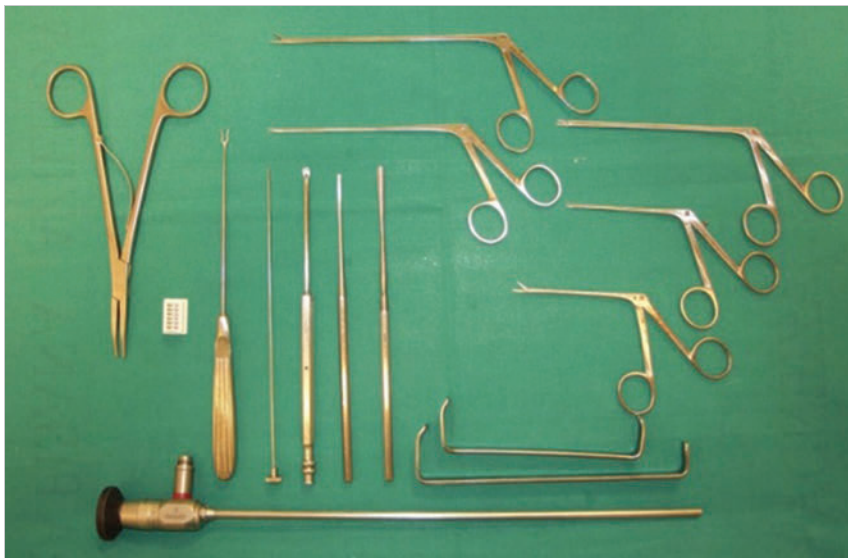


Fig. 14.4 Standard instruments used in minimally invasive video-assisted thyroid surgery.

flipped downside-up and, looking in the cephalic direction, the upper pedicle will be visualized at the top of the screen. This requires a complete rotation of 180°, with the 30° tip looking upward and held in a parallel direction with the thyroid lobe and trachea, in order to better visualize the upper portion of the operative field where the superior thyroid vein and artery are running (► Fig. 14.5).

The upper pedicle has to be exposed by retracting the thyroid lobe downward and medially by gently loading it with the retractor and the assistant spatula. In the meantime the vessels are pulled laterally in order to provide the correct space for the Harmonic scalpel to be introduced. This will allow the external branch of the superior laryngeal nerve (SLN) to be easily identified during most procedures (► Fig. 14.6). SLN injury must be avoided and is prevented by keeping the inactive blade of the energy instrument facing the laryngeal muscles so as not to

transmit excessive heat to this delicate structure. At this point, division of the upper pedicle can be performed with the Harmonic scalpel en bloc or selectively, depending on the diameter of the single vessels or the anatomical situation.

14.3.3 Step 3: Identification of the Important Structures of the Region: The Recurrent Laryngeal Nerve and the Parathyroids

After retracting the thyroid lobe medially and ventrally, the tip of the endoscope is again oriented downward and slightly medially, and the deeper fascia can be opened with gentle spatula dissection. The RLN generally appears at this point, lying in the thyrotracheal groove and posterior to the tubercle of

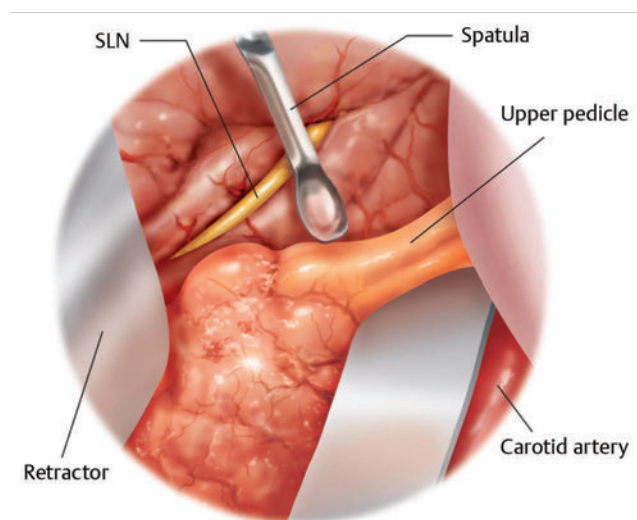


Fig. 14.5 Endoscopic dissection of the superior vascular pedicle, revealing the vessels and superior laryngeal nerve (SLN).

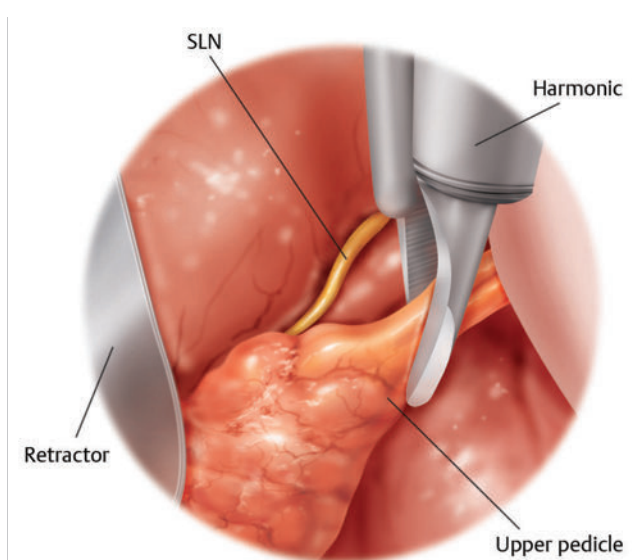


Fig. 14.6 Ligation of the superior vascular pedicle with a Harmonic device. SLN, superior laryngeal nerve.

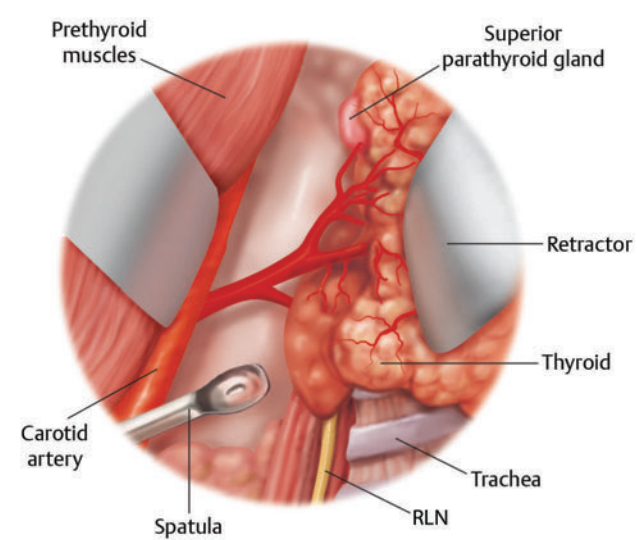


Fig. 14.7 Endoscopic view of the recurrent laryngeal nerve (RLN) and parathyroid glands.

Zuckerkindl (posterior lobe), which constitutes an important landmark in this step. Also, both parathyroid glands are generally easily visualized thanks to the endoscope magnification (► Fig. 14.7). Their vascular supply is preserved by selective ligation of the branches of the inferior thyroid artery. During dissection, hemostasis is achieved with 3 mm titanium vascular clips when dividing the small vessels that often cross the recurrent nerve.

The RLN must be dissected and carefully traced until its insertion near Berry's ligament. This is of paramount importance in order to avoid excessive traction on this delicate structure once the thyroid lobe is delivered through the skin incision (following step). The typical shape and color are of great help for recognition of the parathyroid glands, and these characteristics are greatly enhanced by the endoscopic view. Once identified the parathyroid can be gently dissected, with care to

preserve its small pedicle, and delicately moved away from the thyroid gland, to avoid any damage to its vascular support during the mobilization and extraction of the lobe.

14.3.4 Step 4: Extraction of the Thyroid Lobe Outside the Neck and Completion of the Lobectomy

Once the lobe is completely mobilized the endoscope and retractors are removed, and the surgeon delivers the lobe through the incision. This is accomplished by grabbing the superior pole of the thyroid with conventional Kelly or Crile forceps, and then gently extracting it through the incision by rotating the entire lobe on its longest axis (► Fig. 14.8). Once the lobe is exteriorized the operation proceeds under direct visualization as in open surgery. The lobe is freed from the trachea by ligating the small vessels and dissecting Berry's ligament. It is very important to recheck the course of the RLN at this point to avoid its injury before the final step. The isthmus is then dissected from the trachea and divided. After completely exposing the trachea, the lobe is finally removed by the conventional open technique. This completes the unilateral thyroid lobectomy. In cases where total thyroidectomy is necessary the procedure is simply repeated on the opposite side.

14.3.5 Step 5: Access Closure

Drainage is not necessary. The strap muscles are approximated with a single stitch. The platysma is sutured with a subcuticular resorbable running suture, and the skin is closed by means of a sealant skin glue.

14.4 Results and Outcome

Since June 1998, when the technique was conceived and developed in Pisa, more than 3,000 MIVATs have been performed at

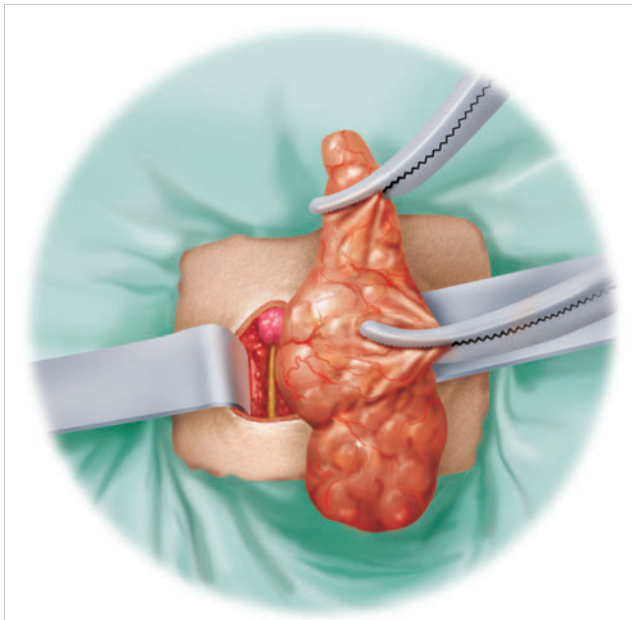


Fig. 14.8 The thyroid lobe is delivered through the incision to facilitate further dissection.

the Department of Surgery, University of Pisa. In a recently published series of nearly 2,000 of these patients, the female to male ratio was 5:1, with a mean patient age of 40.2 years (range 8–85 y) and a total thyroidectomy to hemithyroidectomy ratio of nearly 3:1.⁵ The mean operative time was 31 minutes (range 20–120 min) for hemithyroidectomy and 41 minutes (range 30–130 min) for total thyroidectomy. Surgical indications included follicular lesions, low-risk papillary carcinomas, toxic multinodular goiter, Graves' disease, and familial medullary carcinoma (prophylactic operation for *RET* [rearranged during transfection] gene mutation carriers).⁵ Intraoperative conversion from MIVAT to conventional thyroidectomy (Kocher incision) was necessary in 1.9% of cases, primarily due to intraoperative bleeding, difficult dissection for thyroiditis, and unexpected tracheal or esophageal infiltration from carcinoma.⁵ A review of 10 years of experience with MIVAT showed that complication rates for laryngeal nerve injury, hypoparathyroidism, and postoperative bleeding were similar to those of conventional thyroid surgery.⁷

A prospective, randomized study clearly demonstrated that MIVAT achieves the same clearance at the thyroid bed level and the same outcome as the conventional thyroidectomy technique when dealing with low-risk papillary carcinoma.⁸ At the same time, MIVAT patients can benefit from the main advantages of this minimally invasive technique: reduced postoperative pain, a faster postoperative recovery, and an excellent cosmetic outcome.

14.5 Postoperative Care

After surgery, patients undergoing MIVAT require strict observation during the first 5 to 10 hours on the ward. Dysphonia, airway obstruction, and neck swelling must be carefully evaluated. No drain is left, so careful surveillance for postoperative

Table 14.2 Management of hypocalcemia following thyroidectomy on the first postoperative day

Symptoms	Treatment
Acute symptomatic	Calcium gluconate intravenously
Asymptomatic calcium $\leq 7.5^a$ mg/dL	Calcium (3 g) + vitamin D (0.5 μ g) orally, daily
Asymptomatic calcium 7.5–7.9 mg/dL	Calcium (1.5 g) orally, daily
^a Normal range: 8–10 mg/dL.	

hematomas is required during the immediate postoperative period. The postoperative bleeding risk is very low and dramatically decreases after 5 hours; therefore, patients should lie in bed at least for 5 to 6 hours. Oral feeding should be avoided during the same observation period in order to decrease the risk of postoperative nausea and vomiting. Patients can be discharged the day after surgery (in Italy, “one day surgery” [same day discharge] for thyroidectomy is not allowed by law) and they can return to normal activities. Substitutive therapy with levothyroxine beginning on the first postoperative day is strongly suggested, especially in cases of total thyroidectomy for carcinoma.

No care is required for the wound because the glue protects the wound from any mechanical trauma or external contamination. Frequently, oral anti-inflammatory drugs are prescribed in the postoperative period in order to decrease pharyngeal and cervical back pain (the latter should be moderate, however, because patients undergoing MIVAT are positioned on the operating table without neck hyperextension).

14.6 Management of Procedure-Specific Complications

In the setting of postoperative hematoma, if compressive symptoms and airway obstruction are present, surgical intervention and immediate hematoma evacuation are strongly recommended.

Patients can start oral intake on the evening of the day of surgery and are discharged the day after surgery. On the first and second postoperative days, serum calcium must be checked to control hypoparathyroidism by substitutive therapy, as described in ► Table 14.2.

Voice impairments and subjective or objective dysphonia require immediate postoperative vocal cord evaluation by an otolaryngologist. In asymptomatic patients, this evaluation may be delayed for 3 months.

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15 Remote Access Thyroid Surgery

Katrina Chaung and William S. Duke

15.1 Introduction

Recent technological innovations have addressed growing patient interest in reducing the cosmetic impact of surgery, leading to the development of alternative approaches to thyroid surgery. These approaches have developed along two distinct pathways: minimally invasive techniques that create small anterior cervical incisions and remote access approaches that eliminate any anterior neck incision. Although minimally invasive techniques result in a small cervical scar that is well hidden in a natural skin crease, some patients regard the prospect of any publicly visible scar as unacceptable. Remote-access techniques remove the incision from the visible portion of the neck and conceal it in a distant, hidden location. Endoscopic or robotic techniques are then used to access the thyroid compartment. For the appropriate patient who regards cosmesis as a priority, remote-access techniques can safely and effectively achieve both the surgical and the cosmetic goals.^{1,2}

15.2 Background

The “conventional” thyroidectomy technique was developed by Emil Theodor Kocher in the late 1800s. His methods, which used a 7 to 10 cm transverse cervical incision,³ elevation of subplatysmal flaps, and meticulous dissection techniques, transformed thyroid surgery into a procedure that was so safe and universally accepted that, for more than 100 years, it was performed on all patients undergoing thyroid surgery, regardless of their gland size or disease.

The first endoscopic cervical surgery was described by the Gagner group⁴ in 1996 to perform a subtotal parathyroidectomy. Although this procedure exposed many limitations of endoscopic neck surgery, including prolonged surgical time, mild hypercarbia and subcutaneous emphysema related to the CO₂ insufflation, and a prolonged postoperative hospital stay, the cosmetic outcome was reported as excellent.⁵ This experience attracted the interest of surgeons and patients and suggested the possibility of alternative approaches to thyroid surgery that could minimize the cosmetic impact of the procedure.

This growing interest resulted in the development of minimally invasive and remote access approaches. The minimally invasive approaches include both the minimally invasive video-assisted thyroidectomy (MIVAT)^{6,7} and the minimally invasive nonendoscopic thyroidectomy (MINET).⁸ These techniques employ incisions hidden in natural skin creases that are significantly smaller than those used for conventional thyroid surgery. The extent of dissection is reduced, and the procedure can be performed without a drain and on an outpatient basis.⁹ Despite the limited incision length used in minimally invasive surgery and the predictably excellent cosmetic results achieved in the majority of patients, these procedures may result in a conspicuous anterior cervical scar that can be difficult to camouflage, an unacceptable possibility for some patients.

To further reduce the cosmetic impact of thyroid surgery, remote-access approaches were developed, which completely

remove the scar from the visible portion of the neck and hide it in a concealed, distant location. These approaches primarily emerged in Asia, where poor wound healing and a cultural bias against visible neck scars are common.^{10,11} It is important that patients realize that these approaches hide the scar but are not scarless. As a result of the remote access site, a longer and more extensive dissection is required, and structures that are not usually encountered during thyroid surgery may be at risk with these approaches.

Due to the heterogeneity of access sites and instrumentation that has been employed in remote access procedures, it is difficult to directly compare the overall degree of postoperative pain or duration of recovery for this group to that of conventional thyroid surgery.^{12,13,14} Given the increased dissection extent and unconventional anatomical vantage point, the surgeon's experience and comfort level can significantly impact operative times.^{14,15} These approaches are generally more expensive than conventional or minimally invasive procedures. Currently, there are no reimbursement strategies in place in the United States to offset these increased costs.^{16,17} Additionally, surgeon training and robotic equipment may not be widely available. Despite these challenges, remote access procedures are an attractive alternative for select patients who consider any visible cervical scar an undesirable result.

15.3 Remote Access Endoscopic Procedures

15.3.1 Chest/Breast Approaches

The first completely remote access thyroidectomy was performed by Ohgami et al¹⁸ in 2000. The procedure used incisions at the parasternal border of one breast and along the superior margins of both areolas. Low-pressure CO₂ insufflation and endoscopic equipment were also used to dissect across the chest and gain access to the thyroid compartment. Several variations of this technique have been described, including isolated anterior chest wall approaches¹⁹ as well as bilateral²⁰ and unilateral^{21,22} transareolar approaches. Use of chest/breast approaches are generally reserved for unilateral benign lesions <3 cm and small papillary thyroid carcinomas in patients with no suspicious lymphadenopathy or prior neck surgery or irradiation.^{19,20,21,22}

These approaches avoid a visible neck scar but have a number of limitations. First, incisions on the anterior chest are prone to hypertrophic scarring.²³ Additionally, incisions on the breast may be an unappealing consideration for North American patients.^{24,25} Due to the particular course of dissection, the operative field is narrow, restricting the range of movement of the rigid endoscopic instrumentation.²³

15.3.2 Axillary Approaches

Ikeda et al^{26,27} described the endoscopic axillary approach as an alternative to the anterior chest and breast approaches. The

incision is hidden in the axilla, and CO₂ insufflation and endoscopic dissection are used to access the thyroid compartment. The cosmetic sequelae of this approach are less conspicuous as compared to those of conventional surgery; however, disadvantages include a significantly longer operating time, a narrow operative field, the need for endoscopic visualization, and potential morbidity associated with CO₂ insufflation.²⁸ To avoid some of these limitations, “gasless” remote techniques were developed that used specialized retractor systems rather than CO₂ insufflation.²⁹ The gasless approach has been described for thyroidectomy and central compartment node dissection in patients with low-risk papillary thyroid carcinoma, and postoperative thyroglobulin levels and iodine-131 scans reflect acceptable oncological outcomes.^{29,30} Additional experience and longer follow-up periods will be needed to define the exact inclusion criteria for the treatment of malignant disease using this remote approach.

The axillo-bilateral-breast approach (ABBA)²³ and the bilateral axillo-breast approach (BABA)³¹ are among several hybrid endoscopic procedures developed. These techniques combine axillary and areolar incisions for the cosmetic benefit of the axillary approaches while granting an additional anterior chest working port without necessitating a transverse parasternal scar. Several complications not typically linked to traditional thyroid surgery, including transient neuropraxia of the brachial plexus³² and pneumothorax,³¹ have been reported with these approaches. Although these endoscopic remote access approaches are still used in some Asian centers, they have failed to gain significant traction in Western practices.

15.4 Remote Access Robotic Procedures

To overcome the limitations of the endoscopic approaches, in 2009 a group of surgeons in South Korea introduced the concept of robotically assisted remote access thyroid surgery.³³ The introduction of the da Vinci Surgical System (Intuitive Surgical, Inc.) offers several critical advantages over endoscopic technology. The high-definition binocular camera system provides surgeons with a three-dimensional view of the operative field. Many of the robotic instruments are articulated in such a way that they offer as many or more degrees of freedom than the human wrist can achieve, allowing for improved mobility in tight operative spaces. The robot also faithfully reproduces the movements of the surgeon's hands, permitting safe dissection around critical structures. These robotically assisted remote access procedures can be accomplished without the use of CO₂ insufflation. Dual-incision axillary and chest wall,³³ single-incision axillary³⁴ and facelift³⁵ approaches have been developed. The technology also permits central and lateral neck dissections for malignant disease.³⁶

15.4.1 Robotic Axillary Thyroidectomy

The gasless robotic axillary thyroidectomy (RAT) was described in South Korea in 2009.^{13,33} The initial cases were performed as dual-incision approaches using a second parasternal incision on the anterior chest wall.^{13,30} Chung et al subsequently refined

the approach, which is now most commonly accomplished through a single axillary incision.^{33,34,37} In this technique, an axillary incision is performed, and a soft tissue pocket is developed across the anterior chest. A specially designed retractor (Chung retractor) maintains the pocket, and the thyroid compartment is accessed by separating the sternal and clavicular heads of the sternocleidomastoid (SCM) muscle.³⁰ The robot is introduced and the gland is removed. RAT has been used to treat benign thyroid nodules as well as small, well-differentiated thyroid cancers with outcomes comparable to treatment with conventional or endoscopically assisted approaches.^{13,15,30,38}

Although this approach has remained popular in South Korea, the enthusiasm that RAT initially enjoyed in Western practices has waned. In the United States, where 2% of cases have required conversion to an anterior cervical approach,^{39,40,41} there have been a number of significant complications not usually encountered in thyroid surgery, including brachial plexus injury, esophageal perforation, and significant blood loss from large-vessel injury. RAT also requires postoperative drainage and inpatient care—a step backward from many of the advances achieved with the minimally invasive anterior cervical approaches.^{1,17,37,39,42,43} For these reasons, this procedure has been abandoned in many Western centers.

15.4.2 Robotic Facelift Thyroidectomy

The robotic facelift thyroidectomy (RFT) was developed to overcome the disadvantages associated with RAT (► Table 15.1).^{35,44} In this technique, robotic assistance is used to remove the thyroid gland through a postauricular modified facelift incision.⁴⁴

Recent assessment of more than 60 RFT procedures performed in our center found this technique to be safe and clinically feasible.³⁹ Though the first patient received a drain and overnight observation, every subsequent procedure has been performed on an outpatient basis without a drain. One incidence of transient vocal fold weakness and two seromas have been reported, all of which resolved without intervention. There were no cases of permanent recurrent laryngeal nerve injury or hypocalcemia. No conversions to an anterior cervical approach were required. This complication profile compares favorably to that reported for RAT. The initial mean operative time for a lobectomy was 157 minutes, which decreased to less than 2 hours with increasing surgeon experience.^{35,39} The RFT approach has been replicated in at least four other centers with similar safety profiles.^{2,35,44}

Although no remote access procedure can be considered minimally invasive, the extent of dissection in RFT is approximately 38% less than that required for RAT (► Fig. 15.1).⁴⁵ This translates into expedited recovery time, reduced postoperative discomfort, and drainless outpatient surgery.^{1,2,45} The cervical course of dissection is more familiar to the head and neck surgeon than that of the transaxillary approach,⁴⁴ and the cephalad approach allows the recurrent laryngeal nerve (RLN) to be encountered early in dissection at its most constant location, which is advantageous in preventing nerve and parathyroid gland injury.^{35,37,44} A disadvantage of RFT is transient hypesthesia in the great auricular nerve distribution even when the nerve is carefully preserved.⁴⁴

Table 15.1 Advantages and disadvantages associated with alternative approaches to thyroid surgery

Approach	Advantages	Disadvantages
Endoscopic	- Decreased incision length - Hidden incision sites - Decreased extent of dissection - Drainless surgery - Outpatient surgery	- Some techniques use CO₂ insufflation - Some techniques involve chest and/or breast incisions - Narrow operative field - Decreased range of motion of rigid endoscopic instrumentation - Increased operative time
Robotic	- Single incision site - Incision hidden in remote location - Robotic system provides binocular high-definition, three-dimensional view - Robotic instrumentation allows equal or greater degrees of freedom than the human wrist - No CO₂ insufflation required	- Increased operative time, dependent on surgeons' experience - Increased costs compared to traditional or endoscopic approaches - Limited by equipment availability - Requires careful patient selection
Axillary	Does not use a head or neck incision	2% conversion rate to anterior cervical approach - Drain required - Postoperative inpatient care - Dissection approach unfamiliar to the head and neck surgeon - Risk of brachial plexus injury, esophageal perforation, high-volume blood loss
Facelift	- Anatomical perspective familiar to the head and neck surgeon - Early identification of the recurrent laryngeal nerve (RLN) helps prevent RLN and parathyroid gland injury - Drainless surgery - Outpatient surgery - Favorable safety profile - Low rate of conversion to anterior cervical approach	Transient great auricular nerve hypesthesia even when the nerve is preserved

15.4.3 Selection Criteria for RFT

Robotic facelift thyroidectomy is a viable option for the highly motivated patient who places a premium on cosmetic outcome. The patient should also be willing to accept an increased surgical time, greater extent of dissection, and the possibility of conversion to an open anterior cervical approach in return for elimination of a visible neck scar.

Careful consideration of patient characteristics should also be made to ensure eligibility for RFT.^{1,35,39,44} The requirements include a body mass index <40, the absence of previous neck surgery, and the lack of significant medical comorbidities. Selection criteria in regard to disease features^{1,35,39,44} are also important. The thyroid disease should be amenable to unilateral surgery because the vector of approach in this technique does not permit bilateral surgery. Staged bilateral surgery through a contralateral incision can be performed if indicated. The largest nodule should be ≤4 cm in its largest dimension, and there should be no substernal or extrathyroidal extension. Additionally there should be no clinically apparent thyroiditis or lymphadenopathy (► Table 15.2).

15.4.4 RFT Procedure and Anatomical Landmarks

Preoperative Considerations

Preoperatively, the patient is marked in the upright position. The modified facelift incision begins adjacent to the postauricular crease and extends approximately 1 cm into the occipital

hairline, continuing inferiorly as far as necessary (► Fig. 15.2).^{1,2,35,44} An anterior cervical incision is also marked in the unlikely event that conversion to an open approach is necessary.

Laryngeal nerve monitoring is used; therefore, a short-acting muscle relaxant is given during induction, but no paralytics are used during dissection. The patient is intubated with an electromyographic endotracheal tube for laryngeal nerve monitoring (NIM-3, Medtronic, Inc.) under GlideScope video laryngoscope (Verathon) visualization to ensure appropriate placement. The operating table is rotated 180° from the anesthesia team, requiring extension tubing for the anesthesia circuit. Upon conclusion of the surgery, deep extubation is performed to minimize the coughing and bucking that can occur during emergence.^{1,39}

Open Dissection

Establishing the operative pocket to access the thyroid compartment is essential for robotic excision of the gland. The modified facelift incision is made. As a subplatysmal musculocutaneous flap is developed, the sternocleidomastoid muscle (SCM) is identified and traced inferiorly to the clavicle. The proper dissection plane is superficial to the great auricular nerve (GAN) and external jugular vein (EJV) to avoid injuring these structures (► Fig. 15.3). The anterior aspect of the GAN is usually encountered ~4 cm from the apex of the incision.³⁷ The EJV is usually identified 2 to 3 cm anteromedial from the GAN.³⁹ Depending on its position, the EJV can be reflected dorsally, left down on the SCM, or divided for improved access.^{1,2,35,37,44}

The dissection is aided by progressively deeper retraction with Terris thyroid retractors (Medtronic, Inc.) and renal vein retractors. A malleable retractor is used to reflect the SCM dorsally and laterally.

The muscular triangle defined by the anterior surface of the SCM, posterior border of the sternohyoid muscle, and superior border of the omohyoid muscle is delineated.¹ On average, the omohyoid muscle is located 12 cm from the apex of the incision.³⁷ The omohyoid is reflected ventrally while the sternohyoid and sternothyroid muscles are reflected anteriorly and medially, exposing the superior pole of the thyroid gland

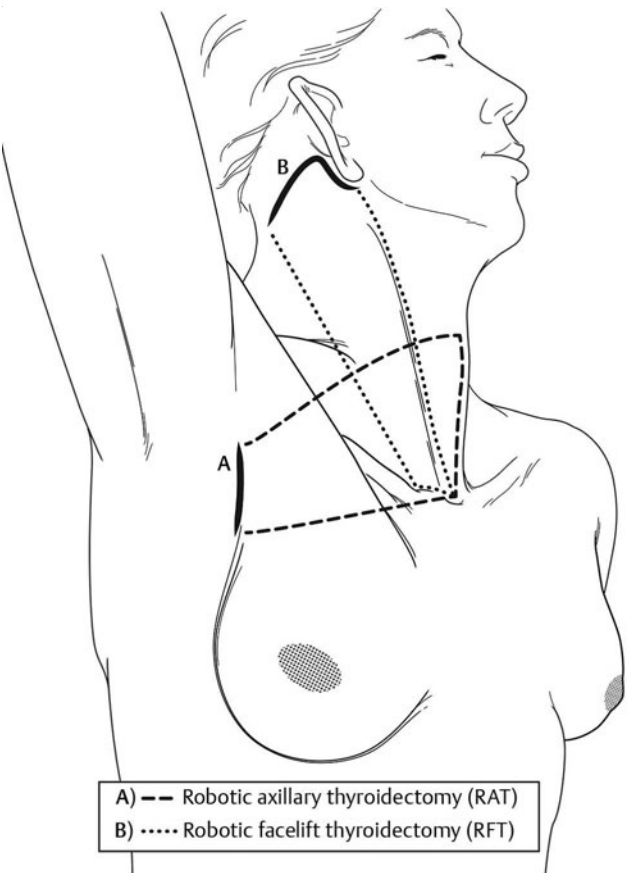


Fig. 15.1 Comparison of the extent of dissection required for the robotic axillary thyroidectomy (RAT) and robotic facelift thyroidectomy (RFT). (Reprinted with permission from Duke WS, Terris DJ. Alternative approaches to the thyroid gland. *Endocrinol Metab Clin North Am* 2014;43[2]:459–474)



Fig. 15.2 The remote-access robotic modified facelift thyroidectomy incision. (Reprinted with permission from Terris D, Singer MC, Seybt MW. Robotic facelift thyroidectomy: patient selection and technical considerations. *Surg Laparosc Percutan Tech* 2011;21[4]:237–242.)

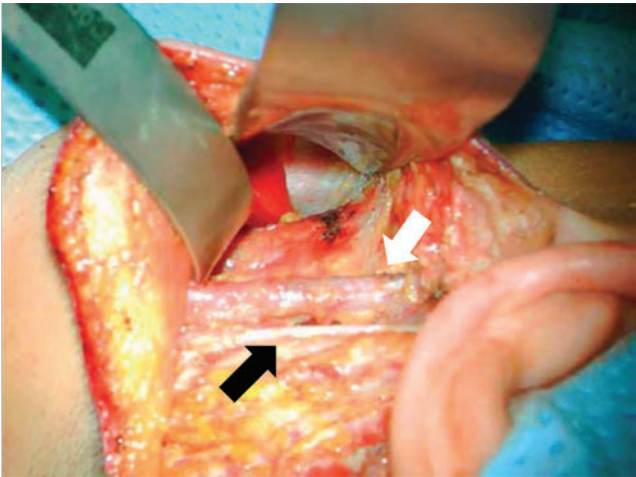


Fig. 15.3 Dissection of the robotic facelift thyroidectomy operative pocket, revealing the great auricular nerve (black arrow) and external jugular vein (white arrow). The strap muscles are retracted ventrally. (Adapted with permission from Terris DT, Singer MC, Seybt MW. Robotic facelift thyroidectomy: patient selection and technical considerations. *Surg Laparosc Endosc Percutan Tech* 2011;21:237–242.)

Table 15.2 Selection criteria for robotic facelift thyroidectomy

Patient factors	Disease factors
• Highly motivated to avoid cervical scar • Understands possibility of conversion to an anterior cervical approach • American Society of Anesthesiologists class 1 or 2 • No prior neck surgery or irradiation • No morbid obesity	• Extent of disease appropriate for unilateral surgery • Largest nodule ≤ 4 cm • No substernal extension • No extrathyroidal disease extension • No pathological lymphadenopathy • No clinically apparent thyroiditis

Source: Adapted from Terris D, Singer MC, Seybt MW. Robotic facelift thyroidectomy: patient selection and technical considerations. *Surg Laparosc Percutan Tech* 2011;21(4):237–242.

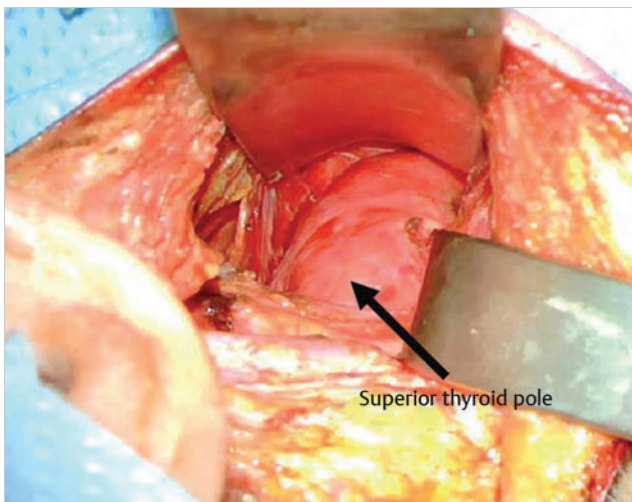


Fig. 15.4 Access to the thyroid compartment from a right remote-access robotic facelift thyroidectomy, with the omohyoid muscle reflected ventrally and the sternohyoid and sternothyroid muscles reflected anteriorly and medially to reveal the superior aspect of the thyroid gland. (Reprinted with permission from Terris DJ, Singer MC, Seybt MW. Robotic facelift thyroidectomy, II: Clinical feasibility and safety. *Laryngoscope* 2011;121[8]:1636–1641.)

(► Fig. 15.4). Through direct visualization, the thyroid gland is mobilized as much as possible and the superior vascular pedicle defined to facilitate the robotic dissection.^{1,2,35,39,44}

Fixed retractors are used to maintain the operative working space. A modified Chung retractor (Marina Medical, Inc.) is introduced underneath the strap muscles to provide ventral retraction. A Singer hook retractor (Medtronic, Inc.) on an adjustable Greenberg Retractor arm (Codman & Shurtleff, Inc.) is applied for posterior retraction of the SCM.^{1,2,35,39}

Robotic Deployment

After the operative pocket is secured, the da Vinci Surgical System is deployed. The robotic pedestal is positioned on the side contralateral to the dissection at an angle ~ 30° from the operating table. Fine adjustments are more easily accomplished by moving the operating table position rather than the robot.

Three robotic arms are employed (► Fig. 15.5). The center camera arm holds a 30° downfacing endoscope and is positioned parallel to the long axis of the modified Chung retractor with its arm almost fully extended to minimize collisions of the elbow joint with the other arms. The dominant instrument arm holds a Harmonic ACE curved shears (Ethicon Endosurgery, Inc.), and the nondominant instrument arm holds a Maryland grasper. These two instrument arms are situated on either side of the center camera arm and adjusted to avoid collisions with the other arms.^{1,2,35,44}

Robotic Dissection

During the robotic dissection, a field surgeon is seated at the patient's side and assists the dissection with a Terris atraumatic suction (Medtronic, Inc.). The console surgeon begins by ligating the superior vascular pedicle with the Harmonic device,

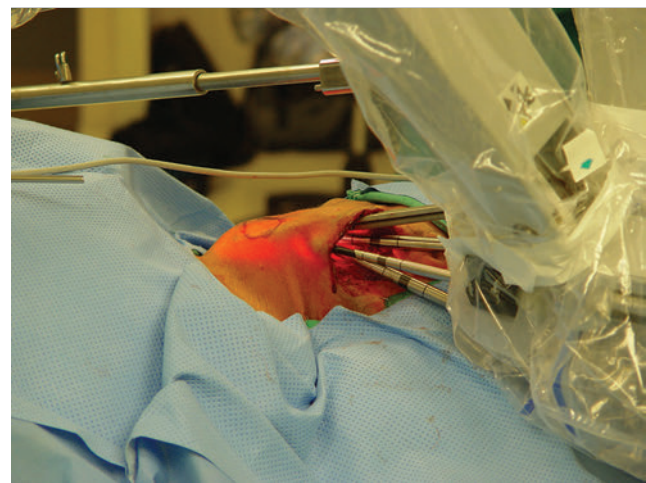


Fig. 15.5 Robotic arms deployed along the axis of the fixed retractor system. (Reprinted with permission from Terris D, Singer MC, Seybt MW. Robotic facelift thyroidectomy: patient selection and technical considerations. *Surg Laparosc Percutan Tech* 2011;21[4]:237–242.)

which allows the superior pole of the thyroid to be mobilized inferiorly and ventrally away from the inferior constrictor. The external branch of the superior laryngeal nerve can usually be visualized traversing the inferior constrictor muscle. The superior parathyroid gland is generally intimately associated with the posterior surface of the thyroid gland and is carefully dissected away and preserved.^{1,2,35,44}

The RLN is identified just proximal to its entrance into the larynx as it courses underneath the inferior constrictor (► Fig. 15.6) at a point approximately 1.2 cm lateral to the muscle origin on the cricoid cartilage.³⁷ By dissecting the RLN inferiorly for a short distance, the ligament of Berry is exposed. The ligament of Berry is divided with the Harmonic device with the RLN under direct visualization. Next, the isthmus is defined and divided with the Harmonic device.^{1,2,35,39,44}

The lateral border of the thyroid gland is mobilized by blunt dissection of the surrounding tissues. The middle thyroid vein followed by the inferior thyroid vessels are isolated and ligated with the Harmonic device, taking care to identify and preserve the inferior parathyroid gland. At this point, the remaining attachments between the thyroid and anterior trachea are divided with the Harmonic device, and the thyroid lobe is delivered from the surgical pocket.^{1,2}

Closure

Meticulous hemostasis of the surgical field is obtained, and a sheet of Surgicel (Ethicon, Inc.) is placed in the thyroid bed. The deep aspect of the incision is closed with interrupted, buried 4–0 Vicryl Sutures (Ethicon, Inc.). The skin edges are sealed with skin adhesive and a quarter-inch Steri-Strip (3M Corp.) No drains are used.^{1,2}

Postoperative Considerations

Because no drain is placed after the robotic facelift thyroidectomy, the patient is discharged on the day of surgery, provided there are no immediate postoperative complications or other

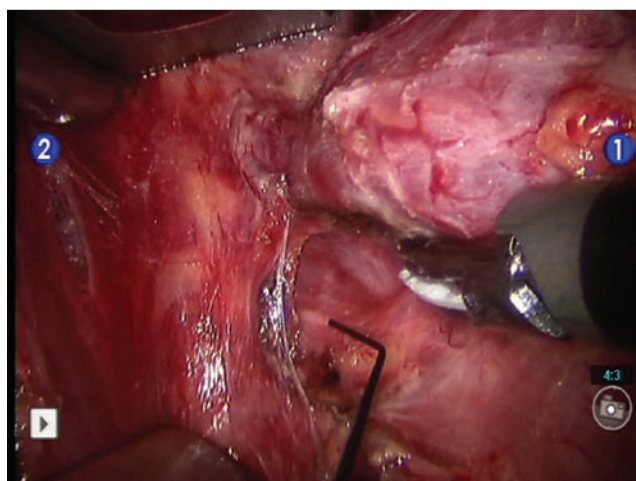


Fig. 15.6 Retraction of the thyroid ventrally allows identification of the recurrent laryngeal nerve seen at the tip of the nerve stimulator just inferior to the inferior constrictor muscle during robotic facelift thyroidectomy. The two active robotic arms are indicated by numbers 1 and 2, respectively, on the robotic screen. (Reprinted with permission from Terris DJ, Singer MC, Seybt MW. Robotic facelift thyroidectomy, II: Clinical feasibility and safety. *Laryngoscope* 2011;121[8]:1636–1641.)

medical contraindications. Patients should be counseled regarding the potential for mild neck edema due to the more extensive dissection, as well as expected transient hypoesthesia in the GAN distribution for several months postoperatively.

15.5 Conclusion

Patient-driven desires to improve cosmetic outcomes have fueled the development of alternative approaches to thyroid surgery. Remote access techniques exchange a visible anterior cervical scar for a distant, concealed scar. Although all of these approaches involve a greater extent of dissection, the robotic facelift thyroidectomy technique can be performed as an outpatient procedure without the use of a postoperative drain. Appropriate patient counseling and selection are essential, and staged procedures for bilateral surgery are feasible. In the hands of an experienced surgeon, remote access thyroidectomy can provide carefully selected patients with a surgically sound and cosmetically excellent result that is not achievable by other methods of thyroid surgery.

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16 Substernal Goiter

Sara L. Richer, Brian Hung-Hin Lang, Chung-Yau Lo, Dipti Kamani, and Gregory W. Randolph

16.1 Introduction

In 1920, William Stuart Halsted wrote “the extirpation of the thyroid gland for goiter better typifies perhaps more than other operations, the supreme triumph of the surgeon’s art.” The extension of a goiter from its original cervical position into the mediastinum, known as substernal goiter, presents unique challenges for the thyroid surgeon. The anatomical distortion, restricted surgical access of the thoracic inlet, and unpredictable vascularity can make substernal goiter surgery challenging and technically demanding. This chapter reviews the definition, clinical presentation, and surgical technique of substernal goiter with an emphasis on the appropriate preparation for achieving optimal surgical outcomes.

16.2 Definition and Classification of a Substernal Goiter

The word *goiter* is derived from the Latin word *gutter*, meaning *throat*, and is an enlargement of the thyroid gland. Although it has been difficult to define what constitutes a goiter (some have defined it based on varying weights or lengths), the definition of a substernal goiter is even less clear. Multiple surgeons have described the substernal goiter in different ways. Early surgeons defined the substernal goiter by position. Kocher defined a substernal thyroid as a gland in which some portion remains permanently retrosternal, and Crile defined the substernal goiter as thyroid growth down to the aortic arch.¹ Other positional definitions include a goiter with its lower position permanently remaining below the sternal notch with the neck in hyperextension or a goiter totally or partially located in the mediastinum that in operating position has its edge at least 3 cm below the sternal manubrium.^{2,3,4} It has also been defined radiographically as thyroid growth to the level of the fourth thoracic

vertebrae on X-ray examination.⁵ Other definitions have focused on the technique required to remove the goiter, such as one that requires mediastinal exploration and dissection for removal.⁶ In a review of the intrathoracic goiter definitions, the clinical definition found to be most relevant defined an intrathoracic goiter as a thyroid gland that has a portion which remains permanently retrosternal on neck examination without hyperextension.⁷ This classification can be made on physical exam and was found to be as sensitive as the other definitions for determining the presence of compressive clinical features and development of postoperative complications.

In addition, several authors have offered various classification schemes for substernal goiter in order to objectively describe the degree of substernal extension. Lahey classified substernal goiters into two grades according to the relationship to the aortic arch: grade I includes those extending nearly to the arch of the aorta, and grade II includes those extending to the arch of the aorta or beyond.⁸ Higgins described a classification scheme based on the percentage of goiter in the chest; goiters with > 50% in the neck are substernal, those with > 50% in the chest are partially intrathoracic, and those with > 80% in the chest are completely intrathoracic.⁹ Similarly, Cohen and Cho graded substernal goiters according to the percentage of mediastinal or intrathoracic component of the goiter (grade 1: 0–25%, grade 2: 26–50%, grade 3: 51–75%, grade 4: > 75%).¹⁰ A more practical classification scheme with associated anatomical correlates is useful for surgical planning and is demonstrated in ▶ Table 16.1.¹¹

16.3 Pathogenesis of Substernal Goiter

The vast majority of substernal goiters derive from a caudal migration of cervical goiters. This downward migration of the

Table 16.1 A substernal goiter classification based on anatomical relationships

Type	Location	Anatomy	Prevalence	Approach
I	Anterior mediastinum	Anterior to great vessels, trachea, recurrent laryngeal nerve	85%	Transcervical (sternotomy, only if intrathoracic goiter diameter is greater than thoracic inlet diameter)
II	Posterior mediastinum	Posterior to great vessels, trachea, recurrent laryngeal nerve	15%	As above; also consider sternotomy or right posterolateral thoracotomy if type IIB
IIA	Ipsilateral extension			
IIB	Contralateral extension			
IIB1	Extension posterior to both trachea and esophagus			
IIB2	Extension between trachea and esophagus			
III	Isolated mediastinal goiter	No connection to orthotopic gland; may have mediastinal blood supply	< 1%	Transcervical or sternotomy

Source: Reproduced from Randolph¹¹ with permission from Saunders.

cervical goiters into the thorax has been attributed to a combination of factors, such as the negative intrathoracic pressure generated during inspiration, repetitive forces of deglutition, the effect of gravity, and the large potential space of the mediastinum. The substernal components tend to migrate anterior to the trachea, esophagus, recurrent laryngeal nerve (RLN), and subclavian vessels in 85 to 90% of the cases.^{12,13} They may extend evenly on both sides or asymmetrically. Although some series reported a higher incidence of substernal extension on the left side, others have reported the opposite phenomenon.^{6,14,15,16}

In approximately 15% of substernal goiters, the goiter involves the posterior mediastinum. The posterior mediastinal goiter descends behind the trachea, great vessels, and RLN. The thyroid surgeon must be aware of this ventral position of the RLN so that it may be recognized before it is cut or stretched. The nerve may also be trapped between components of a posterior mediastinal goiter. The posterior mediastinal goiter may rest in a space bounded by the azygous vein inferiorly, vertebral column posteriorly, trachea and esophagus medially, and subclavian and innominate vessels anteriorly.^{17,18} Posterior

mediastinal goiters are more commonly found on the right side than the left, explained by the presence of the aortic arch and descending aorta, which obstructs the posterior descent on the left side.¹⁹

Even rarer, approximately 1% of substernal goiters are isolated to the mediastinum without any connection to the normal cervical thyroid. Several interesting theories have been put forward to explain the pathogenesis of such goiters. Some isolated mediastinal goiters may form from embryological fragmentation with hyperdescent of thyroid anlagen associated with cardiac and great vessel descent. Another theory proposes that such goiters form as exophytic nodules from the thyroid inferior pole, and over time there is attenuation of the nodule-thyroid stalk.¹¹ Finally, there is the “forgotten goiter,” which is a nodule representing a thyroid tissue fragment in the upper mediastinum from past goiter surgery. Recognition of the isolated mediastinal goiter is critical for presurgical planning because these goiters tend to derive their blood supply from the internal mammary and innominate arteries or directly from the intrathoracic aorta. ▶ Fig. 16.1 demonstrates a forgotten goiter recognized after hemithyroidectomy over 20 years prior.

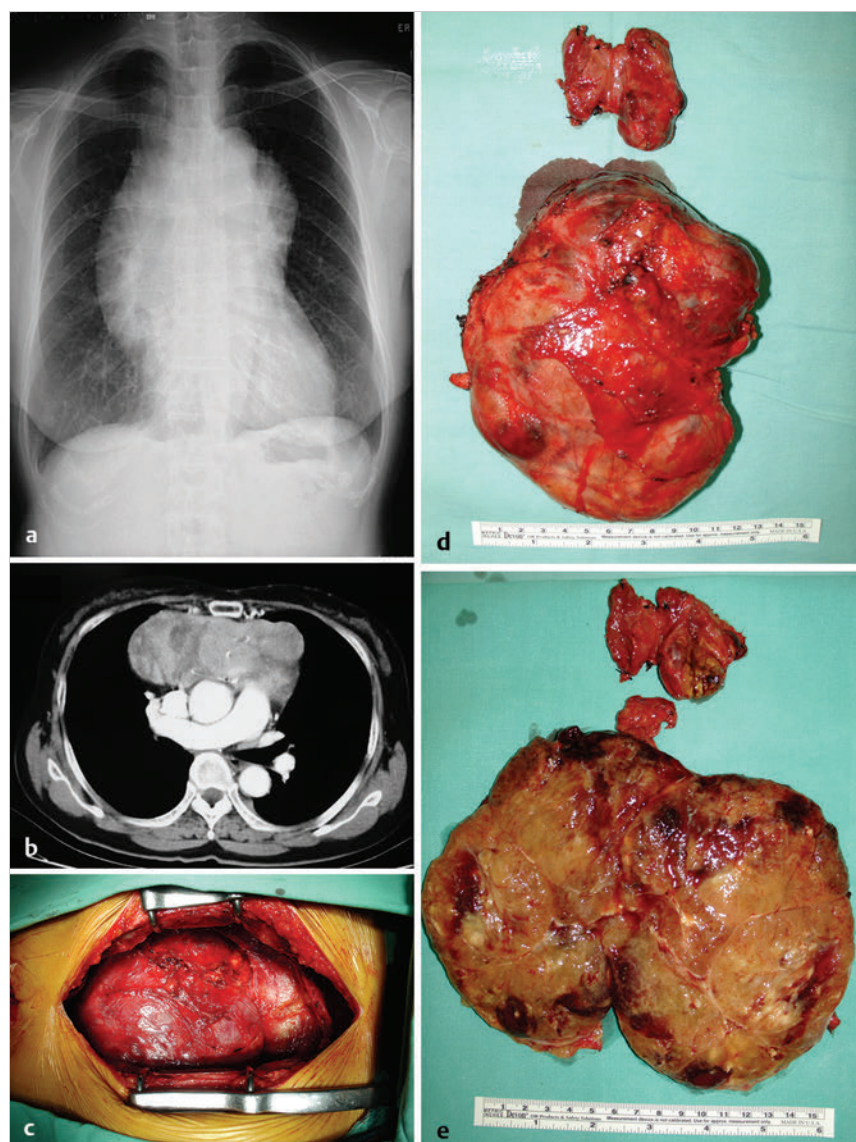


Fig. 16.1 (a) A posteroanterior chest radiograph and (b) a computed tomographic film of a large mediastinal goiter that developed after a hemithyroidectomy over 20 years ago. (c) An additional median sternotomy was required for the complete removal of (d, e) the mediastinal component.

16.4 Incidence and Prevalence

Multinodular goiter is common, affecting 4% of the US population and 10% of the British population. Iodine deficiency contributes to goiter formation, especially in noncoastal mountainous and lowland regions which are especially at risk for endemic goiter. The prevalence of substernal goiters is difficult to determine based on the various definitions and since the number of non-operative substernal goiters remains largely unknown. It is estimated to be present in 0.02% of the general population and 0.05% of females older than 40, based on screening radiography in Australia and the United States.^{20,21} The incidence of substernal goiter significantly increases with age; 60% of substernal goiters occur in patients older than 60.²⁰ In surgical series, the rates of substernal goiters in patients undergoing thyroidectomy have been estimated to be between 2.6 and 21%.^{22,23,24}

16.5 Clinical Presentation and Physical Exam

Most substernal goiters arise in the setting of a preexisting cervical goiter, grow slowly, and are infrequently malignant. Most patients present in the fifth decade or later, and there is a female preponderance, with a female to male ratio of 3:1.²⁵ A positive family history can be present in up to 30% of patients.²⁶ Although some patients are asymptomatic, presenting after an incidental finding on radiographic studies, others present with a palpable neck mass or with respiratory symptoms varying from a simple irritative cough to hoarseness, inspiratory stridor, or frank shortness of breath.^{2,13,27} Acute airway obstruction is an uncommon but life-threatening emergency for benign goiters and occurs almost exclusively in patients with substernal extension.²⁸ ► Fig. 16.2 demonstrates a patient with acute airway obstruction. The exact reason for the sudden onset of airway obstruction is unclear, but this has been thought to be related to sudden enlargement of the goiter due to hemorrhage, cystic degeneration, or malignant change within the substernal component.²⁹ In addition to respiratory distress, dysphagia and

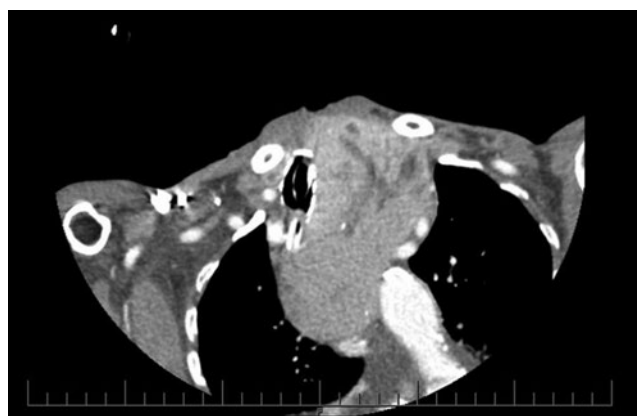


Fig. 16.2 Computed tomographic scan of a patient intubated emergently for respiratory compromise from a substernal goiter. The patient and family decided against surgery, and the patient died from airway compromise after elective extubation.

globus sensation are symptoms suggestive of local compression. Every patient should be questioned about signs of dyspnea, dysphagia, and dysphonia. When the neck vasculature is compressed, superior vena cava (SVC) syndrome or even cerebral edema may occur.³⁰ True SVC syndrome is almost exclusively associated with substernal malignancy and should be carefully radiographically assessed preoperatively. Hematemesis secondary to esophageal varices, chylothorax secondary to thoracic obstruction, and transient ischemic attack through “thyroid steal syndrome” have all been reported as initial presentations of substernal goiters.^{28,31}

16.6 Physical Examination

The physical exam of a patient presenting with a substernal goiter should focus on the airway. The larynx and trachea should be assessed for deviation from the midline, typically to the contralateral side of an asymmetrically enlarged cervical goiter. It is imperative to endoscopically examine the vocal cords in all patients with a substernal goiter. Vocal cord palsy without previous surgery is suggestive of the presence of invasive thyroid malignancy until proven otherwise. Occasionally, vocal cord paralysis may occur as a result of the mass effect of the large goiters, and bilateral vocal cord paralysis in a nonmalignant substernal goiter has been reported.³² Patients should be asked to raise both arms above the neck to elicit the Pemberton's sign (flushing of the face, dilation of the external jugular veins, and/or symptomatic airway compression).^{4,30} Other clinical features, such as Horner's syndrome, can occur occasionally.²⁷ The size and consistency of the thyroid enlargement should be noted, although up to 30% of patients with substernal goiters may have no palpable cervical component.^{6,13} The physical exam can underestimate the goiter, especially in patients with a short neck or morbid obesity. The World Health Organization grading system for goiters can be documented (► Table 16.2). Finally, the cervical lymph nodes should be adequately assessed.

16.7 Preoperative Assessment

16.7.1 Thyroid Function Testing

After a complete history and physical examination, the preoperative assessment in substernal goiter focuses on adequate surgical preparation. All patients should undergo thyroid function testing. Hyperthyroidism is not uncommon in substernal goiters.^{4,13,33,34,35} Screening for hyperthyroidism is especially important because iatrogenic iodine exposure should be

Table 16.2 The World Health Organization grading system for goiters

Grade	Description
Grade 0	Impalpable/invisible
Grade 1a	Palpable but invisible even in full extension
Grade 1b	Palpable in neutral position/visible in extension
Grade 2	Visible but no palpation required to make diagnosis
Grade 3	Visible at a distance

avoided due to the risk of development of overt hyperthyroidism.^{36,37} In particular, elderly patients with hyperthyroidism may be more prone to cardiac complications, such as atrial fibrillation. Additionally, hypothyroidism has been reported in up to 16% of cases.¹³ A massive, firm goiter can result from a fibrotic variant of Hashimoto's disease.

16.7.2 Imaging

A CT scan is essential in the assessment of patients with substernal goiters. The CT scan provides important information for surgical planning, including the intubation and airway management, great vessel management, and the anticipation of invasive malignancy. It provides important information, such as tracheal deviation, tracheal compression, retrotracheal extension, as well as esophageal and major vessel displacement and/or compression.³⁸ The demonstration of these relationships by preoperative CT assists not only in surgical planning but also in the anesthesia provider's intubation approach. In addition, CT findings, such as mediastinal lymph nodes and loss of tissue planes, provide information for diagnosing invasive malignancy. Determining the relationships of mediastinal structures by CT allows for safe operative management for large posterior mediastinal goiters. CT scan is also essential in planning for the potential need for sternotomy.

16.7.3 Fine-Needle Aspiration

The routine use of fine-needle aspiration (FNA) is controversial in substernal goiters. The risk of malignancy ranges from 3 to 16% in selected series.³⁰ Because there is already an indication for surgery on the basis of a substernal goiter, FNA can be omitted if it would not alter the plan of management.^{6,14,39,40} Furthermore, there is a small potential risk of bleeding into a substernal nodule, which may convert a compromised airway to an acute obstruction. However, if there is any suspicion of malignancy during history taking, physical examination, or radiographic evaluation, FNA evaluation may enhance an accurate preoperative diagnosis and facilitate perioperative planning.

16.7.4 Other Studies

Plain chest radiography provides limited information on the size or extent of the substernal goiter, though in some patients the first sign of a substernal goiter may be a mass associated with tracheal narrowing, tracheal deviation, or superior mediastinal widening on the chest radiograph.⁴¹ Up to 41% of patients with substernal goiters have a normal chest radiograph preoperatively.^{13,35,42,43,44} Interestingly, tracheal diameter estimated on plain chest radiography films is significantly larger than that measured on axial CT scan and in cadaveric studies.^{38,45} Therefore, the CT scan is a better preoperative tool for airway measurement and planning. Functional tests, such as pulmonary studies and flow volume loops, have not been considered as a routine part of preoperative workup. Although the presence of airway obstruction can be accurately determined with these studies, they do not significantly affect the management of patients.

16.7.5 Extent of Thyroidectomy

Total thyroidectomy should be carried out in patients with bilateral goiters. If the substernal goiter involves only one lobe, and the contralateral lobe is essentially normal, lobectomy can be carried out to relieve tracheal compression with a lower risk of complications.⁴⁶ In experienced centers, the rates of permanent recurrent laryngeal nerve paralysis and hypoparathyroidism for total thyroidectomy did not appear to be significantly greater than those undergoing less extensive thyroid resections.⁴⁷ Therefore, a total thyroidectomy is recommended as the procedure of choice for the majority of patients with bilateral substernal goiters treated in experienced centers.

16.8 Surgical Technique in Substernal Goiter

16.8.1 Intubation

The intubation of a patient with a substernal goiter should be carried out carefully to avoid laryngeal trauma and edema or loss of airway control. Tracheal deviation does not result in a difficult intubation, and there is no benefit to routine fiberoptic intubation.⁴⁸ One series reported difficult intubation was present in 11.9% of goiter surgeries, with patient age being the only significant factor.⁴⁹ Intubation should be carried out carefully by an experienced anesthesiologist because an emergency tracheotomy is not an easy option for airway management in the patient with substernal goiter.

16.8.2 Early Surgical Steps

Most of the surgical principles in thyroid surgery originally defined by Theodore Kocher remain relevant to goiter surgery and should be similarly applied in substernal goiter procedures.⁵⁰

Upon induction of general anesthesia and endotracheal intubation, the patient is placed in a supine position with the neck extended. The patient is then placed in a semisitting position in order to reduce the neck venous congestion because substernal goiters may extend into the thorax, causing compressive venous engorgement. If a sternotomy is considered, the chest should be prepped and draped, with the thoracic surgeon on standby.

A collar skin incision should be made. A slightly higher skin incision (1–2 cm more cephalad than normal) is useful in a low-lying goiter because it allows better access to the lobe inferiorly by facilitating upward traction on the gland after ligation and division of the upper pole vessels. Upper and lower subplatysmal flaps are developed and sutured or retracted.

The strap muscles can be mobilized from the sternocleidomastoid muscles to facilitate subsequent mobilization of the thyroid lobes. The strap muscles are separated in the midline. Some surgeons routinely transect the strap muscle to improve access of the gland, but this is frequently not necessary in substernal goiter surgery.^{14,15} In case of strap transection, the muscles should be divided as cranially as possible so as to lessen the effect of nerve denervation.

16.8.3 Thyroid Mobilization, Parathyroid Glands, and Recurrent Laryngeal Nerve

An important first step in goiter surgery is to identify the carotid sheath because this is the landmark for the lateral boundary of the goiter. Locating the carotid sheath contents also allows a surgeon to “follow the neck into the chest” and become oriented as to the best approach for the specific goiter one is facing. It is not necessary to deliberately look for and ligate the middle thyroid vein as the first step because the vein is often pushed and compressed by the enlarged thyroid lobe. Dissection should be kept close to the thyroid capsule and move cranially toward the upper pole. Once the lateral aspect of the upper pole has been mobilized, the medial space between the cricothyroid muscle and thyroid lobe is opened. This step is best facilitated by gentle lateral retraction of the upper pole. The usual precaution of identifying and preserving the external branch of the superior laryngeal nerve should be made. Once the upper pole has been mobilized and delineated, the upper pole vessels are doubly ligated close to the thyroid capsule.

The superior parathyroid gland should be identified next and should be considered for reimplantation if its viability is doubtful. The parathyroid glands may be adherent to the thyroid capsule or considerably displaced; therefore special attention should be made to the superior parathyroid because the inferior parathyroid may not be readily identifiable. After removal, the thyroid should be carefully examined for capsular parathyroid glands, which should be reimplanted as necessary.

The substernal goiter can significantly alter the position of the RLN, which should be identified before goiter delivery. In one series, the RLN was entrapped in fascial bands or splayed on the goiter in 16% of cases.⁵¹ This puts the nerve at high risk for traction or avulsion injury if not properly identified. The RLN can be identified where it crosses the inferior thyroid artery and can be traced superiorly in some cases. In many large goiters, the RLN must be identified through a superior approach and dissected away from the goiter in a retrograde fashion off the posterior surface of the gland. The superior approach involves identifying the RLN entering the larynx once the upper pole has been fully reflected. As in all thyroidectomies, when contemplating bilateral surgery, the ipsilateral vagus and RLNs should have adequate electromyographic (EMG) activity prior to proceeding with dissection on the other thyroid lobe.

The substernal component can then be retracted into the neck base. Upward traction allows rotation of the cervical portion of the gland from lateral to medial and also facilitates gentle, blunt finger dissection on the surface of the capsule through areolar planes around all borders of the goiter. Attachments to the great vessels are generally loose areolar tissue, which can be easily separated, though attachments to the carina can be more difficult to dissect.⁵² The surgeon's finger should be used to confirm that all palpable adhesions have been divided, and the substernal component could now be delivered into the neck. Apart from using the surgeon's finger, instruments, such as a sterile tablespoon, delivery forceps, and Foley catheters, have been employed in the past to facilitate the delivery of the substernal portion out to the cervical wound.^{53,54} Once the intrathoracic component has been delivered into the wound,

the gland is retracted medially, and the remainder of the operation proceeds in the typical fashion.⁵⁵

A drain can be considered for patients with obesity, significant dead space, or physical limitations, which would make detection of a hematoma more difficult. However, drain placement should not be expected to reduce the rate of postoperative hemorrhage.

16.8.4 Sternotomy in Substernal Goiter

Most authors have demonstrated convincingly the feasibility and safety of operating and delivering a substernal goiter through a standard cervical approach in the vast majority of cases.^{2,3,6,15,30,39,56,57} In fact, the routine or liberal use of a sternotomy or thoracotomy should be avoided unless it is absolutely necessary. The adoption of more routine sternotomy appears to be associated with an increased operative morbidity and the length of hospital stay.³⁹ Authors have shown that the need for sternotomy is related to the position of the goiter, rather than size.⁵⁸ Several surgical series have reported sternotomy use with a goiter that extends beyond the aortic arch.^{19,58} Others have reported extension below the carina or a “conical shape” of the goiter to be associated with sternotomy use.⁵²

► Fig. 16.3 demonstrates a patient with a subcarinal goiter that required a partial sternotomy for adequate exposure. Other factors associated with sternotomy include loss of fat planes on CT and recurrent or malignant disease.^{19,59} Primary substernal goiters or those with posterior mediastinal extension have an intrathoracic blood supply, which may necessitate sternotomy. When required, a partial sternotomy is typically used, reserving a full sternotomy for exceptional cases. Another potential, but rare, situation requiring a sternotomy or a thoracotomy is the so-called crossed substernal or posterior mediastinal goiter (type IIB). This is a rare variant of substernal goiter in which there is extension from one side to the opposite side of the posterior mediastinum. A right anterolateral thoracotomy through



Fig. 16.3 Computed tomographic scan of a substernal goiter extending below the carina. The patient required a partial sternotomy for successful removal.

Table 16.3 Comparison of the proportion of substernal goiters, need for sternotomies/thoracotomies/tracheostomies and the number of in-hospital deaths in substernal goiters in surgical series reported over 2 decades

First author, year	No. of thyroid resections	No. (%) of substernal goiters	No. (%) of sternotomies/ thoracotomies	No. of postoperative tracheostomies	No. of hospital deaths
Sand 1983 ⁷³	n/a	31	6 (19.4)	0	0
Allo 1983 ³⁰	872	50 (5.7)	1 (2.0)	0	0
Katlic 1985 ²	n/a	80	2 (2.5)	0	0
Melliere 1988 ⁷⁴	2,908	58 (2.0)	5 (8)	0	0
Michel 1988 ³⁵	170	34 (20.0)	4 (11.8)	1	0
Shaha 1989 ⁴⁶	370	72 (19.5)	1 (13.9)	2	0
Madjar 1995 ⁴	222	44 (19.8)	6 (13.6)	0	0
Torre 1995 ⁶⁵	3,338	237 (7.1)	8 (3.4)	5	2
Hsu 1996 ⁴⁷	1,585	234 (14.8) ^a	4 (1.7)	3	0
Moron 1998 ⁷⁵	234	16 (6.8)	3 (1.9)	0	0
Nervi 1998 ⁷⁶	5,263	621 (11.8)	44 (7.1)	1	0
Netterville 1998 ⁵⁷	150	23 (15.3)	0 (0.0)	0	0
Pulli 1998 ³⁹	n/a	21	3 (14.3)	0	0
Vadasz 1998 ⁶⁰	1,458	175 (12.0)	42 (24.0)	2	2
Rodriguez 1999 ²⁷	780	72 (9.2)	7 (9.7)	0	0
Abdel Rahim 1999 ⁶²	n/a	103	0 (0.0)	13	0
Dedivitis 1999 ⁷⁷	204	32 (15.7)	2 (6.3)	0	1
Ozdemir 2000 ⁷⁸	1,320	30 (2.3)	2 (6.7)	0	0
Mussi 2000 ¹⁶	7,480	374 (5.0)	43 (11.5)	0	0
Hedayati 2002 ¹²	381	116 (30.4)	2 (1.7)	2	1
Erbil 2004 ¹³	2,650	170 (6.4)	12 (7.1)	0	0
Shen 2004 ³	n/a	60	1 (1.7)	0	1
Chow 2005 ²⁴	287	24 (8.4)	2 (8.3)	1	0
Sancho 2006 ⁷⁹	n/a	35	13 (37.1)	3	2
Chauhan 2006 ¹⁴	755	199 (26.4)	0 (0.0)	0	0
Ahmed 2006 ¹⁵	267	40 (15.0)	9 (22.5)	5	0

Abbreviation: n/a, not available.

^a Recurrent substernal goiters.

the fourth interspace is recommended for this type of substernal goiter.⁶⁰

16.8.5 Tracheomalacia and Tracheostomy

At the end of the thyroidectomy, prior to the closure of the wound, the surgeon should check the integrity of the trachea by observation during the respiratory cycle and by gentle pressure between the thumb and index finger. This can be done more effectively by asking the anesthesiologist to pull out the endotracheal tube slightly while the surgeon applies gentle pressure to the trachea. An obvious collapse or softening of the

tracheal rings indicates tracheomalacia, a condition that is poorly understood, extremely rare, and reversible.^{3,61,62,63} Tracheomalacia will manifest as postoperative airway obstruction with paradoxical collapse of the airway during inspiration because the tracheal ring softens and loses strength secondary to chronic extrinsic compression. The reported incidence of tracheomalacia secondary to large goiters ranged from 0.001 to 1.5% in surgical series.^{33,42,63} With the advances in anesthesia techniques and the early treatment of large substernal goiters, the true incidence of tracheomalacia from goiter compression is likely lower. In situations when the presence of tracheomalacia is certain, some authors would recommend keeping the endotracheal tube in place for 24 to 48 hours before attempting a controlled extubation.⁶⁴ Other options, including continuous

positive pressure ventilation, tracheal grafting, tracheopexy, and postoperative tracheostomy, have been described.⁶⁵

Although tracheostomy is rarely indicated in the postoperative period after thyroidectomy, the incidence ranged from 0 to 12.6% in reported thyroidectomy series for substernal goiters (► Table 16.3). Apart from tracheomalacia, other indications for tracheostomy would include bilateral vocal cord palsies, laryngeal edema, postoperative bleeding, and traumatic endotracheal intubation.^{47,62}

16.8.6 Outcomes

The complications of substernal goiter resection are primarily hemorrhage, RLN paralysis and hypoparathyroidism. Substernal goiter surgery can be associated with higher complication rates, which are reported to be as high as 30 to 44% in some series.^{19,66} Patients with recurrent goiter and malignancy lead to this increased complication rate.¹⁹ Others have demonstrated no increased complication rate but did report longer operative times and hospital stay.⁵⁹ The rates of postoperative RLN paralysis vary in the literature from 2 to 27%.^{67,68,69} Similarly, rates of permanent hypoparathyroidism vary in the literature from 1 to 8% of patients undergoing goiter resection.^{67,70} It is encouraging to note that the complication rate in expert hands is expected to be low.^{27,70,71} Also encouraging, after goiter resection, positional dyspnea improves in 82.4% of patients.⁷² Therefore, although the standard risks apply to substernal goiter surgery, in expert hands the rate of risk is low and the patient benefit is high.

16.9 Conclusion

Surgical management of substernal goiters poses a challenge to thyroid surgeons but reflects the ultimate triumph of the surgeon's art in thyroid surgery. The majority of the procedures can be accomplished through a cervical incision, and an additional sternotomy, thoracotomy, or tracheostomy is reserved for a small subset of patients only. Because the condition was first described more than a century ago, improvement in preoperative diagnosis and evaluation and refinements in surgical technique have ensured safe and excellent outcomes in patients undergoing thyroidectomies for substernal goiters.

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17 Surgical Management of Medullary Thyroid Cancer

Jennifer Yu and Jeffrey F. Moley

17.1 Introduction

Medullary thyroid carcinoma (MTC) is an uncommon malignancy with unique clinical and pathological features that influence patient evaluation and surgical approach. MTC accounts for 5 to 10% of all thyroid cancers. MTCs arise from the parafollicular or thyroid C cells and do not take up iodine, whereas differentiated thyroid cancers (papillary and follicular) arise from the thyroid follicular parenchyma and do concentrate iodine. MTC is hereditary in 25% of cases (multiple endocrine neoplasia type 2 syndromes).¹ Early surgical intervention is the cornerstone of treatment with complete excision of the primary tumor and nodal metastases. Residual and/or recurrent disease in the neck is also generally managed by surgical resection because adjuvant therapies have yet to demonstrate a durable benefit. New systemic treatments with targeted molecular therapies have shown promise in clinical trials.

17.2 Pathology

C cells constitute approximately 1% of thyroid cells, contributing 0.1% of the normal thyroid mass, and are derived embryologically from the ultimobranchial body and the fourth branchial pouch. They are found throughout the thyroid but are concentrated in the posterior upper third of the gland, generally arranged in groups of six to eight cells at the edge of thyroid follicles. C cells are responsible for the production of several peptides and hormones, the most notable of which is calcitonin, a polypeptide hormone whose physiological effect is to decrease serum calcium. Calcitonin has minimal, if any, effect on normal calcium homeostasis in humans, and no appreciable functional deficit has been identified with loss of C cells following total thyroidectomy. However, as a product of C cells, and therefore of MTC cells, calcitonin has been shown to be a highly sensitive and specific tumor marker. It can be measured in the blood, both in the basal state and after stimulation, by administration of a secretagogue, such as calcium or pentagastrin (not available in the United States). Calcitonin is useful in prethyroidectomy screening of patients with hereditary MTC and in posttreatment surveillance of all MTC patients.

Tumors of MTC are usually slow-growing and indolent, grossly noted to be gray and firm with well-demarcated margins, and they are commonly found in the upper portion of the thyroid lobes. On histology, cells are uniform and generally polygonal or spindle shaped, with central nuclei and finely granular eosinophilic cytoplasm (► Fig. 17.1). Most MTC cells also stain positive for carcinoembryonic antigen (CEA) and negative for thyroglobulin.² A feature of MTC tumors found in one-third of cases is the presence of stromal amyloid, which is composed of calcitonin or procalcitonin molecules. Sporadic tumors vary considerably in size, but most are solitary, whereas the majority of tumors in familial forms are multifocal and bilateral.³ C-cell hyperplasia, believed to be a precursor to malignant transformation in MTC, is most commonly present in familial forms and can often be found distant to the primary carcinoma within the gland.^{4,5,6,7}

17.3 Clinical Course

Patients with sporadic MTC or index cases of familial MTC often present with a palpable mass within the thyroid or neck. Sporadic MTC may arise clinically at any age, but the incidence typically peaks between the fourth and sixth decade of life, considerably later than in patients with known familial syndromes. Sporadic MTC also demonstrates a slight female predominance.^{8,9} Approximately 15% of patients who present with clinically apparent disease may be symptomatic with dysphagia, dyspnea, or hoarseness; nodal metastases are present in regional lymph nodes in more than 50% of patients who present with palpable primary tumors.¹⁰ The most frequently involved lymph nodes reside in the central compartment (level VI), followed by levels II through V in the ipsilateral jugular chain of nodes, then the contralateral lateral nodes.¹¹ Metastatic spread to the upper and anterior mediastinum may be observed, and hematogenous dissemination to distant sites, including the liver, lungs, bone, brain, and soft tissues, may occur throughout the course of MTC.^{1,11} Diagnosis of distant metastases may be made more difficult due to the fine miliary pattern of metastatic disease, which is poorly visualized by standard imaging; however, diagnostic laparoscopy with direct visualization of the liver may help to identify small metastatic deposits in 25% of patients with elevated calcitonin levels following therapeutic surgery.¹²

Per the American Joint Committee on Cancer (AJCC) TNM classification system, the 10-year survival rates for patients with stages I through IV disease are 100%, 93%, 71%, and 21%.¹³ Adjusted 10-year survival rates range from 70% to >85%; however, higher long-term survival rates up to 98% have been reported for patients whose serum calcitonin levels return to normal after surgery.^{11,13,14,15,16,17} In a series of 1,252 patients diagnosed with MTC between 1973 and 2002 who were monitored by the Surveillance, Epidemiology, and End Results (SEER)

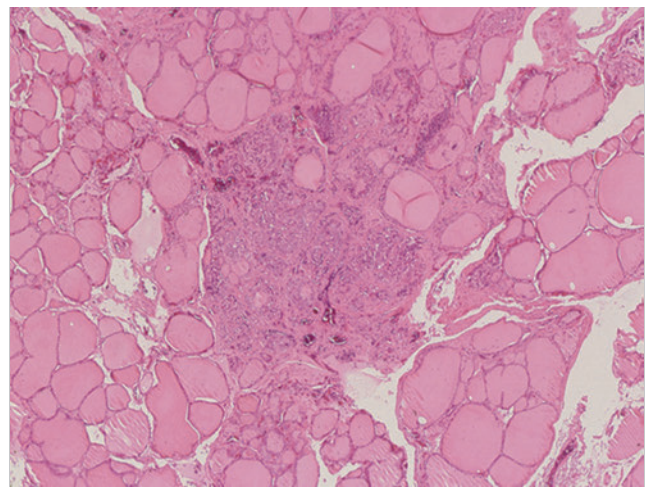


Fig. 17.1 Micrograph of medullary thyroid carcinoma (hematoxylin-eosin staining).

registry, 48% were diagnosed with localized disease, 35% with extension beyond the thyroid and regional disease, and 13% with distant metastases. A similar trend was revealed in 10-year survival rates at 95.6%, 75.5%, and 40%, respectively. The average size of primary tumor at the time of diagnosis was 2.8 cm. Multivariate analysis indicated that older age, higher tumor stage at diagnosis, lesser extent of thyroidectomy, and external beam radiation therapy (EBRT) were significant negative predictors of overall survival.¹⁸ In several other studies, age at diagnosis and tumor stage were the most sensitive prognostic factors; other predictors included postoperative basal calcitonin levels, extent of surgical intervention, and presence of distant metastases.^{16,19}

17.4 Familial MTC Classification

Though the majority of MTC is sporadic in origin, a familial syndrome must be considered in any patient presenting with a new diagnosis of MTC. Multiple endocrine neoplasia types 2A and 2B (MEN 2A and MEN 2B) are the hereditary syndromes that include MTC as a hallmark, though these vary in aggressiveness of malignancy and associated conditions. Familial non-MEN MTC (FMTC) is characterized by the presence of MTC only and has been designated a variant of MEN 2A by the new American Thyroid Association (ATA) guidelines (Wells, et al).⁸² All are autosomal-dominant conditions and have a high penetrance for MTC (>90% of affected patients will develop MTC during their lifetime). MEN 2A is the more common syndrome, accounting for more than 90% of hereditary cases. Other features of MEN 2A are unilateral or bilateral pheochromocytoma (40–50% penetrance), and hyperparathyroidism (10–30% penetrance); less common findings include a cutaneous condition (lichen planus amyloidosis) or Hirschprung's disease.^{20,21,22}

MEN 2B patients develop MTC in 100% of cases, and pheochromocytoma in 40%, but this group of patients is distinguished by different comorbid conditions, which include multiple mucosal neuromas, "marfanoid" habitus, intestinal ganglioneuromatosis, medullated corneal nerve fibers, and megacolon.²³ MEN 2B accounts for approximately 5% of patients with familial disease, and these MTC tumors are often present at birth. MTC in MEN 2B is a more aggressive variant, with early metastasis, making early diagnosis and treatment critical for successful management. Thyroidectomy is recommended in infancy, when possible (► Fig. 17.2).²¹ Lastly, FMTC is a variant of MEN 2A characterized by predisposition to MTC only, though caution is warranted because some kindreds designated as FMTC have subsequently developed pheochromocytoma and parathyroid abnormalities.

17.5 Genetic Analysis

The *RET* (rearranged during transfection) proto-oncogene on chromosome 10q11.2 plays a critical role in the understanding of MTC, both in diagnosis and in familial screening. *RET* encodes a tyrosine kinase receptor protein that is composed of an extracellular domain containing a ligand-binding site with a cysteine-rich region, a transmembrane domain, and two intracellular tyrosine kinase domains.^{3,24} All of the hereditary MTC syndromes are caused by missense germline mutations in *RET*. Interestingly, these mutations are "gain of function" mutations



Fig. 17.2 Total thyroidectomy specimen with multiple enlarged central lymph nodes from multiple endocrine neoplasia 2B patient. Photo courtesy of Dr. Jeffrey F. Moley.

as opposed to "loss of function" germline mutations seen in all other hereditary cancer syndrome genes. Somatic (non-germline) mutations of *RET* have also been identified in 40 to 50% of sporadic MTC cases.²⁵ In sporadic MTC, patients with somatic codon 918 *RET* mutations have been found to have more aggressive disease progression and worse prognosis.²⁵

There are strong genotype–phenotype correlations in the MEN 2 syndromes. Disease severity and expression of associated pathologies (pheochromocytoma, hyperparathyroidism, Hirschprung's disease, lichen planus amyloidosis, and MEN2B phenotype) correlate with the codon and functional domain of mutation within the *RET* protein. For virtually all MEN 2A patients, the mutation occurs within the cysteine-rich extracellular domain, which results in ligand-independent receptor dimerization and constitutive activity.²⁶ In the FMTC variant, mutations are usually similar to those in MEN 2A, but some families have mutations in the intracellular domain. Unlike MEN 2A and FMTC, MEN 2B nearly always involves the same codon 918 mutation, in the intracellular tyrosine kinase domain.²⁷

The increasing availability of genetic analysis over the last 20 years has revolutionized treatment of patients with hereditary syndromes. Now, based on identification of a mutated *RET* allele, tumor aggressiveness and disease course can be much more clearly predicted, and this greater knowledge of

genotype–phenotype correlations translates into timely and appropriate patient counseling. The ATA recommends *RET* testing as early as possible to patients with family history consistent with MEN 2 or FMTC; for MEN 2B, this should occur shortly after birth, and for MEN 2A and FMTC, testing should be performed before 5 years of age.²⁸ In families with a known specific *RET* mutation, a targeted approach can be employed to detect its presence. For patients with newly diagnosed MTC or in families with uncharacterized *RET* mutations, the usual strategy currently employed is to sequence exons 10 and 11 (codons 609, 611, 618, 620, 634) and exons 13, 14, 15, and 16 where the majority of mutations are found.

17.6 Diagnostic Evaluation

In the initial consultation of a patient presenting with MTC, a full patient and family history should be obtained, and particular attention should be placed on the history of any thyroid or parathyroid disease, uncontrolled hypertension, sudden death, or adrenal tumors. Every patient should be considered to have possible familial MTC until proven otherwise, and genetic screening should be offered to patients with MTC or with other associated features, including lichen planus amyloidosis or Hirschsprung's disease.^{3,22} On physical exam, any palpable mass should be assessed for size or fixation to surrounding structures, and the presence of multiple nodules, lymphadenopathy, or evidence of distant metastases should be noted. Computed tomography of the neck and chest is especially helpful. Particularly in MEN 2B patients, several overt clinical features, such as tongue nodules or a prominent mid-upper lip, may be present. In patients presenting with symptoms of respiratory difficulty or hoarseness, direct laryngoscopy for examination of the vocal cords should be done as this could indicate extensive local disease and possible involvement of the recurrent laryngeal nerve. Patients with high levels of calcitonin or metastatic disease may also present with symptoms of flushing, diarrhea, and weight loss.

Diagnostic workup should proceed with fine-needle aspiration (FNA) biopsy of the dominant nodule and include immunohistochemical staining for calcitonin. This has been shown to be successful in diagnosing MTC in approximately 50 to 80% of patients.^{9,29,30}

Preoperative laboratory testing should include measurement of serum calcitonin, CEA, metanephrines, normetanephrines, and calcium levels. *RET* proto-oncogene analysis should be performed for any newly diagnosed MTC patient. Serum calcitonin has proven to be a sensitive and cost-efficient marker in detecting MTC; however, routine measurement in patients with nodular thyroid disease has remained controversial. Several studies have demonstrated an incidence of MTC in 0.5 to 2% of patients without suspected malignancy, and the benefit in reaching an earlier diagnosis and subsequent treatment suggests that implementation of routine calcitonin measurement may be an effective surveillance option.^{30,31,32} Though calcitonin levels may be mildly elevated in other clinical conditions (e.g., renal insufficiency, neuroendocrine tumors), a basal or stimulated calcitonin level > 100 pg/mL strongly suggests the presence of MTC, and the extremely elevated level alone is an indication for surgery. Similarly, a basal level > 10 to 20 pg/mL necessitates further workup of possible MTC.^{23,30,31,32,33,34}

Serum CEA levels are also helpful in the risk stratification of patients with MTC. Preoperative levels > 30 ng/mL have been

shown to portend a poor prognosis for surgical curability and are associated with involvement of local lymph nodes in approximately 70% of patients; at levels > 100 ng/mL, 90% of patients had contralateral neck lymph node involvement, and 75% were found to have distant metastases.³⁵ All MTC patients > 8 years of age should undergo biochemical testing for pheochromocytoma with plasma metanephrines and catecholamines or 24-hour urine collection for metanephrines or catecholamines. If positive, the patient should undergo treatment for the pheochromocytoma prior to definitive thyroidectomy for MTC. Finally, hyperparathyroidism found by elevated calcium and parathyroid hormone levels is managed with concurrent parathyroidectomy at the time of surgery for MTC.

Imaging plays a vital role in the assessment of MTC and first involves a neck ultrasound with lymph node mapping of the cervical compartments. This is critical in the preoperative setting because the sensitivity of intraoperative palpation to detect nodal metastases is only 64%, even when performed by experienced surgeons.¹⁰ Sonographic findings of MTC commonly include hypoechogenicity, internal vascularity, and calcifications similar to other thyroid malignancies.³⁶ In MTC patients presenting with a palpable thyroid nodule, more than 75% will have associated nodal metastases, and 10 to 15% will also demonstrate evidence of distant disease.^{10,37} MTC does not concentrate iodine and will appear as a cold nodule on thyroid scintigraphy. Computed tomographic (CT) imaging of the neck, chest, and abdomen may reveal distant sites of involvement, particularly in the lungs, liver, and mediastinal lymph nodes, and local mass effects (► Fig. 17.3). Primary tumors have relatively nonspecific CT features but generally appear as nodules with calcifications. As mentioned earlier, lung and liver metastases can be quite small, numerous, and have a miliary appearance. Magnetic resonance imaging (MRI) with contrast administration can also be used in evaluation of metastatic disease and is considered the most sensitive imaging technique for detecting liver metastases. Bone lesions are typically best seen either on axial MRI or on bone scintigraphy.³⁸ Use of fludeoxyglucose positron emission tomography (FDG-PET) remains controversial because some studies have shown FDG-PET to have low sensitivity.^{38,39,40} Serum calcitonin levels have been shown



Fig. 17.3 Computed tomographic scan of advanced medullary thyroid carcinoma with tracheal compression.

to correlate well with tumor volume, and distant metastases are generally associated with elevated calcitonin levels; imaging is therefore recommended for these patients and for those with local lymph node metastases.⁴¹

17.7 Initial Surgical Approach

Surgery for MTC is the most important initial patient treatment, and early intervention is of paramount importance due to the more aggressive nature of MTC and the higher rates of recurrence and mortality when compared to differentiated thyroid cancer. Surgery also offers the only possible definitive cure for MTC and is a very effective option for palliation. Systemic therapies, while showing promise, are not curative.⁴² Outcomes are improved in patients with complete remission following surgical resection when compared to patients with biochemically persistent disease (i.e., persistent elevation of calcitonin levels) or to those with distant metastatic disease.

For patients with familial syndromes, the best curative option is complete surgical resection before malignant transformation or before spread beyond the thyroid gland.^{3,43} Per the ATA, prophylactic thyroidectomy should be recommended to all patients with positive genetic testing for hereditary MTC who have not yet developed clinically apparent disease.²⁸ Timing of surgery differs based on the genotype–phenotype correlations, and risk levels developed by the ATA regarding aggressiveness of disease are used as guidelines for patients with hereditary syndromes. For instance, patients with mutations involving codon 918, associated with MEN 2B and the youngest age of onset of MTC, highest risk of metastases, and disease-specific mortality, are given an ATA level D and are recommended to undergo prophylactic total thyroidectomy in infancy. This is in contrast to patients with ATA level A mutations, considered at lowest risk, who are advised to undergo thyroidectomy prior to 5 years of age but who may consider the option to delay surgery beyond age 5 years if certain screening criteria are met (i.e., normal annual basal serum calcitonin, normal annual neck ultrasound, less aggressive MTC family history).²⁸

In our 2005 study of children with MEN 2A *RET* mutations, no evidence of persistent or recurrent MTC (as indicated by elevated serum calcitonin levels) was found in 44 of the 50 children who underwent total thyroidectomy and central lymph node dissection before age eight years.⁴³ A European series of 207 patients with MEN 2A reported that none of the children younger than 14 years of age developed lymph node metastases.⁴⁴ We have treated bulky nodal metastatic disease in a 9-year-old index MEN 2A patient, and cervical lymph node metastases developed in a teen 10 years after a preventive thyroidectomy. The performance of a central neck lymph node dissection should be based on the calcitonin level and the preoperative physical exam and ultrasound. Current recommendations for MEN 2A patients advise total thyroidectomy alone prior to age 5 years if preoperative ultrasound demonstrates thyroid nodules < 5 mm and the basal serum calcitonin level is < 40 pg/mL. Current ATA guidelines suggest that central neck dissection should be done in patients with a basal serum calcitonin > 40 pg/mL, and/or clinical evidence of cervical lymph node involvement.^{28,43,44,45,46}

All patients with MTC, both sporadic and hereditary, who present with palpable disease should undergo total thyroidectomy with varying extents of concurrent systematic lymph

node dissection and parathyroid autotransplantation. Given that lymph node metastases may be difficult or impossible to detect either by imaging or by palpation, selective node dissection (“berry picking”) is discouraged because this has been shown to have higher rates of recurrence, lower rates of biochemical cure, and worse survival when compared to meticulous compartment-oriented dissection (► Fig. 17.4).^{10,47} In a series of 73 patients treated at the authors’ institution who had presented with an initial palpable mass, 80% were found to have central node (level VI) involvement, 75% had ipsilateral jugular node (levels II–IV) involvement, and 47% had contralateral jugular node involvement.¹⁰ Therefore, at a minimum, central and ipsilateral lateral compartment node dissection should be performed at the time of thyroidectomy in patients with a palpable primary tumor. Further compartment-oriented dissection may be warranted based on preoperative imaging, calcitonin and CEA levels, and intraoperative findings.^{3,10} Of note, in patients with sporadic MTC, the incidence of bilateral tumor is relatively low, and a 2002 study examined the utility of total versus unilateral thyroidectomy in patients with sporadic MTC and no identified *RET* germline mutation.⁴⁸ With 22 patients in retrospective review and 15 patients treated prospectively, unilateral thyroidectomy with isthmusectomy, systematic bilateral central lymph node dissection, and ipsilateral modified radical neck dissection was performed. The prospective population was found to have a biochemical cure rate of 80%, with no recurrences in the remaining thyroid lobe.⁴⁸ Although unilateral thyroidectomy offers the advantages of lower risks of hypoparathyroidism and recurrent nerve injury and no need for thyroid supplementation, further investigation will be needed to elucidate the risks and benefits of unilateral thyroidectomy in comparison to removal of all thyroid tissue. Current recommendations remain that the operative procedure should remove all thyroid and nodal tissue from the level of the hyoid bone superiorly to the innominate vessels inferiorly and to the carotid arteries laterally.⁴⁹

Ultrasound mapping of regional lymph nodes prior to surgery is particularly useful, and suspicious nodes can be marked on the skin preoperatively, which is helpful to the surgeon in planning extent of surgery, and whether contralateral level II through V node dissection will be necessary. In a study of 195 patients with MTC, it was found that as the number of central node metastases increased, the frequency of ipsilateral and contralateral lateral compartment lymph node metastases also increased in direct relation. When 10 or more central compartment lymph nodes were involved, nearly all patients had ipsilateral node involvement, and 77% had contralateral metastases, which supports undertaking bilateral lateral compartment dissection during thyroidectomy when numerous central node metastases are identified.⁵⁰ Discontinuous lymphatic spread (“skip metastases”) have also been described in the literature and underscores the importance of a thorough preoperative evaluation to determine lymph node involvement sites.^{10,51}

Preoperative basal serum calcitonin levels are also useful in estimating the extent of possible nodal involvement and need for dissection. A report of 300 patients with MTC treated by compartment-oriented surgery identified different thresholds at which lymph node metastases were found in different compartments; none of the patients with calcitonin levels < 20 pg/mL had evidence of lymph node involvement, which contrasted

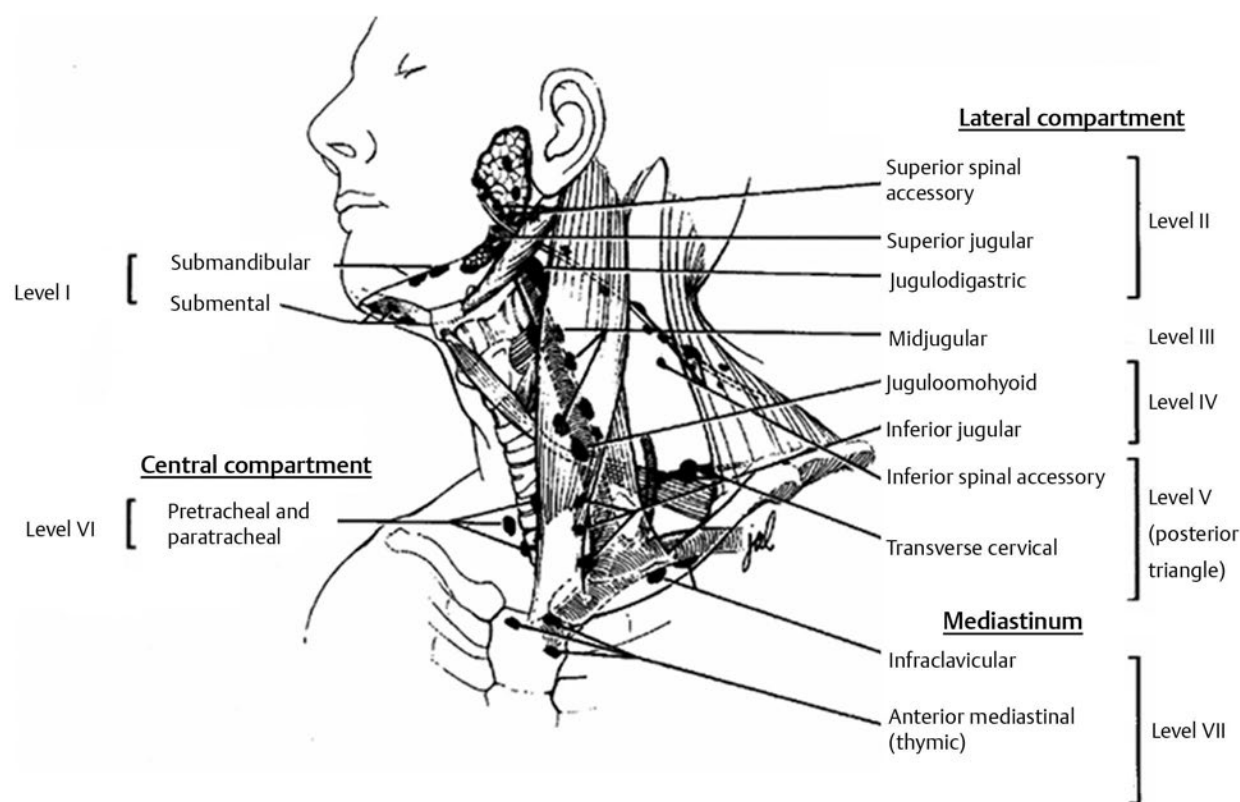


Fig. 17.4 Lymph node levels of the neck with compartment group designations. Adapted with permission (Musholt et al, J Surg Oncol. 2006 Dec 15;94(8):737-47)

sharply with patients with calcitonin levels $>10,000$ pg/mL, who demonstrated $>80\%$ with lymph node involvement in the neck, $>50\%$ in the upper mediastinum, and $>70\%$ prevalence of distant metastases.⁵² This can assist decision making in operative planning for the index procedure, and, in patients with elevated basal calcitonin levels >200 pg/mL, contralateral lateral neck dissection is recommended as well.

Careful management of the parathyroids is critical to preserve function during total thyroidectomy and neck dissection. The extent of surgical manipulation has been controversial because the adequacy of central compartment dissection is arguably compromised by leaving the parathyroids in place with sufficient blood supply. The previous approach at the authors' institution included routine four-gland parathyroidectomy with autotransplantation during central neck dissection; however, our current practice entails resection and autotransplantation of one or two parathyroids on the side of the primary tumor and the contralateral lower parathyroid, if it is not able to be preserved on a viable vascular pedicle. The contralateral upper parathyroid is left in place on its native vascular supply. Preservation of parathyroid function can then be accomplished by transplanting minced 1 mm fragments of the removed parathyroid tissue into individual muscle pockets created in the sternocleidomastoid muscle or a forearm muscle.^{1,53} Due to the risk of subsequent graft-dependent hyperparathyroidism, a nondominant forearm muscle may be used for MEN 2A patients, whereas the sternocleidomastoid is usually used for patients with sporadic disease, MEN 2B, or FMTC. All

parathyroid tissue should be left in the patient if possible, and transplantation of whole glands is not advised. If a patient has already developed primary hyperparathyroidism before thyroidectomy, appropriate parathyroidectomy should be performed. Surgical options include intraoperative parathyroid hormone monitoring with removal of only visibly enlarged glands, subtotal parathyroidectomy leaving one gland or a piece of one gland in situ, or total parathyroidectomy with forearm autotransplantation.

17.8 Postoperative Management

Total thyroidectomy has relatively low morbidity and mortality, but important complications of hypoparathyroidism and recurrent laryngeal nerve injury must be carefully avoided. According to the American College of Surgeons Commission on Cancer Patient Care Evaluation Study, the overall risk of recurrent laryngeal nerve injury during thyroid cancer procedures is approximately 1.3%, ranging from 0.7% for total thyroidectomy alone to 2.7% if concurrent lymph node dissection is performed.⁵⁴ Rates of temporary hypocalcemia, a common postoperative occurrence, also vary from 12% without to 14% with lymph node dissection. The risk of long-term hypoparathyroidism remains low with routine use of parathyroid autotransplantation, ranging from 1 to 4%.^{53,55}

Patients should be started on replacement therapy of levothyroxine with titration to a goal serum thyroid-stimulating

hormone (TSH) level between 0.5 and 2.5 mIU/L when checked 2 to 3 months after surgery. Suppression of TSH is not indicated in MTC patients. Appropriate supplementation is particularly crucial in children following thyroidectomy. Monitoring for possible hypocalcemia should also be implemented, and symptomatic treatment with calcium and vitamin D can be administered temporarily as symptoms resolve or indefinitely if the patient is determined to be permanently hypoparathyroid.²⁸ For patients with hereditary MTC and no evidence of associated endocrine lesions prior to thyroidectomy, routine surveillance for pheochromocytoma in MEN 2A and MEN 2B patients should begin at age 8 years with annual plasma metanephrines. Similarly, to monitor for primary hyperparathyroidism in MEN 2A patients, serum calcium levels should be checked annually for at least 5 years.²²

Calcitonin levels usually decrease to a new baseline by 72 hours after surgery, but, because they may continue to fall, serum calcitonin should be checked 3 months postoperatively to allow levels to reach a nadir.^{8,56,57} A postoperative decrease in the calcitonin level to within normal limits is associated with decreased long-term risk of MTC recurrence and improved survival rates.⁵⁸ Normalization of the calcitonin level is more commonly achieved in patients with disease confined to the thyroid. Among patients with lymph node metastases normalization occurs in 20 to 30% (<5% in patients with 10 or more lymph node metastases).⁵⁹ Radioactive iodine ablation is not effective in MTC; therefore, a thorough, compartment-oriented operation is recommended. Calcitonin levels may be checked every 6 months for 1 year, and less frequently thereafter if levels remain unchanged.

17.9 Residual or Recurrent Disease

In some instances, patients may undergo hemithyroidectomy with a postoperative diagnosis of MTC based on pathology. For patients with hereditary MTC, completion thyroidectomy should be performed because the risk of present or subsequent malignancy in the contralateral lobe nears 100%. However, since the incidence of bilateral MTC in patients with sporadic disease is generally <20%, completion thyroidectomy is not necessarily indicated unless a *RET* germline mutation is discovered, serum calcitonin levels are significantly elevated, radiological evidence of residual MTC is present postoperatively, or pathology demonstrates C-cell hyperplasia, multicentric disease, positive surgical margin, or extrathyroidal extension.^{28,60}

Persistently elevated calcitonin levels in a postoperative patient suggest residual disease, and imaging should be performed to localize any remaining tumor burden. For patients with postoperative calcitonin levels that are elevated but <150 pg/mL, an ultrasound of the neck and mediastinum is adequate. Suspicious lymph nodes or soft tissue lesions may be biopsied or removed. If nothing is found on imaging, patients should undergo calcitonin- and CEA-level testing every 3 months and physical examination with ultrasound every 6 months. For patients with serum calcitonin levels >150 pg/mL, a full metastatic workup should be initiated with additional imaging, including neck and chest ultrasound and CT scan, contrast-enhanced CT or MRI of the liver, bone scintigraphy, MRI of the spine and pelvis, and FDG-PET scan.²⁸ Calcitonin and CEA doubling times have also been found to be an efficient measure of

disease progression in the majority of patients and have been related to overall survival rate, time to recurrence, and time between recurrence and death.^{61,62} Significantly improved long-term prognosis has been demonstrated in patients whose calcitonin-doubling time was >2 years when compared to those <6 months; in one series of 65 patients, 100% of patients in the former category were alive at 10 years compared to only 8% in the latter.⁶²

Even with a successful index procedure, some patients who achieve biochemical remission may later develop elevated calcitonin levels, indicative of persistent or recurrent disease.⁶³ These patients should undergo imaging, as already described, to look for recurrent or metastatic disease. If imaging demonstrates isolated locoregional disease within the neck, patients may undergo additional surgical resection with curative intent.^{11,46} Complete clearance of the tumor burden at reoperation for patients without distant metastases or with minimal distant metastases has been shown to improve long-term survival and prevent further recurrence in the neck (► Fig. 17.5).¹¹ Durable biochemical cure with disease-free survival >10 years may be achieved in more than 25% of these patients following reoperation.^{64,65,66} Therefore, reoperation should be considered in patients whose postoperative calcitonin levels remain elevated following an inadequate initial operation, if imaging demonstrates residual or recurrent disease, or in whom the tumor burden poses a risk of invasion or compression of the trachea, esophagus, or great vessels.

In spite of the presence of occult disease, many patients with elevated calcitonin levels do very well clinically without any radiographic or symptomatic evidence of disease recurrence. This is attributed to the often indolent disease course and variable tumor biology of MTC. Consequently, management of these patients remains controversial because survival rates of patients with persistent hypercalcitonemia have been found to be as high as 86% at 10 years in the absence of distant metastases.⁶⁷ If no anatomical evidence of disease is apparent on physical exam or imaging, conservative management with close surveillance is recommended. Alternatively, a thorough extirpation of central and lateral nodal groups not previously removed may be pursued and may result in removal of subclinical nodal metastatic disease, with normalization of calcitonin (though this has not been proven to result in improved survival).^{10,11,28}

The surgeon must approach reexploration of the neck with caution given the presence of scarring and altered anatomy. There is an increased risk of complications, such as thoracic duct leak, hypoparathyroidism, and injury to a recurrent laryngeal nerve. Risk of injury to the recurrent laryngeal nerve increases to 8% in the reoperative setting, and frequency of hypoparathyroidism may be up to four times higher than after the initial operation.⁶⁶ The surgical procedure is performed through the prior low collar incision with extension laterally and superiorly along the sternocleidomastoid. In reoperative central compartment dissection, a “backdoor” or lateral approach may facilitate appropriate identification of structures because the central neck is thus accessed via a tissue plane that has not undergone prior dissection.⁶⁸ Differing from the anterior approach, the strap muscles are now mobilized medially off of the carotid sheath, exposing the deep central compartment and allowing for clear identification of the recurrent laryngeal nerve and the parathyroids.⁶⁹ At the authors’ institution, in a series of

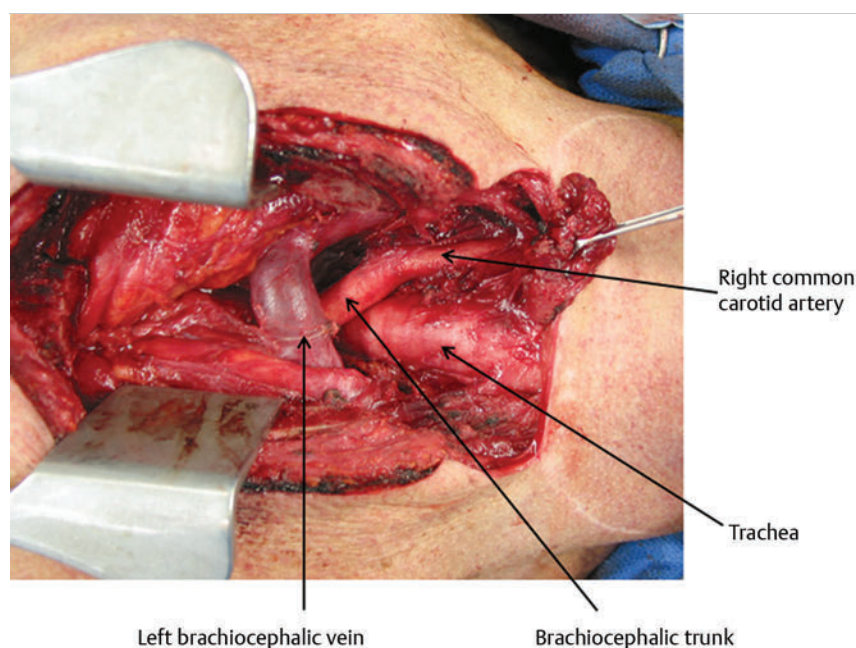


Fig. 17.5 Mediastinal dissection for medullary thyroid carcinoma.

100 central neck reoperations, no recurrent laryngeal nerve injuries were sustained with this technique.⁶⁸ All residual thyroid and nodal tissue is removed from the central compartment (level VI and VII), extending from the hyoid bone at the superior margin along the larynx to an inferior margin of the innominate artery on the right and a similar level approaching the aortic arch on the left with the carotid arteries as the lateral margins. Any tissue remaining anterior to the trachea and superior thymic tissue is also resected. Compartmental dissection of image- or biopsy-proven disease in the central or lateral neck compartments with guidelines similar to those at initial operation should then be performed. For patients who have not undergone parathyroid autotransplantation, it is critical to identify any parathyroids prior to removal of lymph nodes. Resection of normal parathyroid tissue with autotransplantation may be performed at this point, or the surgeon may leave viable glands in situ if oncologic resection is not compromised.⁷⁰ Due to the increased difficulty of identifying the parathyroids in children, reoperative neck exploration is not recommended unless previous autotransplantation has been confirmed, if limited exploration avoiding the remaining parathyroids can be performed, or if bulky tumor burden is compromising surrounding structures.

17.10 Treatment of Advanced Disease

In patients with significant local involvement or distant metastases indicative of advanced disease, treatment options are unfortunately limited by poor response, even to multimodal therapy. Because MTC does not concentrate radioactive iodine, postoperative treatment with this therapy is not recommended in the absence of concurrent differentiated thyroid cancer.^{28,42} The goals of surgical intervention in these patients become more palliative with an aim of reducing symptomatic progression or associated complications. Maintenance of function in swallowing and speech and decreasing bulky tumor burden

within the neck may allow the patient an improved quality of life, and additional adjuvant therapies, including EBRT or hepatic embolization of liver metastases, can be considered. For patients with limited extracervical metastatic disease, a more radical locoregional approach, including resection of a unilateral recurrent laryngeal nerve, may be of benefit to prevent tumor recurrence. In the setting of more significant locally invasive disease involving the trachea, esophagus, or other surrounding structures, the extent of surgical intervention within the neck should be carefully considered in the context of life expectancy and other medical comorbidities. Similarly, for distant metastases, the risks and benefits of surgery or systemic therapies must be weighed against the often slow rate of progressive disease and relatively sustainable patient quality of life, particularly if the patient is asymptomatic with minimal distant disease.

Palliative tumor debulking may benefit patients who develop systemic symptoms, such as pain, flushing, or diarrhea.^{28,65} Systemic metastases are most commonly reported in the liver, lungs, bone, and brain. Liver metastases have been reported in up to 45% of patients with advanced MTC, and definitive treatment should be considered in patients whose hepatic lesions are large, progressive, or symptomatic.^{28,67} For isolated, large metastases, surgical resection may be possible, and some studies have found variable success with radiofrequency ablation and percutaneous ethanol ablation.^{71,72} However, because hepatic lesions are commonly small (1–5 mm) and multiple, other therapies, such as chemoembolization or systemic therapy, may be of greater potential value.^{12,73,74} Lung and mediastinal metastases are also similarly multiple and may require surgical resection to alleviate airway compression or bleeding. Radiofrequency ablation is also recommended in patients whose lung lesions are peripheral and <40 mm in diameter.⁷⁵ However, for significant airway compromise and invasion, airway stenting can be considered and has been successful in provision of symptomatic relief and improvement of respiratory and performance status.⁷⁶ For bone and brain metastases, surgical excision may be necessary to prevent fracture in weight-bearing

bones, to relieve spinal cord compression, or if a patient demonstrates concerning neurological symptoms with radiological evidence of brain metastasis.

EBRT remains limited in its utility as adjuvant therapy for patients with MTC, and current usage varies with institutional preference. Benefit from EBRT occurs mainly with palliation of bone metastases, but it has largely remained ineffective in treatment of disease within the neck. In one series, 46 patients at differing stages of disease underwent EBRT with no significant difference in recurrence rates; however, upon subgroup analysis of 40 patients with "high-risk features," including microscopic residual disease, extraglandular invasion, or lymph node involvement, 86% of the patients who had received EBRT had not experienced local/regional recurrence, whereas only 52% of the patients who had not received EBRT were disease-free.⁷⁷ This supports the argument that EBRT may improve symptoms and quality of life in patients who have unresectable local disease or compromise of critical local structures.

Standard systemic chemotherapy showed little clinical effect and only partial responses at best in small populations of patients treated with different regimens, including dacarbazine, fluorouracil, and doxorubicin.^{78,79,80} Consequently, current recommendations advise against standard chemotherapy in first-line treatment of patients with persistent or recurrent MTC.²⁸ New molecular therapies are very promising, and the increasing understanding of MTC oncogenesis has led to identification of multiple molecular targets. Because all of the hereditary syndromes and up to 50% of sporadic MTC can be related to mutations of the *RET* receptor protein, kinase inhibitors have been under considerable investigation, and agents such as vandetanib, cabozantinib, sorafenib, and sunitinib have shown promise in improving progression-free survival. However, only vandetanib and cabozantinib are currently approved by the Food and Drug Administration, and significant short-term toxicity with little long-term data should be considered before using these agents.^{75,81}

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18 Surgical Management of Anaplastic Thyroid Cancer

Brian R. Untch and Luc G. T. Morris

18.1 Introduction

Anaplastic thyroid cancer (ATC) is a rare thyroid cancer characterized by an aggressive disease course and a high mortality rate.^{1,2} Commonly, patients will present with a rapidly growing neck mass and symptoms related to invasion or compression of structures within the neck. At diagnosis, many patients will already have widespread metastatic disease.³ Clinical decision making in a majority of cases is directed toward palliation. This chapter discusses treatment approaches for patients with ATC and reviews the limited role for surgical intervention.

18.2 The Spectrum of Thyroid Cancers

Well-differentiated thyroid cancers arising from follicular thyroid cells are associated with excellent disease-specific survival outcomes. Localized tumors are managed with thyroidectomy and, in select cases, lymph node dissection and/or adjuvant radioactive iodine therapy.⁴ Even patients with metastatic differentiated thyroid cancer can experience prolonged survival.⁵ This is in stark contrast to patients with ATC, the course of which is as aggressive as any other human cancer. ATCs are composed of undifferentiated cells that do not have the ability to take up radioactive iodine. These tumors are highly fludeoxyglucose (FDG)-avid on positron emission tomography (PET).⁶ Characteristic histological findings include necrosis, local invasiveness, large nuclei, and frequent mitotic figures (► Fig. 18.1).⁷ The spindle cells found in ATC can easily be mistaken for other spindle cell neoplasms, including sarcoma. A pathologist experienced with ATC is critical in cases of diagnostic uncertainty. This is because histopathologic diagnoses (particularly in the setting of a metastatic biopsy) can be complicated by a loss of typical differentiated thyroid-specific immunohistochemistry (IHC) markers that identify a thyroid origin. Accordingly, given the highly undifferentiated nature of these tumors, pathological diagnosis of ATC often requires knowledge of the location of the tumor biopsy site and careful consideration of the patient's clinical history.

Histological evidence suggests that some anaplastic cancers may originate from antecedent thyroid disease. Both goiter and well-differentiated thyroid cancers can be seen adjacent to

anaplastic cells in resected specimens. Molecular analyses demonstrate that mutually exclusive genomic changes in mitogen-activated protein kinase (MAPK) pathway genes (*RAS*, *BRAF*, *RET/PTC* fusions) contribute to thyroid cancer pathogenesis. Additional genetic changes in DNA repair genes (*p53*) and the telomerase promoter may trigger genomic instability and cell immortalization that is required for transformation to an undifferentiated tumor.^{8,9} Given the high incidence of clinical and subclinical thyroid cancers in the general population, clearly this transformation occurs at a very low rate. The incidence of ATC in the United States has been stable over time, ranging between 0.1 and 0.2 per 100,000 persons, accounting for fewer than 1% of thyroid cancer diagnoses.¹⁰

ATCs are responsible for a large percentage of deaths related to thyroid cancer in the United States. Although few large series of patients exist, ATC is thought to have one of the shortest median survival rates of all cancers, ranging from 3 to 5 months.¹¹ A majority of patients will have metastatic disease at presentation (► Fig. 18.2). In addition, many patients will have large, rapidly growing neck tumors that can compress the airway. Surgical series frequently report patients who underwent thyroidectomy and received an incidental diagnosis of ATC at the time of pathological analysis. These are uncommon entities and are not representative of the vast majority of patients presenting with clinically evident ATC. Thus the outcomes of these single-institutional experiences should be interpreted cautiously. In the majority of cases, ATC is unfortunately a disease rarely able to be effectively treated with surgical resection.

18.3 Initial Evaluation of a Rapidly Expanding Neck Mass

Patients presenting with an enlarging neck mass require a histological diagnosis and imaging of the head and neck (► Fig. 18.3). Percutaneous core or fine-needle biopsy under ultrasound guidance provides excellent visualization and can confirm tumor sampling while avoiding vital structures. Open biopsy is rarely performed given the success of percutaneous techniques, but it is occasionally needed. Once the diagnosis has been established, staging workup should include laboratory testing and contrast-enhanced imaging of the head and neck, including brain magnetic resonance imaging (MRI) with full-body FDG-PET (► Fig. 18.4 and ► Fig. 18.5).¹²

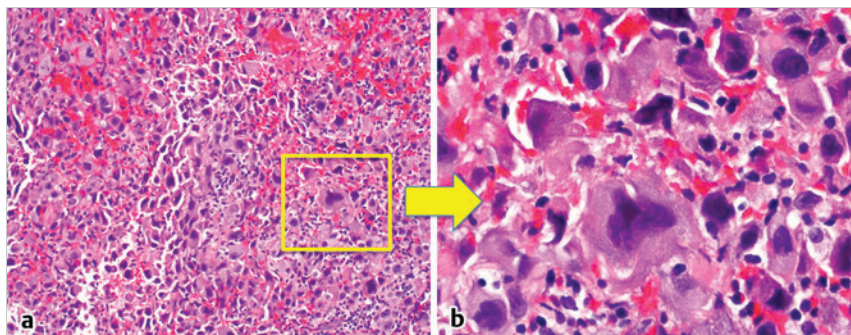


Fig. 18.1 Histology of anaplastic thyroid cancer (ATC). (a) Low-power view demonstrating abnormally shaped cells without papillary or follicular architecture. (b) High-power view demonstrating irregularly shaped cells and heterogeneity of nuclei, features typical of ATC.

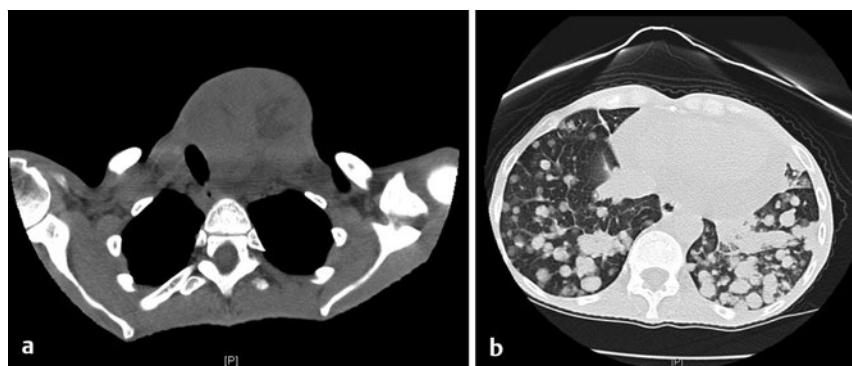


Fig. 18.2 Computed tomographic scans of a patient presenting with anaplastic thyroid cancer. (a) The neck mass results in tracheal and superior mediastinal shift. (b) Extensive lung metastases in the same patient.

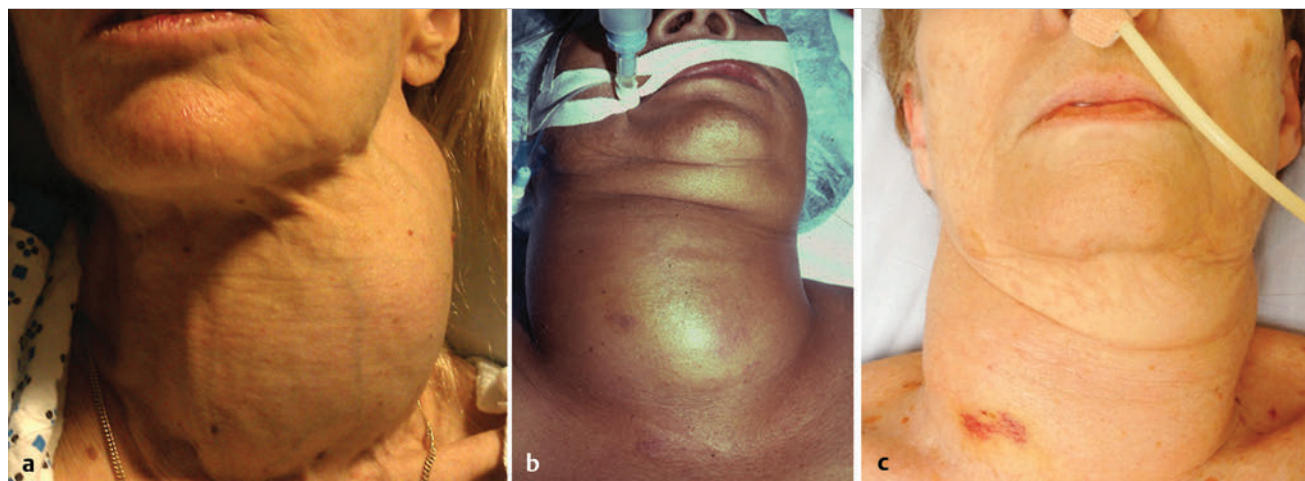


Fig. 18.3 (a-c) Three patients presenting with rapidly enlarging neck masses.

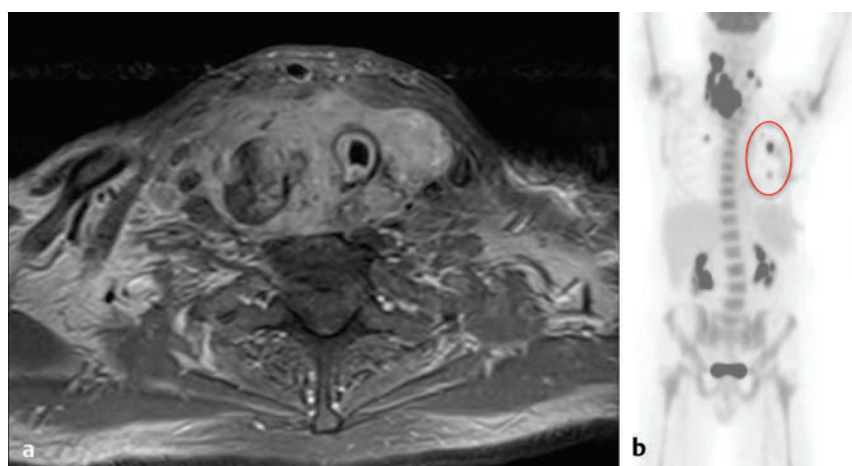


Fig. 18.4 (a) Magnetic resonance imaging (MRI) of the neck in a patient with anaplastic thyroid cancer. The mass is infiltrative and involves multiple structures within the neck. The trachea is displaced laterally. (b) Fludeoxyglucose (FDG) positron emission tomography of the same patient. Locally advanced disease with lymph node metastases can be seen within the neck. Metastatic disease to the lungs is also observed (circled in red).

Thyroid function tests, blood counts, and full chemistry panels should be checked in anticipation of multimodality therapy (surgery, chemotherapy, and radiation). Laryngoscopy to assess vocal cord mobility should be performed in all patients. Locally unresectable tumors invade and surround the carotid artery, prevertebral fascia, mediastinal structures, trachea, larynx, or esophagus.¹³ For localized tumors thyroidectomy with lymph node dissection is reasonable, but this is an extremely uncommon presentation of ATC.¹² Tumors that extensively invade local structures are not appropriate for surgical resection. En bloc resection would

often require extensive surgery with laryngectomy, pharyngectomy, and esophagectomy, and is unlikely to be of value, given the high likelihood of residual gross disease even after extensive resection together with the high likelihood of the development of distant metastases within a short time interval. For patients with metastatic disease identified on cross-sectional imaging/PET it should be noted that this may represent a more well-differentiated component of the tumor. High FDG avidity suggests ATC, but if there is suspicion of low-grade metastatic disease, serum thyroglobulin levels can be helpful.

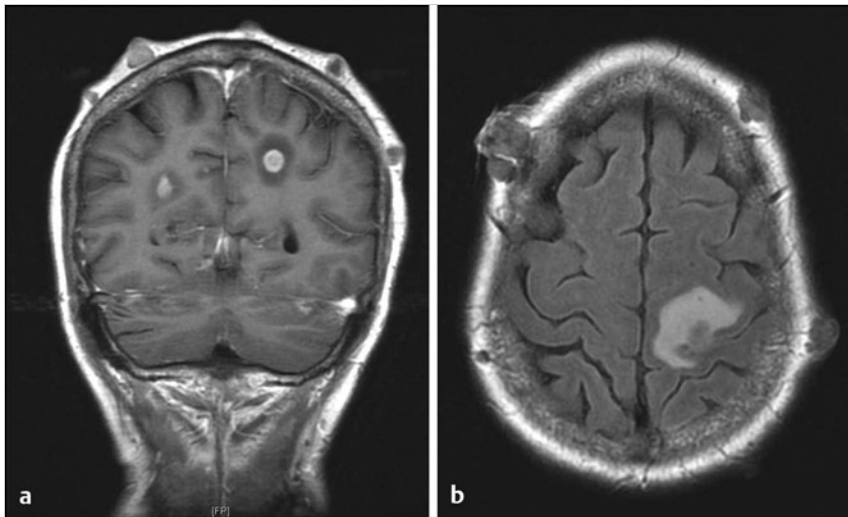


Fig. 18.5 Coronal (a) and axial (b) computed tomographic images of a patient with metastatic anaplastic thyroid cancer. Multiple metastases can be seen within the bones of the skull and the brain.

Patients with distant metastatic disease should be referred for systemic therapy or multimodality treatments that include radiation.¹⁴ Data to suggest one particular treatment approach over another are lacking, and the authors suggest referral to a multidisciplinary group with experience in treating ATC. Enrollment in a clinical trial is optimal. Timely coordination of care across experienced specialists is critical to providing optimal palliative care.

18.4 Resection of Anaplastic Thyroid Cancer

Patients presenting with resectable anaplastic thyroid tumors are rare. Although prolonged survival after complete resection is reported in some series, these patients typically have an incidental diagnosis of ATC after thyroidectomy or have disease biology that portends a better prognosis.¹⁵ After resection of small incidental lesions, patients can be followed closely with cross-sectional imaging. Consideration should be given to adjuvant treatment.

For patients with large tumors and/or lymph node metastasis, resectability should be based on imaging characteristics. In general, removal of gross disease should be the goal, including lymph node dissections as needed. In patients with extensive bilateral lymph node metastasis or upper mediastinal disease, resection should be part of multimodality treatment. Numerous retrospective series associate complete resection (R0, no residual microscopic tumor remaining) with survival.^{16,17} Unfortunately, these analyses are complicated by significant selection bias. Thus surgical resection should be considered only after appropriate metastatic workup, patient counseling, and multidisciplinary discussion. Adjuvant treatments in the form of radiation and systemic treatments are acceptable in this setting.

In some cases it may be reasonable to resect a symptomatic primary tumor in a patient with distant metastatic disease. Patients may have progressive upper aerodigestive symptoms that require palliation. If a tumor is small, resectable, and does not involve vital structures (i.e., an R0 resection is anticipated) then resection can be attempted. It should be noted that this

situation is very unusual. Because recurrent laryngeal nerve involvement is common in ATC, the contralateral nerve should be carefully considered and should be confirmed to be functioning preoperatively. If a total thyroidectomy is performed, the contralateral nerve should be fully dissected and confirmed to be intact and functioning before placing the ipsilateral nerve at risk. If symptomatic improvement is likely from a lobectomy then the contralateral lobe should remain in situ. “Debulking” surgery has no role in treatment of ATC patients. R2 resections (macroscopic residual disease present) are unlikely to benefit patients, as observed in numerous other aggressive malignancies.

18.5 Neoadjuvant Multimodality Therapy

Although most patients undergo palliative multimodality therapy in the form of radiation and systemic treatment, in theory patients with locally advanced unresectable ATCs could respond to treatments, thereby downstaging the tumor and making it resectable. This was illustrated in a dramatic treatment effect seen with the targeted agent vemurafenib in a patient with ATC.¹⁸ Akin to the treatment of patients with borderline resectable pancreatic adenocarcinoma, systemic treatment before operation downstages tumors, but, perhaps more importantly, it selects patients with favorable disease biology who may benefit from resection. This therapeutic strategy could be feasible for ATC patients. Unfortunately, at the current time, systemic agents infrequently “downstage” ATC, and few patients present with localized disease in the absence of distant metastases. Accordingly, there is currently no defined role for neoadjuvant therapy in ATC.

18.6 Chemoradiation Therapy

Because of the very limited role for surgery in patients presenting with ATC, the majority of patients are treated with cytotoxic chemotherapy and radiation therapy. There are no level I data to suggest the standard of care. A standard approach is concurrent radiation therapy with low-dose doxorubicin.

Unfortunately, early reports of effective local control with this regimen were probably overstated, perhaps due to misdiagnosis of some more favorable thyroid histologies as ATC. Contemporary data reveal a 1-year survival rate of only 28% in patients treated with this regimen, although toxicity is quite manageable in most patients.¹⁹ In the highest-risk patients, the added value to intensive chemoradiation therapy is often marginal, underlining the importance of early and informed patient input into the decision-making plan.²⁰

18.7 Tracheostomy

Most patients with ATC will not be candidates for surgical resection. In fact the American Thyroid Association guidelines for ATC suggest that palliative and end-of-life discussions should be initiated at the first office visit.¹² For patients who are not surgical candidates, treatments should be focused on relief of symptoms. In ATC, these symptoms are most commonly airway related and include dyspnea, stridor, aspiration, and hoarseness (from vocal cord paralysis).

In some cases, tracheostomy offers the option of preventing death from airway obstruction. However, "prophylactic" tracheostomy should not be uniformly performed in patients who do not have symptoms of airway obstruction because of the significant symptoms and sequelae that result from having a tracheostomy tube in the presence of an uncontrolled ATC in the neck. Unfortunately, even with a tracheostomy tube tumor growth can still result in asphyxiation. Tumor can also grow through the stoma, resulting in bleeding, aspiration, and continued airway symptoms. For this reason, tracheostomy often worsens, rather than palliates, symptoms, and should not be uniformly recommended for patients with ATC. For patients who present with ATC and do not have symptomatic airway obstruction, the possibility of tracheostomy should be discussed with patients and families in the context of the overall prognosis and goals of care. Given these potential sequelae of tracheostomy, this should be offered to patients on a case-by-case basis, rather than being universally performed.

In recent years, tracheal and esophageal stents have become available for the management of obstructive airways. However, given the rapidity of ATC progression, these interventions should have considerations similar to those associated with tracheostomy. Stenting of the upper airway can be challenging in the most experienced hands, and complications of tumor overgrowth and tracheoesophageal fistula can be anticipated.

In addition to airway disease, ATC patients can have difficulty swallowing. Managing these symptoms with surgically placed feeding tubes may be a reasonable approach for some patients. The decision to pursue this palliative intervention should be based on the goals of care, in a similar manner as for tracheostomy.

18.7.1 Metastasectomy

Metastasectomy has a very limited role in patients with ATC. In the authors' experience patients with dramatic responses to systemic therapy or with a long interval between resection of the primary tumor and recurrence (> 1 y) could be candidates for metastasectomy. This highly select patient population likely

includes rare variants of ATC that have much slower progression than what is typically observed. Even so, a decision to pursue metastasectomy in this setting should be made by a multidisciplinary team of physicians experienced in the care of ATC patients. An untimely operation (or complications thereof) could delay the systemic treatments that will ultimately determine the patient's survival. It is important to note that, even in more common diseases, such as colorectal cancer and non-small cell lung cancer, metastasectomy has not been proven to extend survival but is thought to be a reasonable treatment approach in certain instances.

18.8 Clinical Trial Enrollment

For a rare, aggressive disease with limited therapeutic options there is an obvious need for clinical trials. Multi-institutional collaborative clinical trials represent a way to standardize and optimize therapy. Any patient with ATC should be considered for a clinical trial. Patients with metastatic disease with good performance status should be enrolled in a trial that includes chemotherapeutic and targeted therapy regimens. Given the pace of disease progression and the mortality rate, ATC patients should initiate treatments as soon as possible after diagnosis (days rather than weeks). At Memorial Sloan Kettering, for example, clinical trials to target specific driver mutations, identified by targeted sequence strategies, are under way.

18.9 Conclusion

ATC is a highly lethal cancer associated with distant metastatic disease at presentation and compressive symptoms of neck structures by the primary tumor. Surgical intervention in the form of curative resection is rare and more commonly aids in palliation in select patients. For patients with a new diagnosis of ATC, palliative and end-of-life discussions should be initiated at the first patient visit. Because surgeons are often the first specialists to see a patient with newly diagnosed or suspected ATC, they serve a critical role, even if surgery is rarely performed. It is obligatory that surgeons be prepared to take the time necessary to have frank and empathetic conversations with patients about the natural history of ATC. Furthermore, the surgeon can be invaluable in coordinating expedient referral to medical and radiation oncology colleagues so that treatment, if desired, can be initiated as soon as is practicable. Clinical trial enrollment is critical to making progress in treatment of such a rare disease.

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19 Surgical Management of the Central Neck Compartment for Differentiated Thyroid Cancer

Salem I. Noureldine and Ralph P. Tufano

19.1 Introduction

Cervical lymph node metastases are known to significantly correlate with both the persistence and the recurrence of thyroid cancer, and they may impact survival.¹ Central neck dissection (CND) plays an important role in the management of thyroid malignancy. The primary treatment for locally advanced differentiated thyroid cancer (DTC) should consist of a total thyroidectomy, with both a therapeutic neck dissection and thyroid remnant ablation as indicated.² Yet, because occult lymph node metastases are common in DTC, some have advocated elective CND (in the absence of any clinically or radiologically detectable nodal metastases) as part of routine surgery for DTC.

Nevertheless, the pertinent medical literature indicates that there is no standardization of this operation among surgeons. Boundaries and compartments are not well defined, and the operative reports often fail to mention whether these procedures were being performed in the presence or absence of gross lymph node metastases (clinically or radiographically apparent). These shortcomings prompted the convergence of a subgroup of thyroid cancer specialists under the auspices of the American Thyroid Association (ATA) to formulate a consensus statement on the anatomy and terminology pertinent to CND.³ The group concluded that CND should consist of levels VI and VII of the neck and must contain the prelaryngeal, pretracheal, and at least one paratracheal nodal basin. The surgery should be designated as elective or therapeutic.

Clinically or radiographically apparent cervical lymph node metastases in the central neck should be treated with a therapeutic intent accomplished by a compartmental dissection. Although elective CND is advocated for medullary thyroid cancer (MTC) and other aggressive histologies, controversy still exists for its application to DTC.⁴ This chapter discusses the technique for performing a CND and the considerations for when it should be performed.

19.2 Incidence and Prevalence

DTC, specifically papillary thyroid cancer (PTC), has a tendency for cervical lymphatic spread. Cervical metastases are found in 20 to 50% of patients, with the use of standard pathological techniques, and have been reported by some authors to occur in up to 90% of those examined for micrometastases.^{5,6} Thyroid tumor cells spread through the lymphatic system in a sequential fashion, starting in the perithyroidal, pretracheal, paratracheal, and prelaryngeal lymph nodes of the central neck compartment, and then progress to the lymph nodes of the lateral cervical compartments and the superior mediastinum.⁷

Although occult micrometastases in the lymph nodes of the central neck have been reported to occur in 31 to 62% of patients with PTC, the available evidence suggests that most remain dormant, rarely become clinically apparent, and are of little clinical significance.^{8,9} The incidence of lymph node

metastases in follicular thyroid cancer is 20 to 25% in the American population. In patients with MTC, clinically detectable cervical lymph node metastases are found in at least 50% of patients.

19.3 History, Physical Examination, and Preoperative Planning

Patients will usually present with a mass in the thyroid that has been detected by palpation or discovered incidentally on radiographic imaging for evaluation of other disease processes (e.g., carotid ultrasound, imaging of the cervical spine). A diagnosis is usually established by ultrasound-guided fine-needle aspiration (FNA) biopsy. Most patients with a thyroid malignancy, with or without central neck lymphadenopathy, are usually asymptomatic. Patients with larger or more aggressive tumors can present with hoarseness, dysphagia, and dyspnea.

A patient with suspected thyroid cancer should undergo a detailed examination of the thyroid gland and the cervical lymph node compartments. Cervical ultrasound is often the initial imaging modality employed in the assessment because it is readily accessible, inexpensive, and noninvasive. It is also an important tool for postoperative surveillance of patients with PTC.^{10,11} High-resolution ultrasonography can detect cervical nodal metastasis in up to 20% of patients with PTC. These ultrasound findings may alter the planned surgical procedure in up to 39% of thyroid cancer patients.² Pathological lymph nodes usually have concerning sonographic features that include a round shape, absent hilum, calcification, intranodal necrosis, reticulation, matting, and peripheral vascularity.¹² A detailed cervical ultrasound to include nodal levels II through VI should be performed, ideally by a dedicated clinician, such as the thyroid endocrinologist, the operating surgeon, or a radiologist with a vested interest, to detect nonpalpable lymph node metastases in patients undergoing surgical evaluation for any thyroid cancer.¹¹ However, ultrasound can miss as many as 50% of the involved lymph nodes in the central neck because the overlying thyroid gland may hinder adequate visualization.¹³

In patients with suspected mediastinal disease or with bulky (clinically palpable, >3 cm in size) cervical lymphadenopathy, cross-sectional imaging with computed tomography (CT), magnetic resonance imaging (MRI), and/or positron emission tomography (PET) should be considered. Though the sensitivities of these modalities for the screening and detection of cervical lymph node metastases can be relatively low (30–40%),¹⁴ they can aid in the planning of a neck dissection and often identify pathological level VII lymph nodes within the superior mediastinum and parapharyngeal, retropharyngeal nodes that are not detected on cervical ultrasound or physical examination.¹¹

A CT scan with iodinated contrast may be extremely helpful in evaluating the extent of cervical lymphadenopathy when there is gross nodal disease present, and can help define the extent of surgery necessary to plan clearance of all gross disease in the neck.¹¹ CT with contrast may delay postoperative thyroid scanning and radioactive iodine (RAI) administration for 4 to 8 weeks, but in the scenario of bulky lymphadenopathy or concern for locally invasive disease, it appears justified because complete surgical resection of gross disease is of paramount importance for disease control.¹⁵

19.4 Indications for Central Neck Dissection

There are several indications for therapeutic or elective CND. Patients with thyroid cancer and evidence of central neck lymphadenopathy confirmed by physical examination, radiologic imaging, or intraoperative inspection should undergo therapeutic CND. CND is also indicated in patients with recurrent laryngeal nerve (RLN) invasion or medullary thyroid cancer. Elective CND may be considered in select patients with T3 and T4 differentiated thyroid cancer cases or when there is suspicion of a more aggressive variant of thyroid cancer (including medullary thyroid cancer).

19.5 Contraindications

Just as there are times that CND may be indicated, there are also times where the potential morbidity of the procedure may outweigh the benefit. Surgeons should be very cautious when considering elective CND of the paratracheal nodal basin on the side of the only functioning RLN (i.e., when there is a preexisting vocal fold paralysis contralateral to the paratracheal nodal basin where the positive lymph node is located). Patients with stable recurrent or persistent disease that is away from vital structures, such as the trachea, may be considered for observation rather than surgery. Finally, CND may not be appropriate in patients with known systemic metastases that are progressive and outpacing the recurrent or persistent central nodal metastasis.

19.6 Elective versus Therapeutic Central Neck Dissection

A therapeutic CND should be performed for patients with DTC and pathological lymph node involvement noted on preoperative clinical exam or imaging, or during intraoperative inspection.² The goal of removing these lymph nodes is to aid in local control, prevent recurrence, and perhaps improve survival.

The role of elective CND remains a contentious issue regarding its benefits and risks. An essential component of any discussion about the need for lymphadenectomy is whether patients derive any additional benefit from having a CND with total thyroidectomy and whether this can be done without significantly increasing the morbidity of the operation. Because microscopic nodal disease is rarely of clinical importance, many authors argue that elective CND of microscopic lymph node metastases that are not clinically identifiable at the time of surgery may

not improve long-term outcome and could subject patients to more risk than benefit.² Also, if removal of subclinical metastases alone were an indication for surgery without an appreciation for the clinical significance of this disease (which certainly is debatable), then the same should theoretically apply to the lateral neck. Opponents also fear that, if elective CND were universally adopted by all surgeons performing thyroidectomy, the risk of parathyroid and nerve injury may increase in the absence of significant oncological benefit to the patients.^{4,5,6}

Nonetheless, no consensus yet exists regarding the addition of CND for clinically node-negative patients with DTC. To date, no study has demonstrated significantly reduced recurrence or mortality rates with elective CND. A recent meta-analysis found no difference in the recurrence rates between those treated with or without elective CND at the time of thyroidectomy.⁴ A different study suggested that when elective CND is performed by experienced surgeons it may be associated with a lower risk of disease recurrence, and that the number of patients that would need to be treated to prevent a single recurrence is 31.¹⁶ In light of these discordant findings, the rationale for routine elective CND to prevent either recurrence or death is questionable in DTC. Conversely, there are strategic uses for elective CND that may have justification. These include patients with higher-risk tumors, such as T3 or T4 lesions, or those exhibiting extrathyroidal extension, or more aggressive histologies, such as diffuse sclerosing, insular, or poorly differentiated tumors. Elective central neck dissection is also recommended for medullary thyroid cancer. The pros and cons of therapeutic and elective CND are outlined in ► Table 19.1.

19.7 Surgical Technique

A complete central neck dissection requires removal of all lymph nodes in the prelaryngeal, pretracheal, and paratracheal regions. The surgical borders of the central compartment are outlined in ► Fig. 19.1 and ► Table 19.2 and should include levels VI and VII.

19.7.1 Primary Central Neck Dissection

Primary CND is usually performed at the time of total thyroidectomy and may be performed en bloc with the thyroid or separately. If not already dissected during the thyroidectomy, the prelaryngeal and pretracheal nodes are excised.

The standard thyroidectomy incision is used. A vertical incision opens the midline between the strap muscles, from the thyroid notch to the sternal notch. Adequate exposure of the central neck must be obtained to permit a comprehensive compartmental dissection. The strap muscles must be elevated over the carotid sheath laterally and to the sternum inferiorly.

The prelaryngeal nodes are easily visualized during the resection of the pyramidal lobe. They can be dissected at the time of thyroidectomy or after. The prelaryngeal dissection starts inferiorly at the upper margin of the thyroid isthmus and extends superiorly to the hyoid bone. The fibroadipose tissue overlying the cricothyroid and thyrohyoid membranes is incised and dissected off of these structures. It is important to avoid injury to the cricothyroid muscle or the membranes when performing this maneuver.

Table 19.1 Pros and cons of central neck dissection

	Therapeutic CND	Elective CND
Pros	- Decreases risk of disease recurrence - Improves survival - May reduce the need for reoperation	- May decrease risk of recurrence - May improve survival - Reoperative surgery becomes complicated - Provides accurate staging, thus eliminating need for postoperative RAI therapy in select cases
Cons	- Postoperative hypocalcemia - Postoperative RLN paralysis	- Increases postoperative temporary hypocalcemia - May increase rate of RLN paralysis - Survival and recurrence benefit yet to be proven

Abbreviations: CND, central neck dissection; RAI, radioactive iodine; RLN, recurrent laryngeal nerve.

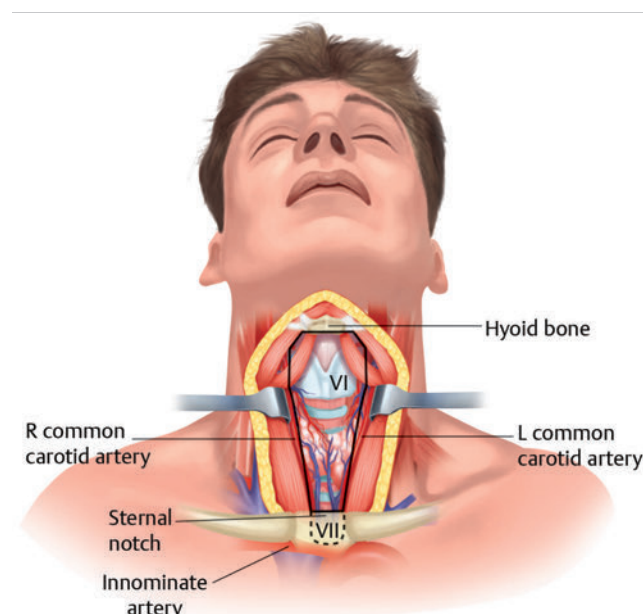


Fig. 19.1 The borders of the central neck dissection are outlined and should include both levels VI and VII lymph node basins.

The pretracheal dissection starts at the lower margin of the isthmus and strips the fibrofatty tissue and nodes from the front face of the trachea down to the level of the innominate artery crossing the trachea. Care is taken to avoid injury to the innominate artery and the brachiocephalic vein. It is important when performing a pretracheal dissection not to extend the dissection down into the paratracheal region. This can jeopardize the RLN, especially on the left side.

Identification and excision of the right paratracheal lymph nodes, which may be found both anteriorly and posteriorly relative to the ipsilateral RLN and inferior thyroid artery main trunk, require careful exploration in the vicinity of these delicate structures. Due to the relatively medial and ventral course of the right common carotid artery, paratracheal lymph nodes may exist posterior to this artery on the right side. Thus adequate central neck dissection may require limited mobilization of the right common carotid artery. The right paratracheal dissection begins with skeletonization of the common carotid artery from the thyroid cartilage superiorly to the innominate artery inferiorly. The dissection should not proceed deep to the common carotid artery to avoid injury to the RLN. Once the

Table 19.2 Surgical anatomical landmarks for levels VI and VII of the central compartment for central neck dissection

Border	Surgical anatomical landmark
Superior	Hyoid bone
Inferior	Axial plane of the innominate artery
Posterior	Prevertebral fascia
Anterior	Sternothyroid muscle
Lateral	Common carotid artery
Medial ^a	Medial edge of contralateral strap muscles

^aIn cases of unilateral central compartment neck dissection.

carotid sheath is fully dissected, the vagus nerve can be stimulated at 1 mA to determine the neurophysiological integrity of the RLN. The RLN is then identified again in the area of where it was exposed for the thyroidectomy. The RLN must be dissected from its laryngeal point of insertion to its most inferior extent in the neck to be able to safely remove all of the lymph nodes in the right paratracheal compartment. On the right side, it travels more ventrally and obliquely than the left RLN (► Fig. 19.2 and ► Fig. 19.3).

It is followed inferiorly until it can no longer be traced under the common carotid artery. Minimizing tension is important in preserving RLN function and avoiding neuropraxia. Prudent use of fine-tip bipolar cautery away from the RLN to cauterize small vessels is recommended. Once the nerve is completely transposed, the lymph node-bearing tissue posterior and medial to the carotid artery and posterior and lateral to the RLN can be delivered anteriorly. The RLN laryngeal entry point is usually used as the superior border of the dissection. It is essential to preserve the main trunk of the inferior thyroid artery and all of its superior branches to maintain a blood supply to the superior parathyroid gland. The inferior parathyroid gland may need to be dissected away from the adjacent lymph nodes to save its blood supply. If the viability of the parathyroid gland appears compromised, it should be harvested and kept in cooled saline for later reimplantation. Approximately 10% of it should be sent for frozen section to confirm parathyroid tissue and avoid inadvertent autotransplantation of a pathological lymph node. The dissection then proceeds over the esophageal muscularis with gentle anterior retraction. The tissue is dissected over the trachea, and the pretracheal lymph nodes are elevated and ligated approximately at the medial edge of the left strap muscles. The

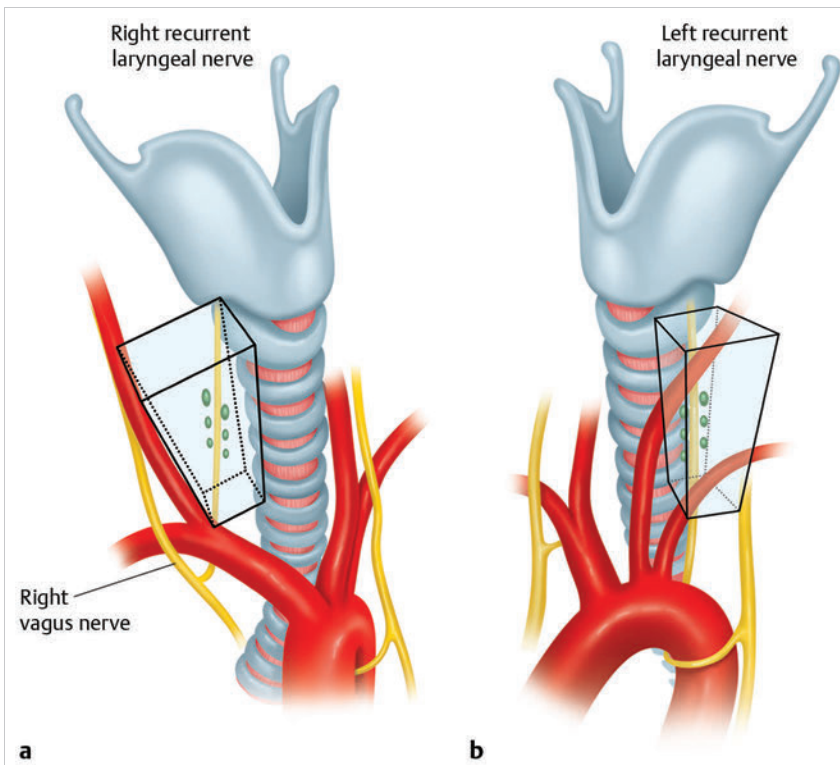


Fig. 19.2 (a) The right recurrent laryngeal nerve (RLN) has greater depth due to it entering more ventrally underneath the bifurcating innominate artery, which lies ventral to the trachea. The right RLN then extends medially and descends to its laryngeal entry point at the right lateral inferior edge of the cricoid cartilage. The right paratracheal region therefore can be divided into two triangles: an upper lateral triangle and a lower medial triangle. The RLN divides the compartment into an anterior and posterior compartment. (b) The left paratracheal region is much flatter and more two-dimensional because of the tracheoesophageal groove location typical of the left RLN as it traverses the region.

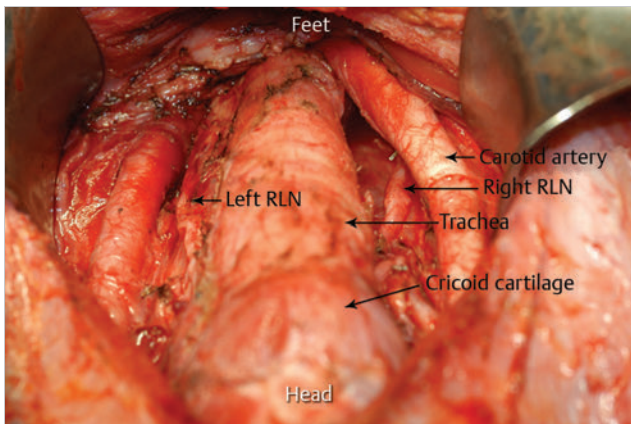


Fig. 19.3 A completed reoperative bilateral central neck dissection with removal of the prelaryngeal, pretracheal, and bilateral paratracheal nodal basins. Notice on the right side, the recurrent laryngeal nerve (RLN) travels more ventrally and obliquely than the left RLN, which runs in a more craniocaudal course and in the tracheoesophageal groove.

inferior dissection is completed by careful ligation of all tissue anterior and superior to the innominate artery. Level VI does extend to the hyoid bone, but it is uncommon to see lymph node metastasis superior to the level of the RLN laryngeal insertion site. Any lymphadenopathy that does exist in this area should easily be seen with ultrasound, and the dissection should be extended to include this area accordingly.

The left paratracheal dissection starts with identifying the common carotid artery. Unlike the right, the left common carotid artery has its own takeoff from the aorta and is dissected inferiorly to the level of the clavicle and superiorly to the

thyroid cartilage. The RLN is then traced inferiorly from where it was identified during the thyroidectomy. Unlike the right RLN, the left RLN runs in a more craniocaudal course and in the tracheoesophageal groove (► Fig. 19.2 and ► Fig. 19.3). It does not need to be circumferentially dissected and transposed because there are seldom lymph nodes deep and medial to the left RLN. It is followed inferiorly to the level of the clavicle. The lymph node tissue medial to the carotid artery is brought over the esophageal muscularis and the RLN. The anterior border of the RLN must be freed from the specimen. One must be careful when dissecting the RLN inferiorly. The RLN is usually tented up with the lymph node-bearing tissue from the superior mediastinal paratracheal region and thymus. An arbitrary termination of the dissection is then made at the level of the superior border of the innominate artery, taking care to meticulously ligate all tissue in this area and avoid injury to the RLN. Dissection continues superiorly to the RLN insertion point. The parathyroid glands are managed in the same way as described for the right parathyroid glands. Similarly, the remaining pretracheal lymph nodes are elevated and ligated at the medial border of the right strap muscles.

The operative bed is then inspected, and the parathyroid gland viability is visually assessed. Liberal use of autotransplantation is advocated if the status of the parathyroid gland is questionable. The physical continuity of the RLNs is evaluated. Nerve monitoring, if used, may provide valuable information on the neurophysiological integrity of the RLN. This may influence the decision on whether to proceed with an elective contralateral CND. A Valsalva maneuver is performed, and hemostasis is achieved with the judicious use of bipolar cautery or sutures. Hemostatic agents may also be used. The strap muscles are closed with an absorbable suture. The use of a drain is left to the discretion of the surgeon. The closure proceeds similar to

that used for thyroidectomy, and medical-grade skin adhesive glue may be used to seal the skin edges.

19.7.2 Reoperative Central Neck Dissection

Reoperative CND may be considered when there is FNA-confirmed evidence of disease or growth of a mass not amenable to biopsy. It is generally accepted that reoperative CND imparts a higher complication rate than primary surgery. We believe that reoperative CND for nodal metastases alone may be as safe as primary CND.¹⁷ Nonetheless, the recommendation for surgery versus observation should be made in a multidisciplinary fashion and tailored to the patient's needs.

All patients undergoing reoperative CND should undergo a fiberoptic laryngoscopy to assess vocal fold mobility. Often, the localization and confirmation of metastatic cancer are made with ultrasound and FNA biopsy. It is important to have a clear understanding of the location of the cancer and its relationship to surrounding structures. The cancer may be in lymph nodes or at the primary site. This is important to distinguish because reoperation for metastatic cancer versus recurrence at the primary site has a strikingly different risk profile. In our experience, when the recurrent disease is at the primary site, there is a much higher risk of vocal fold paralysis (33%) versus metastases to the lymph nodes (<1%).¹⁷ If ultrasound cannot resolve this issue, then axial imaging with contrast may be helpful, especially if there is also concern for local invasion. Ultrasound is also very helpful in defining whether a unilateral or bilateral paratracheal lymph node dissection will be required. This may be due to the improved sensitivity of ultrasound to detect subcentimeter lymph node metastasis in the central neck when the thyroid is not present.

Reoperative CND can be performed through the existing thyroidectomy incision. Excision of the original incision may be performed if necessary and is generally recommended to achieve the best cosmetic result. The approach may be either through the midline raphe of the strap muscles with elevation of the strap muscles over the thyroid bed or from a lateral approach. The lateral approach may be warranted when extensive scarring is present. In this circumstance, the carotid sheath is identified, and the strap muscles are elevated over the thyroid bed from lateral to medial. It may be advantageous to divide the sternothyroid muscle to achieve better access to the paratracheal nodal compartment. The strap muscles are then elevated over the thyroid bed superiorly and inferiorly, taking great care to avoid excessive cautery as dissection proceeds superiorly to avoid injury to the RLN.

The main difference in the technique for reoperative CND compared to primary CND is in the method used to identify the RLNs. The region where the RLN is typically found during thyroidectomy may be scarred, and familiar landmarks for identification of the RLN are not present. RLN monitoring may be useful during reoperative CND. The vagus nerve can be stimulated at 1 mA prior to beginning the dissection to get the baseline amplitude on the electromyographic waveform. Once the carotid artery is identified in the same fashion as in primary CND, the right RLN may be searched for, medial and deep to the common carotid artery above the innominate and subclavian artery junction, and the left RLN medial to the common carotid

artery inferior in the neck and in the tracheoesophageal groove. The remainder of the operation proceeds in the same fashion as described for primary CND (► Fig. 19.1).

19.8 Postoperative Management

Patients undergoing CND may be admitted overnight for observation. Postoperative considerations are similar to those of total thyroidectomy. Patients who have undergone a CND are at increased risk for temporary and permanent hypoparathyroidism.¹⁸ Therefore, patients should be followed per individualized institutional protocols for managing hypocalcemia. Alternatively, routine administration of oral calcium and vitamin D supplementation has been shown to be feasible. Fiberoptic laryngoscopy should be performed to confirm true vocal fold mobility as an important measurement of surgical quality. Observation for bleeding and hematoma formation is also important.

Oncological long-term results will be determined by serial follow-up with ultrasound and serum thyroglobulin (Tg) examination. Ultrasound is typically used for surveillance of the central neck after thyroid surgery with or without CND. Any suspicious lymphadenopathy in the previously operated central neck should be monitored if it is ≤ 0.8 cm and biopsied if it is > 0.8 cm.¹⁹

Recurrence is defined as biochemical or structural identification of disease in a patient previously thought to have no evidence of disease (undetectable baseline or stimulated Tg, and negative ultrasound and cross-sectional imaging). Biochemically detectable disease is defined as an elevation in the serum Tg level. Patients who present with a detectable serum Tg level after RAI or an increasing serum Tg level if no RAI has been administered are most likely to have disease in the nodal groups, which may be in the central compartment (level VI), the lateral neck (commonly at levels II, III, IV, and V), or level VII (upper mediastinal nodes).²⁰ All structural and biochemical disease identified before a patient is classified as having no evidence of disease is considered persistent disease.^{21,22}

19.9 Complications

The complication profile of CND is similar to that of total thyroidectomy. The most common complication associated with CND is hypoparathyroidism. Temporary hypoparathyroidism following CND occurs in 14 to 40% of cases.^{23,24} This wide range of incidence can be partially attributed to the different normal reference levels and the definition of hypoparathyroidism. The high incidence of temporary hypoparathyroidism is likely due to inadvertent inclusion of parathyroid glands in the nodal dissection. Though reports are mixed regarding the incidence of permanent hypoparathyroidism, a meta-analysis performed by Chisholm et al²⁵ reported a 1.2% incidence as defined by the requirement for calcium supplementation surpassing the 6- to 12-month period postoperatively. This low incidence of permanent hypoparathyroidism may be due to the increasing practice of parathyroid autotransplantation at the time of surgery.

Injury to the RLN or the external branch of the superior laryngeal nerve occurs in 1 to 2% of patients.²⁶ In experienced hands the addition of CND to total thyroidectomy for the

treatment of thyroid cancer has not increased the nerve injury rates.²⁵ However, the recent ATA recommendations regarding therapeutic or elective CND should be interpreted in the light of available surgical expertise. Although observation may increase the chance of future locoregional recurrence, overall this approach may be safer in less experienced surgical hands. Sosa et al and others found that high-volume surgeons (> 100 cases/5 y) had 75% fewer complications related to thyroid surgery than low-volume surgeons (4.3% vs. 16.1%).^{27,28} However, there are no similar comparative studies done for outcomes related to CND. In cases of reoperative CND after either previous thyroidectomy or CND, reports have noted increased nerve injury rates up to 12%,² whereas others have shown no increase.¹⁷

19.10 Pearls and Pitfalls

- The RLN divides the right paratracheal space into an anterior and posterior compartment as well as a lateral and medial compartment.
- It is necessary to skeletonize the RLN along its entire cervical course to achieve a complete compartmental dissection. Avoid excessive or unintentional traction on the nerve.
- Attempts to preserve the inferior parathyroid glands and their blood supply may result in incomplete lymph node clearance.
- Preserving the main trunk of the inferior thyroid artery and superior terminal branches helps to minimize hypoparathyroidism by preserving the viability of the superior parathyroid glands.
- Liberal autotransplantation of compromised parathyroid glands (after frozen section confirmation) will help to minimize long-term hypocalcemia.
- Compartmental dissection must be performed. "Berry picking" may necessitate future additional surgery and is discouraged.
- Reoperative CND poses unique challenges for RLN and parathyroid gland preservation, and its risk–benefit profile must be carefully weighed in a multidisciplinary fashion.

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20 Surgical Management of the Lateral Neck in Thyroid Cancer

Daniel Kwon and Alfred Simental, Jr.

20.1 Introduction

The propensity of differentiated thyroid cancer (DTC), especially papillary thyroid cancer (PTC), with its predilection for lymphatic metastases, to demonstrate early spread to cervical lymph nodes has been well described in the literature over the past several decades.¹ The first echelon of thyroid cancer metastases are found in the paratracheal and central neck lymph node compartments, with the lateral cervical lymphatic chain along the jugular vein comprising the second echelon of lymph nodes. The rate of metastases, including micrometastases, for PTC ranges from 50 to 90%.^{2,3,4,5} The central compartment is a frequent site of lymph node recurrence in thyroid cancer. This has prompted considerable debate regarding the need for prophylactic central neck dissection in an attempt to avoid the increased risk of complication associated with reoperative surgery. The debate on the initial surgical management of regional lymph nodes also includes the lateral neck, because recurrence is possible there in up to 30% of cases.⁶ It is undeniable that clinically evident or progressive cervical metastases require treatment to improve outcome, but the treatment of subclinical disease is less clear with regard to cost, risks, and benefit of treatment. Additionally, although cervical metastatic disease has been implicated in some studies as an independent risk factor for locoregional recurrence, its effect on overall mortality is inconclusive.^{7,8} There is potentially significant additional morbidity and surgical risk associated with lateral cervical lymph node dissection compared with thyroidectomy and central neck dissection alone. As methods of thyroid cancer detection have improved significantly over the past several decades, an increasing number of patients face the possibility of neck surgery. This chapter addresses the evaluation, treatment, and implications of lateral neck lymph node metastases in thyroid cancer.

20.2 Risk Factors

A number of risk factors are associated with the presence of lateral neck metastases in thyroid cancer. Papillary carcinoma often demonstrates early lymphatic spread, and therefore has a high incidence of lateral cervical lymph node metastasis. Follicular and Hürthle cell carcinomas have lower rates of lateral cervical nodal metastases, though these do infrequently occur.⁹ In addition to primary tumor histology and the presence of central compartment disease, lateral neck metastases are more likely in the presence of the following factors: younger patients, male sex, increased size of primary tumor, lymphovascular invasion, extrathyroidal extension, multifocal disease, and *BRAF* mutations.^{5,10,11,12,13}



The following are factors affecting lateral neck nodal metastases in well-differentiated thyroid cancer:

- Primary tumor histology.
- Primary tumor size.
- Age.
- Extrathyroidal extension.
- Gender.

Molecular markers have recently been investigated regarding their utility to predict aggressive disease and lymph node metastasis, as well as their being a basis for targeted therapy. *BRAF* is a gene that codes for B-raf, a protein in the mitogen-activated protein kinase cell signaling pathway. Mutations in the *BRAF* gene have been implicated in a variety of human cancers, including melanoma and lung and thyroid cancers. In papillary thyroid cancer, mutations have been demonstrated in some studies to be the most important independent clinicopathologic feature of aggressive disease, including lymph node metastasis, recurrence, and death.¹⁴ However, some of the more recent studies are demonstrating a much higher prevalence of *BRAF* mutations than previously described and fail to find an association with lateral cervical lymph node metastases.^{15,16,17,18} Other molecular markers, such as the expression of tumor-suppression protein p53, have also been investigated as risk factors for disease aggressiveness and nodal metastasis.¹⁹ These markers have not been established to be independent indications for elective neck dissection in thyroid cancer but may serve to stratify risk and guide further preoperative evaluation. Patients with additional risk factors will be the most likely to benefit from either ultrasound or advanced imaging, such as computed tomography (CT) and magnetic resonance imaging (MRI), to evaluate the central and lateral lymphatic compartments for the presence of metastatic disease.

20.3 Preoperative Evaluation

The lateral neck should be assessed in all patients undergoing surgery for thyroid cancer. A complete history should inquire about the presence of any new neck masses or any first-degree relatives with a history of metastatic thyroid carcinoma. Physical examination should include laryngoscopy to determine vocal fold mobility and careful bimanual examination of the neck for abnormal lymph nodes. In postoperative patients, elevated levels of thyroglobulin (Tg) and Tg antibody can serve as a harbinger of recurrent primary or metastatic disease.

20.3.1 Imaging

Radiographic detection of macroscopic cervical lymph node metastases is crucial because removal of macroscopic disease at the initial surgery will decrease the need for revision surgery as well as repeated radioactive iodine (RAI) treatments. High-resolution ultrasound of the thyroid and lateral neck has been found to be reliable and low cost for the evaluation of thyroid cancer when employed by experienced clinicians. Unfortunately, routine diagnostic thyroid ultrasound frequently does not address the lateral neck. However, a protocol employing dedicated, comprehensive, consistent preoperative ultrasound assessment of the lateral neck results in the detection of suspicious lymphadenopathy in up to 20 to 30% of patients with known thyroid cancers, and ultimately alters surgical treatment in approximately 20% of these patients.^{20,21} The sensitivity of ultrasound in detecting cervical lymphadenopathy in the central compartment has been reported as 30 to 50%, largely due to the shadowing effect of the thyroid gland. The low sensitivity of ultrasound (US) in the central neck is one reason why CT imaging is preferred by many surgeons in the initial imaging evaluation of high-risk patients. However, in the lateral neck, ultrasound has up to 90% sensitivity in detecting suspicious lymph nodes. Specificities approach 90% in both central and lateral compartments using US.^{15,22} Concerning features of lymph nodes on US include size > 1 cm, hypoechoic consistency, round shape, irregular borders, absence of hilum, peripheral vasculature, calcifications, and cystic changes.^{23,24,25}

Below are US features of lymph nodes suggestive of metastases in thyroid cancer:

- > 1 cm in size.
- Hypoechoic lymph node/cystic changes.
- Irregular border.
- Absence of normal hilum architecture.
- Peripheral vasculature.
- Calcification.

US has many advantages over other imaging modalities, such as CT and MRI. There is no radiation exposure with US, it can be performed in the outpatient office during the initial visit, and it is rapid, easily repeatable, and relatively inexpensive. Fine-needle aspiration (FNA) biopsy has been shown to be more accurate when coupled with US guidance and has become the standard for thyroid and cervical biopsies.²⁶ Despite these advantages, limitations in evaluating substernal regions and invasion of surrounding organs, as well as interoperator reliability, present some challenges for the universal acceptance of US as the sole imaging modality for initial or recurrent high-risk thyroid cancers. Advanced imaging modalities, such as CT, MRI, or positron emission tomography (PET-CT) have similarly high sensitivity and specificity in assessing central compartment and lateral neck lymph nodes.^{27,28} They offer the advantages of better visualization of adjacent neck tissues and periclavicular neck levels and less operator dependence. Additionally, combining imaging modalities, such as US and CT, has been shown to offer higher sensitivity than the individual modalities.²⁹ At

this time, most surgeons are more comfortable reviewing CT or MRI scans, rather than US images, to determine the locations of metastases. Thus these modalities are widely preferred for preoperative planning and locating metastases in uncommon locations. However, the routine use of CT results in considerable expense and additional radiation exposure. The Food and Drug Administration (FDA) has begun to consider the effects of CT radiation on long-term health and has issued several statements requesting the decrease of exposure to medical radiation.³⁰ Also, the use of CT contrast dye may delay the administration of postoperative RAI for at least 3 months after administration while the stunning effect of the contrast on the thyroid wears off.

Despite these limitations, CT imaging will provide the most reliable clinical staging and surgical planning of any current imaging modality. The use of MRI has similar advantages to CT, but the presence of vascular flow voids, movement artifacts, and inferior osseocartilaginous delineation limit its utility in imaging advanced thyroid malignancy.

20.3.2 Pathological Staging

Cervical lymphadenectomy is associated with increased morbidity, and every effort should be made preoperatively to establish a cytological diagnosis of suspicious lateral cervical nodes. FNA has remarkably improved the ability to pathologically detect malignancy in central compartment and lateral cervical lymph nodes.³¹ However, the accuracy of cytopathologic diagnosis is highly dependent on adequate sampling of the lesion and the proficiency of the pathologist. Palpation-guided FNA results in a false-negative rate of ~ 6%, with an additional 10% of samples found to be inadequate.³² However, when US-guided FNA (US-FNA) is performed, the diagnostic yield improves, and inadequate sampling rates decrease to approximately 3 to 7%.^{26,33} This is possible due to real-time visualization of needle passes through the targeted lymph node.³⁴ The diagnostic yield of US-FNA can also be increased by selecting nodes with more suspicious features (as listed in the previous section), with sensitivities and specificities approaching 100% when multiple features are present.³⁵

Sensitivity and specificity of US-FNA can be further increased when Tg assay of the aspirated fluid is performed in addition to routine cytopathologic analysis.³⁶ This is especially helpful for sampling small-volume lymph nodes or nodes with significant cystic components, which might yield an inadequate number of cells.^{37,38} The utility of Tg serology in FNA is limited for sampling undifferentiated, anaplastic, or medullary thyroid cancers, which do not typically produce Tg. In addition, the presence of Tg antibody may theoretically affect the measurement of Tg, although studies have shown that FNA-Tg measurement is useful, even in the presence of circulating serum Tg antibody.³⁶ Inclusion of any thyroid tissue would obviously create a false-positive; however, this is typically more relevant to central compartment nodes where the needle could mistakenly pass through the thyroid gland and where small foci of remnant thyroid may mimic lymph nodes.³⁹ Thus Tg assessment with FNA is most useful when sampling lateral neck nodes in athyrotic, Tg antibody-negative patients after RAI administration.⁴⁰ With or without Tg, US-FNA should be performed in all clinical

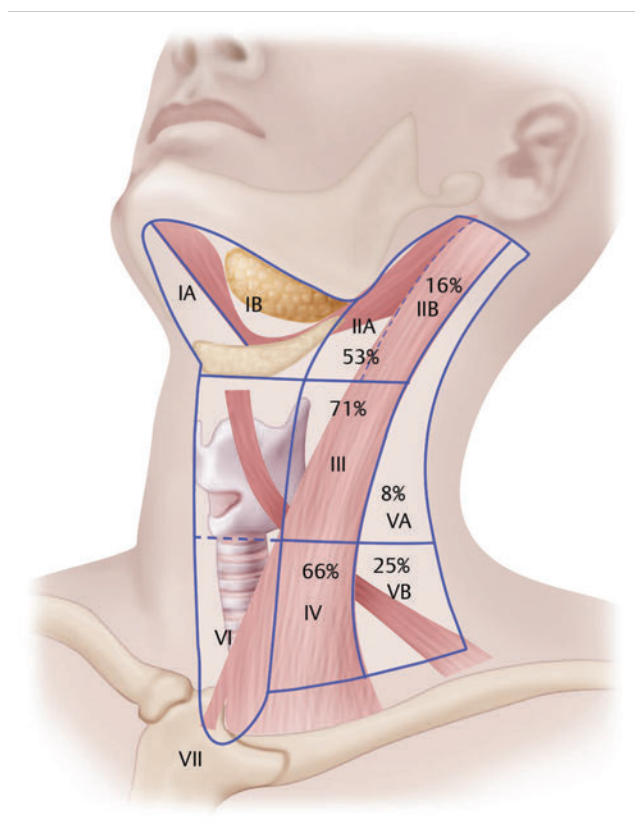


Fig. 20.1 Prevalence of lateral lymph node metastasis by compartment. (Adapted from Robbins et al.⁴⁹)

scenarios with suspected lymph node metastasis, whether primary or recurrent.

20.3.3 Laboratory Evaluation

Serum Tg and Tg antibodies are useful tools in surveillance and are thought of as surrogate measures of functional thyroid tissue, benign or malignant.^{41,42} The presence of a progressively rising Tg or Tg antibody after surgery and primary ablation of thyroid tissues may be a sign of persistent or recurrent thyroid malignancy. In addition, testing for the presence of certain biomarkers, such as *BRAF* mutations, which has been associated with lymph node metastases, may aid in risk stratification.^{17,43,44,45} Studies have explored the utility of gene assays for *BRAF* in FNA samples to predict disease behavior, including lymph node metastases.⁴⁶ However, the significance of many of these biomarkers are still under investigation and the assays are not widely available.

20.4 Cervical Lymph Node Compartments

The neck compartments have been standardized for several decades based on well-studied lymph node drainage pathways and oncological patterns of spread.^{47,48,49} Defining key boundaries and landmarks has been instrumental in relating metastatic cancerous deposits with likely sites of unknown primary tumors in squamous cell carcinoma of the upper aerodigestive

tract and also for defining lymph node basins most appropriate for evaluation when treating patients with these malignancies. This has resulted in standardized nomenclature for communication of lymph node basins most likely to be affected by well-differentiated cancer as well. For practical purposes, there are six lymph node compartments or “levels” in the neck that are described following here (► Fig. 20.1). These compartments encompass the lymph nodes in the fibro-fatty soft tissue located between the superficial investing fascia superiorly, and the visceral and prevertebral fascia layers deep. Level I is known as the submandibular space, and levels II through IV, the jugular nodes.

20.4.1 Level I

Level I is bound by the mandible superiorly and the body of the hyoid inferiorly. The anterior border is the anterior belly of the contralateral digastric muscle, and the posterior border is the stylohyoid muscle. Level I is divided into IA and IB by the anterior belly of the ipsilateral digastric muscle.

20.4.2 Level II

Level II is bound superiorly by the skull base and inferiorly by the horizontal plane of the inferior border of the hyoid bone. The anterior border is the stylohyoid muscle, whereas the posterior border is the lateral border of the sternocleidomastoid (SCM) muscle. Level II is also divided into two sublevels, IIA and IIB, by the vertical plane of the spinal accessory nerve.

20.4.3 Level III

Level III is bound superiorly by the horizontal plane of the inferior border of the hyoid bone and inferiorly by the horizontal plane created by the inferior aspect of the cricoid cartilage. The lateral sternohyoid muscle is the anterior border, and the lateral border of the SCM and/or cervical rootlets serve as the posterior border.

20.4.4 Level IV

Level IV is bound superiorly by the horizontal plane of the inferior cricoid cartilage and inferiorly by the clavicle. Similarly to level III, the anteromedial border is the lateral sternohyoid muscle, and the lateral border is the lateral SCM and cervical rootlets posteriorly.

20.4.5 Level V

Level V is bound superiorly by the convergence of the SCM and trapezius muscles and inferiorly by the clavicle. The lateral edge of the SCM and/or cervical rootlets is the anterior border, whereas the anterior border of the trapezius muscle serves as the posterior border. This level is divided into VA and VB by the horizontal plane of the inferior cricoid cartilage.

20.4.6 Level VI

Level VI is bound by the hyoid bone superiorly and laterally by the common carotid arteries. The inferior limit is sometimes

defined as the sternal notch, whereas others use the innominate artery as the inferior border. These lymph nodes inferior to the sternal notch in the anterior mediastinum are often included in the definition of the central compartment due to the contiguous lymphatic drainage of the perithyroidal and paratracheal lymph nodes into the mediastinum. Superior mediastinal lymph nodes accessible through the neck are often referred to as level VII lymph nodes, though this is not supported by the consensus statement of the American Head and Neck Society as well as the American Academy of Otolaryngology–Head and Neck Surgery.⁵⁰

20.5 Lateral Neck Dissection Definitions

Similar to the definition of the cervical lymph node compartments, nomenclature and definitions of neck dissections are important for consistency in the medical literature and research and for communication among clinicians. Lateral neck dissections have been relatively well defined in the literature, based on the previously described lymph node levels.

The radical neck dissection (RND), popularly described by Crile in 1906, is defined by removal of all ipsilateral cervical lymph node structures in compartment levels I through V along with the spinal accessory nerve, SCM, and internal jugular vein. The boundaries of this dissection are the mandible superiorly, the clavicle inferiorly, the lateral hyoid bone, the sternohyoid muscle, and the contralateral anterior digastric muscle medially, and the anterior border of the trapezius laterally.

The modified radical neck dissection (MRND), introduced several decades later, refers to the removal of all lymphatic structures included in the radical neck dissection (levels I–V), but with the preservation of at least one of the nonlymphatic structures (spinal accessory nerve, SCM, internal jugular vein). Despite the preference for the terms *radical neck dissection* and *modified radical neck dissection*, there is some variety in the nomenclature found in the literature in reference to the removal of lymph node levels I through V, including *complete neck dissection* or *comprehensive neck dissection*.⁵¹

Most recently, *selective neck dissection* (SND) has emerged as a general term that refers to the removal of some but not all of the lymphatic compartments of the lateral neck. The use of SND represents one of the major changes in head and neck oncological surgery, where targeted lymphadenectomy is guided by knowledge of lymphatic drainage patterns specific to the primary malignancy site and histology.⁵² Due to this more selective approach to the neck, the literature refers to several classifications, such as supraomohyoid neck dissection, antero-lateral neck dissection, lateral neck dissection, and extended neck dissection. However, the extent of excision described by these terms varies among institutions. Therefore the extent of neck dissection, according to the individual levels excised, should be specifically described when departing from the more standardized terminology of RND and MRND. This includes comments on inclusion or exclusion of lymph node sublevels as well as lymph nodes not included in the compartment classifications, such as perifacial, periparotid, parapharyngeal, superior mediastinal, and suboccipital lymph nodes. Additionally, any sacrificed nonlymphatic structure should be noted as well. This

is especially important when one is dealing with the lateral neck in thyroid cancer because cervical metastases may vary, especially in the setting of recurrent disease.

Traditionally, the extent of lateral neck dissection for thyroid cancer had been largely left to the discretion of the individual surgeon, leading to disparate procedures and operative descriptions. To codify these differences, the 2009 American Thyroid Association (ATA) guidelines recommended “therapeutic lateral neck compartmental lymph node dissection” for lateral cervical metastases.⁵³ With the exception of RND and MRND, lateral neck dissections for thyroid cancer should now specifically describe the nodal compartments, which are dissected, and excision of individual nodes (“berry picking”) is no longer recommended.

20.6 Cervical Lymph Node Metastasis in Differentiated Thyroid Cancer

Papillary thyroid cancer is the predominant thyroid cancer resulting in cervical lymph node metastasis due to its prevalence and high propensity for lymphatic spread.

20.6.1 Drainage Patterns

Cervical metastasis in differentiated thyroid cancer typically occurs in the central compartment, the first nodal basin, with subsequent stepwise spread to the lateral neck in levels II through V. There is also evidence of spread to the lateral neck directly from the thyroid gland.⁵⁴ These “skip metastases” have been shown to occur in up to 38% of cases, most commonly from upper pole lesions.⁵⁵ Level I is not commonly affected by thyroid cancer metastasis. Levels III and IV are the most common sites of lateral cervical metastases, but the incidence of multilevel disease affecting all levels II through V is high once the disease has progressed to the lateral neck.^{56,57} Spread to level IIB is less common (~15%), with rates of involvement ranging from 5 to 62%. Similarly, level VA is only involved in approximately 8% of cases (► Fig. 20.1).⁵⁶ Finally, it is important to recognize that contralateral neck metastasis may occur, especially in multifocal tumors and tumors involving the isthmus. Even in cases of unilateral thyroid cancer, contralateral or bilateral lateral neck metastases have been seen in up to 24% of cases in one study.⁵⁸ These cases correlated highly with the presence of clinically evident ipsilateral lateral and contralateral paratracheal nodal metastases, leading the authors to suggest bilateral neck dissection in those cases.

20.6.2 Prognostic Significance of Nodal Metastasis

When stratified by low- and high-risk differentiated thyroid carcinoma, large, single-institution studies have demonstrated no changes in survival among patients with or without nodal disease.⁵⁹ Other institutions have suggested decreased survival in patients with nodal metastasis in certain populations, such as older patients and patients with follicular carcinoma.^{8,60} Large-population studies also have conflicting reports regarding the survival implications of nodal metastases.^{61,62,63} It is

important to recognize that most of the retrospective survival outcome data in thyroid cancer are plagued by selection bias, with different subjects receiving different treatments. The long survival in differentiated thyroid cancer makes it difficult to design a prospective study with enough patients and follow-up length to reach significance.⁶⁴ However, in terms of locoregional control after primary treatment, the presence of nodal disease in the lateral neck at initial presentation has been shown to be a positive predictive factor for recurrence, even after neck dissection and adjuvant treatment.⁶⁵ There is no conclusive evidence that RAI treatment is effective in eradicating occult lateral neck metastasis, and it has been shown to be relatively ineffective in treating clinically apparent disease.⁶⁶ Therefore, although its effect in overall survival is controversial, lateral neck disease in thyroid cancer should be addressed with surgery in an attempt to control regional disease progression and improve quality of life.

20.6.3 Elective/Prophylactic Neck Dissection

Though much more common in other countries, a minority of centers in the United States advocate prophylactic lateral neck dissection to prevent the need for future treatment-related quality-of-life issues. Each time a patient undergoes another surgical intervention, there is a “time packet” related to preparation and recovery from the given procedure. Thus, even though survival is not changed, repeated interventions at temporally distinct times decrease the patient’s nontreatment-related survival. A patient may be subjected to two separate 6-week recovery periods instead of one, thus doubling the treatment-related recovery.

Studies reporting on prophylactic lateral neck dissection have demonstrated occult disease rates of up to 50% and have advocated prophylactic lateral neck dissection, either routinely or in the presence of central compartment lymphadenopathy.^{67,68} In order to improve the detection and removal of occult metastasis, while minimizing the morbidity of surgical therapy, the use of sentinel lymph node mapping and biopsy has been employed. However, the sentinel lymph node is almost always located in the central compartment; therefore sentinel lymph node mapping seldom provides guidance in addressing the lateral neck.⁶⁹ Proponents for prophylactic neck dissection including the lateral neck cite the benefits of more accurate staging and subsequent changes in the management algorithm.⁷⁰ But, despite good evidence demonstrating the prevalence of occult lateral neck disease, there are no data indicating a long-term survival benefit of lateral neck dissection in these patients.^{71,72}

It is possible that microscopic nodal disease and clinically apparent nodal disease are separate entities in terms of their biological behavior. A meta-analysis by the ATA reported that the data indicated that small-volume micrometastases had a significantly more benign behavior when compared to clinical apparent disease.⁷³ Microscopic metastases discovered only by prophylactic neck dissection had recurrence rates of approximately 6%, which were similar to the 4% recurrence rates in clinically N0 patients that did not undergo neck dissection. This rate of clinical recurrence contrasted greatly when comparing overall recurrence rates between cN0 and cN1, which were 2% versus 22%, respectively. In a double-armed study from Japan,

where RAI is not routinely used, prophylactic neck dissection in low-risk (micropapillary) thyroid cancer discovered metastatic disease in approximately half of the cases. However, clinically apparent lymph node disease developed in only 1.2% of patients who opted for observation alone after 8 years of follow-up.⁷⁴ These studies suggest that microscopic cervical metastases may not necessarily progress to clinical disease in the majority of patients. A meta-analysis examining the role of lateral neck dissection in well-differentiated thyroid cancer concluded that, when considering the risks and benefits, there was no definitive role for elective lateral neck dissection.⁷⁵ Although there are practical reasons for performing concurrent prophylactic central neck dissection during thyroidectomy, the cost and morbidity of lateral neck surgery, combined with the small decrease in clinical recurrence, greatly limits the benefit of routine lateral neck dissection in a clinical N0 patient.

20.6.4 Therapeutic Neck Dissection

A wide range of neck dissection techniques have been described in the literature and used in practice. Limited neck dissections include “berry picking,” the selective removal of macroscopically involved lymph nodes, as well as “superselective” neck dissection, which is the removal of only the compartments that have involved lymph nodes. These methods were popular in the past because the disease course of differentiated thyroid cancer is so indolent. These limited approaches also require less surgical proficiency and typically result in less morbidity. However, routine use of noncomprehensive cervical lymphadenectomy for the primary treatment of the lateral neck results in a higher risk of recurrence and subsequently increases treatment-related recovery and morbidity. The presence of lateral neck disease suggests that the biology of the cancer is more aggressive than most clinically occult variants. Thus the micrometastases that accompany the clinical disease are likely to recur if it is not addressed surgically. Preoperative imaging has been reported to be highly specific involved compartments or the number of involved nodes.⁷⁶ The use of limited neck dissection makes reoperation more difficult and increases the chance of treatment-related morbidity in the previously violated surgical field. These minimal methods may be of some utility when dealing with recurrent neck disease following a previous comprehensive neck dissection for local control. Based on the foregoing data describing patterns of lateral neck spread in thyroid cancer, the 2009 ATA guidelines have advocated for a “comprehensive lateral neck dissection.” This was later clarified as removal of levels IIA, III, IV, and VB in the presence of lateral neck disease.¹³ The Triological Society similarly recommended either selective neck dissection, including levels II through V with or without the inclusion of IIB and VA, or MRND for therapeutic treatment of clinically positive lateral neck metastasis in differentiated thyroid cancer (► Fig. 20.2 and ► Fig. 20.3).⁷⁷ Because level I involvement is rare, it typically does not need to be involved in the dissection.

20.6.5 Recurrent Neck Disease

In the case of reoperation for recurrent lateral neck disease, a compartment-based neck dissection should generally be considered because extensive scarring increases the risk of

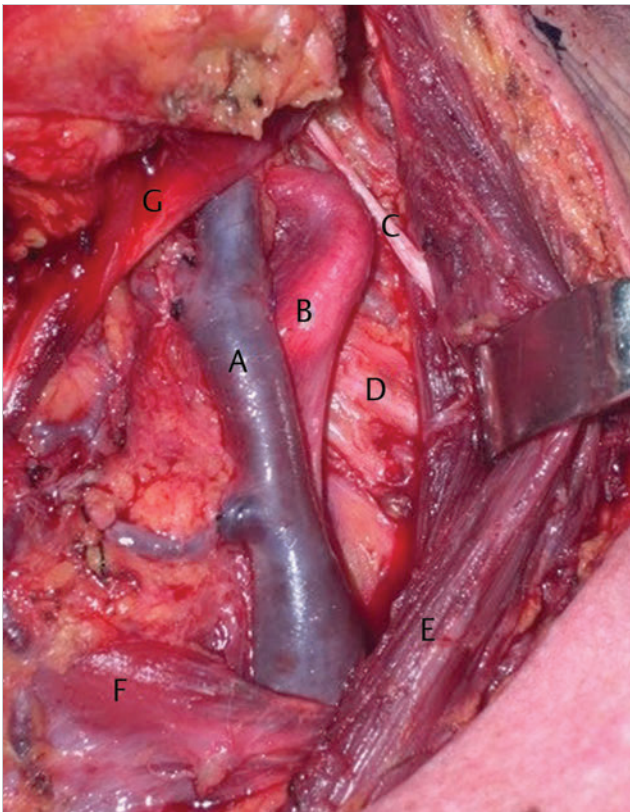


Fig. 20.2 Left neck after dissection. A, internal jugular vein; B, carotid artery; C, spinal accessory nerve; D, cervical rootlet; E, sternocleidomastoid muscle; F, omohyoid muscle; G, digastric muscle.

neurovascular injury. Careful evaluation with preoperative imaging should evaluate possible involvement of the carotid sheath or deep cervical musculature. Recurrent cancers will typically occur outside of the field of dissection and may be relatively simple to remove. However, in field recurrences treatment may require resection of important neurovascular structures, such as the phrenic nerve, spinal accessory nerve, and brachial plexus, which may result in significant morbidities. When the recurrence is in a surgically tenuous location and is small, close observation with maximal thyroid-stimulating hormone (TSH) suppression may be a reasonable option. In a series of 166 patients with lymph node recurrence detected on surveillance US that were followed for 3.5 years, the majority of the lymph nodes remained stable, with 29% eventually growing and 14% resolving on their own.⁷⁸ This study suggests that immediate surgical treatment of nodal recurrence may not be necessary and that active surveillance may be a reasonable alternative, reserving treatment for progression. In these progressive cases, if patient preference, high risk of morbidity, or medical comorbidity precludes reoperation, external beam radiation or systemic therapy may be employed with reasonable results.

20.7 Medullary and Poorly Differentiated Thyroid Cancer

Medullary thyroid cancer (MTC) should be considered a distinct entity when compared to DTC and portends a worse prognosis.

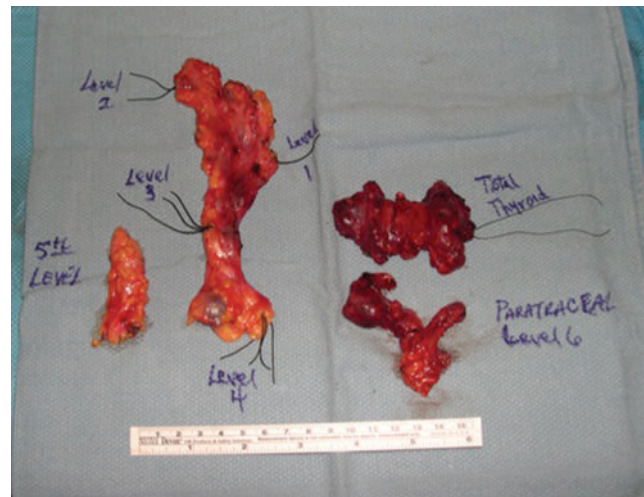


Fig. 20.3 Surgical specimen showing total thyroidectomy and central and lateral neck contents.

Clinically apparent cervical metastases are common on presentation due to early lymphatic spread, and distant metastases may be present in up to 50% of cases.⁷⁹ The pattern of lymphatic spread tends to be stepwise, and the presence of central compartment lymphadenopathy has been shown to be indicative of ipsilateral and contralateral lateral neck spread in more than 70% and 38% of cases, respectively. These numbers increase dramatically when there are multiple (> 10) central compartment nodes.⁸⁰ This has led some to advocate for elective lateral neck dissection when there is central compartment involvement.⁸¹ Unfortunately, it has been demonstrated that it is difficult to achieve biochemical remission of MTC in cases of cervical lymph node spread, with reports as low as 10% despite neck dissection.⁸² However, resection of neck disease has been shown to decrease local complications, such as invasion into adjacent neck structures (e.g., the aerodigestive tract).⁸³ Therefore, the 2009 ATA MTC guidelines recommended a lateral neck dissection of levels IIA, III, IV, and V when there are clinically apparent lymph node metastases, without the need for biopsy. In the setting of distant metastasis, lateral neck dissection should be employed only in the presence of clinically positive nodes in order to control regional disease that may eventually result in airway, phonatory, or swallowing dysfunction.

Anaplastic thyroid cancer is extremely aggressive and typically presents with distant metastases and extensive local invasion.⁸⁴ Locoregional invasion into the carotid artery, internal jugular vein (IJV), cranial nerves, and aerodigestive tract is common. Therefore, usual considerations assessing lymph node involvement and cervical spread typically do not apply. Isolated intrathyroidal tumors represent 10% of cases of anaplastic thyroid cancer and are usually an incidental finding. In these cases, the ATA recommends therapeutic removal of central and lateral lymph node compartments along with thyroidectomy.⁸⁵ The role of surgery is otherwise based on whether complete resection with gross negative margins is possible with reasonable morbidity.⁸⁵ Even in the presence of distant metastasis, palliative locoregional surgery may be considered to preserve airway obstruction.

20.8 Surgical Considerations, Risks, and Postoperative Care in Lateral Neck Dissection

All proven or potential benefits of lateral neck dissection in thyroid cancer must be weighed against the risks and morbidity of lateral neck dissection.

20.8.1 Skin Incision and Wound Complications

An important aspect of lateral neck dissection in thyroid cancer is the surgical incision and scar. Considering the indolent nature of the disease and the relatively high prevalence in younger patients, optimizing the cosmetic appearance of the neck should be among the goals of treatment. When treating the lateral neck concurrently with thyroidectomy, extending the anterior neck incision along a natural skin crease laterally may help minimize noticeable scarring. A purely lateral neck incision may be employed, but often this incision must be extended superiorly behind the SCM muscle for adequate exposure of the level II basin. Trifurcating scars or multiple skin incisions (MacFee) should not be necessary, and they increase the risk of wound dehiscence, scar contracture, and flap necrosis.⁸⁶ Basic wound-healing principles should be followed with tension-free closure, optimizing nutrition and minimizing risk factors for wound complications. Risk factors for wound healing frequently include previous radiation, diabetes mellitus, malnutrition, and tobacco use. When lateral neck dissection is performed after previous thyroidectomy, an effort to use the same neck incision is prudent. Although cosmesis is taken into account, successful extirpation of disease and safety should be of ultimate importance.

20.8.2 Drains and Fluid Collections

The dissection and disruption of vascular, lymphatic, and adipose tissues during neck dissection predispose to the collection of fluid in the potential space formed underneath the skin flap and under the SCM muscle. Postoperative seromas, formed by the collection of serous fluid, are relatively common, with rates as high as 20%. Fortunately, hematoma formation occurs in only ~ 1% of cases.^{87,88} Fluid collections are usually detected on physical exam and can generally be evaluated with US, reducing the need for radiation and contrast from CT imaging. Typical presentations include loss of the normal neck contour, expanding neck mass, firmness to palpation, and skin ecchymosis. Seromas are largely prevented by using closed suction drains after neck dissection, but they may occur with incorrect drain placement, drain clotting, or premature removal. Most small seromas may be observed and allowed to reabsorb, but because these collections may predispose the patient to wound infection or dehiscence, removal of fluid may sometimes be necessary with needle aspiration or drain replacement.

Hematomas similarly increase the risk of wound complications and should be removed with either bedside evacuation or

return to the operating room for evacuation and control of any continued bleeding. Meticulous intraoperative hemostasis and avoidance of anticoagulant and antiplatelet medication should be used to prevent hematoma. Surgical drains do not prevent hematoma (as they do in seroma) but may aid in recognizing and localizing bleeding.

Chyle leaks may occur after left neck dissection in level IV near the site of the thoracic duct, but up to 25% may result from injury of the right lymphatic duct.⁸⁹ Because the thoracic duct and right lymphatic duct often present as a plexus of vessels, intraoperative ligation with clips or suture ties of the inferior aspect of neck dissection is prudent. Intraoperative Valsalva may be done when there is suspicion of a chyle leak during neck dissection. Additionally, application of hemostatic materials, sclerosing agents, and fibrin products has been described as adjunctive treatment.⁹⁰ Chyle leaks may occur in up to 2% of cases and are usually discovered after postoperative resumption of enteral feeding when drain fluid changes from a serosanguinous to a milky color. Sending drain fluid for triglycerides or chylomicrons helps confirm the presence of chyle. Rarely, chyle leaks may progress into the chest through the mediastinum and cause chylothorax. Treatment for chyle leaks typically starts with conservative management consisting of a medium-chain fatty acid diet and continuing suction drains.⁹¹ Unfortunately, pressure dressings seldom work. If the patient is able to tolerate oral intake, strict adherence to a diet of fruit and non-fried vegetables, excluding avocado, for several weeks, is usually effective in reducing chyle flow. Somatostatin may also be administered to reduce splanchnic blood flow and chyle production from the gastrointestinal tract.⁹² Chyle leaks are usually considered high-flow when daily drainage exceeds 500 to 1,000 mL. Needle drainage may be helpful, but high-flow chyle leaks and those that fail to stop after conservative treatment typically require reoperation to avoid malnutrition and immunologic dysfunction.

20.8.3 Vascular Injury

Complications involving the common carotid artery are the most life-threatening encountered during neck dissection. Intraoperative injury should be repaired primarily with vascular surgery techniques and specialty consultation, if possible. Postoperative carotid artery blowout occurs in up to 4% of radical neck dissections and is typically associated with other wound complications, such as infection, wound breakdown, and salivary fistulas.⁹³ Carotid blowout is associated with a 50% mortality risk and carries an additional morbidity risk, such as neurologic stroke from acute blood loss or intervention attempts, including surgical ligation, endovascular angiography, and embolization. IJV injury is also potentially life threatening but can usually be controlled intraoperatively with relative ease. During modified or selective neck dissection, every attempt should be made to preserve the IJV, especially in cases of bilateral neck dissection. Loss of bilateral IJV flow is associated with head and neck edema, elevated intracranial pressure, stroke, and blindness.⁹⁴ In addition to surgical ligation of IJV, thrombosis of the IJV may occur in up to 10 to 30% of MRND due to extensive handling and catheterization leading to adventitial damage and intimal dissection.^{95,96}

20.8.4 Nerve Injury

The lower divisions of the facial nerve are at risk for injury during dissection of levels I and II and when raising skin flaps. When operating in level I, past series have reported permanent paralysis of the marginal mandibular nerve in approximately 1% of cases, but rates may increase to 6% in cases of malignancy.^{97,98} Vagal nerve injury, although uncommon, is particularly undesirable because it typically results in dysphonia and dysphagia due to loss of both motor and sensory function to the larynx and pharynx, and it has greater morbidity when compared with isolated recurrent laryngeal nerve injury from thyroid and central compartment surgery.

The spinal accessory nerve in the neck is composed entirely of motor fibers to the SCM and trapezius muscles. Injury or sacrifice to the spinal accessory nerve causes shoulder droop and weakness, range of motion limitation, "winged scapula," and pain due to adhesive capsulitis of the shoulder joint. With the increased efforts to preserve this nerve, including departure from routine radical neck dissection and selective dissection of IIB and VA, rates of shoulder dysfunction have decreased over the past several decades. Now SND involving levels II through IV are associated with a 5% incidence of postoperative shoulder dysfunction, though this increases to 30% when level V is included.⁹⁹ This dysfunction may be permanent, although patients can have at least some return of function over time when the nerve is not completely transected. Even with complete transaction, many symptoms of spinal accessory nerve injury may be ameliorated by physical therapy and shoulder rehabilitation. Prevention of injury is best employed by early identification and careful handling of the nerve. It is important to recognize the variable course of the nerve in respect to the IJV as well as variable insertion into the SCM muscle.¹⁰⁰ Additionally, avoidance of muscle relaxants intraoperatively and use of a nerve stimulator may be helpful in locating and preserving the spinal accessory. Whether transected unintentionally or sacrificed, primary neurotomy or cable nerve grafting should be attempted. Injury to other motor nerves in the neck, including the hypoglossal nerve and phrenic nerve, are relatively rare, but similarly should be identified and repaired primarily or with a graft when transected.

Sympathetic chain injury typically occurs due to compression during retraction of the carotid sheath in neck dissection. Deficits are rare and typically temporary but may result in Horner's syndrome, which manifests as ipsilateral ptosis, miosis, and anhidrosis.¹⁰¹

Morbidity from injury to sensory nerves of the neck, including cervical rootlets, the great auricular nerve, and the lingual nerve, can be very bothersome to patients and adversely affect satisfaction and quality of life. Sensory deficits typically have a greater likelihood for recovery due to regeneration over time from adjacent sensory networks. Amputation neuromas may develop from transected sensory nerves causing firm, tender neck masses and may be treated with excision and reimplantation of the nerve stump.

The addition of lateral neck dissection in the surgical treatment of thyroid cancer confers significant additional risk of complications and morbidity when compared to thyroid surgery or central compartment surgery alone. This is especially important in the treatment of thyroid cancer, which is

commonly treated by low-volume surgeons in low-volume centers. Similar to studies demonstrating improved outcomes in high-volume thyroid surgical centers, neck dissection at high-volume centers has been associated with improved survival outcomes.¹⁰² Proper preoperative planning, meticulous surgical technique, and early recognition and treatment of complications are most effective in the prevention of complications in lateral neck dissection.

20.9 Conclusion

Thyroid cancer has a high propensity for cervical lymph node metastasis, and the treatment of choice is largely surgical. Due to the behavior and natural course of differentiated thyroid cancer, the treatment of the lateral neck must be properly selected and systematic. The goal is to maximize the oncological and survival benefit to the patient while minimizing risks and complications.

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Part 4

Parathyroid Diseases

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21 Pathophysiology of the Parathyroid Glands

Brendan C. Stack, Jr. and Galimat Khaidakova

21.1 Introduction

The parathyroid glands are four glands located on the posterior aspect of the thyroid. The parathyroids are small (<50 mg each) and produce only one hormone, which is known as parathyroid hormone (PTH) or parathormone. PTH functions to maintain calcium homeostasis by acting on the renal tubules and the calcium stores in the skeletal system, and indirectly on the gastrointestinal tract through 1,25-dihydroxyvitamin D. These glands and their function appear to be simple at first glance; however, clinicians involved in the treatment of patients with parathyroid disorders quickly realize that the pathophysiology involved can be quite complex. To accurately diagnose and adequately manage patients with parathyroid diseases, one must have a thorough understanding of the pathophysiology involved. This chapter reviews the pathological processes that occur with the parathyroids.

21.2 Hyperparathyroidism

The most common derangement in parathyroid function is the excess production of parathyroid hormone, which is called hyperparathyroidism (HPT). Hyperparathyroidism was described simultaneously in Europe and the United States in the 1920s.¹ Patients initially presented with significant renal and skeletal manifestations, including nephrolithiasis, renal failure, osteoporosis, and pathological fractures. With our increased understanding of this disease process, and with the addition of calcium to routine metabolic panels, the clinical presentation has changed drastically. Most patients currently diagnosed with hyperparathyroidism are asymptomatic.² Although this early detection is an accomplishment of screening in modern medicine, the treatment of asymptomatic patients presents a therapeutic dilemma.

Hyperparathyroidism is defined as primary, secondary, or tertiary based on the etiology. Primary hyperparathyroidism implies inappropriately elevated levels of PTH when compared with the serum calcium. In the physiological state, hypercalcemia reduces the PTH level by negative feedback, acting through calcium-sensing receptors (CaSRs) on the parathyroid glands. Secondary hyperparathyroidism is an elevated PTH level due to a lack of negative feedback. The most common disease process leading to chronic secondary hyperparathyroidism is vitamin D deficiency or chronic renal failure. Tertiary hyperparathyroidism occurs when glands affected by secondary hyperparathyroidism have been stimulated to the extent that the glands become autonomous and are no longer governed by the normal feedback mechanisms from CaSRs. Even if the underlying pathophysiology is corrected, the excess production of PTH persists. The classic example of tertiary hyperparathyroidism occurs in a patient who, having secondary hyperparathyroidism due to chronic renal failure undergoes a renal transplant, and the hyperparathyroid state remains.

21.2.1 Primary Hyperparathyroidism

Pathology

Primary hyperparathyroidism (PHPT) is hypercalcemia secondary to excess PTH production from a dysfunctional gland or glands, and is the most common cause of hypercalcemia in the ambulatory setting.³ Primary hyperparathyroidism affects roughly 1% of the adult population, and the incidence increases with age. Women are affected at least twice as often as men.^{3,4,5,6} PHPT can be attributable to a single adenoma (80–90% of cases), four-gland hyperplasia (5–10%), double adenomas (4–6%), and rarely parathyroid carcinoma (<1%) (► Fig. 21.1 and ► Fig. 21.2).^{7,8,9,10,11,12,13}

Genetic alterations have been shown to contribute to the development of primary hyperparathyroidism. Two specific genetic mutations have been demonstrated in nonfamilial parathyroid adenomas.^{1,12,14,15,16} Decreased expression of the multiple endocrine neoplasia type 1 (*MEN1*) tumor suppressor gene has been found in up to 20% of these adenomas. Activation of the cyclin D1 (*CCND1*)/*PRAD1* oncogene results in overproduction of cyclin D1 and is found in up to 40% of adenomas. Parathyroid adenomas with these genetic alterations are hypercellular and have calcium-sensing receptors that do not function properly.

The CaSR plays an important role in calcium homeostasis. This receptor is found in abundance on the surface of the normal parathyroid gland in addition to many other locations in the body, including the renal tubules, bone marrow, osteoclasts, breast tissue, parafollicular cells of the thyroid, and G cells in the gastric mucosa. Adenomatous cells have a decreased concentration of calcium-sensing receptors compared with normal cells, and have altered set points, which allow for inappropriate production of PTH despite normal or high serum calcium levels.^{2,3,17,18,19}

Clinical Manifestations

The clinical spectrum of PHPT involves multiple organ systems. Renal manifestations are the second most common and occur in 20 to 30% of these patients.⁷ Nephrolithiasis accounts for virtually all of the kidney-related complications. PTH increases renal calcium absorption, renal phosphorus excretion, and activity of 1 α -Hydroxylase. 1 α -Hydroxylase converts vitamin D to its active form, which increases intestinal absorption of calcium. The excess of filtered calcium compared with that absorbed leads to hypercalciuria and the predisposition to calcium stones. Hyperparathyroidism also leads to a decrease in the glomerular filtration rate and a mild metabolic acidosis. Nephrocalcinosis is a rare complication of hyperparathyroidism and is diffuse calcification of the renal tubular system and parenchyma, which can be seen on a plain radiograph.¹

Skeletal manifestations of PHPT are the most common when the symptom of bone pain is included. Osteitis fibrosis cystica, Brown's tumors, and fractures were common presenting entities with hyperparathyroidism in the past. With earlier

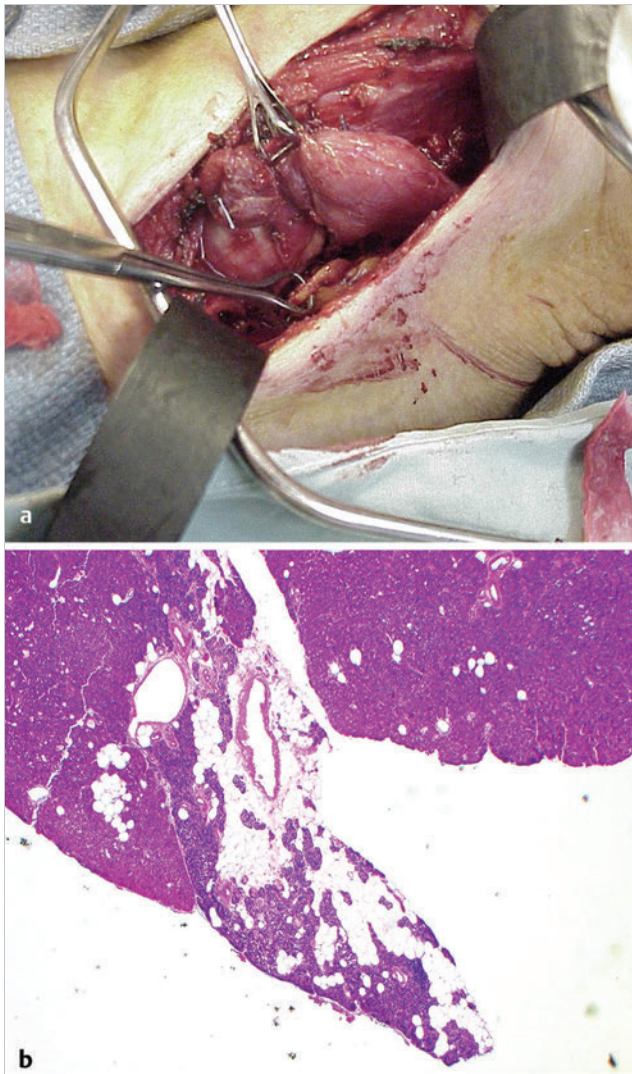


Fig. 21.1 (a) Parathyroid adenoma in vivo. A superior Babcock retracts the thyroid gland anteriorly, and an inferior Babcock retracts the parathyroid adenoma. (b) Histology of parathyroid adenoma surrounding a remnant of normal parathyroid tissue.

detection, these have often been replaced by osteopenia or generalized bone demineralization and bone pain. The osteopenia associated with PHPT continues to carry a fracture rate that is greater than that in controls. In the current form of the disease, this generalized bone loss cannot be visualized well on plain radiographs, but it can be identified early with bone densitometry. A dual energy X-ray absorptiometry (DEXA) scan is used to assess bone density and is typically reported for the lumbar spine, femoral neck, and distal radius. Hyperparathyroidism decreases bone density in cortical bone more than trabecular bone, and therefore the distal radius is often the most affected. The bone density is reported as a T-score, which gives the density as a standard deviation from normal, and a T-score of -2.5 (the defining score for the start of osteoporosis) is often used as an indication for surgical intervention on the parathyroids.^{2,4,20}

Gastrointestinal symptoms are less specific but are part of the clinical picture of HPT. Pancreatitis, peptic ulcer disease, constipation, nausea, and emesis have all been described. Gastroesophageal reflux is most commonly reported, although no clear mechanism has been demonstrated.

There are several “somatic” symptoms associated with HPT; they are nonspecific and include depression, impaired cognition, fatigue, malaise, sleep disorders, and irritability. Although these symptoms are difficult to characterize, they stress the importance of obtaining a thorough neuropsychiatric history since these symptoms have been shown to improve after correction of the underlying hyperparathyroidism.^{4,7,21,22,23,24}

Evaluation

Primary hyperparathyroidism can be diagnosed with precision with a serum calcium level, serum PTH level, 24-hour urinary calcium and creatinine, and an adequate patient history. If the serum albumin levels are normal, total serum calcium is preferred and more reliable than ionized calcium.²⁵ Assays that measure intact, biologically active PTH are preferred when compared with older methods of measuring fragments of the PTH molecule. An elevated serum calcium level in the presence of elevated levels of parathyroid hormone is virtually diagnostic for primary hyperparathyroidism. There are a few exceptions that need to be considered. Thiazide diuretics and lithium

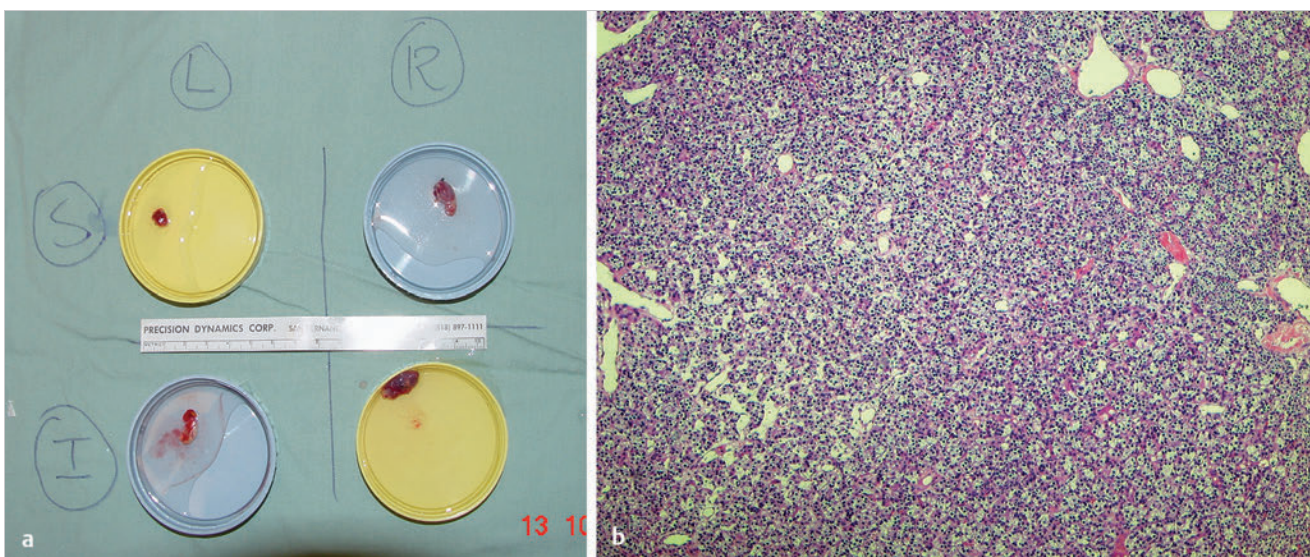


Fig. 21.2 (a) Gross specimen of four-gland hyperplasia. (b) Histology of a hyperplastic parathyroid gland.

Table 21.1 Indications for parathyroidectomy in asymptomatic patients according to 2008 National Institutes of Health guidelines

Parameter	Indication
Serum calcium	> 1 mg/dL above normal range
Age	< 50 years old
Creatinine clearance	< 60
Osteoporosis	T-score < -2.5 standard deviation (forearm)
Neuropsychiatric	Severe psychoneurological disorder
Compliance	Poor compliance
Renal complications	Nephrocalcinosis

excess can produce laboratory findings similar to primary hyperparathyroidism and should be investigated in the patient history.^{3,26} Twenty-four-hour urinary calcium and creatinine excretion is important in the evaluation of hyperparathyroidism. These laboratory results can rule out the possibility of a rare condition known as familial hypocalciuric hypercalcemia (FHH) (see discussion later in the chapter).²⁰ Urinary calcium and creatinine excretion can also help with determining prognosis because total 24-hour calcium excretion > 400 mg/24 h is associated with an increase in renal complications.⁴ Studies have also suggested a role for vitamin D testing, which can help with the evaluation of persistent elevation of PTH levels postoperatively and may help identify patients that are at risk for secondary HPT and postoperative hypocalcemia.^{27,28,29}

All patients who are diagnosed with primary hyperparathyroidism by laboratory data warrant a DEXA scan to assess bone mineral density. This will determine the degree of secondary osteopenia and risk of impending fracture. Any patients who have nephrolithiasis with calcium stones, pathological fractures, or significant osteoporosis should be worked up for hyperparathyroidism with a serum calcium and PTH level to rule out hyperparathyroidism as a cause.³

Management

The typical clinical presentation of PHPT has changed dramatically since its description in the 1920s. When this condition was first described, patients presented with the classic “renal stones, painful bones, abdominal groans, psychic overtones, moans, and fatigue.”²⁷ With increased understanding of PHPT and the addition of calcium to routine metabolic panels, patients are now being identified much earlier in their clinical course. It is estimated that only 20 to 30% of contemporary patients with PHPT present with significant symptoms.^{2,3,4,30} Many argue that a larger number of patients are actually symptomatic but present with nonspecific symptoms, including depression, fatigue, bone pain, or anorexia. This debate aside, 60 to 80% of patients who present with primary hyperparathyroidism presently are asymptomatic or have nonspecific symptoms.^{2,7,30} This can leave practitioners with the therapeutic dilemma of which patients warrant treatment.

This dilemma has been the topic of meetings and recommendations from the National Institutes of Health (NIH) as well as the American Association of Clinical Endocrinologists and American Association of Endocrine Surgeons. It has been

commonly accepted that patients presenting with classic symptoms of hyperparathyroidism, including fracture, nephrolithiasis, and neuromuscular complaints, warrant treatment. More recent reports have indicated that asymptomatic hyperparathyroid patients have a long-term increase in cardiovascular disease and malignancy.^{4,29,30} Furthermore, 23 to 62% of patients who present without symptoms become symptomatic within 10 years of presentation.⁴ For these reasons, in 2008 an NIH consensus panel met and modified its third consensus guidelines and recommended treatment for asymptomatic patients if any of the following apply: serum calcium is > 1 mg/dL above the normal range, age is < 50, creatinine is < 60 mL/min, the patient cannot participate in follow-up, severe psychoneurological disorder, or other complications of PHPT, including nephrocalcinosis or osteoporosis (T-score < -2.5 standard deviation [SD] at the lumbar spine, hip, or wrist) (► Table 21.1).³⁰

An in-depth discussion of all the surgical and medical treatment options can be found in other chapters, so current treatment options and recommendations are only briefly addressed here. There are no long-term studies demonstrating the efficacy of medical management or observation in these patients. Several medications target the effects of hyperparathyroidism without treating the underlying problem. Bisphosphonates have been shown to increase bone mineral density in patients with hyperparathyroidism, with no significant effect on PTH levels.³¹ Similarly, estrogen replacement can stabilize bone loss in postmenopausal women with PHPT.³² Furosemide can help to reduce serum calcium levels acutely. Calcimimetic medications are an intriguing class of medications that target the problem in hyperparathyroidism. With their mimetic activity these medications give negative feedback on the calcium-sensing receptors of the parathyroids and can reduce PTH production. One of these medications, cinacalcet, has been shown to reduce PTH levels and normalize serum calcium.^{33,34} Calcimimetics have shown promising results, and, although studies have found them to be less effective than the gold standard of parathyroidectomy at decreasing PTH levels, there are no statistically significant differences in calcium and phosphate levels between the two groups 1 month after treatment.^{4,33}

If patients with PHPT are managed medically, they require clinical follow-up, biannual serum calcium levels, annual serum creatinine levels, and annual bone densitometry.¹ Associated “somatic” symptoms may not abate with drug therapy, and patients incur the cost of chronic pharmacotherapy.¹

The cost of follow-up after several years of medical management for primary hyperparathyroidism has been shown to exceed the costs of successful surgical management.³⁵ Surgical management has been reported to be 95 to 98% curative, with complication rates of 1 to 2% in experienced hands. It is for these reasons that the recent position statement from endocrinologists and endocrine surgeons recommended surgical intervention in patients who meet the preceding criteria for treatment.

Parathyroid Carcinoma

Another cause of primary hyperparathyroidism that warrants discussion is parathyroid carcinoma (PTC) (► Fig. 21.3). This is a rare condition that accounts for < 1% of hyperparathyroidism. It affects men and women equally, and the average age of presentation is 55 years.

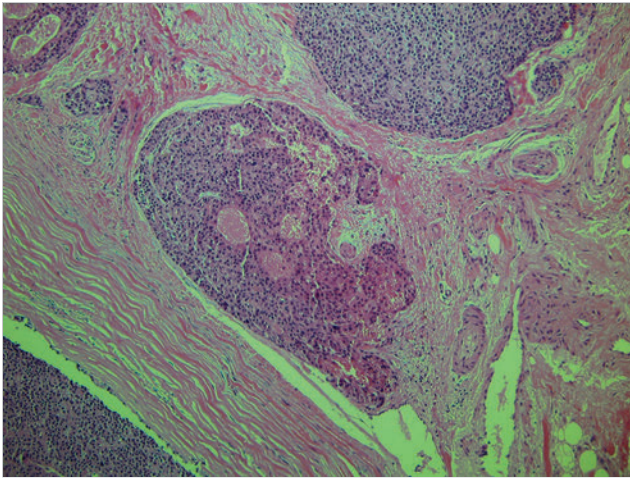


Fig. 21.3 Histology of parathyroid carcinoma with invasion of the capsule.

One challenge is that the diagnosis is rarely apparent on initial presentation because the symptoms are the same as benign causes of hyperparathyroidism. Consistent findings in parathyroid carcinoma are preoperative calcium and PTH levels much higher than those typically found with benign disease.³⁶ The calcium levels for PTC are often >14.0 mg/dL, and PTH levels are commonly >300 ng/dL. The tumor itself is usually larger than the typical adenoma, on average measuring 2 to 3 cm in diameter. A palpable neck mass is present in up to 70% of patients found to have PTC, which is not characteristic of benign disease.³⁷ Cervical lymphadenopathy, which should raise suspicion for a malignant process, is found in one-third of patients presenting with PTC. Patients with parathyroid carcinoma are also more commonly symptomatic. In contrast to reports of 20 to 30% of patients with primary hyperparathyroidism who present with symptoms, in one series eight of nine patients who were found to have parathyroid carcinoma intraoperatively had “somatic” symptoms at presentation.^{16,36,37}

Intraoperative findings that are consistent with parathyroid carcinoma include adherence to or invasion of surrounding structures (thyroid lobe or strap muscles), fibrosis, nodularity, induration, and gray color instead of the typical tan adenoma. Careful attention to these characteristics is important during surgery because the treatment of choice for parathyroid carcinoma is wide surgical excision. Adjuvant treatments, such as external beam radiation and chemotherapy, have not been shown to improve survival. Intraoperative frozen pathology is not reliable, making careful intraoperative examination paramount. Surgical excision should include en bloc excision of the tumor, including the ipsilateral thyroid lobe and straps if involved.^{37,38,39} Consideration should be given to primary level VI dissection if there is a concern for lymphadenopathy discovered at the time of surgery.

Parathyroid carcinoma carries a poor prognosis, with the 5-year survival reported as low as 49%. Interestingly, these patients usually die as a result of their uncontrolled hypercalcemia as opposed to local or metastatic disease. Harari et al³⁸ reported a recurrence rate of 49 to 60% after surgical resection. This recurrence can be determined by monitoring serum

calcium, parathyroid hormone, and carcinoembryonic antigen (CEA), with an increase being an ominous sign of recurrence.

21.3 Secondary Hyperparathyroidism

Any disorder that results in hypocalcemia or vitamin D deficiency will elevate PTH levels and can serve as a secondary cause of hyperparathyroidism. Classically this condition is caused by chronic renal failure, and the resulting alterations in vitamin D, phosphorus, and calcium. Chronic renal failure results in decreased levels of 1,25-dihydroxyvitamin D, hyperphosphatemia, and hypocalcemia. As renal function declines, there is loss of available 1 α -Hydroxylase, resulting in a decrease in active vitamin D (1,25-dihydroxyvitamin D) levels. This occurs when the glomerular filtration rate (GFR) drops below 60 mL/min. Significant increases in the PTH level develop later in the progression, when the GFR drops to 30 mL/min, and significant hyperphosphatemia occurs with a GFR of 20 mL/min or lower.^{1,40,41,42} The elevation in phosphorus levels and the hypocalcemia that develops from decreased vitamin D act to further increase PTH secretion. Early in the disease process, the elevated PTH is appropriate and serves to increase phosphate excretion and calcium absorption in the kidney and counterbalances the metabolic derangement. However, as renal disease progresses and the filtered fraction of phosphate decreases, the ability of PTH to increase phosphate excretion is saturated, and the phosphate released from bone as a result of elevated PTH exacerbates the hyperphosphatemia.⁴³

Over time, chronic stimulation leads to hyperplasia of the parathyroid glands. Histological studies from resected glands of patients with secondary hyperparathyroidism show nodular and diffuse hyperplasia.^{40,41} Decreased expression of the CaSR has been demonstrated in both types of hyperplasia but is more evident in areas of nodular hyperplasia.^{44,45,46} This decreased expression of the CaSR results in decreased negative feedback and explains why PTH levels remain elevated when calcium levels are normal or elevated.

Historical symptoms of secondary hyperparathyroidism include renal osteodystrophy, with spontaneous fractures, bone pain, radiographic bone lesions, and extraskeletal calcifications. However, as with primary hyperparathyroidism, patients now often present prior to the onset of any significant symptoms.⁴⁷ Calciphylaxis, coronary artery calcification, and psychoneurological disorders are more serious manifestations seen in secondary hyperparathyroidism. Calciphylaxis and coronary artery calcification have been shown to be associated with elevated calcium-phosphorus product. A product over 70 has been correlated with an increased risk of developing cerebrovascular accident or death.^{48,49}

Secondary hyperparathyroidism is a diagnosis based on the clinical picture and metabolic derangements. The presence of hypocalcemia and elevated PTH is diagnostic of secondary hyperparathyroidism. When phosphorus levels are also elevated, this points to chronic renal failure as the etiology. If phosphorus levels are low, other anomalies, such as vitamin D deficiency, should be considered. Vitamin D deficiency is an increasingly prevalent cause for secondary hyperparathyroidism with decreasing sun exposure and an aging population.^{28,29,50}

Prevention is truly the best treatment of hyperparathyroidism in chronic renal failure. This is accomplished by aggressive phosphorus management early in the progression of renal failure and adequate replacement of vitamin D. Low phosphorus diets and the use of phosphorus-binding drugs that prevent enteral absorption can decrease the hyperphosphatemia. Phosphorus binders containing aluminum are currently avoided because they can be toxic to bones. The current recommendation is the use of calcium containing phosphorus binders as long as the calcium-phosphorus product is less than $55 \text{ mg}^2/\text{mL}^2$. If the product exceeds 55, or if serum calcium is elevated over 10.2 mg/dL , alternatives such as sevelamer are recommended because they have no calcium or aluminum.⁵¹ This recommendation is an attempt to keep the calcium-phosphorus product $< 70 \text{ mg}^2/\text{mL}^2$, at all costs, because coronary artery calcification and calciphylaxis have been shown to occur at these levels.⁴⁹

Vitamin D or its analogues can be given to reduce PTH levels. Vitamin D can act on the parathyroid to reduce PTH, but it can have the undesired effect of elevating serum calcium and phosphate. Therefore, vitamin D formulations (e.g., calcitriol) are only recommended when phosphorus is $< 6 \text{ mg/mL}$. Newer vitamin D analogues are available that can reduce PTH without undesired effects. Patients taking one such analogue, paricalcitol, experienced fewer episodes of hypercalcemia and a more rapid reduction in PTH as compared with patients taking calcitriol.^{51,52,53} Calcimimetic medications, such as cinacalcet, have promise because they can suppress the parathyroid glands.

The indications for surgical intervention in secondary hyperparathyroidism are not as clear as those for primary disease. There are no National Institutes of Health guidelines addressing surgical intervention. Currently accepted indications for surgery include failure of medical management, calcium-phosphorus products persistently > 70 despite medical intervention, serum calcium $> 11 \text{ mg/dL}$, serum PTH $> 800 \text{ pg/mL}$, severe bone disease, anticipated renal transplant, or severe pruritus.⁴⁷ Some relative surgical indications for secondary hyperparathyroidism include the following:

- Failure of medical management
- Hypercalcemia
- Hypercalciuria
- PTH > 800
- Hyperphosphatemia with calcium-phosphorus product > 70
- Severe bone disease
- Severe symptoms
- Anticipated renal transplant

Surgery for correction of secondary hyperparathyroidism involves subtotal parathyroidectomy with excision of three or three-and-one-half glands, or total parathyroidectomy where all four glands are excised and one of the glands is autotransplanted in the sternocleidomastoid muscle in the neck or in the brachioradialis muscle in the nondominant or shuntless forearm. Cryopreservation may be considered when performing either procedure as an option for hypoparathyroidism.

21.4 Tertiary Hyperparathyroidism

The definition of tertiary hyperparathyroidism is not straightforward. Tertiary HPT results from progression of secondary

HPT and is the least prevalent. In tertiary HPT, PTH, calcium, and phosphorus levels are elevated. It is rare for this condition to occur outside of chronic renal failure. The distinction between secondary HPT and tertiary HPT is that, in tertiary HPT, the glands have become autonomous. This manifests by continuation of the electrolyte derangements despite correction of the underlying renal condition. For example, if a patient with chronic renal failure and hyperparathyroidism undergoes a renal transplant and continues to have hyperparathyroidism, this would be classified as tertiary HPT. The indications for prevention and treatment are similar to those already listed for secondary HPT.

21.5 Familial Hypocalciuric Hypercalcemia

There are many causes of hypercalcemia that must be differentiated from primary hyperparathyroidism. This task is usually not difficult because other causes of hypercalcemia cause a compensatory suppression of PTH by negative feedback. This is in contrast to the elevated PTH seen despite hypercalcemia in primary hyperparathyroidism. One clinical condition where PTH can also be elevated in the presence of hypercalcemia, leading to a diagnostic dilemma, is familial hypocalciuric hypercalcemia (FHH).

FHH is an autosomal dominant condition caused by a defect in the CaSR located on both the parathyroid glands and the renal tubule. The CaSR has been mapped to chromosome 3q21-q24, and multiple inactivating mutations have been described.^{26,52} This inactivation of the CaSR requires a higher serum calcium to act on the parathyroids to suppress PTH, which increases the set point allowing hypercalcemia in the presence of normal to slightly elevated PTH levels. In the renal tubule, the defect in the CaSR leads to increased calcium and magnesium reabsorption.^{19,30,53,54} The net result is hypercalcemia, hypocalciuria, and, frequently, hypermagnesemia.

Patients are rarely symptomatic, which is in contrast to primary hyperparathyroidism, in which 20 to 30% of patients present with symptoms.^{3,7} The distinction between these two disorders is made with family history and laboratory findings. A family history of hypercalcemia should raise the suspicion of this autosomal dominant condition, especially if there is a family history of hypercalcemia that did not improve after parathyroidectomy for presumed hyperparathyroidism. PTH levels are typically normal to mildly elevated in FHH as opposed to primary hyperparathyroidism, in which they are more significantly elevated, but the true laboratory distinction between these two disease processes is made with urinary electrolyte studies. Twenty-four-hour urine collection for creatinine and calcium can confirm the diagnosis of FHH. In FHH 75% of patients have 24-hour calcium excretion levels of $< 100 \text{ mg}$, whereas patients with primary hyperparathyroidism usually have excretions in excess of 200 mg in 24 hours. The calcium/creatinine clearance ratio is < 0.01 in a majority of patients with FHH and > 0.02 in most patients with primary hyperparathyroidism.^{18,30,55,56} The distinction between these conditions is not difficult if urine studies are performed. However, many patients have undergone surgical intervention with no benefit because they were incorrectly identified as having primary

Table 21.2 Clinical presentation of multiple endocrine neoplasia type 1 (MEN1)

Clinical manifestation	Prevalence (MEN1)
Primary hyperparathyroidism	90–100%
Pancreatic islet cell tumors	33%
Pituitary adenomas	20%
Thymic carcinoids	5%
Less common findings: angiofibromas, collagenomas, lipomas, spinal ependymomas, thyroid adenomas, adrenocortical adenomas	

hyperparathyroidism. This underscores the importance of routine use of the 24-hour urine collection for calcium and creatinine to exclude FHH patients from parathyroid surgery. Commercially available genetic testing can also be useful but is only 70% sensitive for diagnosis.

21.6 Multiple Endocrine Neoplasia Syndromes

Multiple endocrine neoplasia (MEN) syndromes are characterized by the presence of functional tumors of endocrine organs that produce hormones that lead to the characteristic symptoms. The current classification divides the syndromes into MEN1 (Wermer's syndrome), MEN2A (Sipple's syndrome), and MEN2B (also known as MEN3). These syndromes are inherited in an autosomal-dominant manner. Hyperparathyroidism plays a significant role in MEN1 and MEN2A but is not part of the spectrum of disease with MEN2B.

21.6.1 Multiple Endocrine Neoplasia Type 1

MEN1 is a disease with a genetic predisposition for tumors of the parathyroids, pancreatic islet cells, and anterior pituitary. This syndrome is also known to include duodenal tumors, adrenal adenomas, thyroid adenomas, carcinoid tumors, and lipomas (► Table 21.2). Parathyroid tumor development in MEN1 occurs decades earlier than in the sporadic forms, and the gastrointestinal tumors have an increased malignant potential.⁵⁷

Primary hyperparathyroidism is the most consistent feature of MEN1 and has been reported to affect 90 to 100% of these patients by the age of 40, making it also the earliest feature of the disease. It is estimated that up to 2% of primary hyperparathyroidism is attributable to MEN1.⁵⁷ As is the case with sporadic primary hyperparathyroidism, most patients are asymptomatic. Symptoms common to MEN1-associated primary hyperparathyroidism are the same as seen in the sporadic forms.⁵⁸ The diagnosis of PHPT in MEN1 is the same as nonsyndromic cases.

Although the presenting symptoms and diagnostic criteria are the same for PHPT in MEN1 as they are for sporadic cases of PHPT, there are significant differences in the patient populations. For example, hyperparathyroidism develops much earlier in patients with MEN1 than it does in the general population. PHPT is almost universal in patients with MEN1 by the age of 40, and annual screening with serum calcium and PTH is

recommended, beginning at 8 years of age.^{59,60} This is 20 years sooner than the average presentation of PHPT in other patients. The female predominance seen in nonfamilial hyperparathyroidism is not seen in MEN1-associated hyperparathyroidism, which has an even male-to-female ratio. Perhaps the most important distinction between the PHPT found in MEN1 patients and the sporadic variety is that multiple gland involvement is characteristic of PHPT in MEN1 patients, where 80 to 90% of nonsyndromic PHPT is caused by a single parathyroid adenoma.^{12,26,59,61}

The multiple gland involvement found in these patients necessitates a therapeutic approach that differs from the approach taken to other patients with PHPT. Patients with sporadic primary hyperparathyroidism who meet the NIH criteria for surgery can undergo surgery directed only at the affected gland or glands assuming adequate preoperative localization. However, the multiple gland hyperplasia seen in the parathyroids of MEN1 patients necessitates a more aggressive approach. Although some parathyroid glands may appear grossly normal during neck exploration of these patients, it is felt that these glands are not histologically normal but represent asymmetric hyperplasia.^{56,59} This explains the increased failure rate found in MEN1 patients who undergo surgical intervention for hyperparathyroidism. It is reported that roughly 50% of these patients will have recurrent hyperparathyroidism 10 to 12 years after surgical correction.^{62,63}

There are two surgical options commonly employed in these patients. The first consists of a bilateral neck exploration with subtotal parathyroidectomy and thymectomy leaving a 20 to 50 mg remnant of vascularized parathyroid tissue in situ. The thymectomy is added due to the increased incidence of supernumerary parathyroid glands found in MEN1, and if the subtotal approach is used, it is advisable to leave a surgical clip at the site of the remnant parathyroid for reference if future neck explorations for recurrent hyperparathyroidism are required. The second option employed is a total parathyroidectomy combined with thymectomy and autotransplantation of a portion of the resected parathyroid tissue into either the sternocleidomastoid muscle in the neck or the brachioradialis muscle in the forearm. There is no consensus regarding which of these two implantation sites is more appropriate.^{15,64,65,66,67,68} Due to the high failure rate of surgical intervention and the known pathogenesis involving multiple-gland hyperplasia, selective parathyroidectomy resecting only grossly involved glands is generally not recommended. Due to the surgical intent of bilateral exploration with exposure of all parathyroid tissue, preoperative localization studies are not necessary for initial surgical intervention, although they may be useful for excluding ectopic glands. Studies have shown technetium-99m sestamibi, single-photon emission computed tomography (SPECT), and positron emission tomography (PET) with ¹¹C-methionine to be of benefit in selected patients undergoing reoperation for recurrent hyperparathyroidism.^{58,69,70} Intraoperative PTH measurements have become popular and useful in determining adequate resection in sporadic cases of HPT, especially when caused by a single adenoma. Recent reports advocate the use of the intraoperative PTH assay for reexploration and for total parathyroidectomy.^{13,71,72} The decline in PTH is not as abrupt as that seen after the resection of an offending adenoma, and more experience with this assay in MEN1 patients is required.

Although this chapter focuses on parathyroid diseases, a discussion of MEN1 without mention of its other manifestations would be incomplete. Pituitary adenomas are another common finding in these patients. Most studies report a 20% incidence of clinically evident pituitary adenomas in MEN1 patients, but one study demonstrated that up to 60% of MEN1 patients will have pathological evidence of a pituitary adenoma if an autopsy is performed.^{60,73,74} The most common pituitary tumor found is prolactinoma. As compared with nonsyndromic patients, pituitary adenomas in MEN1 tend to be larger, more symptomatic, and have a higher recurrence rate after resection.⁷⁵ Pancreatic and gastrointestinal islet cell tumors are another significant component of MEN1. Parathyroid and pituitary involvement with MEN1 can be effectively treated, which leaves the malignant potential of the gastrointestinal and pancreatic islet cell tumors as the major cause of mortality.^{76,77,78,79} As with pituitary disease, there is a discrepancy between clinically apparent islet cell tumors (33% of MEN1 patients) and biochemical involvement (80%). Gastrinomas with Zollinger–Ellison's syndrome are the most common clinical manifestation in this group. Insulinoma is the next most common clinically significant islet cell tumor, followed by rare tumors, including vasoactive intestinal polypeptideoma (VIPoma), somatostatinoma, and pancreatic polypeptidoma. Aside from the classic parathyroid, pituitary, and pancreatic involvement, patients with MEN1 are at an increased risk of developing multiple other manifestations. For example, up to 5% of patients with MEN1 develop thymic carcinoids. Interestingly, these thymic carcinoids are found almost exclusively in male smokers with MEN1.^{15,80} Cutaneous tumors such as angiofibromas and collagenomas are more common in this group, as are adrenocortical adenomas, thyroid adenomas, and spinal cord ependymomas.^{15,81,82}

The MEN1 gene (*MEN1*) has been cloned and mapped to chromosome 11q13.^{58,60,79,80,81,82,83} *MEN1* is a tumor suppressor gene that encodes for a protein named menin, and inactivation of this protein leads to tumorigenesis. Now that the gene is cloned, genetic testing is feasible. Prophylactic surgery is not performed in MEN1, but due to the increased risk conferred by radiological screening, genetic testing is now offered to first-degree relatives of patients with MEN1 in order to decrease unnecessary radiation exposure in unaffected individuals. Genetic testing is also suggested in patients that have multiglandular PHPT or in PHPT patients under 30.^{15,79,84}

21.6.2 Multiple Endocrine Neoplasia Type 2

Multiple endocrine neoplasia type 2 (MEN2) is divided into three subgroups: MEN 2A, MEN 2B, and familial medullary thyroid cancer (FMTC), which is a variant of MEN2A. As in MEN1, these syndromes are inherited by an autosomal-dominant mode of transmission. The three have medullary thyroid carcinoma as a common feature but differ in other clinical manifestations.

MEN2A is characterized by medullary thyroid carcinoma, pheochromocytoma, and hyperparathyroidism. Hyperparathyroidism affects 20 to 30%^{30,60,85} of these patients and is more commonly asymptomatic and milder than the

hyperparathyroidism found in MEN1.^{86,87} As in MEN1, hyperparathyroidism in MEN2A is characterized by multiglandular hyperplasia, and treatment options for symptomatic patients are similar. However, because the symptom complex is milder and the recurrence rate after surgery is much less than that for MEN1, bilateral neck exploration with removal of only grossly enlarged glands without cervical thymectomy is performed for most symptomatic patients.^{88,89} If hypercalcemia is severe, more aggressive approaches, such as subtotal or total parathyroidectomy with cervical thymectomy, can be considered. The absence of hyperparathyroidism in MEN2B and FMTC makes the role of C-cell hyperplasia and elevated calcitonin as a causative factor of hyperparathyroidism in MEN2A less plausible. It has been found that the *RET* proto-oncogene is expressed in the parathyroid tumors of MEN2A, and, furthermore, specific *RET* mutations (codon 634) are found preferentially in families with MEN2A involving hyperparathyroidism. This leads to the conclusion that the parathyroid hyperplasia in MEN2A may be related to the expression of the mutant *RET* protein.⁹⁰ Medullary thyroid cancer is the most consistent finding of MEN2A and is found in 90 to 95% of patients. When MEN2A is confirmed by testing for the *RET* proto-oncogene, prophylactic thyroidectomy is recommended. The age at which this thyroidectomy should be performed is a controversial topic. For high-risk genetic alterations (e.g., codon 634), thyroidectomy is recommended by 5 years of age.^{91,92} For intermediate-risk alterations, it is argued that thyroidectomy can be performed later. Pheochromocytoma occurs in nearly 40% of patients with MEN2A. Biochemical screening by urinary or serum catecholamines is recommended for all patients with MEN2 or with medullary thyroid carcinoma. If patients are found to have pheochromocytoma, this should be surgically addressed prior to considering thyroidectomy or parathyroidectomy.^{85,93,94} MEN2A is also associated with cutaneous lichen amyloidosis as well as Hirschsprung's disease (► Table 21.3).^{15,95} MEN2B also involves medullary thyroid carcinoma and pheochromocytoma but does not have an association with hyperparathyroidism. Medullary thyroid cancer is universal in these patients, is more aggressive than MTC found in MEN2A, and occurs at an earlier age. Timely diagnosis and early prophylactic thyroidectomy are imperative for the patient's ultimate prognosis. When MEN2B is diagnosed by *RET* testing, thyroidectomy is recommended by 6 months of age.^{91,96} Pheochromocytomas occur in 40% of patients with MEN2B and should be evaluated and treated in the same manner as described for MEN2A. Marfanoid habitus, intestinal ganglioneuromas, and mucosal

Table 21.3 Clinical presentation of multiple endocrine neoplasia type 2A (MEN2A)

Clinical manifestation	Prevalence (MEN2A)
Medullary thyroid carcinoma	90–95%
Pheochromocytoma	40%
Hyperparathyroidism	10–25%

Note: Less common features: cutaneous lichen amyloidosis, Hirschsprung's disease.



Fig. 21.4 Calciphylaxis lesion.

neuromas involving the lip and tongue are also common in MEN2B.^{15,85,86}

21.7 Calciphylaxis

Calciphylaxis is a vascular and tissue manifestation of systemic disease.^{97,98} This primarily occurs in patients with secondary hyperparathyroidism and chronic renal failure, but isolated cases have been reported in patients with other underlying pathology, such as alcoholic cirrhosis, vitamin D intoxication, primary hyperparathyroidism, multiple myeloma, and hypercalcemia of malignancy.^{49,99,100,101} The term *calciphylaxis* is somewhat misleading because it implies an immunologic process. Other more specific terms are *calcific uremic arteriopathy*, *uremic small vessel disease*, *uremic gangrene syndrome*, and *uremic small-artery disease with medial calcification and intimal hyperplasia*.^{49,102,103,104,105} As these other more descriptive terms imply, calciphylaxis is characterized by systemic calcification of the tunica media of small vessels. This leads to the clinical manifestation of tissue ischemia and necrosis. Affected areas initially manifest as painful purpuric plaques with nodularity (► Fig. 21.4) and typically progress to necrotic ulcers with eschar. The underlying muscle can be involved by the ischemic and necrotic process. What ultimately leads to the poor prognosis associated with calciphylaxis is the superinfection that often ensues. The mortality rate remains between 60 and 87%, with patients usually succumbing to overwhelming infection and sepsis.¹⁰⁵

Uremic small artery disease has been found to occur in 4% of patients on dialysis. Females are affected much more commonly than males, and the mean age at presentation is between 48 and 57 years.¹⁰⁶ The pathogenesis is not well understood, but certain risk factors have been identified in animal models as well as in patients. Elevated PTH, hyperphosphatemia, and elevated vitamin D levels seem to provide a milieu where calciphylaxis is more common. However, a superimposed event such as local tissue trauma, injection of medications, or elevation of other laboratory values often leads to the development of wounds in these sensitized patients.¹⁰⁷ As previously discussed, chronic renal failure leads to lower levels of vitamin D, which in turn decrease intestinal absorption of calcium leading to

hypocalcemia and elevated PTH levels. This secondary hyperparathyroidism ultimately leads to elevated calcium levels, and, with the addition of phosphate retention common in renal patients, elevated calcium-phosphorous products lead to soft tissue and vascular calcification.¹⁰³ A calcium-phosphorous product ≥ 70 increases the likelihood of developing calciphylaxis. Other factors felt to contribute to calciphylaxis are type 1 diabetes mellitus, protein C or protein S deficiency, calcium carbonate usage, prednisone, and administration of warfarin.^{49,100,101,103,105}

With the lack of a specific test for calciphylaxis, the diagnosis remains a clinical one requiring a high degree of clinical suspicion. The development of a painful purpuric plaque in a dialysis patient should provoke close monitoring. Although laboratory abnormalities, such as leukocytosis, hypercalcemia, hyperphosphatemia, and elevated PTH, have been described, the confirmation of this diagnosis is with tissue biopsy showing medial calcification of small arteries and intimal hyperplasia.¹⁰³ There is no utility in imaging these patients for diagnostic purposes.

Once this diagnosis is suspected or confirmed, aggressive management is critical. The treatment involves attempting to correct the underlying hypercalcemia and hyperphosphatemia. This is accomplished by stopping vitamin D supplementation and prescribing a low-calcium dialysate and phosphate binders that are not calcium based, such as sevelamer hydrochloride (Renagel, Genzyme Corp.).^{95,107,108,109} Dressing changes (with conventional or vacuum dressings) and surgical debridement of the necrotic wounds are important to prevent superinfection and ultimate sepsis.^{101,110} The role of parathyroidectomy for calciphylaxis is controversial. Reports have advocated subtotal parathyroidectomy for improvement in wound healing, increased survival, and improvement of pain with the ulcers.^{103,111} However, other reports have refuted these claims. Currently, there is no clear consensus on the role of, or extent of, parathyroidectomy in this patient population. Calciphylaxis carries such a grim prognosis that prevention is of the utmost importance. Meticulous management of the phosphate and calcium balance in renal patients can prevent the metabolic background, which has been shown to predispose these patients to calciphylaxis. Several recent studies have suggested the use of intravenous sodium thiosulfate, which has previously been used in cyanide poisoning, as a treatment for calciphylaxis. Sodium thiosulfate is a chelating agent that may reduce circulating calcium and aid in the resorption of calcium deposits.^{101,107}

21.8 Hypoparathyroidism

Hypocalcemia can result from multiple factors, including hypovitaminosis D, sepsis, hypoalbuminemia, hypomagnesemia, and fluoride poisoning. Hypoparathyroidism with decreased production of PTH or resistance to PTH can also cause significant hypocalcemia. Hypoparathyroidism is much less common than hyperparathyroidism and is found in congenital as well as acquired forms. The most common cause is iatrogenic following thyroid or parathyroid surgery.^{112,113,114}

Hypoparathyroidism occurring in children is most common in the neonatal period. The most common finding in the neonatal period is physiological hypoparathyroidism with symptoms and biochemical evidence of hypoparathyroidism that are

transient and warrant no treatment. The pathogenesis of this physiological hypoparathyroidism is poorly understood, but known risk factors include maternal diabetes, birth asphyxia, and preterm delivery with low birth weight.¹¹⁵ Other forms of hypoparathyroidism that occur early, in the first 24 hours of life, are caused by hypoplasia or agenesis of the parathyroid glands. DiGeorge's anomaly is one example of parathyroid agenesis associated with other findings. DiGeorge's anomaly is caused by failure of migration of neural crest cells into the third and fourth pharyngeal pouches, which results in failure of appropriate development of the parathyroids and thymus. The clinical picture includes immune deficits secondary to the lack of T-cell function, hypoparathyroidism with hypocalcemia, cardiac defects including truncus arteriosus, and characteristic facies.^{116,117,118} Microdeletions mapped to chromosome 22q11 have been described in up to 90% of patients with DiGeorge's anomaly.¹¹⁹ Congenital hypoparathyroidism can occur in the face of normal-appearing parathyroid glands, and a collection of genetic defects has been described. There is an autosomal-dominant form caused by a mutation in the CaSR. This mutation is an activating mutation that signals parathyroid cells and other cells in the body, indicating that there is adequate serum calcium, despite hypocalcemia. The clinical picture of hypocalcemia and hyperphosphatemia results in the presence of a normal intact PTH. This condition also has a paradoxical high or high normal urinary calcium due to activation of the calcium receptor in the renal tubule.^{53,114} These patients are usually asymptomatic despite significant hypocalcemia, and attempts to treat the hypocalcemia should be reserved for symptomatic patients because treatment can result in elevated urinary calcium excretion, nephrolithiasis, nephrocalcinosis, and renal insufficiency.^{53,114,120,121} There are two other forms of inherited hypoparathyroidism. One is a defect in the signal peptide of the PTH precursor preventing conversion to active PTH, and the other is inherited with sensorineural hearing loss and renal dysplasia, which has recently been attributed to mutations in transcription factor GATA3.^{121,122,123} Autosomal recessive and X-linked recessive forms of hypoparathyroidism have been reported, but specific genetic defects are not yet known.¹²⁴ Late neonatal hypoparathyroidism occurs days after delivery. Two mitochondrial disorders, Kenny-Caffey's syndrome and Kearns-Sayre's syndrome, are associated with late neonatal hypoparathyroidism.¹¹³

Childhood hypoparathyroidism can also be seen as a part of an autoimmune complex. The most common example is hypoparathyroidism in conjunction with adrenal insufficiency and mucocutaneous candidiasis (HAM syndrome). Another syndrome with autoimmune destruction of the parathyroids is autoimmune polyglandular syndrome type I (also known as autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy [APECED] syndrome). Immunologic destruction of the hormone-producing cells in the parathyroids is a common denominator in these two syndromes. Endocrinopathies in APECED, such as diabetes mellitus, hypogonadism, and hypothyroidism, must be excluded.¹²⁵

Pseudohypoparathyroidism is a condition in which hypocalcemia and hyperphosphatemia are accompanied by elevated levels of PTH, indicating that the pathology is not absence of parathyroids or PTH but rather resistance of the end organs to the effects of PTH. There are two distinct forms of

pseudohypoparathyroidism described. Type 1 is attributable to a blunted response of the cyclic adenosine monophosphate (cAMP) cascade to PTH, and is subdivided into type 1a, type 1b, and pseudopseudohypoparathyroidism, which is a related disorder.¹¹⁴ The gene coding for the stimulatory Gs- α 1 protein in the adenylyl cyclase complex (*GNAS1*) has been shown to be involved in all of these disorders. The *GNAS1* gene is known to be imprinted with the maternal allele expressed in the kidney. Therefore, maternal and paternal transmission differ in clinical presentations. Type 1a pseudohypoparathyroidism has a described mutation in *GNAS1*.¹²⁶ Manifestations of this disease include not only the aforementioned metabolic findings but also short stature, round facies, and short metatarsal and metacarpal bones, which is also known as Albright hereditary osteodystrophy. The spectrum of disease in type 1a is the consequence of maternal transmission of a defective *GNAS1*, because the skeletal manifestations are seen in conjunction with renal manifestations.¹¹⁴

In type 1b pseudohypoparathyroidism the defect in *GNAS1* is felt to be limited to the kidney, because these patients have the characteristic hypocalcemia, hyperphosphatemia, and elevated PTH but do not have Albright hereditary osteodystrophy. This suggests that a maternal transmission is responsible in type 1b. There have been a few described defects in *GNAS1* for type 1b that are different from the defect known to be responsible for type 1a and pseudopseudohypoparathyroidism. In type 2 pseudohypoparathyroidism the cAMP response to PTH is intact, but the phosphate excretion in the kidney is altered, leading to the characteristic metabolic findings. It is felt that the downstream effects of cAMP are blunted due to resistance. The signal transduction defects seen in all of these disorders not only affect the response to PTH but also can affect other hormonal responses in the patient. This can manifest as hypogonadism due to resistance to gonadotropins or hypothyroidism due to resistance to thyroid-stimulating hormone (TSH).^{114,124,127} Pseudopseudohypoparathyroidism is the consequence of paternal transmission of the *GNAS1* mutation described in type 1a and includes Albright's hereditary osteodystrophy but does not have hypocalcemia because the normal maternal allele expressed in the kidney preserves normal renal function.^{124,128,129}

Although all of the aforementioned syndromes and disease processes can cause hypoparathyroidism, the most common cause of hypoparathyroidism is iatrogenic following neck surgery. This can occur following thyroidectomy, parathyroidectomy, or central compartment neck dissections. It is estimated that 1 to 2% of patients undergoing total thyroidectomy for thyroid cancer develop hypoparathyroidism and hypocalcemia.^{130,131}

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22 Parathyroid Carcinoma

Jason P. Hunt and Richard B. Cannon

22.1 Introduction

Hypercalcemia in the presence of high parathyroid hormone (PTH) levels usually signifies the presence of hyperparathyroidism. When these calcium levels are extreme in nature, it may raise the concern for parathyroid carcinoma. This is a rare disease that can lead to death by hypercalcemia if not treated. Regardless of the rarity of disease, providers treating hyperparathyroidism should be aware of the unique features that are suggestive of a malignant process of the parathyroid glands. This disease may be difficult to distinguish from a parathyroid adenoma, but malignant parathyroid neoplasms can often be predicted by the pattern of presentation along with intraoperative findings. These indolent tumors behave differently than many head and neck malignancies, and the cause of death is most often related to the degree of hypercalcemia. Although the primary treatment goal should consist of complete surgical excision, residual tumor can persist for long periods of time. Even when surgical cure is no longer possible, managing the patient's hypercalcemia is important. This may require resection of local, regional, or distant metastatic disease. When surgical resection is not possible, medical management of the hypercalcemia is necessary. This chapter discusses the presentation of parathyroid carcinoma as well as current concepts on its management.

22.2 Epidemiology

Parathyroid carcinoma was first described by DeQuervain in 1904.¹ It is interesting that this was a nonfunctioning tumor, whereas the vast majority of parathyroid carcinomas are functioning tumors producing significant levels of parathyroid hormone.^{2,3,4} It wasn't until 1933 that Sainton and Millot described the first functioning parathyroid carcinoma.⁵ Though most parathyroid carcinomas are functioning tumors with severely elevated calcium levels, which aids the diagnosis, nonfunctioning tumors may not be diagnosed until they are more advanced. Without the extreme elevation of serum calcium assisting with the detection of the parathyroid malignancy, these may not be recognized until there is a palpable neck mass or it has invaded structures of the neck that affect voice or swallowing.

Parathyroid carcinoma affects approximately 0.005% of individuals per year according to a review of the 286 cases in the National Cancer Database by Hundahl and colleagues.⁶ In a separate study, Lee and colleagues evaluated the Surveillance, Epidemiology, and End Results (SEER) cancer registry from 1998 to 2003.⁷ They noted that the incidence of parathyroid carcinoma had increased by 60% in the latter half of the study. This increase in incidence may be related to improved rates of diagnosis, but the exact reason is unknown. This incidence also varies geographically per country. In locations such as Japan and Italy, the incidence has been reported as high as 5% of all cases of hyperparathyroidism.^{8,9} However, the incidence in the United States is <1% of all hyperparathyroidism cases.¹⁰ There are many possible explanations for the geographic differences,

including genetic differences, referral patterns, and diagnostic criteria, among others. Although this is a low percentage of patients, the diagnosis must be kept in mind when evaluating a patient with hyperparathyroidism, and understanding the presenting signs and symptoms is helpful in this process. In contrast to primary hyperparathyroidism, which has a 3 to 4:1 female to male distribution, parathyroid carcinoma affects males and females equally.⁶ Most affected individuals are middle-aged, though cases have been reported from 12 to 90 years of age.^{7,11,12,13} We outline epidemiological differences between individuals with primary hyperparathyroidism versus those with parathyroid carcinoma. The following conditions are associated with parathyroid carcinoma:

- Neck irradiation
- Hyperparathyroidism–jaw tumor syndrome
- Familial isolated hyperparathyroidism
- Multiple endocrine neoplasia type 1

Although parathyroid carcinoma is rare, it must be considered in all individuals with primary hyperparathyroidism. Certain warning signs on presentation make the diagnosis more likely. These findings will be presented later in this chapter.

22.3 Tumor Pathogenesis

Parathyroid carcinoma may develop spontaneously or occur as part of a familial syndrome. Several conditions have been associated with spontaneous development of parathyroid carcinoma as already mentioned. Neck irradiation affects parathyroid glands and increases the likelihood of parathyroid disease,^{14,15} and it has been associated with many cases of parathyroid carcinoma.^{16,17} Koea and Shaw found that 1.9% of parathyroid carcinomas were associated with previous radiation.¹⁸ This pathway of parathyroid carcinogenesis has also been suggested in at least one animal study where parathyroid carcinoma was seen in mice after exposure to neck irradiation.¹⁹ This is not surprising because radiation is known to have carcinogenic effects years after exposure. Parathyroid carcinoma has also been associated with primary hyperparathyroidism,^{4,6,20} secondary hyperparathyroidism,²¹ and end-stage renal disease.²² However, the rarity of disease makes strong correlations difficult.

Familial conditions associated with parathyroid carcinoma include familial isolated hyperparathyroidism, multiple endocrine neoplasia type 1 (MEN1), and hyperparathyroidism–jaw tumor (HPT-JT) syndrome. Familial isolated hyperparathyroidism is an autosomal-dominant disease that is distinct from MEN syndromes.²³ It can have pronounced elevations of calcium and parathyroid hormone levels, and it is associated with an increased risk of developing parathyroid cancer. MEN1 is another hereditary syndrome that has an association with parathyroid carcinoma.^{24,25,26} Some studies have suggested that the genetic mutations associated with MEN1 are responsible for the increased risk, but the definitive evidence for this causality is lacking at the present.²⁷

Table 22.1 Clinical features of hyperparathyroidism and hypercalcemia because of parathyroid carcinomas versus benign disease

Organ system	Presenting symptoms and complaints	Percent affected	
		Malignant	Benign
Renal	Polyuria, polydipsia, urolithiasis, and kidney failure	56	20
Bone	Osteopenia, osteoporosis, pathological fractures, and bone pain	63	8
Neuromuscular	Fatigue, muscle aches, proximal muscle weakness, decreased memory, irritability, and depression	74	38
Gastrointestinal	Anorexia, nausea, vomiting, constipation, peptic ulcers, and pancreatitis	18	8
Rheumatologic	Gout, pseudogout, chondrocalcinosis, and calcific tendinitis	12	1
Cardiovascular	Decreased QT interval, arrhythmias, and hypertension	14	1
	Asymptomatic	2	47

Data from Obara and Fujimoto¹², Kvols³⁶, and Uden P, Chan A, Duh QY, Siperstein A, Clark OH. Primary hyperparathyroidism in younger and older patients: Symptoms and outcomes of surgery. *World J Surg* 1992; 16: 791–798.

HPT-JT syndrome is another autosomal-dominant syndrome that has ossifying jaw tumors, renal neoplasms, uterine tumors, and hyperparathyroidism. The genetic defect associated with this disease is a mutation in the *HRPT2* gene that codes for parafibromin.²⁸ This protein is considered to be a tumor suppressor because it can induce apoptosis. This incidence of parathyroid carcinoma has been reported to be as high as 15% in this condition.^{2,29}

Sporadic cases of parathyroid carcinoma are also frequently associated with *HRPT2* gene mutations. Multiple studies have found a high rate of *HRPT2* gene mutations independent of HPT-JT syndrome.^{30,31} Because parafibromin inactivation is linked to a large portion of parathyroid carcinomas, this mutation is considered a marker for parathyroid carcinoma. This gene may be involved in the majority of cases of sporadic parathyroid carcinoma.

22.4 Clinical Presentation

22.4.1 History

Parathyroid carcinomas are rare, typically slow-growing tumors with a tendency to recur locally and metastasize late. As previously stated, parathyroid cancer is equally distributed between men and women, whereas parathyroid adenomas and hyperplasia are three times more common in women.³² Some studies suggest these tumors may present earlier in life compared with benign hyperparathyroidism. The average age at presentation is between 40 and 60, though it has been reported across a wide age range.^{7,33}

Nearly all tumors are functional (95%) and result in severe primary hyperparathyroidism. Typically, serum calcium and PTH levels are significantly elevated, with 70% having serum calcium concentrations > 14 mg/dL, and patients are very often symptomatic from their hypercalcemia.^{12,34} Frequently, patients will present with both bone and kidney disease. In addition, patients can present with voice complaints and recurrent laryngeal nerve dysfunction, which, when coupled with primary hyperparathyroidism, should raise concern for parathyroid cancer. However, some parathyroid cancers may not be functional

and present only with symptoms related to local tumor invasion.

Symptoms of hypercalcemia are not unique to parathyroid carcinoma. In fact, < 1% of patients with hypercalcemia and only 0.5 to 2% of patients with hyperparathyroidism will have cancer of the parathyroid gland.³⁵ However, patients with cancer typically have severe symptoms. Hypercalcemia can cause renal, bone, neuromuscular, rheumatologic, gastrointestinal, and cardiovascular symptoms, as well as form calcium deposits in the skin, cornea, and lungs (► Table 22.1).³⁶ Although these symptoms may raise the level of suspicion for cancer, the degree of hypercalcemia should be the clinician's best warning sign.

22.4.2 Physical Findings

Approximately 40% of patients with parathyroid cancer will present with a neck mass.³⁷ This occurs in the typical location for parathyroid glands: just off midline, on either side, and low in the neck. A neck mass in this location can be confused with level IV cervical lymphadenopathy or a thyroid nodule. Non-functional parathyroid carcinomas also most commonly present with a neck mass. These patients remain normocalcemic and usually have more advanced-stage disease at presentation, and their tumors are more aggressive. In contrast to patients with functional parathyroid cancers, patients with nonfunctional tumors die from mass effect and tumor burden, rather than from hypercalcemia.³⁴

Approximately 10% of patient will present with recurrent laryngeal nerve dysfunction.¹² Vocal fold paresis and paralysis symptoms include dysphonia, a hoarse or breathy voice, shortness of breath, and/or aspiration. The diagnosis is made by direct or indirect laryngoscopy demonstrating unilateral decreased or absent movement of the vocal fold.

22.5 Evaluation

22.5.1 Laboratory Studies

Hyperparathyroidism is typically diagnosed with serum calcium and PTH levels. Studies have shown that serum calcium

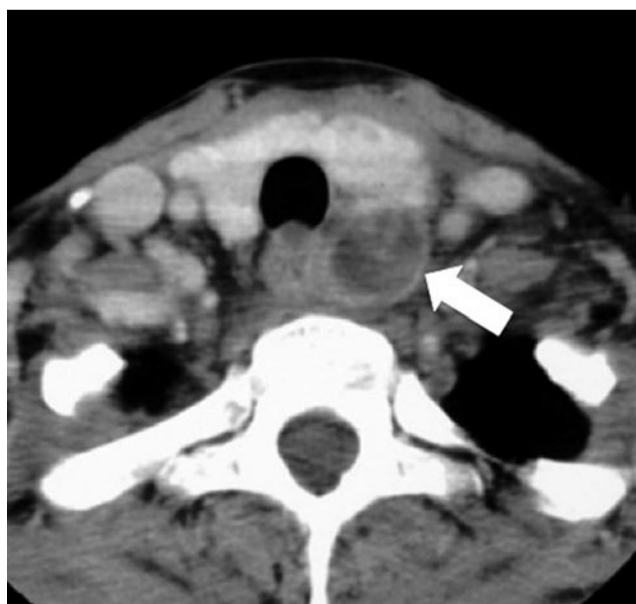


Fig. 22.1 CT image of a parathyroid carcinoma (arrow). (Courtesy of Richard Wiggins, MD.)

levels are > 14 mg/dL in 65 to 75% of patients with malignant hyperparathyroidism compared to only 10% of patients with benign disease.^{12,34} Also, PTH levels are usually very high and at least 5 times higher than the upper limit of normal, with the mean elevation 10.2 times higher than the upper limit of normal.¹¹ In addition, vitamin D deficiency, hypophosphatemia, and hypercalciuria are often seen in patients with parathyroid carcinomas. Renal dysfunction presents with elevated blood urea nitrogen (BUN) and creatinine, and elevated amylase and lipase are hallmarks of acute pancreatitis. Anemia is common in parathyroid carcinoma (~80% of patients), in contrast to benign parathyroid disease ($< 10\%$ of patients).

22.5.2 Imaging

High-resolution ultrasonography is the most commonly employed technique to visualize parathyroid tumors. Ultrasound gives excellent soft tissue resolution, is noninvasive, and is relatively cheap, but its results are operator dependent. Also, it is limited to imaging the anterior neck; retroesophageal, retrotracheal, and mediastinal areas are poorly visualized. Parathyroid carcinomas appear as hypoechoic masses that tend to be larger, more heterogeneous, and more lobulated than benign adenomas, which are smaller, homogeneous, and have smooth borders.³⁸ Infiltrative lesions and those with calcifications are suspicious for cancer.³⁹ In addition, the depth-width (DW) ratios are distinctly different, with a mean near 1.21 for carcinoma versus a mean of 0.64 for adenomas.

Contrast-enhanced computed tomography (CT) is commonly used to visualize the soft tissue of the neck and can be helpful to fully evaluate nearby structures. This is a useful imaging modality in cases of carcinoma because it allows for full evaluation of the local disease extent and metastases. It may give a superior evaluation of the central neck and superior mediastinum for lymph node evaluation. ▶ Fig. 22.1 shows a typical CT image of a parathyroid carcinoma. Magnetic resonance imaging

(MRI) is less commonly used because of the expense, and many studies have shown it is not superior to CT for isolating parathyroid masses.

Finally, a parathyroid scan, or scintigraphy, is commonly used to identify parathyroid tumors. This test uses the radioisotopes thallium-201 and technetium-99 m and computer subtraction techniques to localize enlarged parathyroid glands. Thallium-201 concentrates in both parathyroid and thyroid tissues, and then technetium-99 m concentrates in the thyroid, so subtraction allows imaging of parathyroid glands and tumors. It has good sensitivity, but its specificity can be affected by concomitant thyroid disease, and it is nonspecific for adenomas and carcinomas.

22.6 Differential Diagnosis

The clinician must also rule out other causes of cancer-related hypercalcemia. These include lytic bone metastasis and ectopic production of PTH by nonparathyroid tumors, such as renal, ovarian, bladder, breast, and small cell lung carcinomas. Urinary cyclic adenosine monophosphate (cAMP) and phosphate can be used to help distinguish the underlying cause. Tumors secreting PTH will have a high urinary cAMP and low phosphate, and lytic bone metastases will have a low urinary cAMP and normal phosphate. Also, tumor-excreting ectopic PTH will have low levels of intact PTH, and PTH messenger RNA (mRNA) will not be expressed. Finally, PTH-related protein (PTHrP) is expressed in some cancers (including squamous cell carcinomas of the lung, esophagus, and head and neck) and may cause hypercalcemia. PTHrP can be detected by radioimmunoassay.

The frequent similarity to a benign parathyroid adenoma presents a major diagnostic challenge. In fact, many parathyroid carcinomas are not diagnosed until during surgery or after excision. As previously described the history, physical exam, labs, and imaging can be suggestive of a parathyroid carcinoma, but histological confirmation is required to secure the diagnosis. This can be a difficult task because there is no single histopathological feature that defines a parathyroid cancer. These lesions tend to be large, dense tumors as seen in the gross picture in ▶ Fig. 22.2. A malignant parathyroid neoplasm can be assured only by distinct invasion of the surrounding structures, vascular invasion, or metastases. There are some features that are highly suggestive of parathyroid carcinoma. These include a thick fibrous capsule, capsular invasion, mitotic figures, prominent nuclear enlargement, and pleomorphism (▶ Fig. 22.3). However, these features may occasionally be seen in nonmalignant parathyroid disease. At times, the definitive diagnosis cannot be made until the patient is noted to have recurrence or metastatic disease on follow-up. Individuals with a parathyroid neoplasm that is suspicious, but not diagnostic, for carcinoma should be followed as if the lesion were malignant.

22.7 Treatment

22.7.1 Surgery

Surgical excision is the mainstay of therapy and is the only curative treatment. The thoroughness of the initial operation is crucial, and tumor spillage often results in local tumor recurrence. A preoperative diagnosis is not always secure, and the

surgeon must recognize certain intraoperative findings that suggest a carcinoma. These gross findings include a thick fibrous capsule, gray-white color, invasion into adjacent structures, large size, and hard consistency. The approach to the initial surgery has evolved from an aggressive procedure involving an ipsilateral thyroidectomy, isthmusectomy, excision of the adjacent strap muscles, and a low threshold to remove the recurrent laryngeal nerve, to a more conservative parathyroidectomy or en bloc resection of the tumor with any adjacent invaded structures and a rim of healthy tissue. In the SEER database, 78.6% of parathyroid carcinomas were removed via surgeon-reported parathyroidectomy, and 12.5% were removed by en bloc resection.⁷ The recurrent laryngeal nerve should be

sacrificed, if involved, due to a high rate of local recurrence with attempts to dissect the tumor from the nerve. Elective neck dissection is controversial but generally not recommended due to low rates of regional metastasis. For residual disease with a positive margin or regional recurrence, reoperation is recommended to remove all tumor tissue. Most recurrences occur within the neck.⁴⁰

In addition, due to the limited efficacy of nonsurgical therapies, surgical resection of metastatic disease can be considered, primarily to debulk the tumor and palliate the effects of hypercalcemia. These measures are not likely to be curative but may provide lasting control by reducing the tumor volume. Studies have shown that palliation of hypercalcemia is frequently achieved in reoperations, and responses may last from a few months to several years.^{8,11,13,17} Postoperative management primarily consists of monitoring patients closely for hypocalcemia or hungry bone syndrome and repleting their serum calcium levels with oral and intravenous calcium and vitamin D as needed. These patients may have low levels of vitamin D preoperatively with very high levels of serum calcium. This combination may increase the risk of hungry bone syndrome over that of the routine parathyroid adenoma resection.

22.7.2 Radiation

Parathyroid carcinomas tend to be radioresistant, and the literature is limited to small observational studies without prolonged follow-up. In the primary setting, there is 1 case report of long-term survival, 11 years, of a patient with invasive parathyroid carcinoma treated with definitive radiation.¹¹ A series out of MD Anderson showed that adjuvant radiotherapy had a local recurrence rate of 16.7% (1/6 patients), whereas those without adjuvant radiotherapy had a local recurrence rate of 50% (10/20 patients).³⁷ Also, a series out of the Mayo Clinic demonstrated a lower risk of locoregional disease progression and improved cause-specific survival with adjuvant radiation based on four patients who received adjuvant radiation therapy for locoregional disease progression after initial surgery.⁴¹ In addition, radiotherapy can be considered for palliation of pain from bone metastasis and for symptoms of hypercalcemia.

22.7.3 Chemotherapy

Experience with chemotherapy is limited to case reports in the palliative setting for severe, refractory hypercalcemia. Dacarbazine, 5-fluorouracil, and cyclophosphamide resulted in normalization of serum calcium for 13 months in one patient with pulmonary metastases.² This regimen showed a complete



Fig. 22.2 Gross specimen of a parathyroid carcinoma.

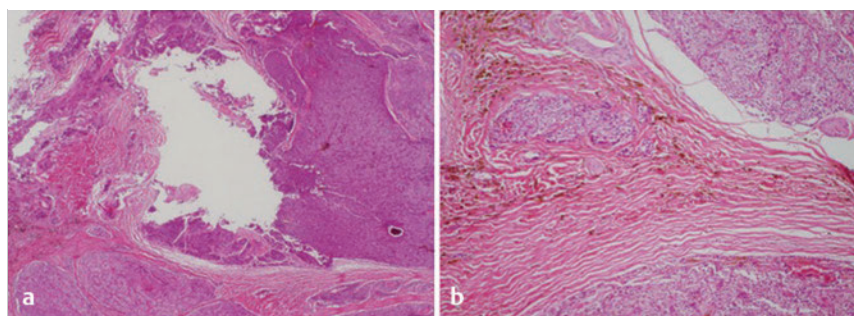


Fig. 22.3 Pathological slides of parathyroid carcinoma. (a) Light microphotograph of parathyroid carcinoma showing thick fibrous bands intersecting the gland with areas of necrosis (hematoxylin-eosin stain; original magnification $\times 4$). (b) Light microphotograph of parathyroid carcinoma further showing thick fibrous bands along with encasement of surrounding vasculature (hematoxylin-eosin stain; original magnification $\times 100$). (Courtesy of Benjamin Witt, MD.)

symptomatic response and a partial biochemical response for 5 months with moderate gastrointestinal side effects.⁴² Dacarbazine alone showed a dramatic response for 2 months with normalization of serum calcium in a patient with aggressive locally recurrent disease despite five previous neck explorations.⁴³ In one patient with a metastatic nonfunctional parathyroid carcinoma, chemotherapy with methotrexate, adriamycin, cyclophosphamide, and lomustine showed a dramatic and complete resolution of their mediastinal mass and pleural effusion after 18 months of treatment.⁴⁴

22.7.4 Medical Management

Mortality from parathyroid carcinoma generally results from uncontrolled hypercalcemia. Controlling hypercalcemia is therefore important and can be a difficult task. Surgical resection of a functioning tumor is the best option, even if limited metastatic deposits exist,² and there may be a role for resecting metastatic disease. When there are no surgical options remaining for treating the cancer, the provider is limited to controlling the calcium levels through medical management. This approach requires aggressive hydration and the use of a calcimimetic agent or intravenous bisphosphonate.

Calcimimetics suppress the production of parathyroid hormone by increasing the sensitivity of the calcium-sensing receptor. Cinacalcet is the agent currently available for treatment of parathyroid related hypercalcemia. It is often used when surgery is not an option and patients have significant hypercalcemia. One study by Silverberg showed that cinacalcet could reduce calcium levels by at least 1 mg/dL in the majority of patients. Other calcimimetics have also been looked at with similar results.^{45,46} Side effects related to calcimimetics include nausea, vomiting, diarrhea, and dehydration. Patients may need continuous hydration to manage these side effects.

Bisphosphonates can also be helpful in reducing calcium levels. They work by suppressing osteoclast-mediated bone resorption and may help control hypercalcemia over an extended time with multiple doses.^{2,47} There are multiple options to choose from, including denosumab, which is a fully humanized monoclonal antibody that has been used to treat postmenopausal osteoporosis and to prevent skeletal events from bone metastases. It has also recently been advocated for use in control of hypercalcemia of malignancy, including that caused by parathyroid carcinoma.^{48,49}

Other potential treatments include immunotherapy and radiofrequency ablation. In some studies, infusing a set of PTH peptide immunogens controlled hypercalcemia and was even seen to induce regression of metastatic tumor.^{50,51} Other studies showed less effectiveness.⁵² Radiofrequency ablation has been used to control focal metastatic lesions that lead to hypercalcemia. It has been shown, in case reports, to control serum calcium levels.^{47,53} The effects have been temporary, but it can be repeated.

22.8 Staging and Survival

There is no standardized staging system for parathyroid cancer. This is in part due to the rare incidence of this entity as well as

the difficulty in making a pathological diagnosis. There are not clear diagnostic histological features of parathyroid carcinoma in the absence of frank tumor invasion or metastases. Typical factors related to disease prognosis, such as the T (size of the primary tumor), N (lymph node status), and M (distant metastases status) status have proven to be less reliable predictors of outcome in parathyroid carcinoma than in other endocrine tumors.^{6,7}

Invasion into adjacent structures is common and often used in the diagnostic criteria. There is also a tendency to invade nerves in the area, such as the recurrent laryngeal nerve (RLN). The impact of RLN invasion on survival is unknown, but it is recommended to sacrifice this nerve if it is found to be invaded. The lymph node status is also not very useful because <5% of parathyroid carcinomas present with lymph node involvement.⁶ Also, lymph node involvement does not appear to impact long-term survival. When lymph node metastases occur, they are more likely to be associated with recurrent cases of parathyroid cancer.

22.9 Outcomes

Parathyroid carcinoma is often a slow-growing indolent disease. The overall survival has been reported from 49 to 95% at 10 years.^{6,7,40} Lee's study using the SEER database did show a trend toward improved survival in more recent years along with a trend toward increased surgical intervention.⁷ Although patients often die of hypercalcemia, aggressive medical management may be able to improve long-term survival by controlling serum calcium levels, and this approach may explain some reports of 10-year survival rates as high as 77%.⁵⁴ Local disease control may be difficult due to the tendency for invasion of surrounding structures, and recurrence occurs in approximately 50% of patients.^{37,40} The time to recurrence averages 3 years, with a range up to 20 years.^{55,56}

Although there are few, if any, prognostic factors that predict outcome, early detection and en bloc resection have been suggested as the best way to control disease. However, patients need long-term follow-up to assess for recurrence as well as the need for possible medical management of hypercalcemia. Follow-up should consist of a clinical evaluation, including a periodic physical examination, laboratory studies, and imaging. Intact parathyroid hormone and serum calcium levels provide an efficient way to follow patients with functioning parathyroid carcinomas. For nonfunctioning cancers, imaging and physical exam are the primary modes of surveillance. Imaging options may vary but would often include ultrasound or CT evaluation of the neck. CT of the abdomen and pelvis may be required to evaluate patients at risk for distant disease.

22.10 Conclusion

Parathyroid carcinoma is a rare disease. Understanding the typical presentation can prepare the clinician for making the correct diagnosis. Surgery is the primary treatment in this indolent malignancy, but controlling the degree of hypercalcemia is important, even in incurable cases, to provide long-term survival.

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23 Parathyroid Imaging

Rosemarie Metzger and Mira Milas

23.1 Introduction

Much time has passed since the days when palpation and barium swallow studies were the preoperative localization methods of choice for primary hyperparathyroidism. Thermography, selenomethionine scintiscanning, and esophageal cineradiography have likewise joined their ranks in the history books.¹ Today, the modalities of choice for parathyroid imaging include ultrasound and technetium-99m (^{99m}Tc)-sestamibi (sestamibi) imaging, and, more recently, four-dimensional-computed tomography (4D-CT) scanning. In combination with the development of intraoperative parathyroid hormone measurement, advances in parathyroid imaging enabled the adoption of focal parathyroid exploration as a surgical strategy. At present, whether surgery is focal or bilateral exploration,^{2,3,4} the role of parathyroid imaging remains critically important. Preoperative knowledge of single versus multigland disease, concomitant thyroid pathology, and ectopic gland location is critical to achieving operative success.

Parathyroid imaging must be performed in the correct context. It is used for localization, to supplement and aid surgical dissection, but never to help attain a diagnosis. The biochemical diagnosis of hyperparathyroidism should be made prior to embarking on localization, and imaging should be pursued in those patients who are surgical candidates. The number and type of imaging studies to perform are based largely on surgeon preference and institutional availability. Study performance and sensitivity are also important, although one must remember when interpreting data on imaging performance and sensitivity that the sensitivity of all modalities is dependent on intraoperative findings, which are influenced by whether or not bilateral exploration was pursued. The prevalence of multigland disease influences the perceived accuracy of localizing studies,⁵ and it varies with the thoroughness of the surgical exploration.⁶

Imaging must also be interpreted with a thorough understanding of parathyroid embryology and anatomy. Most patients have four glands, although supernumerary glands have been reported.⁷ The superior glands are derived from the fourth branchial pouch along with the lateral lobes of the thyroid; the inferior glands arise from the third pouch along with the thymus. Superior glands are located in a more posterior plane when compared with inferior glands, and this plays an important role when reviewing imaging, especially cross-sectional or sagittal images. Although superior glands are typically located behind the midportion of the superior thyroid lobe near the cricothyroid junction, they can also descend into a relatively inferior cervical location. Recognizing this posterior position in the neck can help distinguish them from inferior parathyroid glands, which are typically also found in the low neck in close proximity to the inferior pole of the thyroid, although in a more anterior plane. Likewise, inferior glands that reside within cervical or mediastinal thymic tissue will remain in a relatively anterior plane.

This chapter focuses on the most common parathyroid imaging modalities used today and their roles in both primary and reoperative cases.

23.2 Ultrasound

Reports from 1975 and 1978 were the first to detail the use of ultrasonography to identify parathyroid glands >5 mm in size,^{8,9} and Barraclough et al provided additional support in 1981.¹ For many years now, it has often been the first modality used to detect abnormal parathyroid glands and can be performed in the outpatient office setting. Although radiologists have classically performed or interpreted ultrasounds, surgeon-performed ultrasound is becoming increasingly common.

The patient is positioned supine on the examination table with a pillow positioned at the level of the shoulders to allow for neck extension. A high-frequency linear array transducer of 7.5 to 15 MHz is used to systematically scan the neck to identify both thyroid and parathyroid abnormalities. Normal parathyroid glands are typically too small and structurally similar to adjacent thyroid tissue for sonographic detection, suggesting that almost any gland identified is inherently pathological in nature. On gray-scale imaging enlarged parathyroid glands are uniformly hypoechoic and classically ovoid or teardrop in shape with well-defined margins created by a hyperechoic line of adventitia along the anterior and posterior surfaces (► Fig. 23.1).¹⁰ Large adenomas can appear bilobed or irregularly shaped.^{11,12} Cystic degeneration can be found in 1 to 2% of enlarged glands.¹³ Color Doppler imaging is used to identify the vascular pedicle, the enlarged, extrathyroidal feeding artery that typically arises from branches of the inferior thyroidal artery. This feeding artery typically supplies the adenoma at the pole of its long axis, in contrast to lymph nodes, which have a central, hilar blood supply.^{10,11,12,14} Vascular arcs surrounding parathyroid glands from 90 to 270° have also been described in more than 50% of adenomas.¹⁵ These arcs arise from arborization of the feeding artery around the periphery before smaller branches penetrate deeper, and were first described in angiography literature (► Fig. 23.2).^{12,16} Although these features can be confirmatory in cases of large, more obvious parathyroid adenomas, their value is often greatest for lesions that are smaller and less readily identifiable as an enlarged parathyroid.^{11,12,14}

Gradually applying enough pressure with the ultrasound probe to gently deform the subcutaneous tissue and strap muscles can help elucidate glands that might be otherwise difficult to see, such as those deep in the tracheoesophageal groove or laterally in the carotid sheath.¹² This technique can be valuable even when glands are obvious; enlarged glands may be compressible and can therefore be seen to “move” or change shape during ultrasound with gradual compression by the sonographer. Conversely, enlarged lymph nodes do not exhibit this same deformability.

Superior parathyroid glands are generally found posterior to the upper or middle third of the thyroid lobe and can sometimes be more readily identified with the probe in longitudinal orientation. Inferior glands are typically found immediately adjacent to the lower border of the thyroid lobe or in the fibrofatty central neck tissue.¹² Lymph nodes can also be frequently identified in the central neck spaces and may be difficult to distinguish from enlarged parathyroid glands. One clue to

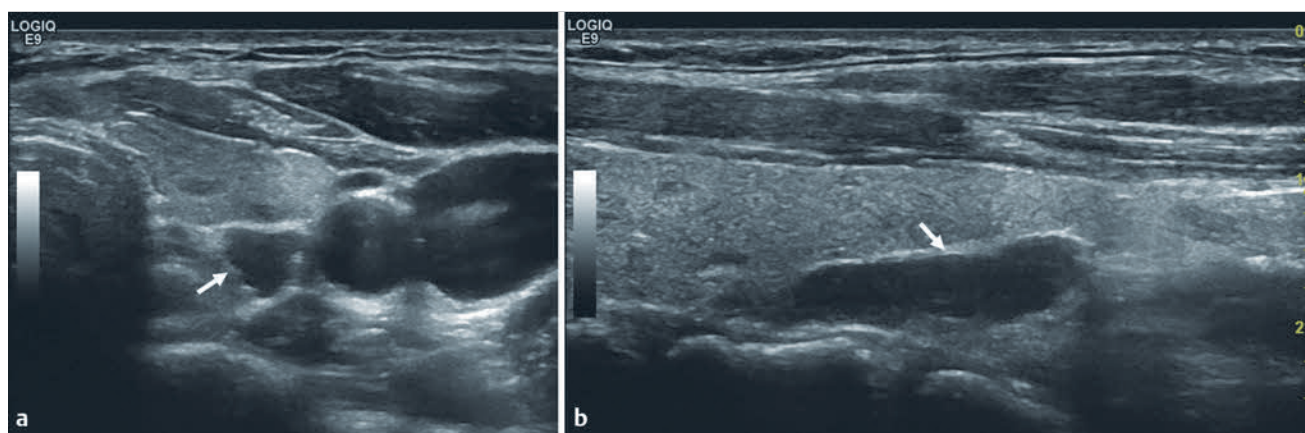


Fig. 23.1 Classical oval shape of enlarged parathyroid gland on ultrasound (arrow). (a) Transverse image. (b) Longitudinal image.

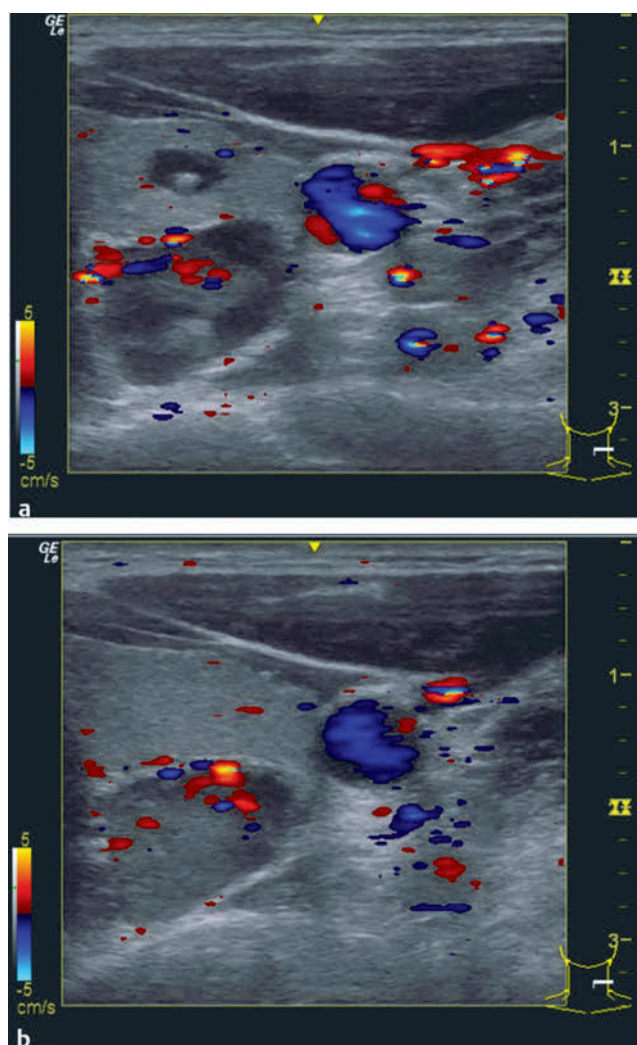


Fig. 23.2 Vascular pedicle (a) and arcs of peripheral arborization (b) on a large left superior parathyroid adenoma.

distinguish lymph nodes from parathyroid glands is to examine the echogenicity of the thyroid gland. Coarse thyroid echogenicity can signify an underlying thyroiditis, such as Hashimoto's thyroiditis. In these cases it is not uncommon to find multiple

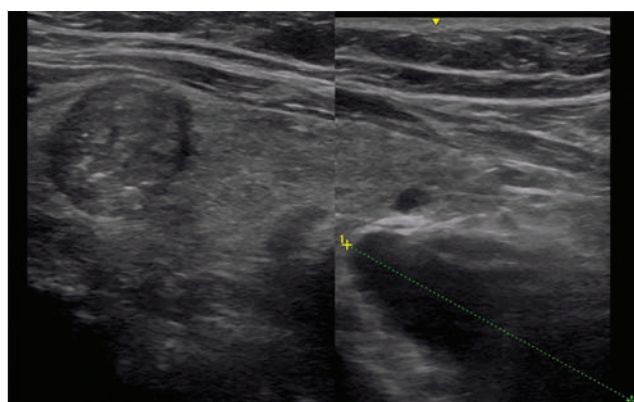


Fig. 23.3 Papillary thyroid cancer within the thyroid lobe adjacent to a large parathyroid gland (dotted line).

enlarged lymph nodes in the central neck spaces. In general, lymph nodes tend to be more round in shape than parathyroid glands, and those associated with subacute thyroiditis may demonstrate central, linear vascular flow that corresponds to the hilum. Lymph nodes in patients with Hashimoto's thyroiditis typically lack any blood flow, reflecting the chronic nature of the inflammatory process.¹⁷

Given its low cost, ease of administration, and lack of ionizing radiation, ultrasound is rapidly becoming the preferred parathyroid imaging modality; many view it as a mandatory localization strategy.^{18,19} This is especially true among surgeons because the superior anatomical resolution provided by real-time ultrasound can be invaluable in operative planning and execution. Sensitivity of surgeon-performed ultrasound is high, ranging from 76 to 88%,^{20,21,22} and has been reported by some to be higher than that of radiologist-performed ultrasound.^{23,24,25} Gland size, weight, and volume can predict the likelihood of sonographic detection, as can sonographer skill. Patient obesity; small, multiple, hyperplastic, or ectopic glands; and thyroid nodular disease are all limitations to successful ultrasound.²⁶ However, visualization of concomitant thyroid pathology, which occurs in 25 to 84% of primary hyperparathyroidism patients and is malignant in nearly 20% of cases, can also be beneficial in the preoperative setting (► Fig. 23.3). This knowledge can alter the planned operative approach, help to

avoid unnecessary thyroid surgery for lesions first encountered intraoperatively, and potentially avoid future reoperative neck surgery for missed pathology.^{27,28} Milas et al determined that preoperative detection and biopsy of thyroid nodules decreased concomitant thyroidectomy to 6%, as opposed to 30% in those who had thyroid nodules discovered intraoperatively at the time of parathyroid surgery.²⁷ Doppler flow can help differentiate thyroid nodules (which lack a polar vascular pedicle) from parathyroid adenomas, as can identification of a well-defined tissue plane separating a parathyroid gland from the thyroid. Thyroid nodules are more likely to be heterogeneous in echotexture, as opposed to the uniform hypoechoic nature of a parathyroid adenoma. Ultrasound can also be useful in identifying intrathyroidal parathyroid glands and facilitating fine-needle aspiration biopsy if necessary. Finally, ultrasound can help differentiate nodular thyroid disease from parathyroid activity, which may be difficult to distinguish on nuclear scintigraphy imaging alone.

Ectopic glands, especially those located in retroesophageal, intrathymic, and mediastinal locations, as well as multigland disease, reduce the overall success of ultrasound. The upper mediastinum and posterior clavicular spaces may be better imaged with a curved probe. Deglutition during examination can help elevate glands in these locations into the field of view.²⁹ Color flow Doppler imaging is less beneficial for ectopic glands in the superior mediastinum because these glands are frequently supplied by the thymic branch of the internal mammary artery and are not sonographically accessible. Adjunctive measures, including axial rotation of the patient's head, may be helpful when searching for ectopic glands. However, interference by osseous structures and those poorly penetrated by ultrasound (esophagus and trachea) can still ultimately limit identification.³⁰ Care must also be taken to evaluate the high cervical region near the carotid bifurcation and along the thyrothymic ligament in the central neck.¹¹

Multigland hyperplasia can be difficult to image because these glands are typically smaller than adenomatous glands, and all involved glands are rarely visualized. In patients with asymmetric hyperplasia or double adenomas, finding of a single enlarged gland on ultrasound may lead to the incorrect conclusion that only one diseased gland is present.^{4,31} Conversely, multigland disease in the setting of secondary and tertiary hyperparathyroidism can lead to four sonographically identifiable glands.

23.3 Nuclear Scintigraphy

Radioisotope imaging of the parathyroid glands requires a source of radioactivity, known as the tracer, as well as a camera with which to capture the emitted radiation. Following marginal success with selenium-75-methionine, thallium-201 (²⁰¹Tl) was the first radiotracer to gain widespread acceptance for parathyroid localization. Originally used for myocardial perfusion imaging, ²⁰¹Tl is a potassium analogue that is rapidly integrated into the intracellular potassium pool.³² Densely hypercellular tissues, such as enlarged parathyroid glands, as well as thyroid tissue, accumulate ²⁰¹Tl. Today, use of ²⁰¹Tl has been abandoned in favor of technetium-99m (^{99m}Tc)-sestamibi (sestamibi) due to superior image quality, improved accuracy, and more favorable dosimetry.³² A lipophilic compound that

becomes trapped intracellularly, primarily by sequestration in the mitochondria,³³ sestamibi was originally designed to be a myocardial perfusion agent; its uptake by parathyroid tissue was serendipitously discovered. Coakley et al reported the first use of sestamibi in parathyroid imaging in 1989.³⁴ Although, like ²⁰¹Tl, it is taken up by both parathyroid and thyroid tissue, sestamibi washout time from parathyroid tissue is longer due to mitochondrial-rich oxyphil cells in hypercellular parathyroid glands.³⁵ Additionally, owing to the superior physical characteristics of sestamibi for gamma camera imaging, the radiation dose to the patient per unit administered is approximately 20 times less than that for ²⁰¹Tl.³⁴

^{99m}Tc-tetrofosmin (tetrofosmin), another myocardial perfusion agent, has also been used for parathyroid scintigraphy. Parathyroid tissue avidly takes up tetrofosmin but dissipates it more quickly than sestamibi.^{36,37} Despite this rapid clearance, some have indicated that the isotopes have similar sensitivities.^{38,39} Most, however, feel tetrofosmin is significantly less sensitive⁴⁰ and less accurate in orienting the surgeon to the diseased gland,⁴¹ and therefore use sestamibi instead.

The techniques used in parathyroid scintigraphy have evolved over time, and there are multiple protocols that remain in use. The two basic protocols are dual-isotope single-phase (subtraction) and single-isotope dual-phase (washout). Both techniques serve to isolate activity attributable to just the parathyroid glands because ²⁰¹Tl, sestamibi, and tetrofosmin all have affinity for both thyroid and parathyroid tissues. Subtraction was popularized by the introduction of ²⁰¹Tl for parathyroid scintigraphy in 1983, and relied on concomitant use of technetium-99m (^{99m}Tc)-pertechnetate chloride (pertechnetate), which accumulates in the thyroid but not the parathyroid glands. ²⁰¹Tl and pertechnetate are administered in a single session, without moving the patient. The pertechnetate, or thyroid image, is then subtracted from the ²⁰¹Tl, or parathyroid image. Residual activity represents abnormal parathyroid tissue.⁴² Iodine-123 (¹²³I) is also used for subtraction, which, along with pertechnetate, is concentrated in thyroid cells via the thyroid Na⁺/I⁻ symporter, although only ¹²³I is organified in thyroid follicles.⁴³ Because of its similar half-lives in both thyroid and parathyroid tissue, tetrofosmin requires that a subtraction protocol be used, as opposed to a washout protocol, for which sestamibi is suitable.⁴⁴

Subtraction imaging may be most useful in patients with thyroid abnormalities because thyroid nodules are the most frequent cause of false-positive results in parathyroid scintigraphy.^{32,45} Many thyroid lesions that accumulate sestamibi or tetrofosmin also accumulate pertechnetate and iodine and can therefore be subtracted. The subtraction technique, though useful, has certain limitations. Patient motion during data acquisition may lead to registration errors of the sestamibi/tetrofosmin and pertechnetate/iodine images, resulting in a false-positive study. Another pitfall of the subtraction technique is decreased or absent thyroid uptake of pertechnetate or iodine, which may render the subtraction image invalid. A detailed thyroid history is valuable, including thyroid hormone supplementation or recent computed tomographic (CT) scan with iodinated contrast. Very intense sestamibi or tetrofosmin uptake by a parathyroid lesion may occasionally cause "shine-through" on the pertechnetate/iodine image and be erroneously interpreted as a thyroid nodule. Occasionally, a

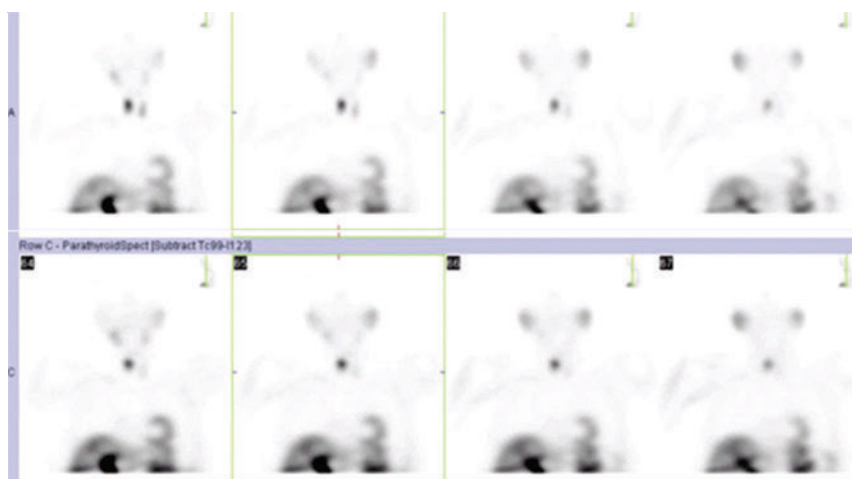


Fig. 23.4 Sestamibi scan with initial (*top row*) and washout (*bottom row*) phases. From left to right, images represent coronal views starting anteriorly and proceeding posteriorly in the neck. A large single focus of residual radiotracer labels a (presumably) single enlarged parathyroid gland in the right neck.

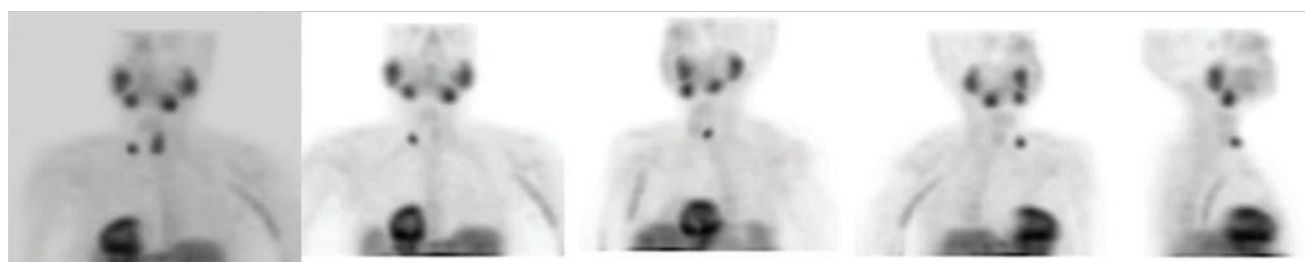


Fig. 23.5 Single-photon emission computed tomography (SPECT) of a patient. From left to right, the first image represents the initial sestamibi image. Radiotracer is seen ascending a vein in the left arm where it was injected, and a smudge representing the left thyroid gland is visible in the left neck. The subsequent four images are after radiotracer washout and show a single abnormal collection of radiotracer marking an abnormal parathyroid gland in the right neck. Four angles are captured to demonstrate the utility of SPECT imaging.

parathyroid lesion will be situated immediately behind a thyroid lesion and is eliminated when the thyroid image is subtracted.³²

Taillefer et al introduced the single-isotope dual-phase imaging (washout) technique in 1992 based on the observation that the washout of sestamibi from abnormal parathyroid tissue is slower than that from surrounding thyroid tissue.⁴⁶ This simple and easy-to-perform study requires only a single injection of sestamibi followed by imaging approximately 15 minutes and 1.5 to 3 hours later. A persistent focus of activity on delayed imaging is indicative of a parathyroid lesion (► Fig. 23.4). Unfortunately, some parathyroid lesions do not retain sestamibi, whereas some thyroid lesions, and even cervical lymph nodes, accumulate and retain sestamibi, resulting in both false-negative and false-positive studies.^{32,43,47} This technique also lacks sensitivity for detecting multigland disease.⁴⁸

The acquisition technique can also affect sensitivity of scintigraphy. Use of a fixed or mobile gamma camera will determine whether planar (two-dimensional) or three-dimensional images are acquired, respectively, whereas the type of collimator (lens equivalent of a gamma camera) used determines their resolution. Collimators filter emitted gamma rays into a singular direction so that a clear image is produced and spatial orientation is maintained, similar to a polarizing lens. Parallel-hole collimators filter a stream of parallel rays allowing for simultaneous imaging of both the neck and the chest. Pinhole collimators provide the highest resolution, limit imaging to the neck

only, magnify the structures being imaged, and can also be positioned so as to obtain oblique views.³² They are significantly more sensitive than parallel imaging for glands of all sizes, including multigland disease.^{49,50}

The addition of single-photon emission computed tomography (SPECT) allows for three-dimensional imaging by using a mobile gamma camera to collect images at multiple angles around the patient (► Fig. 23.5). The multiple images are compiled by a computer and displayed as three-dimensional images, similar to positron emission tomography (PET) imaging. SPECT increases the sensitivity of scintigraphy compared to planar imaging alone.^{51,52} The additional detail is useful for not only detecting but also localizing ectopic parathyroid glands, because tomography provides more detailed anatomical information about the gland, its size, and its relationship to other structures, including the sternum, spine, and heart.⁵³ It is also helpful in differentiating thyroid lesions from parathyroid lesions. Because the parathyroid glands are typically found posterior to the thyroid they can subsequently lie directly behind a thyroid nodule. Planar imaging alone is unlikely to distinguish an anterior thyroid lesion from a posterior parathyroid gland; tomography is able to differentiate these spatial relationships.³²

The latest adjunct to scintigraphy is hybrid SPECT/CT imaging, a modality combining nuclear medicine and CT technology into a single physically integrated instrument (► Fig. 23.6). The CT portion provides an anatomical map, which, when merged with the radiotracer uptake demonstrated on SPECT images, aids in demonstrating the relationship of sestamibi-avid lesions

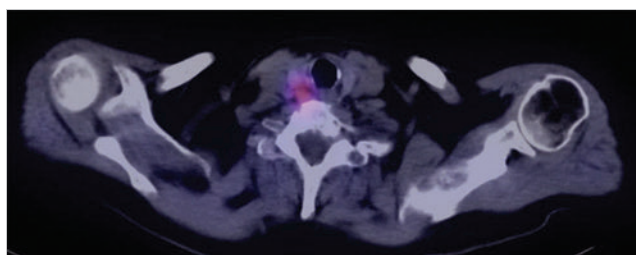


Fig. 23.6 The same focus of parathyroid disease as in ► Fig. 23.4 is shown in an axial single-photon emission computed tomography (SPECT) / computed tomography image.

to adjacent structures. Because CT and SPECT acquisition can be performed in a single imaging session without moving the patient, there is near-perfect coregistration of the images. Attenuation correction afforded by SPECT/CT improves the sensitivity for the detection of deeper lesions, and visualization of corresponding anatomy improves the differentiation of abnormal from physiologic sestamibi accumulation.⁴⁷ These advantages can lead to a significant reduction in false-positive findings over SPECT imaging alone.⁵⁴

The success of scintigraphy is dependent on the particular scanning technique used, and therefore reported sensitivities vary widely. Subtraction scanning has been demonstrated to be superior to single-agent dual phase washout.^{55,56,57} Many advocate for the combined use of both planar and SPECT imaging. Nichols et al⁵⁸ noted that the use of SPECT imaging alone did not afford increased sensitivity from planar imaging, 88% versus 83%, respectively. However, the addition of SPECT to planar imaging led to the greatest sensitivity, specificity, and accuracy (90%, 89%, and 89%, respectively). Multigland disease continues to remain a major challenge in parathyroid imaging, and in this study every technique was significantly less sensitive in the detection of multigland disease (MGD) than in the detection of single-gland disease (SGD).⁵⁸ Specificity was also significantly lower for MGD than for SGD for interpretation of all images (73% vs. 98%, $p < 0.001$).⁵⁸ Lavelly and colleagues also found that SPECT was not more sensitive than planar imaging, but they did find that SPECT/CT was significantly more sensitive than both planar and SPECT imaging (dual-phase imaging; subtraction protocol not used).⁵⁹ Sharma et al, in a study of 833 patients, found that, although accuracy for identifying SGD was equivalent between planar and SPECT modalities (SPECT, SPECT/CT, and SPECT ¹²³I), all SPECT-based scans had a statistically higher rate of disease detection (i.e., lower false-negative rate) than planar imaging.⁶⁰

Regardless of the type of study performed there will always remain biological factors beyond the control of surgeons and radiologists that contribute to the sensitivity and specificity of scintigraphy. These factors, including size, weight, and oxyphil content of parathyroid glands, in addition to P-glycoprotein expression, have all been demonstrated to affect detection by scintigraphy.^{41,61,62,63,64,65} Although positive scans are associated with adenomas of significantly larger volume and weight, many equally large glands can be missed, whereas glands of much smaller stature are identified.^{26,58,61,63,64} These findings suggest there are other factors at play. Successful scintigraphy can be related to an adenoma's oxyphil cell content; oxyphil cells are rich with densely packed mitochondria and rapidly sequester

sestamibi.^{61,63,64} Oxyphil content in parathyroid adenomas is variable, although pure oxyphil cell adenomas are rare.⁶⁶ Erbil et al demonstrated that oxyphil cell content >20% was necessary to obtain positive sestamibi scan results in glands that were <600 mg, whereas in glands >600 mg, low oxyphil cell content did not affect imaging results.⁶¹ In a similar fashion, expression of P-glycoprotein (P-gp) or multidrug resistance-related protein (MRP) can also affect parathyroid scintigraphy results independent of parathyroid size. Specifically, the retention of sestamibi in parathyroid cells depends on the activity of the P-gp coded on the multidrug resistance (*MDR1*) gene, which functions as an adenosine triphosphate (ATP)-dependent efflux pump, preventing the accumulation of lipophilic, cationic radiopharmaceuticals, including tetrofosmin and sestamibi.⁴¹ Mitchell and colleagues elegantly demonstrated that it was not size, but rather another factor, such as P-gp expression, that was the primary determinant of parathyroid retention of sestamibi.⁶⁷ Sun and Kao, in two separate studies, went on to demonstrate that either P-gp expression, MDR expression, or both were present in every single parathyroid with a corresponding false-negative sestamibi scan.^{62,68} Biochemistry is also important, although the correlation between preoperative parathyroid hormone (PTH) and calcium levels and scintigraphy results is variable. Some have found no statistically significant relationship.^{26,61,64,65,69,70} Mehta et al suggested that PTH expression was greatest in glands consisting of predominantly chief cells, and therefore, given the corresponding reduced oxyphil cell concentration, tended to lead to negative studies.⁶³ Conversely, others have found higher preoperative calcium and PTH values are predictive of positive scans.⁷¹ These biological factors are inherently nonmodifiable. However, use of levothyroxine to enhance the sensitivity of sestamibi imaging in euthyroid patients, and discontinuation of calcium channel blockers in patients with primary hyperparathyroidism, have both been suggested as ways in which the sensitivity of imaging can be altered at a biological level.^{72,73}

23.4 Computed Tomography

Conventional axial imaging has never been a preferred method for parathyroid localization, owing to decreased sensitivity largely related to low spatial resolution of early scanners using thick scan slices. Development of very thin acquisition thicknesses and multidetector CT, however, in addition to incorporating the perfusion characteristics of parathyroid adenomas, has brought about the emergence of a new imaging modality, 4D-CT. The fourth dimension relies on time and the rapid uptake and washout of contrast from parathyroid adenomas. Noncontrasted CT of the neck is performed at the outset. Iodinated contrast is then rapidly administered, and imaging is performed at multiple subsequent time points. The initial postcontrast imaging begins at 25 to 30 seconds after the injection and is considered the "arterial" phase. Washout images are obtained between 30 and 60 seconds after the initial arterial image (► Fig. 23.7). The highly detailed, multiplanar images obtained allow for visualization of hyperfunctioning parathyroid glands, which demonstrate rapid uptake and washout compared to normal parathyroid glands and other structures in the neck.^{74,75}

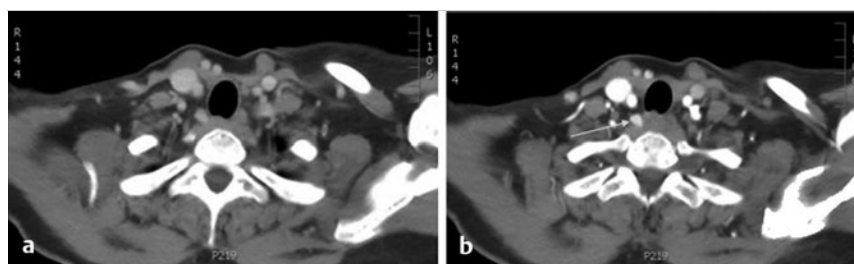


Fig. 23.7 Abnormal parathyroid gland (arrow) in tracheoesophageal groove is better seen in the delayed arterial phase (a) than in the venous phase (b) of a four-dimensional computed tomographic scan.

Separate studies by Rodgers et al and Starker et al demonstrated that the sensitivity of 4D-CT (70% and 85.7%, respectively) was statistically superior to both ultrasound and sestamibi (single-agent dual-phase SPECT/CT and SPECT, respectively) for defining the precise location (quadrant of the neck) of abnormal parathyroid glands.^{75,76} It should be noted that surgeon-performed ultrasound was not included in either study.^{75,76} Multigland disease was variably predicted. In Starker et al's study multigland disease was identified in 6 of 7 patients (85.7%), as opposed to 5 of 11 patients (45%) in Rodgers et al's study, with only 3 of these (27%) having all diseased glands suggested on imaging.^{75,76} Lubitz et al studied a more varied population, including reoperative patients, all of whom had negative, discordant, or otherwise inconclusive standard parathyroid imaging (ultrasound and sestamibi imaging) and also found a high rate (60%) of accurate localization.⁷⁷

There are, however, disadvantages to 4D-CT relating to availability, interpretation, and radiation exposure. Although the calculated effective radiation doses for 4D-CT and sestamibi (single-agent dual-phase SPECT) are relatively similar (10.4 and 7.8 mSv, respectively), the calculated thyroid dose (92 mGy) is significantly higher with 4D-CT (about 57-fold). This corresponds to a calculated lifetime attributable risk of thyroid cancer for a 20-year-old female exposed to 4D-CT of approximately 0.1%, or 1,040/million.⁷⁸ This number tapers precipitously in the following decades of life, which is when those with hyperparathyroidism are most frequently diagnosed.⁷⁸ To minimize radiation exposure, many institutions have altered their 4D technique and now limit the number of phases performed. Raghavan et al retrospectively reviewed 29 4D-CT scans in five different combinations of phases (unenhanced and arterial phase; unenhanced, arterial, and early venous phases; all four phases; arterial phase alone; and arterial and early venous phases) and found that the accuracy, sensitivity, and specificity for localization of the arterial phase alone (91%, 83.6%, and 93.4%, respectively) were comparable to all four phases (90.5%, 82.1%, and 93.2%, respectively).⁷⁹ In a similar study, two-phase (unenhanced and arterial) and traditional four-phase studies were compared. Sensitivity (85.3% and 86%) and accuracy (60.3% and 65.5%) did not significantly differ between the 2- and 4-phase techniques, respectively.⁸⁰

23.5 Other Modalities

Magnetic resonance imaging (MRI) and positron emission tomography (PET) have been used to a lesser degree for parathyroid imaging. Hyperfunctioning glands demonstrate hypointensity to intermediate signal intensity on T1-weighted MRI sequences. Most adenomas demonstrate high signal intensity on T2-weighted images and avid enhancement following

administration of intravenous gadolinium; normal parathyroid glands are not typically visualized.^{47,74,81} Acute hemorrhagic and cystic adenomas can have equally high intensity on both T1- and T2-weighted images. Conversely, low signal intensity on both T1- and T2-weighted images is reflective of cellular degenerative changes, old hemorrhage with hemosiderin-laden macrophages, and fibrosis of the gland.⁸² Concurrent thyroid pathology, in addition to sarcoid nodules, neurofibromas, normal lymph nodes, follicular lymphadenitis, and other lymph node pathologies can appear hyperintense on T2-weighted imaging, leading to false-positive results. MRI is also limited by artifact introduced by patient movement, including physiological motion, and indwelling metal, such as clips from previous surgery. Its use may be best suited for cases with negative or discordant imaging.⁸³

Both fludeoxyglucose (FDG) and ¹¹C-methionine PET have demonstrated reasonably high sensitivity and specificity for localizing parathyroid glands.^{84,85,11} ¹¹C-methionine PET/CT has been shown to perform well, especially in the setting of concomitant thyroid disease.⁸⁶ As with other modalities, however, multigland disease is poorly imaged. As with MRI, cost and accessibility effectively limit the use of PET to cases of negative or discordant prior imaging.

23.6 Study Selection

There is no perfect localization study. Which study to use will depend not only on patient factors, such as renal function and body habitus, but also institutional availability, radiation exposure, and surgeon preference. Success will be inherently limited by the presence of multigland disease as well as institutional differences in imaging algorithms and practices.

A recent meta-analysis suggested ultrasound and sestamibi-SPECT were essentially comparable in terms of accurately localizing abnormal parathyroid glands, whereas 4D-CT was beneficial in those with negative or inconclusive results on other imaging.⁸⁷ Many continue to prefer dual localizing studies because one may be helpful for correlating or confirming uncertain findings in the other. The combination of sestamibi scintigraphy and ultrasound is the preferred approach by a majority of U.S. surgeons.⁸⁸ False-positive sestamibi imaging due to thyroid nodules, inflammatory thyroiditis, and cervical lymphadenopathy can be minimized with ultrasound evaluation to differentiate between thyroid, parathyroid, and other cervical lesions. Additionally, combined ultrasound and sestamibi scintigraphy are reported to have increased sensitivity for the preoperative localization of parathyroid adenomas; when both are positive and concordant the accuracy is approximately 94 to 99%.^{89,90} In fact, some have even suggested that use of intraoperative PTH monitoring is not necessary in these patients.⁹¹ However,

concordance rates range between 42 and 59%, thus limiting the applicability of this approach.^{31,89,91,92} Additionally, even in the setting of concordance and an appropriate drop in intraoperative PTH level following focused exploration, an additional abnormal gland, indicating multigland disease, can be found during contralateral exploration in up to 16% of patients.⁴

There is a movement toward single-modality imaging. Given the accuracy and convenience of surgeon-performed ultrasound, the once gold standard scintigraphy is more often being reserved for cases in which there is an unclear or negative surgeon-performed ultrasound.^{20,22,93,94} In more than 50% of cases, single-gland disease missed on ultrasound but subsequently detected by scintigraphy is due to a posteriorly located upper gland in the tracheoesophageal groove or other retroesophageal location.⁹⁵ However, the added benefit of sestamibi scintigraphy in patients with nonlocalizing ultrasounds can be limited, with success rates of <50% in identifying any abnormal glands.⁹⁶

Cost is another consideration. As our health care system continues to evolve, value will be of equal if not greater importance in choosing among the imaging modalities. Ultrasound is easily the cheapest modality, and when used in isolation, the potential cost advantage is staggering. Of 119 patients undergoing sestamibi scintigraphy, Arora et al reported 57 had correctly localized glands with findings corroborated by surgeon-performed ultrasound.²⁰ Twenty-eight patients had incorrectly localized glands by scintigraphy, but correctly localized ultrasound findings. Therefore, these 85 patients could have theoretically undergone surgeon-performed ultrasound only, representing a potential cost savings of at least \$90,000.²⁰ Wang and colleagues and Lubitz et al, in separate studies, found the most cost-effective strategies to be ultrasound combined with sestamibi-SPECT, then 4D-CT if needed, or an algorithm of ultrasound followed by 4D-CT, when ultrasound was inconclusive. Both, however, rely on the assumption that bilateral neck exploration is a more costly procedure than focal exploration.^{97,98}

23.6.1 Reoperative Neck Surgery

In patients with previous parathyroid or thyroid surgery, scarring and altered tissue planes make localization paramount. Four-gland or multigland exploration in this setting is avoided if possible. Scarring of the operative bed makes for a tedious dissection that can be more prone to bleeding, thus obscuring the otherwise subtle color differences critical to identification of parathyroid glands and the recurrent laryngeal nerve. The approach to these cases should be to find and resect an abnormal gland or glands whose locations are known preoperatively with a high degree of anatomical certainty. Detailed knowledge of the patients' clinical history is critical, so that the surgeon can more accurately predict whether residual single- or multigland disease is present and appropriately interpret localization studies.⁹⁹ If no hypercellular parathyroid tissue was resected during the previous surgery, a single adenoma may be expected; previous removal of hypercellular tissue should raise suspicion for multigland disease.^{99,100}

Although the preferred sequence for reoperative localization is subject to surgeon preference and institutional availability, the general consensus is to begin with noninvasive modalities and progress to those that are invasive.^{99,101,102,103} Whether two concordant studies are necessary is debatable. Udelsman and

colleagues have outlined a sequence beginning with cervical ultrasound and/or scintigraphy with SPECT. Negative or unconvincing studies are followed by a 4D-CT scan. Selective venous sampling or ultrasound-guided biopsy of suspicious cervical lesions (with aspirate sent for PTH measurement as well as cytology) is reserved for cases in which this hierarchical approach has failed to localize an abnormal gland.^{30,104}

It is important to remember all imaging studies are less reliable in the reoperative neck, and as is the case for primary procedures, multigland disease limits localization sensitivity.¹⁰⁴ Although ultrasound can help identify a vascular pedicle, and more precisely pinpoint anatomical location, detection of an abnormal parathyroid gland can be more challenging than in patients without prior surgery, and false-negative rates up to 68% have been reported.¹⁰⁵ For those that have undergone prior partial or total thyroidectomy, the usual anatomical landmarks are altered or absent. Postoperative fibrosis, shifts in vascular structures, and skin scarring all contribute to difficulty in identifying an abnormal gland.¹⁰⁵ Additionally, the high rate of failure is likely reflective of where these glands are located. Reoperative parathyroid surgery performed for persistent disease, as opposed to recurrent disease, implies a missed gland, which is often paraesophageal, mediastinal, or intrathy-mic.^{106,107} These regions are classically not well visualized by ultrasound due to shadowing by the trachea and esophagus or interference from the clavicle or other osseous structures.

Nuclear scintigraphy should be relatively unaffected by scarring. However, especially in cases where the thyroid is surgically absent, it provides little anatomical detail other than cervical versus thoracic. SPECT/CT, and especially 4D-CT, can therefore provide critical structural and anatomical detail to help guide reoperation, although the sensitivity of 4D-CT is significantly greater than that of SPECT/CT for reoperative parathyroid surgery (93% vs. 55%, $p=0.04$).¹⁰⁰ Venous sampling, though lacking acute anatomical precision, can localize to a side when all previous studies have failed to identify any site of abnormal parathyroid tissue.^{108,109} However, challenges arise owing to the aberrant venous anatomy resulting from a previous operation.

23.7 Conclusion

The role and nature of parathyroid imaging continue to expand as the operative approach to parathyroidectomy has evolved. Although localization is paramount for focal exploration, it is equally important prior to planned bilateral exploration to assess for concomitant thyroid pathology and detect any ectopic hyperfunctional parathyroid tissue. Ultrasound, especially surgeon-performed ultrasound, has become a favored approach by many, and, in some cases, the only modality performed prior to primary parathyroidectomy. Nuclear scintigraphy has become increasingly more sensitive and accurate with the addition of SPECT/CT. Newer modalities, such as 4D-CT, have demonstrated consistently high accuracy and have significant utility in the setting of reoperative parathyroid surgery. Multigland disease will continue to limit successful localization regardless of modality. Surgeons are encouraged to learn the modalities available to them and view the images of these studies prior to performing an operation. Ultimately, the imaging technique used is largely based on institutional availability, surgeon preference, and, increasingly, cost.

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24 Renal Hyperparathyroidism

Steven R. Bomeli and David J. Terris

24.1 Introduction

Secondary hyperparathyroidism (HPT) occurs when parathyroid hormone (PTH) levels rise to compensate for another disease process, most commonly vitamin D deficiency or renal failure. The PTH elevation is considered an appropriate physiological response in order to maintain normocalcemia. Tertiary HPT is the condition in which hypercalcemia develops in the setting of long-standing secondary hyperparathyroidism. It occurs due to autonomously functioning parathyroid glands that have lost their ability to respond to negative feedback. The term *tertiary HPT* also refers to HPT that persists after successful renal transplantation, wherein the PTH and calcium elevations persist despite normalization of the metabolic abnormalities inherent to renal failure. Both secondary and tertiary HPT are far less common than primary HPT. Where primary HPT is caused by a single adenoma in the majority of cases, secondary and tertiary HPT involve hyperplasia of all four parathyroid glands, at least at some point throughout the progression of the disease. Because the physiological mechanisms associated with secondary HPT related to renal failure are so specific and unique, the authors prefer the term *renal HPT*.

24.2 Pathophysiology

Renal HPT is common among patients in renal failure, with a prevalence of 90% at the time of initiation of hemodialysis.¹ Vitamin D deficiency, long-term lithium therapy, osteomalacia, rickets, and malabsorption are other causes of secondary HPT, and are exclusively medically managed.^{2,3}

In chronic kidney disease (CKD), hyperphosphatemia occurs as the glomerular filtration rate decreases, and this process, along with reduced conversion of vitamin D to its active metabolite, is thought to be the driving factor in the onset of secondary hyperparathyroidism. There are several separate mechanisms by which hyperphosphatemia results in increased PTH levels. Hyperphosphatemia acts directly on chief cells in the parathyroid glands to stimulate PTH production. Mild hypocalcemia is induced when calcium precipitates with phosphorus as the equilibrium is shifted by hyperphosphatemia. This hypocalcemia further stimulates production of PTH.² Hyperphosphatemia also causes production of a recently discovered protein known as fibroblast growth factor 23 (FGF23), which is secreted by osteocytes.⁴ This novel protein is now thought to be the most important regulator of phosphorus homeostasis. It acts on the kidney to increase phosphorus clearance, and it inhibits the 1- α -hydroxylase enzyme whose baseline production is already reduced by the underlying renal failure, thereby decreasing the active 1,25-dihydroxyvitamin D (calcitriol) levels.⁵ The resulting decreased intestinal absorption of calcium further exacerbates hypocalcemia, which increases PTH secretion. Loss of negative feedback of vitamin D on the vitamin D receptors in the parathyroid glands potentiates PTH secretion.⁶ The factors leading to secondary hyperparathyroidism from chronic renal failure are depicted in ► Fig. 24.1.

Early in renal failure, phosphorus and calcium levels usually remain normal, but PTH and FGF23 are elevated. As the glomerular filtration rate (GFR) drops below 30 mL/min (stage IV kidney disease), PTH is upregulated and decreases phosphorus reabsorption in the kidney while its actions to release calcium and phosphorus from the bone continue. The result is a situation where hyperphosphatemia causes PTH secretion, and elevated PTH levels increase phosphate release from bone, worsening the hyperphosphatemia. This pathophysiology affects all parathyroid glands and therefore results in four-gland hyperplasia, although the enlargement is not always symmetric (► Fig. 24.2).

24.3 Symptoms

Most patients with renal hyperparathyroidism are asymptomatic because patients with CKD are usually screened and treated prior to the onset of symptoms. However, symptoms may occur with advanced and long-standing renal HPT, even despite appropriate medical treatment. The high rate of bone turnover from osteoclast activation by PTH may lead to bone pain, skeletal deformities from weak bone architecture, and even pathological fractures. Neurological symptoms can include irritability, inability to focus, generalized muscle weakness, and pruritis. Calciphylaxis, also known as calcific uremic arteriopathy, occurs when arterial walls become calcified and the blood supply to tissue is compromised. Symptoms begin with painful distal extremities, which develop violaceous nodules. Radiographic imaging of the arterial supply may reveal arterial calcification (► Fig. 24.3).

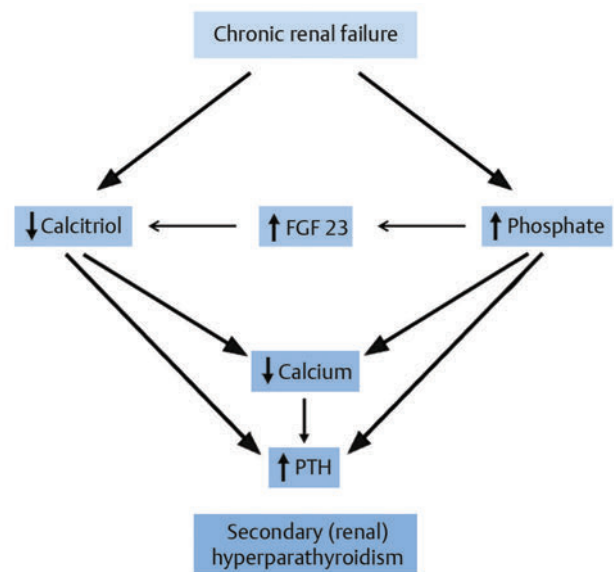


Fig. 24.1 The factors that result in secondary hyperparathyroidism as a consequence of chronic kidney disease. FGF, fibroblast growth factor; PTH, parathyroid hormone.

The progressive ischemic necrosis of skin is a cause of significant morbidity and is associated with a mortality rate as high as 80% once ulcerations develop.⁷ Its presence is, therefore, an indication for emergent parathyroidectomy. In contrast, patients with tertiary disease after successful renal transplantation usually experience the classic symptoms of primary hyperparathyroidism, consisting of bone pain, nephrolithiasis, and mental status changes (including memory loss, irritability, impaired concentration, and poor sleep).

24.4 Diagnosis

Laboratory assessment is essential in confirming the diagnosis of renal HPT. Patients usually have mild hypocalcemia or

normocalcemia, hyperphosphatemia, decreased vitamin D levels, and sometimes dramatic elevations of PTH. In contrast, patients with tertiary hyperparathyroidism typically have laboratory findings consistent with those of primary hyperparathyroidism. The calcium is usually mildly to moderately elevated, vitamin D and phosphate levels may be decreased, and PTH levels are mildly elevated. Alkaline phosphatase may be elevated, signaling high bone turnover. Depending on the duration of untreated disease, bone mineral density assessment (dual-energy X-ray absorptiometry [DEXA] scanning) may indicate osteopenia or osteoporosis. Brown tumors characteristic of osteitis fibrosa cystica are rarely seen and are indicative of severe and protracted disease.

24.5 Medical Management

The majority of patients with renal hyperparathyroidism are now managed medically. The mainstays of therapy are phosphate binders (calcium carbonate, calcium acetate, sevelamer hydrochloride, lanthanum carbonate), vitamin D analogues (ergocalciferol, cholecalciferol, calcitriol, 22-oxacalcitriol, falecalcitriol, alfacalcidol, paricalcitol, and doxercalciferol), and the calcimimetic cinacalcet HCl.⁸ Phosphate binders that do not contain calcium are increasing in popularity because there is a lower risk of hypercalcemia.⁹ Vitamin D analogues, such as cholecalciferol or ergocalciferol, carry a lower risk of hypercalcemia in patients with chronic kidney disease than calcitriol, the most active form of vitamin D.¹⁰ Cinacalcet (Sensipar, Amgen) is a calcimimetic pharmaceutical that increases the sensitivity of the calcium-sensing receptor on the surface of the chief cells of parathyroid glands, which are responsible for negative feedback. It has been shown to reduce PTH, calcium, phosphorus, and calcium-phosphorus product values in randomized, placebo-controlled trials.^{11,12,13} Population studies



Fig. 24.2 Asymmetric four-gland hyperplasia seen in renal hyperparathyroidism.



Fig. 24.3 Clinical and histological presentation of calciphylaxis. (a) Nonhealing ulceration on the left lower leg with a necrotic border. (b) Radiograph of the left lower leg with diffuse calcifications and stenosis of the arteries (arrows). (c) Histological examination of skin biopsy from the ulceration: calcific sclerosis and microthrombi within a small artery (hematoxylin-eosin stain, magnification $\times 200$). (d) Calcium deposition in an artery (von Kossa stain, magnification $\times 200$); calcium deposits are highlighted as dark granules (arrow). (From Zhou Q, Neubauer J, Kern JS, Grotz W, Walz G, Huber TB, Calciphylaxis. *Lancet* 2014;383[9922]:1067. Reproduced with permission.)

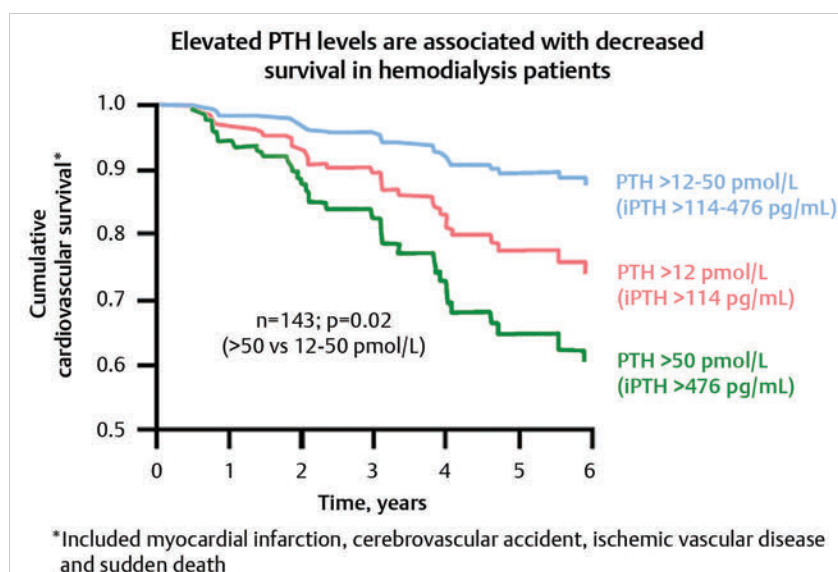


Fig. 24.4 Increased parathyroid hormone (PTH) levels correlate with increased cardiovascular mortality in hemodialysis patients. iPTH, intact parathyroid hormone. (From Marco et al.²⁰ Reproduced with permission.)

of dialysis patients have indicated a decrease in the rate of parathyroidectomy after January 2006, which corresponds to the availability of cinacalcet.¹⁴ Although the advent of cinacalcet has represented a major breakthrough in the medical management of renal HPT, its use is occasionally limited by gastrointestinal side effects and compliance, owing to its oral route of administration.^{12,15} Velcalctide (AMG 416, Amgen) is a novel intravenous calcimimetic drug that has been evaluated for treatment of renal hyperparathyroidism. In a phase 1 trial, it decreased serum PTH and FGF23 levels for a duration of up to 24 hours.¹⁶ Although it appears safe and well tolerated, more studies are necessary before it can be widely recommended.

The need for medical intervention has been supported by observational studies of dialysis patients, which have shown that elevated phosphorus, calcium, PTH, alkaline phosphatase, and FGF23 levels are associated with increased mortality and a higher frequency of cardiovascular events.^{17,18} Furthermore, a high calcium–phosphorus product is associated with the potential for soft tissue and vascular calcifications, with associated increases in morbidity and mortality (► Fig. 24.4).^{19,20} For these reasons, laboratory guidelines for the treatment of HPT in patients with renal failure have been developed. In 2003, the Kidney Foundation of the United States suggested maintaining a calcium level of between 8.4 and 9.5 mg/dL, a phosphorus level between 3.5 and 5.5 mg/dL, a calcium–phosphorus product < 55 mg²/dL,² and a PTH level between 150 and 300 pg/mL.²¹ The most recent Kidney Disease Improving Global Outcome (KDIGO) international guidelines of 2009 suggests that phosphorus levels should be kept just above the normal laboratory range, whereas the PTH level should be maintained between two and nine times the upper limit of normal.²²

Although parathyroidectomy is the treatment of choice for tertiary HPT, medical management with cinacalcet has been described. In several small series, it has been shown to decrease PTH and normalize calcium without compromising renal allograft function.^{23,24} Treatment must be continued indefinitely, however, and there is little justification to withhold parathyroidectomy as the definitive management except in rare circumstances.²⁵

Percutaneous ethanol injection under ultrasound guidance has been described as a nonsurgical alternative to parathyroidectomy in patients with tertiary hyperparathyroidism.²⁶ This approach has not been embraced in the United States, principally because of the risk to the recurrent laryngeal nerve and the inherent scarring that is created, but it has been used in other countries for patients who are not surgical candidates.

24.6 Surgical Indications

Renal transplantation is the surgical treatment of choice for renal hyperparathyroidism. Calcium, PTH, vitamin D, and phosphorus levels generally normalize within 1 year after renal transplantation,²⁷ and patients whose values do not normalize in a year by definition have tertiary HPT. Parathyroidectomy becomes necessary when transplantation is not feasible or when medical management fails. Approximately 1 to 2% of patients with renal hyperparathyroidism will require parathyroidectomy each year.²⁸ Historically, symptoms such as pruritis and bone pain, and findings such as vascular calcifications and calciphylaxis, drove the decision for surgery. Currently, most patients are referred for surgery when laboratory values cannot be maintained within the recommended limits with medical management alone. Although precise clinical indications for surgery vary between experts and among patients, in the hands of expert surgeons significant decreases in the levels of PTH, calcium, and phosphorus may be anticipated with parathyroidectomy.²² For surgical candidates, an objective increase in quality of life through symptom control has been demonstrated for patients with both renal and tertiary HPT.²⁹

The severity of renal and tertiary hyperparathyroidism has been correlated with ultrasonographic characteristics of parathyroid glands. Anatomical features and vascular supply can be used to predict therapeutic response to medical management for renal HPT.^{30,31} Enlarged and nodular parathyroid glands appear to be resistant to cinacalcet.³² Despite the association between these ultrasound findings and failure of medical management, there is not sufficient evidence for ultrasound findings to be considered a surgical indication at the present time.

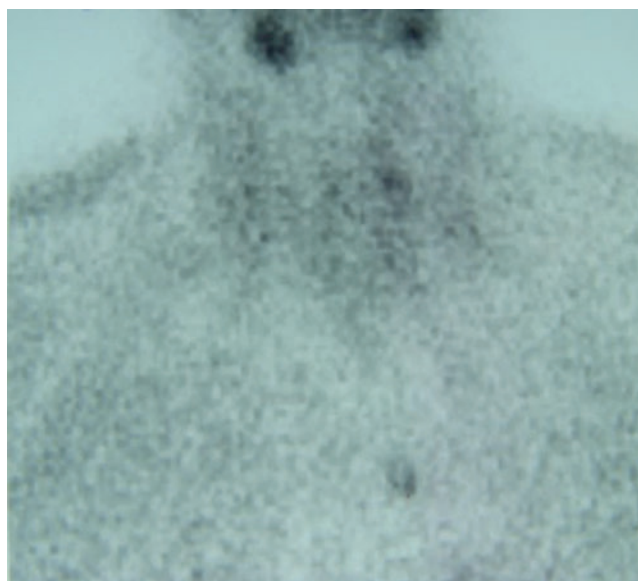


Fig. 24.5 Sestamibi scan indicating a mediastinal parathyroid gland in a patient with persistent hyperparathyroidism after total parathyroidectomy (2 hours after sestamibi injection).

Ectopic vascular calcifications and calciphylaxis top the list of surgical indications because the necrotic skin is not capable of healing due to lack of perfusion, and it can lead to limb loss, sepsis, and death. Fortunately it is rare, occurring in only 4% of patients having surgery.³³ Patients with calciphylaxis due to renal HPT who undergo subtotal parathyroidectomy have improved wound healing and increased survival compared with those managed medically.³⁴ Surgery has also been shown to improve fatigue, musculoskeletal pain, bone density, and rates of limb salvage.³⁵

Parathyroidectomy is the treatment of choice for tertiary hyperparathyroidism. The likelihood of persistent autonomous parathyroid function after renal transplantation is thought to be related to the duration of dialysis prior to surgery.³⁶ Though there are no absolute guidelines for when to consider surgery, hypercalciuria, the associated renal tubular injury, and the increased risk of nephrolithiasis are all particularly threatening for a transplanted kidney.³⁷ Generally patients with persistent hypercalcemia 1 year after transplant are considered candidates for parathyroidectomy. The decision for surgery should be made cautiously, however, because some studies suggest that transplant graft function can be compromised after parathyroidectomy.^{38,39} Others have found that, although the glomerular filtration rate of transplanted kidneys was decreased after parathyroidectomy for tertiary HPT, the long-term graft survival was not affected by the surgery.⁴⁰

24.7 Imaging Studies

Although renal HPT affects all four parathyroid glands, preoperative localization studies have proven to be of considerable value in planning the initial surgical approach. The sensitivities of technetium-99m (Tc-99m) sestamibi scanning for the localization of parathyroid glands in renal HPT are as high as 70%, and are especially helpful in the setting of ectopic glands, which are

known to occur in as many as 40% of patients with renal HPT (► Fig. 24.5).⁴¹ Although a bilateral neck exploration with identification of all four parathyroid glands is always performed, the additional information provided by preoperative imaging studies is particularly beneficial for reoperative parathyroidectomy. For persistent or recurrent hyperparathyroidism after total parathyroidectomy, the sensitivity of Tc-99m has been reported to be as high as 100%.⁴²

24.8 Surgical Approaches

There are three principal options for surgery in patients with renal hyperparathyroidism for whom parathyroidectomy is undertaken. The first option is a subtotal parathyroidectomy, where all four glands are identified, three and a portion of the fourth are resected, and the remnant is preserved with its blood supply intact. The location of the remnant parathyroid tissue is marked with a hemoclip or a permanent suture in case reoperative surgery is necessary. Although the most normal-appearing parathyroid is preferred for selection as the remnant, this consideration is trumped by location. Reoperative surgery is far easier when the remnant is in an inferior location safely removed from the recurrent laryngeal nerve.

Another important principle is the sequence of the operation. Because the vascular integrity of the remnant may be lost during its subtotal resection, it is best to first identify all of the parathyroid glands, and then prepare the remnant. Only when it is apparent that the remnant is healthy and will survive should the remaining three glands be resected (as they can easily serve as a remnant if the initially chosen gland appears compromised after preparation). Finally, although historically this procedure has also been called a $3\frac{1}{2}$ gland parathyroidectomy (or even a $3\frac{3}{4}$ parathyroidectomy), the portion of the gland that is retained as a remnant may vary considerably depending on the size of the parathyroid glands. Instead, the surgeon should endeavor to preserve approximately 30 to 60 mg of parathyroid tissue (approximating the size of a single normal parathyroid gland).

The second surgical option for patients with renal HPT is a total parathyroidectomy with reimplantation of a portion of the most normal-appearing (nonnodular) region of one of the four parathyroid glands. This autotransplantation involves mincing approximately 30 to 60 mg of parathyroid tissue (to increase the surface area) and placing it into a receptive pocket. Although classically the recipient bed chosen was the nondominant brachioradialis muscle, because of the inconvenience of a second site of surgery, and more importantly the substantial potential morbidity associated with its removal, this practice has been largely abandoned.⁴³ We prefer to reimplant the parathyroid tissue into a soft tissue pocket in the presternal region separate from the cervical dissection, but convenient in location (► Fig. 24.6).

The morbidity of resecting this (should it be necessary in the future) is nearly zero.⁴⁴ When autotransplantation is required during thyroid surgery, we prefer using the ipsilateral sternohyoid muscle, and marking the pocket with a 3-0 Prolene suture (Ethicon, Inc.). An alternative to surgical implantation is the subcutaneous injection of resected parathyroid. The tissue is minced, suspended in saline, and then injected into muscle. This approach appears to shorten the median time of



Fig. 24.6 Location for presternal autotransplantation of minced parathyroid gland below the cervical incision after total parathyroidectomy (marked in purple).

parathyroid recovery from 9 months to 2 months.⁴⁵ Reoperation can generally be performed under local anesthesia so long as the recurrence is not due to a gland in the neck that was missed during the initial operation. The choice between a subtotal parathyroidectomy versus total parathyroidectomy with autotransplantation is largely driven by the patient's eligibility for a renal transplant. We prefer to leave a remnant when there is a possibility for transplantation in the future.

The final surgical option for patients with renal HPT is represented by total parathyroidectomy without autotransplantation. Although this may seem extreme, the risk of recurrent disease is close to zero, and the anticipated hypocalcemia may be managed by a combination of oral calcium supplementation and a calcium-rich dialysate bath. When this approach is pursued, communication with the managing nephrologist is particularly important.

A routine transcervical thymectomy to remove potential ectopic parathyroid tissue and parathyroid rests is controversial.³⁷ The authors incorporate this if an inferior gland is not identified or if the intraoperative PTH degradation suggests a supernumerary gland.

Patients with posttransplant tertiary HPT are managed much differently than those with dialysis-dependent renal failure and renal HPT. Their condition is functionally quite similar to primary HPT. Although traditionally a four-gland exploration was pursued in these patients, it has been recognized that the residual parathyroid hyperplasia is sometimes asymmetric. Some of the glands are clearly nonautonomous and dormant. For this reason, many units (including that of the authors) approach these patients with the prospect of doing less than a four-gland exploration, and guide the approach with both preoperative imaging to localize the hyperfunctional gland(s), and intraoperative PTH testing to ensure removal of all hyperfunctional tissue.^{46,47} Through this approach, many patients can avoid the additional risk of temporary and permanent hypoparathyroidism posed by bilateral exploration.

24.9 Intraoperative Parathyroid Hormone

The intraoperative PTH assay has been used in parathyroidectomy for renal HPT. However, the interpretation of the values is complicated because this population has decreased renal function, and, therefore, delayed renal clearance of PTH. The traditional criteria of a >50% drop in PTH at 10 minutes postoperatively has been found by some to be a useful tool when performing subtotal parathyroidectomy in patients with renal HPT.⁴⁸ The rationale is that, although the PTH nadir may not be reached until 30 minutes postexcision in patients with renal failure, the 10-minute value is highly predictive of the 30-minute value.⁴⁹ Ohe et al have suggested that an 80% drop in PTH at 20 minutes predicts cure when performing total parathyroidectomy with autotransplantation, whereas a decay of <70% is indicative of a missed or supernumerary gland.⁵⁰ Other authors have found the same criteria somewhat unreliable in their predictive value of cure, and suggest that these values can be used only as a guide when performing total parathyroidectomy.⁵¹ The use of this assay has not been as well defined as it has been for primary HPT, and the criteria for predicting a curative operation for both renal HPT and for tertiary disease continue to evolve.

24.10 Cryopreservation

Cryopreservation was originally described by Wells in 1974 and involves preserving resected parathyroid tissue at -80°C .⁵² It has been proposed (in the preintraoperative PTH era) as a strategy to prevent permanent hypoparathyroidism. However, the need for parathyroid reimplantation is very low at 1% in experienced hands, the viability of the transplanted tissue is no better than 50%, and it falls to nearly zero after 2 years of cryopreservation.⁵³ With cost containment being an important consideration for health care in the United States, most surgeons have abandoned the use of cryopreservation due to its low cost-efficiency.^{54,55} More stringent criteria are needed to determine if there are patients who would benefit from having parathyroid tissue cryopreserved at the time of surgery.

24.11 Renal Protocol

Patients undergoing parathyroidectomy for renal hyperparathyroidism are treated in a multidisciplinary fashion because of their potential for profound hypocalcemia in the setting of complicated medical management, and occasional large fluid shifts. Nephrology, endocrinology, endocrine surgery, transplant surgery, and social work coordinate the perioperative management of these patients. One week preoperatively, patients are started on 2 to 3 g of oral calcium per day and 2 μg of calcitriol intravenously during each session of dialysis. A subclavian central line is placed by a transplant surgeon after the administration of general anesthesia but before surgery commences. This facilitates phlebotomy and allows administration of intravenous calcium. Postoperatively, calcium and electrolyte abnormalities are managed by the nephrology and endocrinology services. This standardized treatment protocol and enhanced

communication between services allows the management of these complex patients to proceed in a streamlined fashion.

24.12 Conclusion

Renal HPT is a disease of all four parathyroid glands that occurs commonly in dialysis-dependent CKD patients. It is treated with phosphate binders, vitamin D analogues, and calcimimetic agents until PTH and electrolyte abnormalities are within the recommended ranges or renal transplantation occurs. When parathyroidectomy is indicated, it should be performed in high-volume centers by experienced surgeons because of the complex perioperative electrolyte abnormalities, which require a multidisciplinary approach for management. A bilateral neck exploration is performed in all instances, and a subtotal parathyroidectomy, a total parathyroidectomy with autotransplantation, or a total parathyroidectomy without autotransplantation is performed.

Tertiary HPT is diagnosed by elevated calcium and PTH levels, which persist or develop after successful renal transplantation. Surgical management of tertiary disease is similar to that of primary hyperparathyroidism in which only hyperfunctioning parathyroid tissue is removed, and the amount of tissue removed is determined by preoperative localizing studies and intraoperative PTH levels.

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Part 5

Surgical Management of Parathyroid Diseases

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25 Conventional Parathyroidectomy

Jennifer Leonard and Geoffrey B. Thompson

25.1 Introduction

Since the first description of the parathyroid glands by Sir Richard Owen in 1852, great strides have been made in the understanding of diseases of the parathyroid glands and their surgical treatment. The first parathyroidectomy was performed in 1925 by the Viennese surgeon Felix Mandl. The Nobel Prize-winning work of Berson and Yalow in 1963 fundamentally changed the way many hormonally active tumors are diagnosed. With the subsequent development of a highly accurate whole-molecule immunoassay to measure parathyroid hormone (PTH) levels in serum, patients can now be screened with serum calcium and PTH testing instead of waiting for the disease to become advanced and clinically apparent. In addition, it simplifies testing by eliminating the need to rule out all of the other possible causes of hypercalcemia. Today, most patients presenting for parathyroidectomy are minimally symptomatic or asymptomatic without subjective complaints; but few truly have no sequelae.

25.2 Epidemiology and Causes

Primary hyperparathyroidism (HPT) is a common disease affecting approximately 0.7% of the population overall and up to 2% of postmenopausal women. The average age at diagnosis is 55, and the majority of individuals present between the ages of 40 and 70 years.^{1,2} Primary HPT is most commonly sporadic and caused by a single adenoma; however, sporadic multigland disease (MGD) is routinely encountered in up to 15% of patients, with double adenomas and carcinomas occurring less frequently. In a recent review of 828 patients who underwent bilateral neck exploration for parathyroidectomy, 15% were found to have double adenomas and 13% were found to have MGD. Double adenomas most often occur in the superior glands, and preoperative imaging correctly identified them in only 25% of cases.³ Multigland hyperplasia is most commonly sporadic but is associated with a genetic syndrome in 5% of cases. These syndromes include multiple endocrine neoplasia type 1 (MEN1), multiple endocrine neoplasia type 2A (MEN2A), hyperparathyroid-jaw tumor syndrome, and familial isolated HPT.⁴ Acquired predisposing factors for primary HPT include exposure to low-dose ionizing radiation and certain drugs, such as lithium.⁵ Patients with familial hypocalciuric hypercalcemia (FHH) and those taking hydrochlorothiazide may present with similar laboratory findings as those seen in primary HPT without the systemic effects.⁶ These patients will, however, have low urinary calcium excretion.

Secondary HPT and tertiary HPT commonly arise in the setting of renal failure and vitamin D deficiency states and are among the most challenging complications to manage in this patient population. Secondary HPT arises due to a 1,25-dihydroxyvitamin D deficiency and hyperphosphatemia. These factors result in reduced ionized calcium, which directly increases PTH concentrations. Over time this process may result in decreased expression of calcium-sensing receptors in the

parathyroid glands and resultant parathyroid hyperplasia.⁷ There are a number of medical management options available to these patients, and surgery is usually reserved for severe cases refractory to other treatments.⁸ Given that some of the medications used to treat this condition are potentially nephrotoxic and are also expensive, the ideal management strategy for this complex disorder is not well established in patients with renal failure not yet on dialysis. Parathyroidectomy has been shown to be efficacious and cost effective after approximately 7 to 8 months of medical treatment.⁹

Tertiary HPT is the autonomous secretion of PTH that is no longer responsive to plasma calcium concentration and which persists after the correction of end-stage renal failure, usually by renal transplant. Tertiary HPT is likely the result of an increase in parathyroid mass rather than a change in the set point of PTH release, as seen in FHH, or a change in mass and set point that is seen in primary HPT.¹⁰

25.3 Diagnosis

The diagnosis of HPT is most commonly suspected in relatively asymptomatic patients with an elevated serum calcium concentration. However, a minority of patients will present with symptoms of the disease, including renal stones, bone pain, fatigue, weakness, pancreatitis, hypercalcemic crisis, or neurocognitive symptoms. There may be a family history of hyperparathyroidism. All patient evaluations should begin with a careful history and physical examination. The history should elicit both overt and subtle symptoms of HPT as well as a review of previous head and neck procedures and any history of prior radiation exposure. Current and prior medications should be reviewed for evidence of exposure to drugs known to contribute to parathyroid or calcium alterations. It is also important to take a careful family history to elucidate any possibility of an inherited syndrome. Any patients who present with voice changes or those undergoing reoperative surgery should undergo a formal assessment of their vocal fold mobility.

A total calcium level should then be repeated to confirm the measurement and any historical laboratory values reviewed. Long-standing asymptomatic hypercalcemia raises the possibility of familial hypocalciuric hypercalcemia. To confirm the diagnosis of HPT, intact PTH hormone levels should be measured at the same time as the serum calcium. Eighty to 90% of patients with primary HPT will have elevated serum PTH concentrations.¹¹ A minority of patients will present with inappropriately normal PTH levels given their degree of hypercalcemia, and these patients are also considered to have HPT. A 24-hour urine calcium and screening for calcium-sensing receptor mutations should be obtained to rule out FHH. Eucalcemic hyperparathyroidism can also occur.

During the diagnostic evaluation, it is also important to exclude other causes of hypercalcemia, including the use of thiazide diuretics or lithium. Thiazide diuretics increase calcium reabsorption in the distal renal tubules and can result in mild hypercalcemia. Patients with mild HPT may be prescribed

thiazide diuretics for hypertension, with an even further increase in their serum calcium. Some of these patients will have true HPT that has been unmasked by the thiazide diuretics but a large proportion will not. Therefore, in asymptomatic patients on thiazide diuretics with biochemical HPT it is recommended to stop the medication for 3 months and then repeat testing before any surgical therapy is undertaken.

Lithium is another drug associated with HPT. It interferes with calcium metabolism by decreasing the sensitivity of the parathyroid glands to calcium and reducing urinary calcium excretion. A minority of patients on this drug develop elevated PTH with increased serum calcium and hypocalciuria. Treatment of this is discontinuation of lithium if the psychiatric condition of the patient permits. After cessation of the drug, serum calcium will likely normalize if the duration of therapy has been short but may persist if the patient has been taking the medication for more than 10 years, necessitating parathyroidectomy.

Other conditions that are associated with hypercalcemia include vitamin D excess, sarcoidosis, malignancy, prolonged immobilization, or FHH. In all of these conditions except FHH, the PTH values will be very low. FHH is a hereditary disorder caused by an inactivating mutation in the calcium-sensing receptor in the parathyroid glands and renal tubules.¹² Up to 20% of these patients will present with asymptomatic hypercalcemia and an elevated PTH, making it difficult to distinguish from primary HPT. Patients with FHH, however, will have very low levels of urinary calcium excretion and a low calcium/creatinine clearance ratio. The distinction between these two diseases is important because FHH is a benign inherited condition, and parathyroidectomy will not cure these patients. This disorder is not associated with the sequelae seen in primary HPT, and there is often a family history of failed neck explorations and lifelong hypercalcemia.

25.4 Indications for Surgical Management

Surgical therapy offers the only definitive treatment for patients with HPT. Emerging data suggest that even patients with subclinical HPT and mild elevation in PTH and calcium levels can benefit from treatment.¹³ Surgery for HPT has grown safer and more common over time. From 1999 to 2008, the annual case volume has risen 177%. With this rise in case volume, complication rates have declined from 5.2 to 3.8%, with the highest-volume centers reporting the lowest complication rates.¹⁴ Indications for surgical management of HPT fall under three categories, symptomatic disease, asymptomatic disease, and HPT associated with renal disease.

Patients presenting with bone disease, kidney stones, muscle weakness, or a serum calcium > 12 mg/dL are considered symptomatic and should undergo operative management. The decision to operate on asymptomatic or minimally symptomatic patients balances the risk of developing long-term complications with the risks of surgery. Rao and colleagues conducted a randomized prospective clinical trial evaluating surgery versus expectant management for patients with asymptomatic HPT. In this study, 53 patients were randomly assigned to either parathyroidectomy or routine follow-up. Following parathyroidectomy, there was an increase in bone mineral density

as measured at the femoral neck and a modest increase in quality of life scores.¹⁵ These results suggested that even patients with mild asymptomatic HPT could benefit from surgical therapy. The current guidelines for operative management of asymptomatic disease were elucidated at the fourth international workshop on the management of primary HPT in 2014 and are generally accepted. These include a serum calcium > 1 mg/dL above the upper limit of normal, creatinine clearance < 60 in the absence of another cause, patients < 50 years of age presenting with primary HPT, or bone mineral density that is reduced by > 2.5 standard deviations (by T-score) measured at the at lumbar spine, total hip, femoral neck, or distal 1/3 radius.¹⁶

25.5 Indications for Bilateral Neck Exploration (Conventional Parathyroidectomy)

Until the last decade, bilateral neck exploration (BNE) was the primary procedure performed for HPT. With improved intraoperative PTH monitoring and preoperative localization studies, minimally invasive parathyroidectomy (MIP) has recently become the more common procedure.¹⁷ There are, however, multiple clinical circumstances for which BNE is the most appropriate procedure because it has over time been proven to be safe and effective. The following are some indications for conventional parathyroidectomy:

- Negative or discordant preoperative imaging
- MIP with failure of decrease in intraoperative PTH
- Concomitant thyroid pathology
- MEN1
- MEN2A
- Familial isolated HPT
- History of neck irradiation, including radioiodine treatment
- History of lithium use
- Certain reoperative settings
- Secondary and tertiary HPT

In our experience at Mayo Clinic, the cure rate for patients undergoing standard BNE for nonfamilial, nonmalignant primary operations is 99.5%, with an operative mortality of 0.3%. Complication rates were low and included persistent vocal cord paralysis (0.8%) and permanent hypocalcemia (0.3%).¹⁸

MIP relies on accurate preoperative localization studies to direct and limit surgical exploration (► Fig. 25.1, ► Fig. 25.2, ► Fig. 25.3, ► Fig. 25.4, and ► Fig. 25.5). Preoperative localization studies using sestamibi scintigraphy and/or ultrasound are variably successful in identifying a single adenoma in 61 to 93% of cases.¹⁹ In a recent prospective analysis of factors contributing to negative preoperative localization, ultrasound was shown to be superior to sestamibi for the detection of abnormal glands. On multivariate analysis, body mass index, gland size, and gland volume were statistically significant independent factors influencing the predictive ability of both ultrasound and sestamibi scanning.²⁰ When preoperative imaging is negative or discordant, BNE is the preferred procedure.

There is also some argument that, even with concordant preoperative imaging studies, a significant proportion of patients with MGD could be missed. Siperstein et al analyzed the success

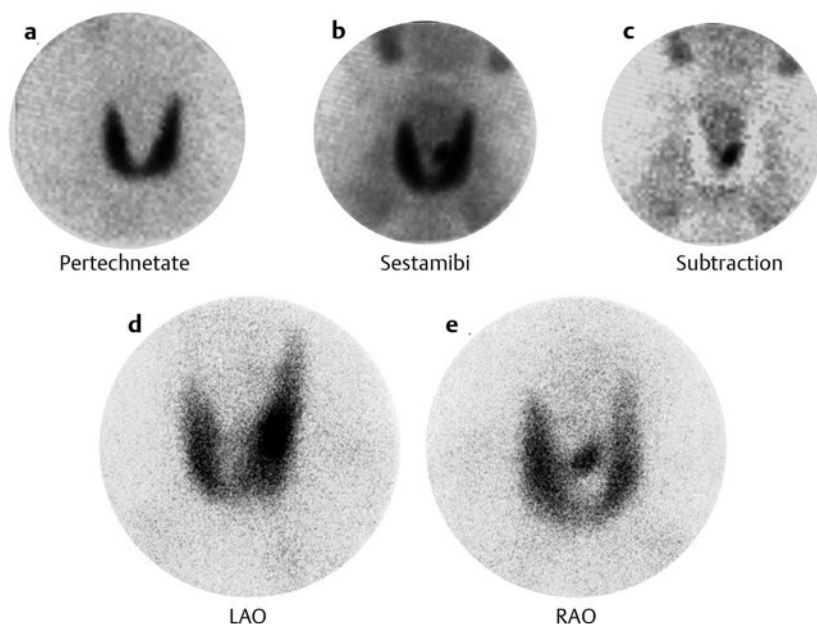


Fig. 25.1 (a-e) Sestamibi subtraction scan demonstrating a left inferior parathyroid adenoma. LAO, left anterior oblique; RAO, right anterior oblique.

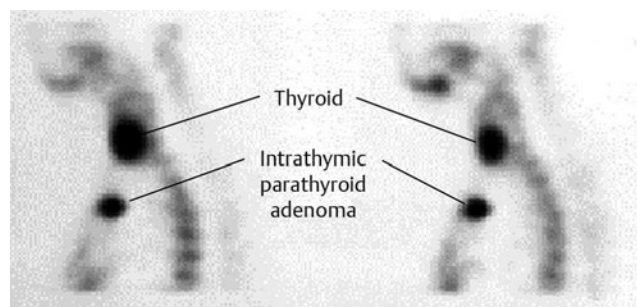


Fig. 25.2 Sestamibi scan (lateral view) demonstrating an intrathyroidic parathyroid adenoma.

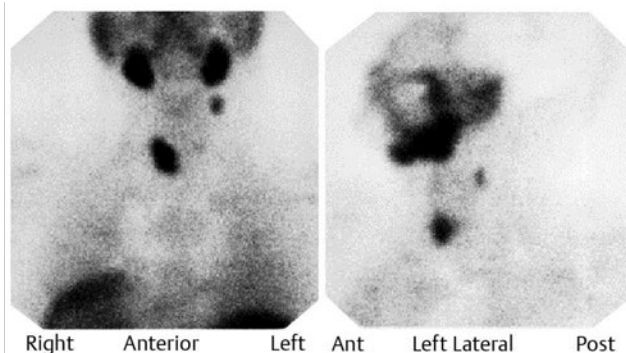


Fig. 25.3 Sestamibi scan demonstrating an undescended (inferior) parathyroid adenoma overlying the carotid bifurcation.

of limited exploration using sestamibi, ultrasound, and intraoperative PTH monitoring.²⁰ Over a 9-year period, 1,158 patients underwent MIP followed by BNE to identify additional parathyroid pathology. The authors showed that, even with concordant preoperative imaging and intraoperative PTH monitoring, MIP failed to identify MGD in up to 20% of cases.²⁰ Other data show that in 50% of patients with recurrent HPT following initial surgical treatment the recurrence is due to the presence of MGD.²¹ These data demonstrate that surgeons must be proficient in both MIP and BNE to adequately treat all patients with HPT.

Bilateral neck exploration is accepted as the procedure of choice in cases of suspected or confirmed familial HPT. Often these patients will require subtotal parathyroidectomy or total parathyroidectomy with autotransplantation along with transcervical thymectomy. Because patients with inherited HPT are susceptible to recurrent disease and other pathologies, the goals of parathyroidectomy are to achieve and maintain normocalcemia for the longest time possible while avoiding potential complications associated with surgical therapy and facilitating future surgery for recurrent disease.

MEN1 is an autosomal-dominant disorder caused by mutations in the *MEN1* gene. Individuals with MEN1 are at risk for

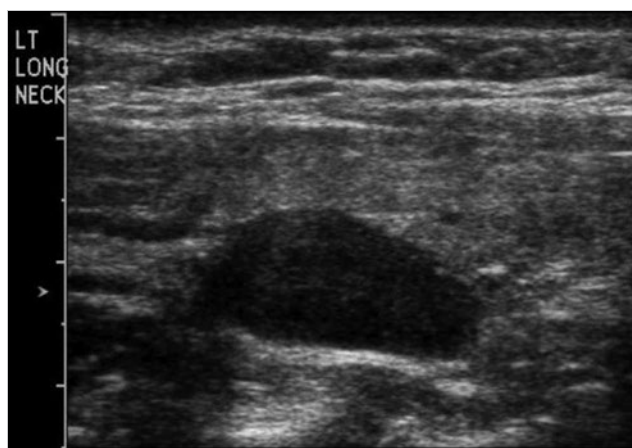


Fig. 25.4 Neck ultrasound demonstrating a classic hypoechoic bean-shaped parathyroid adenoma.

anterior pituitary tumors, pancreatic neuroendocrine tumors, foregut carcinoid tumors, and a variety of skin lesions.²² Virtually all patients with this disorder develop primary HPT by the third to fifth decade. All parathyroid tissue in these individuals is abnormal, and the risk of recurrent disease with any parathyroid tissue left in situ is high. However, total parathyroidectomy with autotransplantation can be complicated by graft failure and permanent hypocalcemia in up to 33% of patients.^{23,24,25}



Fig. 25.5 Four-dimensional computed tomographic scan demonstrating a left paraesophageal parathyroid adenoma (arrow).

Given the rarity of this condition, with approximately 1:30,000 individuals being affected, there are no large studies to evaluate the best operative approach. We analyzed our experience with 106 patients who underwent surgery for MEN1. MGD was identified in 90% of patients and primary exploration resulted in surgical cure in 94%. After 10-year follow-up, 16% had recurrence of hypercalcemia after primary exploration and 30% after reoperative procedures. From this experience we concluded that all patients with MEN1 should undergo four-gland exploration with subtotal resection to ensure initial cure while facilitating possible reoperation. Due to the high likelihood of supernumerary thymic parathyroid glands in this population we also recommend transcervical thymectomy at initial operation.²⁶

MEN2A is an autosomal-dominant condition caused by mutations in the *RET* oncogene and is characterized by the development of medullary thyroid cancer, pheochromocytoma, and HPT. The incidence of HPT in this patient population is significantly lower than in MEN1, occurring in 19 to 34% of patients.²⁷ Compared with MEN1, HPT associated with MEN2A is milder and less symptomatic, with a majority of patients possessing a single adenoma and a small minority with MGD. In our analysis of parathyroidectomy for patients with MEN2A we found that, whether treated by total, subtotal, or more limited resections, all patients were cured and none had recurrence after a median of 5.8 years of follow-up. Thus, in this patient population, we do not recommend routine subtotal resection because the HPT is readily cured and the recurrence is rare when addressing visibly enlarged glands alone.²⁶

25.6 Operative Technique

The patient is placed in the supine position with both arms loosely tucked. The neck is slightly hyperextended in the sniffing position (► Fig. 25.6). We routinely use an intraoperative nerve monitor and intraoperative PTH monitoring. Because identification of the parathyroid glands relies on discriminating subtle differences in color and texture, meticulous hemostasis

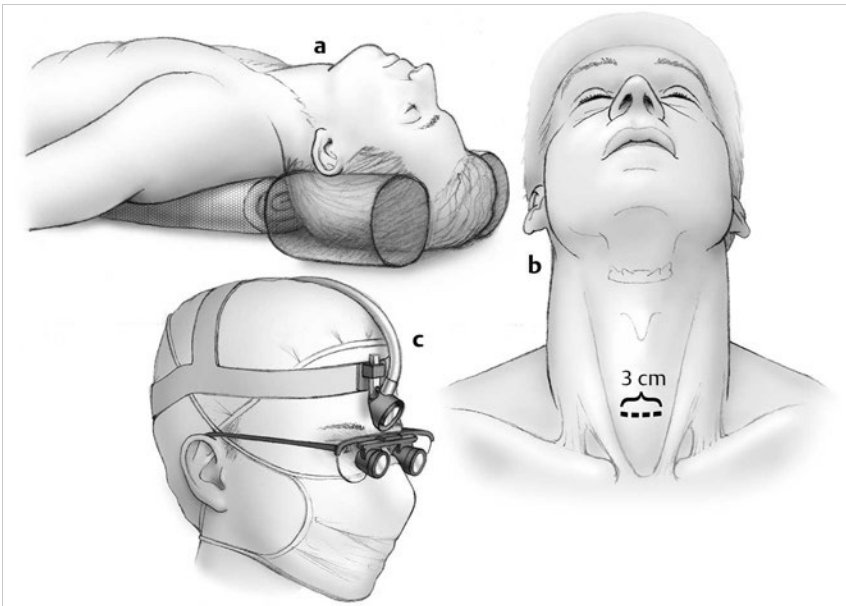


Fig. 25.6 Positioning (a) and planned incision (b) for bilateral neck exploration. (c) Dissection is aided with loupe magnification and appropriate illumination.

is necessary during exploration. It is nearly impossible to accurately identify the parathyroid glands in a bloody field. We begin with a Kocher incision approximately two fingerbreadths above the sternal notch. The length of the incision is determined by the patient's body habitus. The subcutaneous tissues

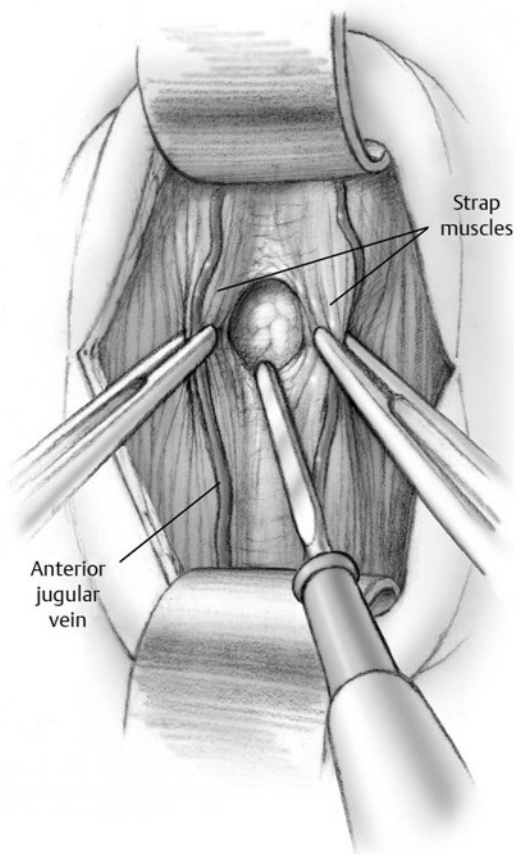


Fig. 25.7 Strap muscles divided along median raphe.

are dissected with electrocautery through the platysma muscle. Subplatysmal flaps are then raised carefully, remaining superficial to the anterior jugular veins. The strap muscles are divided along the median raphe (► Fig. 25.7). This is typically an avascular plane, but care must be taken to ligate small vessels crossing between the anterior jugular veins. It is usually possible to retract the strap muscles laterally at this point, but in difficult cases they may be divided to improve access. With retraction of the strap muscles, the thyroid gland will be exposed. Application of gentle pressure will deliver the gland medially, exposing the middle thyroid vein. This vein should be divided to facilitate additional mobilization of the thyroid gland (► Fig. 25.8). After medial mobilization of the thyroid the recurrent laryngeal nerve should be identified and carefully preserved (► Fig. 25.9).

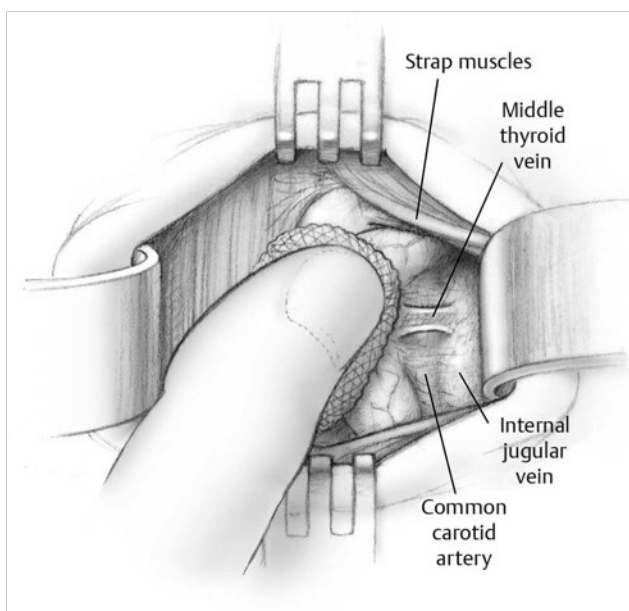


Fig. 25.8 Exposure of the middle thyroid vein.

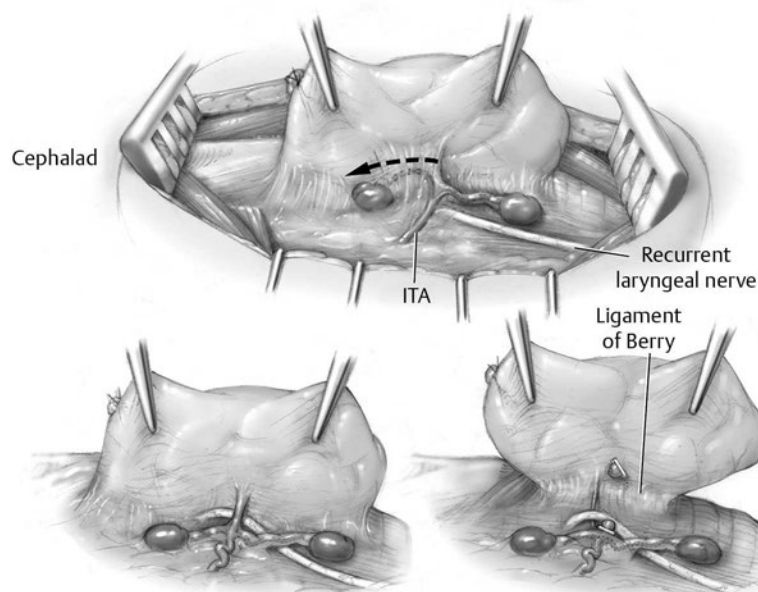


Fig. 25.9 Exposure of the recurrent laryngeal nerve with parathyroid glands in their classic anatomical position. The inferior parathyroid gland is ventral to the plane of the recurrent laryngeal nerve, whereas the superior parathyroid gland is dorsal. ITA, inferior thyroid artery.

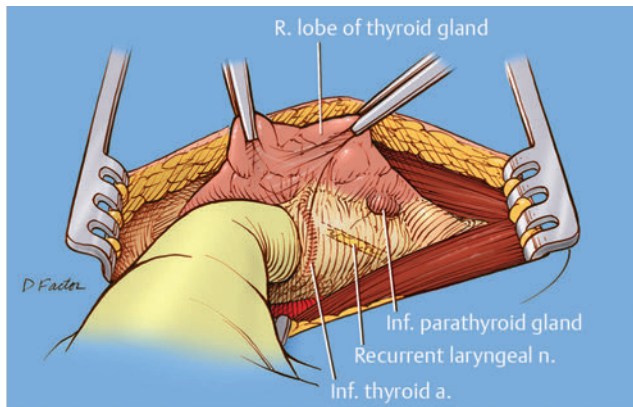


Fig. 25.10 Inferior parathyroid gland anterior to the plane of the recurrent laryngeal nerve.

The recurrent laryngeal nerve classically is identified near the tracheoesophageal groove within 3 mm of the ligament of Berry and rarely may be located within the ligament. Similar exposure is obtained on the contralateral side along with demonstration of the prevertebral fascia, carotid artery, and esophagus.

At this point, all four parathyroid glands are identified. The superior thyroid glands originate from the fourth branchial pouch and migrate caudally with the thyroid. They are embryologically and anatomically related to the tubercle of Zuckerkandl and usually found on the posterior aspect of the upper two-thirds of the thyroid gland, approximately 1 cm superior to the intersection of the recurrent laryngeal nerve and the inferior thyroid artery. It is often necessary to fully mobilize the thyroid to expose the superior parathyroid glands. If the thyroid is not fully mobilized the glands can be missed because their migration can take them into the tracheoesophageal groove, retroesophageal area, or posterior mediastinum. The inferior glands arise from the third branchial pouch and migrate caudally with the thymus. They are usually found anterior or posterolaterally to the lower pole of the thyroid, although ectopic glands may be found anywhere along their path of descent from the proximal neck (undescended at the carotid bifurcation) to the mediastinum. The inferior glands are located more ventrally than the superior glands in the plane anterior to the recurrent laryngeal nerve (► Fig. 25.10).

All four glands should be exposed and inspected before any resection is completed. Multiple studies have shown that the most common location for a missing parathyroid adenoma found on reoperation is in the normal anatomical location.^{28,29} Other potential sites for missing adenomas include intrathyroidic, retroesophageal, carotid sheath, or mediastinal locations.

If MGD is suspected based on preoperative imaging or the patient has confirmed hereditary HPT, a subtotal parathyroidectomy with or without autotransplantation may be required. Typically the smallest gland is left in situ. If this gland is found to be more than twice the normal size, partial resection may be required. The decision to undertake subtotal resection should be made on the basis of patient disease characteristics and visual inspection of all glands. Although some studies show good sensitivity and specificity for a >50% decrease in PTH levels, the role of intraoperative PTH values in the setting of MGD has

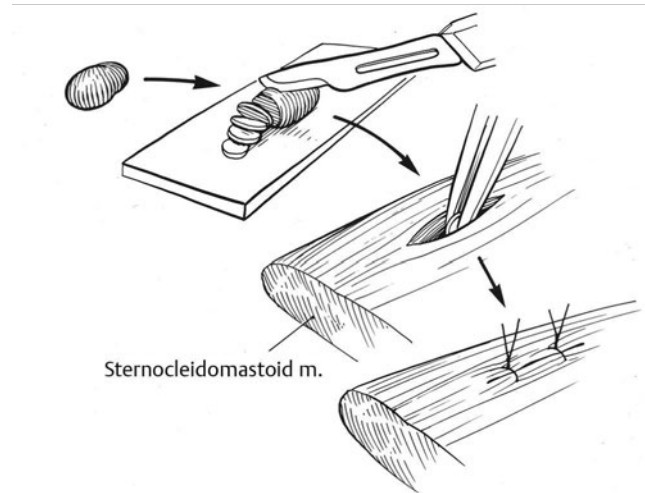


Fig. 25.11 Autotransplantation of parathyroid tissue into the forearm brachioradialis muscle following total parathyroidectomy.

been controversial.³⁰ These patients have altered kinetics of PTH release and degradation as well as asymmetric proliferation and secretory status.³¹ Most of the available studies are limited by small size, short follow-up, heterogeneous patient populations, and different surgical techniques. We routinely use intraoperative PTH monitoring in patients with MGD to limit the extent of resection and to prevent operative failure, especially in patients with nonlocalizing or discordant preoperative imaging studies. In this circumstance, we look for a return to normal PTH values in addition to a 50% decrease from baseline. Total parathyroidectomy with forearm autotransplantation is another option for patients with MGD and is not favored by the authors due to a greater risk of permanent hypoparathyroidism (► Fig. 25.11).

25.7 The Missing Gland

One of the greatest challenges in parathyroid surgery is what to do when three normal glands are found and the sought-after fourth gland remains occult. Biopsy of normal glands should be considered, but great care must be taken to avoid iatrogenic injury of normal glands. A sound knowledge of the embryonic development of the parathyroid glands is essential in parathyroid surgery (► Fig. 25.12).

If a superior gland is missing one should mobilize the upper pole of the thyroid by dividing and ligating the superior pole vessels. This will often bring the superior gland and the distal recurrent laryngeal nerve into view. If not, the dissection should extend along the tracheoesophageal groove where the missing gland can often be carefully palpated (► Fig. 25.13 and ► Fig. 25.14). Further exploration should continue behind the esophagus and down into the upper posterior mediastinum. These maneuvers will usually result in success; otherwise a deep-seated mediastinal gland should be suspected. Mediastinal procedures (median sternotomy, thoracotomy, or thoracoscopy) should never be performed without preoperative localization.

If an inferior gland is missing, first a transcervical thymectomy should be performed (► Fig. 25.15). If negative, the carotid

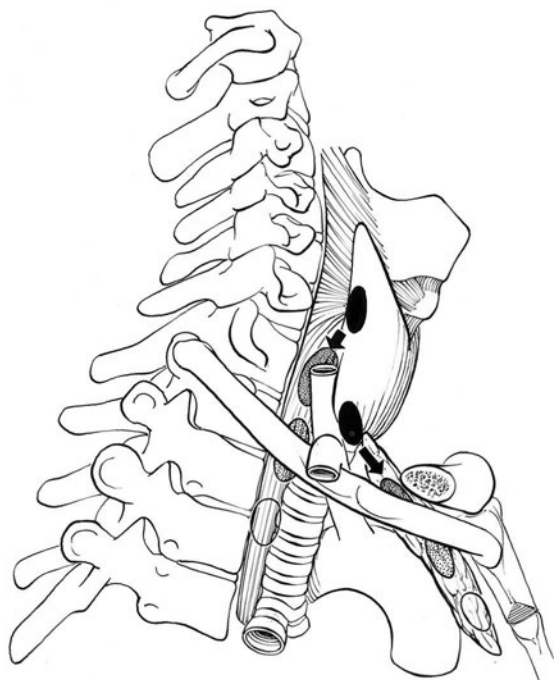


Fig. 25.12 Migration of the superior and inferior parathyroid glands. The superior parathyroid gland may descend into the posterior mediastinum, whereas the inferior gland may descend into the chest with the thymic tissue.

sheath should be opened up to the carotid bifurcation. Finally, a thyroid lobectomy (partial or complete) with ultrasound guidance should be considered. Approximately 10 to 15% of patients have supernumerary glands, most often in the neck or thymus. Ectopic glands outside the reach of a collar incision account for 1 to 2% of cases of HPT.

After all four glands are visualized and abnormal glands resected, closure is performed in layers with an interrupted absorbable suture and a running 4-0 absorbable subcuticular suture (► Fig. 25.16).



Fig. 25.14 Right superior parathyroid adenoma (*held in forceps*). Note the normal inferior parathyroid gland in its usual anatomical location surrounded by a halo of fat (*arrow*).

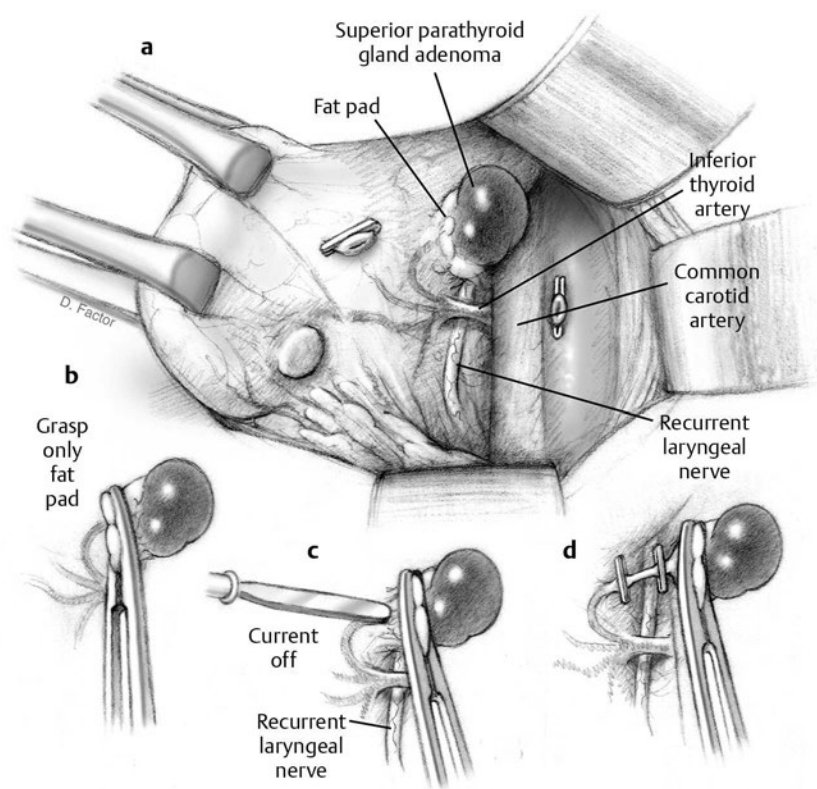


Fig. 25.13 Excision of the left superior parathyroid adenoma. (a) The middle thyroid vein has been divided between clips and the thyroid gland rotated medially, exposing the superior parathyroid adenoma, inferior thyroid artery, and recurrent laryngeal nerve. (b) The fat pad attached to the adenoma is gently grasped and used to manipulate the gland. (c) Blunt dissection is used to expose the vascular pedicle of the adenoma. (d) The vascular pedicle is clipped and divided.

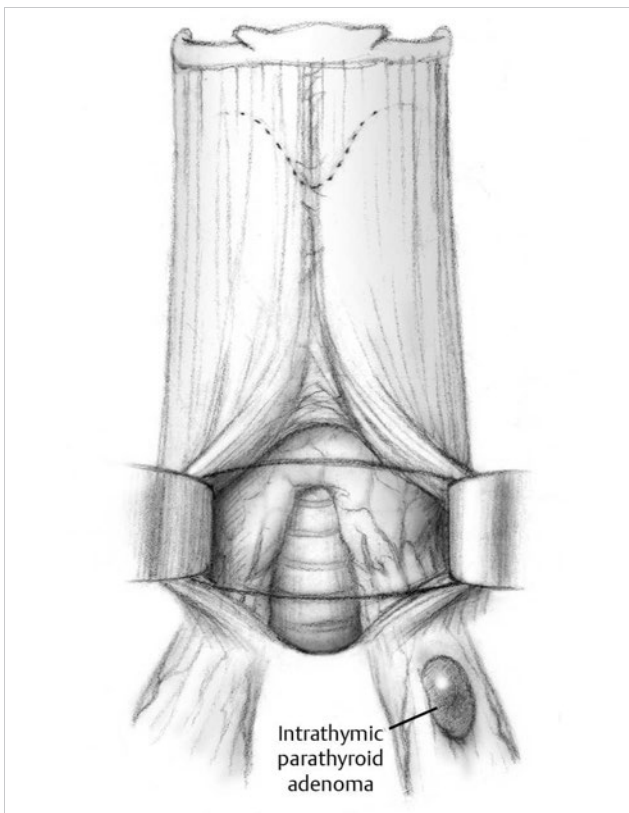


Fig. 25.15 Partial transcervical exposure of an intrathyroidal inferior parathyroid gland.

25.8 Postoperative Care

Postoperatively, all of our patients undergoing bilateral neck exploration are observed overnight in the hospital, and repeat serum calcium and PTH values are obtained the next morning. If patients have very low serum calcium levels or symptomatic hypocalcemia we administer supplemental oral calcium with or without activated vitamin D, depending on their PTH values. Rarely, severe hypocalcemia will require intravenous calcium administration via a central venous catheter. Most patients requiring an autotransplant will require supplemental calcium and activated vitamin D until the autograft begins to function.

In our practice, permanent recurrent laryngeal nerve injury is rare, at 0.8%. If this occurs on one side the patient will experience hoarseness, if bilateral injury occurs this can be devastating and require tracheostomy. Rarely, bleeding associated with the procedure will require a return to the operating room for hematoma evacuation. The small space and close proximity to the airway make meticulous hemostasis during this operation exceedingly important. Most patients are dismissed the next morning and follow-up serum calcium is obtained in 2 weeks to ensure cure.

25.9 Conclusions

Diagnosis and treatment of primary HPT have advanced significantly over the last several decades, and surgery remains the only definitive curative therapy. Surgery is recommended for

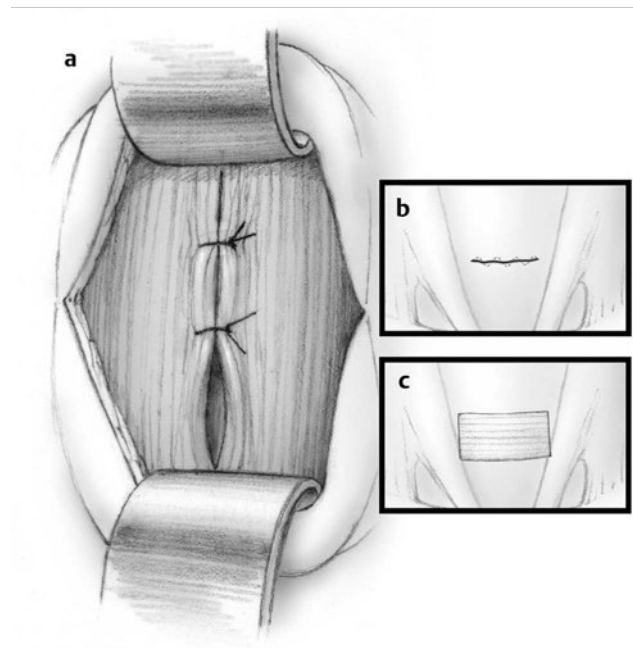


Fig. 25.16 Wound closure. (a) The strap muscles are reapproximated in the midline with absorbable sutures, leaving space for egress of fluid from the thyroid compartment. (b) A layered skin closure is performed with interrupted absorbable sutures and a running 4-0 absorbable subcuticular suture. (c) An adhesive bandage is applied.

patients with symptomatic disease, familial disease, and asymptomatic disease associated with reduced renal function, osteoporosis, serum calcium > 1 mg/dL above normal, or age < 50 years. Parathyroidectomy has been shown to be cost-effective compared with medical therapy, and even patients with mild disease can benefit from treatment. Although MIP is appropriate in selected patients with good preoperative localization studies, bilateral neck exploration is recommended for patients with negative or discordant imaging, MGD, familial disease, renal disease, or lithium-induced HPT, and in some cases of persistent or recurrent disease. The most common cause of failed parathyroid operations is a missed adenoma, and these are usually found in normal anatomical locations on reoperation. A good understanding of the anatomy and embryology of the parathyroid glands and surrounding structures is critical for safe and effective surgery. Meticulous dissection is mandatory to minimize the risk of complications, which, although rare, can be severe. Conventional parathyroidectomy remains an excellent treatment option in the hands of an experienced parathyroid surgeon in the absence of good preoperative localization and the availability of intraoperative PTH monitoring.

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26 Minimally Invasive Parathyroidectomy

William S. Duke and David J. Terris

26.1 Introduction

Traditional parathyroid surgery required a large transverse cervical incision, bilateral neck exploration with identification of all four glands, and removal of any visibly abnormal glands. Patients typically were managed with drains and were admitted to the hospital for postoperative monitoring. Although there are patients who still clearly require bilateral exploration, the majority of hyperparathyroidism is due to single-gland disease.¹ In recent years, significant advances in early disease detection, improved preoperative localization modalities, and innovative surgical adjuncts, such as rapid intraoperative parathyroid hormone (IOPTH) assays and hand-held gamma probes, have made minimally invasive, drainless, outpatient procedures a feasible and appropriate alternative for most patients requiring parathyroid surgery.

There is no consensus as to what defines minimally invasive parathyroid surgery.² There are numerous different surgical access options, recommended incision lengths, and extents of exploration that may be performed.^{2,3,4,5} In a broad sense, minimally invasive surgery significantly reduces the tissue trauma required compared with traditional surgical exposures.⁶ Although no strict definition exists, minimally invasive parathyroid procedures generally limit the length of the skin incision and more importantly reduce the extent of dissection to only that which is necessary to locate and safely remove the hyperfunctional gland(s). Exposure of all four parathyroid glands, regardless of the size of the incision, cannot be considered minimally invasive surgery.⁷ Although completely endoscopic parathyroid surgery using CO₂ insufflation of the neck has been reported,⁸ minimally invasive parathyroidectomy (MIP) is now most commonly performed using an open gasless technique, either with or without endoscopic assistance.

26.2 Indications for Minimally Invasive Parathyroidectomy

Primary hyperparathyroidism (PHPT) is one of the most common causes of hypercalcemia, and its prevalence is increasing.⁹ Appropriate candidates for parathyroid surgery in general should have a secure diagnosis of PHPT and have no contraindications to surgical intervention. Most patients are either symptomatic or meet consensus indications for surgery¹⁰; however, surgery is not withheld simply on the basis of those relatively strict criteria. The following are some indications for parathyroidectomy in asymptomatic patients¹⁰:

1. Serum calcium > 1 mg/dL above upper limits of normal
2. Creatinine clearance < 60 mL/min
3. Twenty-four-hour urinary calcium > 400 mg/d and increased risk of nephrolithiasis
4. Nephrolithiasis or nephrocalcinosis
5. Bone mineral density T-score < -2.5 at the lumbar spine, femoral neck, total hip, or distal radius, or a vertebral fracture
6. Age < 50 years old

7. Patient requests surgery or is poor candidate for long-term observation

As many as 85% of patients with PHPT have single-gland disease and therefore may be candidates for MIP if other criteria are met.⁴ Patients considered for MIP generally do not have a diagnosis associated with multigland disease, such as multiple endocrine neoplasia (MEN) types 1 or 2A, prior cervical radiation, a history of lithium use, or renal hyperparathyroidism.¹ Although minimally invasive concepts, incision lengths, and dissection techniques can be applied to some patients with these conditions, they generally require four-gland exploration and often removal of multiple glands. Although not absolute contraindications for MIP, surgeons should also be cautious about offering the procedure to patients who have a history of prior central compartment surgery, thyroiditis, or large goiters.

Once the diagnosis of hyperparathyroidism is confirmed and the decision is made to proceed with surgery, patients being considered for MIP should undergo at least one preoperative imaging study to identify the location of the abnormal parathyroid tissue. It should be emphasized that localization studies play no role in the diagnosis of primary hyperparathyroidism, nor are the results used to determine if a patient requires surgery.¹¹ Imaging studies are used only to identify the likely site of the hyperfunctioning parathyroid tissue and determine the most appropriate operation for the patient.¹¹ Although many preoperative localization studies are available, technetium-99m sestamibi (sestamibi) and a cervical ultrasound are the most commonly used techniques for initial parathyroid surgery. MIP requires that findings suggestive of abnormal parathyroid tissue be present on at least one of the studies; optimally the sestamibi and ultrasound will be concordant and identify a suspected parathyroid adenoma in the same quadrant. Sestamibi is particularly important in evaluating for the presence of an ectopic adenoma, which may not be amenable to resection with MIP. The details of preoperative localization studies are presented more fully in Chapter 23.

26.3 Techniques for Minimally Invasive Parathyroidectomy

26.3.1 General Considerations

Though there are many variations of minimally invasive parathyroid surgery, the unifying determinant that qualifies a procedure as a MIP is a limited exploration that does not expose all four parathyroid glands to the risks of surgical trauma; secondary elements are a small incision (generally < 4 cm),² and reduced extent of dissection. It is recognized that current minimal-access techniques allow all four glands to be identified with minimal dissection through a very small, centrally placed incision.¹² MIP may be performed as an open or endoscopically assisted procedure, under local or general anesthesia.^{2,12} This chapter presents a general description of these approaches,

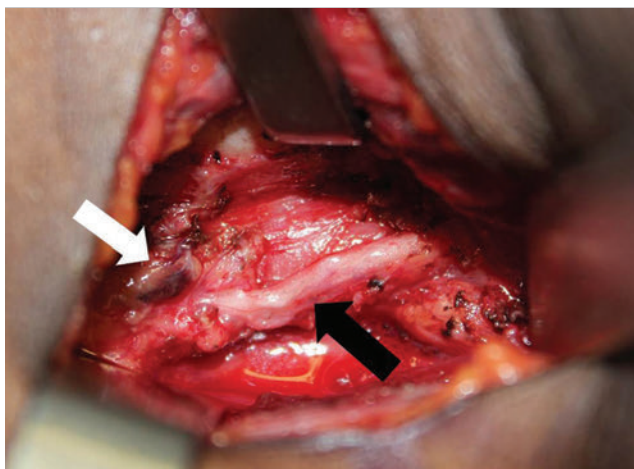


Fig. 26.1 The inferior parathyroid gland (white arrow) is always ventral to the recurrent laryngeal nerve (black arrow), whereas the superior parathyroid gland is dorsal.

although they may be tailored to fit the preferences of the individual surgeon and needs of each specific patient.

Knowledge of the usual and potential ectopic gland locations is critical for successful parathyroid surgery. The superior glands are usually located within a 2 cm region whose center is 1 cm cranial to the intersection of the recurrent laryngeal nerve and the inferior thyroid artery,¹³ and they are always dorsal to the recurrent laryngeal nerve. The location of the inferior parathyroid glands is more variable. They are typically located within 1 cm of the inferior aspect of the thyroid gland, anterior to a coronal plane drawn through the recurrent laryngeal nerve (► Fig. 26.1), but they may be intimately associated with the thymus or thyrothymic tract in up to 26% of patients.^{13,14} Although most parathyroid adenomas are found in these predictable locations within the central neck compartment, up to 13% of patients have supernumerary glands, which may be pathological, and as many as 11% of patients have more than one adenoma.^{1,14}

Minimally invasive parathyroid surgery relies on intraoperative adjuncts, rather than visual inspection of all four parathyroid glands, to ensure the complete removal of all hyperfunctional parathyroid tissue. These adjuncts include IOPTH assays, which are discussed here and in Chapter 27, and handheld gamma probes, discussed further in Chapter 28.

26.3.2 Minimally Invasive Parathyroid-ectomy (Nonendoscopic)

The nonendoscopic MIP technique uses retractors to maintain the operative space, which is accessed through a small cervical incision. To ensure the final scar will be predictably concealed in a naturally occurring neck crease, the procedure begins by marking the planned incision site while the patient is awake and upright in the preoperative holding area.^{1,15} The patient is placed supine on the operating table, and general anesthesia is induced. A laryngeal electromyographic endotracheal tube is used to intubate the patient if nerve monitoring is desired. Generally no shoulder roll is required, but gentle neck extension is obtained by slightly lowering the head rest of the bed. The table



Fig. 26.2 Mobile intraoperative parathyroid hormone assay equipment in the operating room.

is rotated 180° so the patient's lower extremities face the anesthesia station. This allows the anesthesia team to obtain blood from veins in the patient's foot for IOPTH assessment, and obviates the need for an arterial line. A baseline IOPTH level is obtained before the incision is made. The PTH assay is performed by a technician with a mobile workstation in the operating room, eliminating the transport time associated with sending the specimens to the main laboratory (► Fig. 26.2). Once the patient is in the final operative position, the surgeon performs an ultrasound to help guide the subsequent dissection. The planned incision site is then infiltrated with a local anesthetic with epinephrine.

A 2 to 2.5 cm incision is made in the midline. The platysma is divided, and dissection continues deeply until the strap muscles are identified.⁴ A guarded electrocautery tip prevents inadvertent tissue injury in the narrow operative space. Meticulous attention must be given to hemostasis because any bleeding can obscure the critical visualization of deeper structures. No subplatysmal flaps are elevated. The strap muscles are separated vertically in the midline and the thyroid isthmus is identified. The strap muscles are bluntly elevated off the anterior and lateral face of the thyroid lobe on the side to be explored first and secured under retractors (► Fig. 26.3).

Attention is then directed toward the most likely location of the pathological gland, as predicted by preoperative localization studies. Exploration of the superior gland is facilitated by retracting the thyroid lobe ventrally and medially, exposing the posterior aspect of the thyroid and the paratracheal region. This exposure can usually be achieved without division of the middle thyroid vein, though ligation of this vessel is occasionally necessary to sufficiently mobilize the thyroid. The inferior parathyroid gland may be found by gently dissecting the soft tissue ventral to the inferior pole of the thyroid gland or may be identified dorsal to the gland after gentle retraction of the thyroid lobe. The coronal plane of the recurrent laryngeal nerve, if



Fig. 26.3 Proper placement of retractors for minimally invasive parathyroid surgery.

identified, provides a good reference point to help determine the appropriate depth of dissection.

Because there are often no normal glands exposed for reference, the ability to visually distinguish a normal from abnormal parathyroid gland is crucial to successful minimally invasive parathyroid surgery. Normal parathyroid glands are typically flat, light brown to tobacco color and are 3 to 8 mm long with an average weight of 40 mg.^{1,13} They are usually surrounded by or capped with fat (► Fig. 26.4).

Parathyroid adenomas are typically larger, more rounded or nodular, rubbery, and a darker red-brown in color (► Fig. 26.5). Gentle spreading of the overlying tissue may help reveal the enlarged glands. Once identified, blunt dissection is used to liberate the gland from the surrounding soft tissue, until only the vascular pedicle remains attached to the gland. Soft tissue adherent to the capsule of the gland may be grasped to facilitate retraction and dissection, but care should be taken to avoid grasping the gland itself or applying excessive manipulation. Such forceful maneuvers may stimulate the release of stored parathyroid hormone and alter subsequent IOPTH levels,¹⁶ or violate the capsule of the gland, risking parathyromatosis.

The recurrent laryngeal nerve may be identified and is preserved during this dissection. Once free from the surrounding tissue, the vascular pedicle of the adenoma may be coagulated with electrocautery or ligated with vessel clips and sharply divided if it is near the recurrent laryngeal nerve. Frozen sections are not generally required. Once the suspicious gland has been removed the surgical field is irrigated, hemostasis assured, and half a sheet of Surgicel (Ethicon, Inc.) is placed into the wound bed. The strap muscles are either left open or reapproximated in the midline with a single 3-0 Vicryl (Ethicon, Inc.) figure-of-eight suture. The subcutaneous tissue is closed with buried interrupted 4-0 Vicryl sutures, and the skin edges are closed with tissue adhesive and a single transverse Steri-Strip (3M Corp.) (► Fig. 26.6). No drains or external sutures are used.

Postexcisional IOPTH levels are drawn at 5 and 10 minutes after removal of the affected gland. This may be extended to a 15-minute interval if necessary. Obtaining levels at these time points allows the surgeon to assess the PTH decline and make a

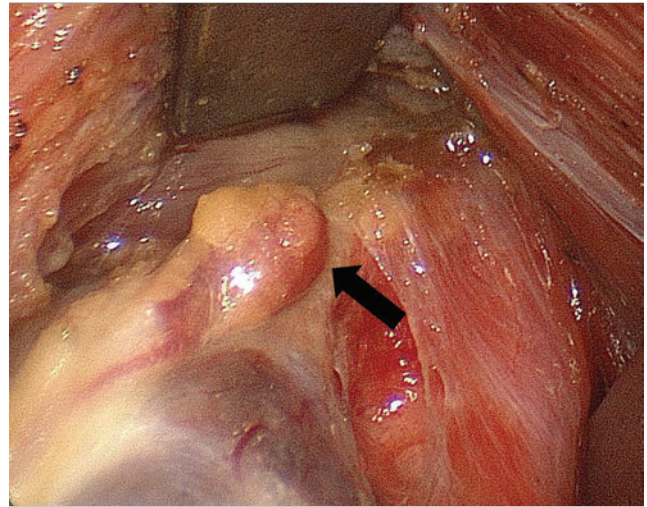


Fig. 26.4 Normal parathyroid gland (arrow) demonstrating surrounding fat.



Fig. 26.5 Parathyroid adenoma.

decision about the likelihood of a successful operation. The procedure is usually considered successful and terminated if the postextirpation IOPTH level has fallen at least 50% below the baseline value and is within the normal range.^{17,18,19} In our practice, patients are discharged home on the day of surgery with a prescription for a short-term tapering oral calcium regimen.²⁰

Failure of the IOPTH levels to decrease as anticipated should raise the surgeon's suspicion for multigland disease. If there is any doubt about the ability to adequately identify the glands or if an ectopic gland is suspected, the procedure should be

converted to a standard bilateral exploration and all potential gland locations explored as indicated. This can commonly be done without extending the incision. In challenging cases, frozen section confirmation that parathyroid tissue has been correctly identified is sometimes pursued, and bilateral PTH sampling from the internal jugular veins may prove to be helpful.

26.3.3 Minimally Invasive Video-Assisted Parathyroidectomy

Drawing on the success of other minimally invasive experiences, a hybrid procedure, the minimally invasive video-assisted parathyroidectomy (MIVAP), was described by Miccoli et al in 1997.²¹ In this approach, the incision can be reduced to as little



Fig. 26.6 The skin is closed with tissue adhesive and a quarter inch Steri-Strip, which facilitates removal of the adhesive at 3 weeks postoperatively.

as 1.5 cm,¹² and endoscopic visualization is used to assist the identification and extirpation of the abnormal gland(s). The limited amount of dissection associated with this approach facilitates a rapid recovery with less pain than conventional parathyroid surgery.²² Although this approach is primarily used to perform focused surgery on a single abnormal gland, by using a midline neck incision bilateral exploration is still easily accomplished if necessary.

The patient is marked, positioned, and prepared for surgery as described above for the open MIP procedure. The surgeon stands to one side of the patient (generally the right). One assistant stands at the patient's head and uses retractors to maintain the operative space while a second assistant stands opposite the surgeon and controls the endoscope. A video monitor placed on both sides of the patient's head allows all surgeons to ergonomically view the procedure (► Fig. 26.7).

The initial steps of the procedure are similar to the open MIP technique. Retractors are used to maintain the operative space. Though many retractor types may be suitable for this task, the Terris thyroid retractors (Medtronic, Inc.) are angled to provide improved visualization of the surgical field and are particularly beneficial when working in such narrow confines.

The strap muscles are divided vertically in the midline and are bluntly elevated off the thyroid lobe on the side of the suspected adenoma. Once the lateral aspect of the thyroid is identified, it is secured under a retractor and pulled medially and ventrally while a second retractor directs the strap muscles laterally (► Fig. 26.3). This vector of retraction is critical in exposing the proper tissue planes. While the assistant at the head of the bed maintains the operative space, the camera operator introduces a 30° 5 or 7 mm endoscope through the incision with the lens initially oriented inferiorly.

Under endoscopic visualization, blunt dissection with elevators is used to gently separate the tissue overlying the suspected location of the adenoma (► Fig. 26.8). Once identified, continued circumferential blunt dissection is used to free the adenoma until only the pedicle remains. The pedicle is then cauterized and divided or clipped and sharply divided if there is any concern about its proximity to the recurrent laryngeal nerve. The adenoma and endoscope are removed, and the wound is closed as already described. IOPTH levels are obtained.

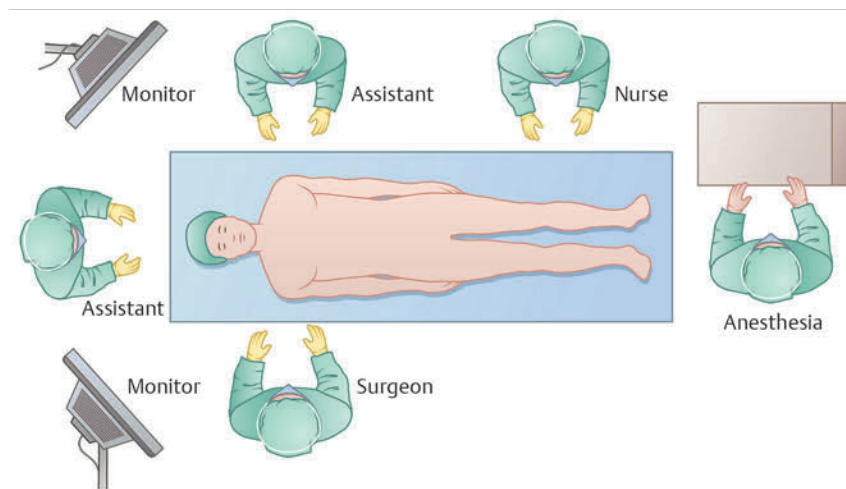


Fig. 26.7 The operating table is rotated 180° so the patient's lower extremities are facing the anesthesia team. Using two video monitors gives the entire surgical team an ergonomic view of the procedure.

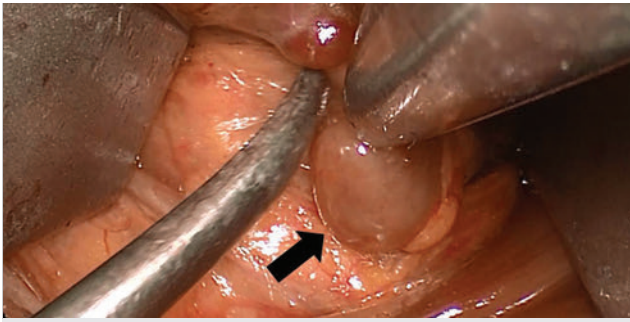


Fig. 26.8 Endoscopic visualization facilitates blunt dissection of the adenoma (arrow) away from the surrounding tissue.

26.3.4 Minimally Invasive Parathyroidectomy Modifications

As with any operation, minimally invasive approaches to parathyroid surgery can be modified to suit the particular requirements of an individual patient's disease. The procedures can be performed under local anesthesia using a cervical block and monitored anesthesia care, which may be an attractive option for patients with medical comorbidities that preclude the safe use of general anesthesia.^{23,24} Incision lengths can be adjusted relative to the patient's body habitus, although previous work in thyroidectomy patients has shown that minimally invasive, video-assisted endocrine surgery through a small incision is safe in patients with an elevated body mass index.²⁵ If necessary, MIP can often be converted to a bilateral exploration without extending the midline neck incision. This may be useful for identifying and obtaining a biopsy of a second, normal-appearing gland in institutions that rely on frozen-section analysis rather than IOPTH assays or in cases where the previously suspected abnormal gland on preoperative imaging appears to be normal on intraoperative inspection.

MIP may be performed through a lateral approach in carefully selected patients with posteriorly based adenomas. A lateral neck incision is made, and dissection is directed between the lateral aspect of the strap muscles and the sternocleidomastoid muscle to access the region posterior to the thyroid gland. This approach may offer fast, more direct access to deep adenomas and may be more comfortable for patients undergoing local anesthesia for their procedure. It may also be beneficial in reoperative cases when significant midline and thyroid compartment scar tissue after prior central neck surgery is expected to complicate the dissection.³

Minimally invasive parathyroid surgery may also be accomplished with the assistance of radioguidance technology. Minimally invasive radioguided parathyroidectomy (MIRP) is performed using a handheld gamma probe to either localize or confirm the removal of hyperfunctional parathyroid tissue after an injection with technetium-99m sestamibi.²⁶ This technique is more fully described in Chapter 28.

26.4 Outcomes

Numerous studies have shown that the MIP approaches yield cure rates that are comparable to or exceed those of traditional four-gland exploration,^{4,12,27,28,29} and are associated with less

pain, faster operative times, and less cost than bilateral surgery.^{12,30,31} Miccoli et al¹² reported an initial success rate of 99% in 652 patients undergoing MIVAP, with a mean operative time of 30 minutes. Similarly, Udelsman et al⁴ reported a 99.4% cure rate in 1,037 patients undergoing MIP, with a significantly lower complication rate, length of stay, and cost than traditional bilateral surgery.

Despite these advantages, only about 70% of patients with PHPT may be candidates for MIP.¹ Patients may have underlying conditions that predispose to multigland disease, such as MEN, or may have imaging studies that fail to localize the hyperfunctional gland. Surgeons should always be prepared to perform bilateral surgery if dictated by intraoperative findings, such as failure of the IOPTH assay to drop as expected.

26.5 Conclusion

Minimally invasive parathyroidectomy techniques have revolutionized the management of primary hyperparathyroidism. The durable cure rates of these procedures match or exceed those of conventional open four-gland exploration, and they are associated with a faster, less morbid recovery with a reduced cosmetic impact. Minimally invasive parathyroidectomy is appropriate for most patients requiring surgery and should be considered for all patients with sporadic, localizing disease.

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27 Intraoperative Parathyroid Hormone Assay

Latha V. Pasupuleti and James A. Lee

27.1 Introduction

Over the past few decades the surgical management of primary hyperparathyroidism has evolved dramatically. Historically, all patients underwent a bilateral neck exploration to assess all four parathyroid glands, and any grossly diseased glands were resected. Today, with the advent of improved localization studies combined with intraoperative parathyroid hormone (IOPTH) monitoring, minimally invasive parathyroidectomy has gained widespread acceptance, particularly among experienced endocrine surgeons. This chapter discusses the development of the IOPTH assay as well as the current recommendations and techniques for its usage.

27.2 History of the Intraoperative Parathyroid Hormone Assay

In the 1970s, physicians at the University of Miami first began using a radioimmunoassay to measure parathyroid hormone (PTH) levels for patients undergoing parathyroidectomy. However, this early assay measured fragments of the molecule, rather than the intact molecule, which often led to inconsistent results. In 1987, Samuel Nussbaum at the Massachusetts General Hospital reported a highly sensitive two-site antibody immunoradiometric assay to measure intact PTH. The surgeons at Massachusetts General Hospital subsequently reported their results at the American Association of Endocrine Surgeons (AAES) annual meeting and proposed that their assay could be used as an intraoperative tool, because it had a short, 15-minute turnaround time. However, their report was received with skepticism as being an unnecessary test in the hands of an experienced endocrine surgeon. Shortly thereafter, surgeons at the University of Miami started to perform their own intraoperative assay with a similar turnaround time of 15 minutes. Their “quick” PTH (QPTH) assay had similar results to the standard assay. Using their assay, these surgeons studied samples measured at various operative intervals. They also learned that manipulating the gland raised intraoperative measurements. Through their various lab value comparisons, they discovered that the half-life of PTH was 3.5 to 4 minutes.¹

Around this time, surgeons in France published reports of using a new, limited approach to parathyroidectomy performed with ultrasound localization, local anesthesia, and confirmation of excision of an adenoma with PTH assays and cyclic adenosine monophosphate (cAMP) levels. However, their assays took more than 45 minutes to run, and they often did not confirm removal of disease until long after the operation was concluded. If there was evidence of multigland disease based on the IOPTH assay values, the patient had to undergo a second operation.^{1,2,3}

Nichols Institute Diagnostics finally brought a major advancement to IOPTH monitoring in the United States with an immunochemiluminometric assay (ICMA) in 1993. This method did not use radioisotopes, thus making it portable. The assay was rapid, stable, and showed no cross-reactivity with PTH fragments like previous assays did.¹

In 1992, surgeons at the University of Miami began using sestamibi scans for preoperative localization of parathyroid adenomas. Combining preoperative localization with intraoperative PTH assays, they shortened their operative times for parathyroidectomy. At around the same time, Boggs et al showed that ICMA had a sensitivity of 97%, specificity of 100%, and overall accuracy of 97% for predicting postoperative calcium levels.^{1,4} These results were presented at the AAES in 1996, after which a sudden interest was spurred in the focused parathyroidectomy method now widely performed.¹

However, the cost of using this new intraoperative PTH assay technology was initially high, slowing adoption by surgeons. The University of Miami evaluated the decreased costs associated not only with shorter operative times, but their ability to perform the surgery as an outpatient. They showed that same-day parathyroid surgery versus an overnight stay cost 39% less.¹ Thus cost-effectiveness was another driving factor in support of using IOPTH monitoring to help perform more focused parathyroidectomies.

27.3 Differences in the Molecular Structure of PTH and Its Effect on the Assay

The molecular pathway and structure of PTH have a significant effect on how the assay is measured. PTH is first translated in the endoplasmic reticulum of the parathyroid chief cell as a 115-amino-acid-sequence molecule called preproPTH. Subsequently, two amino acid sequence cleavages occur, first to create proPTH and then to create the final 84-amino-acid-length intact PTH molecule termed (1–84) PTH. Less than 1% of (1–84) PTH reaches the PTH receptors in target organs after being released from the parathyroid glands. When PTH is metabolized, only the inactive C-terminal portions (cPTH) are rereleased into the circulation. The N-terminal products (nPTH) have biological activity but make up a much smaller portion of circulating hormone. In contrast, cPTH has a longer half-life and is secreted primarily by the kidneys. Thus cPTH fragments are elevated in patients with renal dysfunction, which may adversely affect the results of assays measured in patients with renal failure. ► Fig. 27.1 depicts the production and degradation pathway of PTH.⁵

“Intact PTH” assays are two-site sandwich assays in which the nPTH and cPTH ends are bound by separate antibodies. Ideally, a PTH assay will selectively bind and measure (1–84) PTH. However, (1–84) PTH circulates in much smaller numbers than the various PTH fragments, making its measurement challenging. In fact, most of the early assays reacted with the more abundant, smaller cleavage products and fragments of PTH (which are devoid of bioactivity) more than with the active (1–84) PTH molecule. Additionally, the ratio of (1–84) PTH to its fragments can vary significantly in patients with renal dysfunction and varying parathyroid gland activity. These challenges associated with the accuracy of IOPTH assays and which

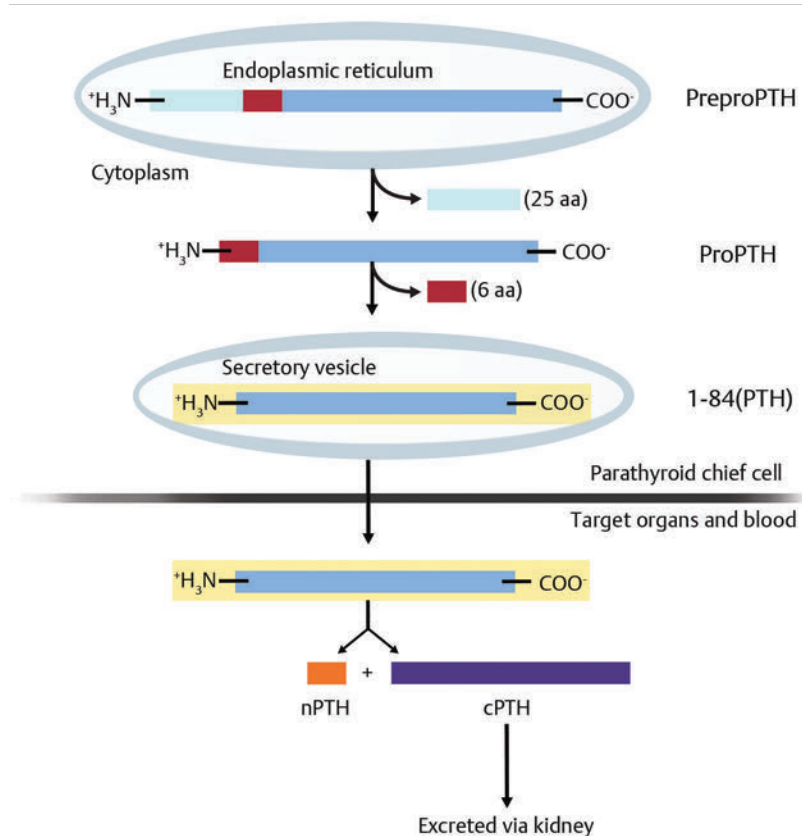


Fig. 27.1 Production and degradation of parathyroid hormone. Molecules highlighted in yellow are biologically active. aa, amino acids; PTH, parathyroid hormone; nPTH, amino-terminal fragment of PTH; cPTH, carboxy-terminal fragment of PTH. (Reproduced from Carter AB, Howanitz PJ. Intraoperative testing for parathyroid hormone: a comprehensive review of the use of the assay and the relevant literature. Arch Pathol Lab Med 2003;127:1425, with permission from Archives of Pathology and Laboratory Medicine. Copyright 2003 College of American Pathologists.)

molecules were actually being measured have been studied and evaluated extensively. Fortunately, newer generations of IOPTH assays have improved rates for detecting the actual (1-84) PTH molecules, rather than the inactive fragments.^{5,6}

27.4 Intraoperative PTH Monitoring Improves the Success of Minimally Invasive Parathyroidectomy

With the increased accuracy of preoperative localization studies, many surgeons have shifted toward minimally invasive parathyroidectomy rather than routine four-gland exploration. Minimally invasive parathyroidectomy techniques use focused, unilateral, and often endoscopic methods.⁷ However, during minimally invasive parathyroidectomy, because all four glands are not directly visualized, the surgeon does not necessarily know whether or not all of the diseased parathyroid tissue has been removed. By incorporating IOPTH assessment, surgeons can excise the image-localized adenoma and immediately assess for biochemical resolution of the hyperparathyroidism to determine if the operation has been successful. If intraoperative PTH levels fail to decline appropriately, the surgeon can immediately convert to a bilateral neck exploration, thus potentially avoiding a second operation for the patient.

When ultrasound identifies a single adenoma, the addition of IOPTH measurements increases the operative success from 71 to 86%.⁷ Likewise, when sestamibi scan localizes a single

adenoma, use of IOPTH improves the operative success from 83 to 92%.⁷ When both ultrasound and sestamibi scan are used and have concordant results, their combined accuracy in localization is 95%.⁷ When IOPTH assessment is added to ultrasound and sestamibi in this setting, the operative success increases to 97%.⁷ Some argue that this gain of 2% does not justify the use of IOPTH monitoring in this setting and increases the length of operation and costs.⁷

IOPTH assessment is especially helpful in the setting of discordant findings on preoperative imaging studies. About half to two-thirds of patients with hyperparathyroidism will have discordant imaging findings.⁷ The use of IOPTH monitoring in this setting has been shown to guide the operative management in 74% of these patients, leading to an operative success rate of 93%. Sixty-six percent of these patients were able to have successful unilateral exploration.⁷

Cayo et al prospectively studied more than 755 patients with primary hyperparathyroidism and found that IOPTH monitoring accurately predicted success of parathyroidectomy in 97.5% of patients with multigland disease.⁸ However, other studies report that IOPTH is not as successful with multigland disease.^{9,10} Siperstein et al reported that, when a bilateral neck exploration is routinely performed, even when preoperative localization studies identified a single adenoma, unsuspected additional morphologically abnormal parathyroid glands are identified in 20 to 22% of patients. Adding IOPTH only reduced the rate of identifying unsuspected multigland disease to 16 to 17%. However, one criticism of this study is that, although the additional glands were morphologically abnormal, they may not have been functionally abnormal. Overall, IOPTH

assessment correctly predicts multigland disease in only 22% of patients who have it.¹¹

27.5 Application of the IOPTH Assay

Logistical considerations in using IOPTH monitoring include location of blood draws, location of the lab running the assay, type of IOPTH assay used, and timing and number of blood draws required to accurately determine biochemical cure.

Surgeon preference usually dictates whether the samples are drawn from the internal jugular vein or a peripheral intravenous site. Central venous sampling is convenient because the internal jugular vein is in the operative field, though a peripheral sample obtained away from the surgical field may be less susceptible to fluctuations in PTH related to manipulation of the parathyroid glands. Centrally collected samples have higher PTH values on average, but this does not cause a statistically significant difference in percentage drop that affects the outcome of the operation.^{12,13,14} Regardless of site used, all samples should be drawn from the same location.^{12,13,14}

High-volume centers are often able to use the highest-quality, fastest assays, and often have either a dedicated lab facility adjacent to the operating room or the capability to perform the assay in the operating room to enable faster turnaround time. One option, the STAT IO-iPTH assay (Future Diagnostics) can be performed in 8 minutes and offers portable, point-of-care results within the operating room. At low-volume centers, the samples may have to be sent to the standard hospital lab for processing, thus taking much longer to get results. This delay in lab results can prolong the operation, thereby negating some of the benefit of having a shorter, more focused operation.

PTH samples are most commonly drawn as a baseline (prior to the start of the operation), time 0 (T0) (just prior to ligating the vascular pedicle), and 5 and 10 minutes after excision of the adenoma (► Fig. 27.2a). The baseline and T0 samples are referred to as the preexcision values, whereas the 5- and 10-minute samples are called the postexcision values. Two preexcision values are drawn because the T0 is often higher than the baseline value due to manipulation of the diseased parathyroid(s). However, the T0 is sometimes lower than the baseline if the blood supply had already been ligated prior to drawing of the T0 sample.^{15,16} Of note, preoperative PTH values should not be used in the intraoperative determination of biochemical success.

Because the half-life of PTH is 3.5 to 5 minutes, the 10-minute value should have fallen by more than half of the higher of the two preexcision values to be considered a successful operation, a guideline often referred to as the Miami criterion. Many surgeons believe that, in addition to a 50% drop, IOPTH levels should also normalize to avoid missing persistent disease. If the PTH has fallen by more than 50% but remains elevated above normal at 10 minutes, samples at later time points may be sent. Frozen-section analysis can be used if there is uncertainty about the resected specimen.⁵ Other reasons for a prolonged decline in PTH values include a reduced renal clearance of PTH in cases of overt or subclinical renal insufficiency and incidental intraoperative PTH spikes from excessive gland manipulation

(► Fig. 27.2b).^{15,16} Obtaining a delayed value at 30 minutes post-excision can help discern if there was truly persistent disease.

Although the Miami criterion is the most commonly employed standard for IOPTH monitoring, numerous others have also been advocated as being the most effective at determining a successful operation. ► Table 27.1 summarizes the Miami, Vienna, Halle, and Rome criteria.¹⁷ A number of studies have compared the effectiveness of the various criteria on the same set of patients. In a comparison of various intraoperative PTH criteria, Carniero et al reported the best results with the Miami criterion, which achieved the highest accuracy (97%), with a false-positive rate of 0.9% and a false-negative rate of 2.6%.^{16,18} The Miami criterion has been compared to other more stringent criteria that focused on detecting multiglandular disease with a higher sensitivity. However, any attempts to lower the number of false-positive results and decrease the number of operative failures traded an increased specificity in predicting complete resection for a lower sensitivity and lower overall accuracy, leading to further unnecessary neck explorations and a prolonged operative time.^{16,18}

Barczynski et al performed a retrospective review of 260 patients with sporadic primary hyperparathyroidism and concordant sestamibi scanning and ultrasound results to compare the predictive values of the Halle, Miami, Rome, and Vienna criteria (► Table 27.2). They concluded that the Miami criterion, followed by the Vienna criterion, was the most balanced, with the highest accuracy for predicting cure. However, the Rome criterion, followed by the Halle criterion, was noted to be the most useful in intraoperative detection of multiglandular disease. Despite this finding, they believed that, in patients with concordant sestamibi and ultrasound results, using the Rome or Halle criterion would result in a significantly higher number of unnecessary conversions to bilateral neck explorations and only a marginal improvement in the success rate of primary operations.¹⁸

27.6 Limitations of the Parathyroid Hormone Assay

There are multiple reasons for inaccurate IOPTH results. The metabolism and clearance of PTH vary greatly between patients and are influenced by the rate of the production of PTH as well as by its metabolism, the patient's renal function, and the type of parathyroid disease that is present.⁵ Hemolysis of postexcision blood specimens may artificially decrease the PTH level, resulting in false-positive IOPTH levels.¹⁹ Multigland disease can cause misleading IOPTH values (► Fig. 27.2c). For instance, more than half of patients with double adenomas are reported to have false-positive IOPTH results.²⁰ This error may be due to size differences between the adenomas; if the larger gland is removed first, there may be a larger drop in PTH initially that may lead a surgeon to conclude that the only diseased gland was removed.²⁰ As discussed earlier, as PTH is processed, there are many degradation products and fragments produced. The ideal IOPTH assay selectively detects the actual (1–84) PTH molecules. However, there is cross-reactivity of fragments that can alter IOPTH results, especially when older assays are used for measurements.^{5,6}

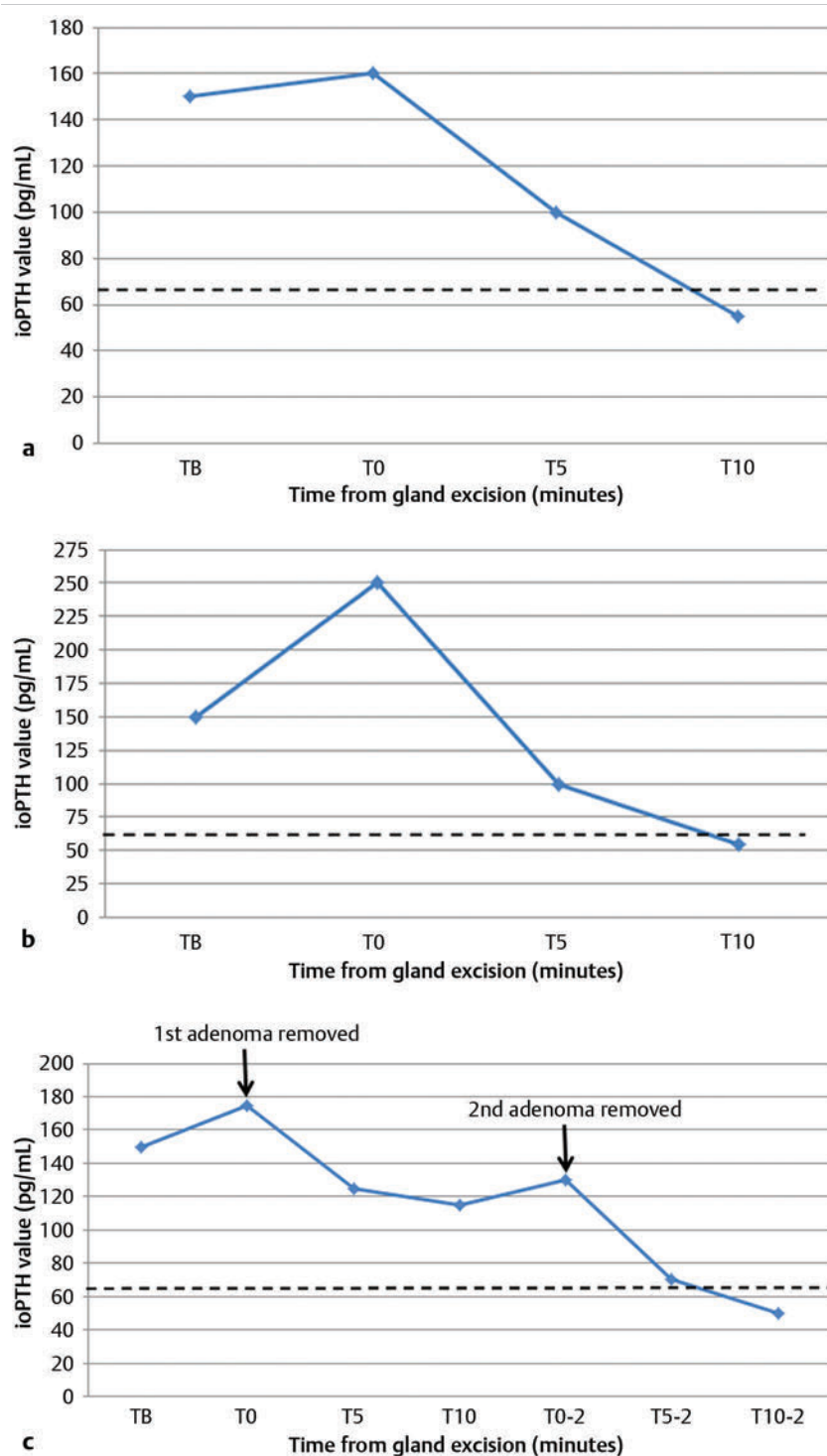


Fig. 27.2 Patterns of intraoperative parathyroid hormone (ioPTH) decline after parathyroid adenoma excision. The dotted line represents the assay upper limits of normal. **(a)** Decline to cure after removal of a single adenoma. **(b)** Parathyroid hormone spike at T0 from excessive gland manipulation, followed by decline to cure. **(c)** Initial failure to decline, followed by appropriate decline to cure after resection of a second adenoma. TB, baseline; T0, time of excision.

Table 27.1 Comparison of the major criteria used to guide intraoperative decision making with intraoperative parathyroid hormone

Criterion	Description
Miami	>50% decline from either the highest preincision or preexcision parathyroid hormone (PTH) value within 10 minutes of gland removal
Rome	>50% decline from the highest preexcision level, and/or PTH level within the reference range at 20 minutes after excision, and/or a PTH value <7.5 ng/L lower than the value at 10 minutes after excision
Halle	Decline into the low normal range (PTH <35 ng/L) within 15 minutes of gland removal
Vienna	>50% decline from the preincision value within 10 minutes of gland resection

Table 27.2 Comparison of the effectiveness of the major criteria used for intraoperative parathyroid hormone decision making

Criterion	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Overall accuracy (%)
Miami	97.6	93.3	99.6	70	97.3
Rome	82.9	100	100	26.3	83.8
Halle	62.9	100	100	14.2	65
Vienna	92.2	93.3	99.6	60.9	92.3

Abbreviations: NPV, negative predictive value; PPV, positive predictive value.

Source: Data from Barczynski M, Konturek A, Hubalewska-Dydejczyk A, et al. Evaluation of Halle, Miami, Rome, and Vienna intraoperative iPTH assay criteria in guiding minimally invasive parathyroidectomy. *Langenbecks Arch Surg* 2009;394:846.

27.7 Conclusion

Improved preoperative localization studies combined with faster, more accurate IOPTH assays have spurred the wide adoption of minimally invasive parathyroidectomy. Various criteria have been used to assess IOPTH results for biochemical cure. Currently, the Miami criterion ($\geq 50\%$ decrease in the IOPTH levels at 10 minutes from the higher of the preexcision values) is the most widely used and has an accuracy above 97% with the lowest false-positive and -negative rates. The advent of IOPTH monitoring is a prime example of how an improved understanding of hormonal pathways and kinetics and evolving technology can drive innovations in medicine.

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28 Radioguided Parathyroid Surgery

Sarah C. Oltmann and Herbert Chen

28.1 Introduction

As the surgical management of primary hyperparathyroidism (PHPT) has transitioned from routine, bilateral neck exploration to a more focused, minimally invasive approach, parathyroid surgeons have developed multiple preoperative and intraoperative tools to improve treatment outcomes.¹ These tools include advanced imaging techniques to identify and localize the parathyroid adenoma prior to surgery, rapid intraoperative parathyroid hormone (IOPTH) measurements to indicate when all hyperfunctioning parathyroid tissue has been removed, and detection methods of technetium-99m sestamibi within the pathological parathyroid gland(s).^{2,3}

Technetium-99m sestamibi was initially used in cardiac imaging for its ability to concentrate in mitochondria-rich tissues.⁴ During its initial years of use, "hot spots" were observed in the neck of some patients. These patients were noted to have primary hyperparathyroidism, with adenomas in locations corresponding to the areas of increased activity. The use of technetium-99m sestamibi in parathyroid surgery was first described in 1989 by Coakley et al for purposes of preoperative localization imaging.⁵ Over the following 10 to 15 years, the tendency of abnormal parathyroid tissue to concentrate this isotope was further exploited, leading to the development of radioguided parathyroid surgery. This technique uses an injection of technetium-99m sestamibi on the day of surgery to allow intraoperative detection of the gamma rays, which guides the dissection and confirms the identity of the resected tissue.^{6,7,8} This technique, which is applicable in both four-gland explorations and directed approaches, is still in use today and is taught by some of the dedicated endocrine surgery fellowships.⁹

28.2 Patient Selection

After making the decision to operate for hyperparathyroidism, there are few things to consider before determining if radioguided parathyroid surgery is appropriate. It is important to note that a successful radioguided surgery program requires significant coordination and cooperation between several areas and teams within the hospital. The isotope injections are usually performed in nuclear medicine, and for optimal use, need to be timed roughly 90 minutes prior surgery.¹⁰ To accomplish this, communication between departments, including preoperative holding and nuclear medicine, and the operative team, is crucial to ensure the patient has returned from nuclear medicine in a timely fashion, and that the injection does not occur too soon prior to the operation. The authors have found that, through the consistent use of this technique, all involved parties develop a routine, ensuring the patient is prepared for surgery with the isotope at optimum strength for detection during the procedure.

28.2.1 Primary Hyperparathyroidism

Patients with a diagnosis of primary hyperparathyroidism make up the vast majority of patients undergoing radioguided

parathyroidectomy. Regardless of preoperative sestamibi scan results or suspicion for single-gland versus multigland disease, parathyroid uptake of technetium-99m sestamibi on the day of surgery can provide helpful guidance in the operating room.^{6,11} When performing a focused, directed parathyroidectomy in a well-localized patient, the gamma probe provides the surgeon with instantaneous feedback that the excised tissue is parathyroid in origin, and not lymph node, adipose, thymus, or thyroid nodule tissue.⁸ During a four-gland exploration, a minimally invasive incision can accommodate the probe and direct the surgeon to the gland(s) of interest.

28.2.2 Secondary and Tertiary Hyperparathyroidism

Patients with a diagnosis of secondary or tertiary hyperparathyroidism generally have diffuse parathyroid gland hyperplasia in response to long-standing renal disease or other disorders of calcium metabolism. For this reason, the operative procedure of choice is a subtotal or total parathyroidectomy. This results in the exploration of both sides of the neck; thus preoperative imaging is not often obtained. However, because these patients may often have supernumerary glands due to hyperplasia of parathyroid rests, the gamma probe is a helpful tool to ensure that additional hot spots are not being left behind.¹² Although the underlying etiology of hyperplasia may differ from that in primary hyperparathyroidism, the concentration of sestamibi within the glands is equivalent.

28.2.3 Ectopic Glands

For patients noted to have a mediastinal gland on preoperative imaging, a laparoscopic gamma probe provides an excellent guide to dissection of the mediastinum during video-assisted thoracoscopic surgery (VATS).^{13,14} VATS provides a minimally invasive alternative to median sternotomy for mediastinal adenomas. The gamma probe also provides measurements of ex vivo counts, which immediately confirm that a parathyroid adenoma is contained within the specimen versus the need for additional resection while awaiting IOPTH or frozen-section results.

When a missing gland is encountered during the course of a four-gland exploration, or a supernumerary gland is suspected, in vivo counts with the gamma probe can also detect glands in ectopic locations (retro-esophageal, carotid sheath, etc.).^{15,16}

28.2.4 Extremes of Patient Age

Use of the gamma probe during parathyroidectomy has been extensively studied in patients of all ages.^{17,18} Adjustments in the dose of technetium-99m sestamibi administered to children must be made. However, low-dose protocols for patients of all ages also exist.¹⁹ In the very young and the very old, decreasing the extent of dissection when possible is advantageous. Regardless of the technique used for resection, surgical

management of primary hyperparathyroidism should not be deterred based on patient age because excellent outcomes can be achieved at any age when the procedure is performed by a high-volume surgeon.^{20,21,22,23,24,25,26}

28.2.5 Obesity

Obese patients present a challenge to the parathyroid surgeon. The amount of subcutaneous adipose tissue may limit the quality of preoperative images, although several studies have demonstrated equivalent performance of both ultrasound and sestamibi when high-quality studies are performed.^{27,28,29} The additional soft tissue may also increase the need for larger incisions in order to ensure adequate exposure.²⁹ And lastly, the weight of the soft tissue on the relaxed airway raises concerns for airway protection, both during the procedure and immediately after.^{27,29} Given the ability to improve gland detection within a limited field and discern parathyroid tissue from surrounding neck structures, radioguided parathyroidectomy can be advantageous to the parathyroid surgeon for this difficult patient population.

28.2.6 Reoperative Surgery

In patients with persistent or recurrent disease or a history of extensive previous cervical operations, the surgeon must deal with dense scarring, disrupted tissue planes, and altered anatomy. Previous explorations may have displaced the parathyroid glands from the typical locations.^{30,31} For these reasons, the parathyroid surgeon needs precise information regarding the target for resection in order to optimize success.³² This can be obtained via preoperative imaging in some instances, but intraoperative detection with the gamma probe can isolate the area of dissection. This focus can minimize the amount of scar tissue that needs to be disrupted, and theoretically keep the critical structures of the neck safe.

28.2.7 Forearm Grafts

Forearm grafts may be required for those patients undergoing subtotal or total parathyroidectomy. Indications for this more extensive parathyroid excision include familial causes of primary hyperparathyroidism, secondary hyperparathyroidism, and occasionally tertiary hyperparathyroidism. Because these patients often have either ongoing physiological stimulus to the remnant or genetic alteration leading to persistent proliferation, the forearm graft can become hyperplastic with time. The very reasoning for placing the graft within the forearm was to be able to differentiate recurrent disease in the neck from hyperplasia in the graft. Once the graft is determined to be the culprit, it must be debulked. If the graft location(s) were not appropriately marked with clips or permanent suture at the time of implantation, it can be difficult to find the parathyroid tissue within the forearm musculature.¹² Several authors have described the successful use of radioguidance to aid in the resection and debulking of forearm grafts.^{33,34,35} When using radioguidance for this patient population, it is critical to ensure the isotope is injected in the contralateral upper extremity or either lower extremity. This minimizes issues with high background counts.

28.2.8 Parathyroid Carcinoma

Parathyroid carcinoma is a rare entity.³⁶ Invasion of adjacent structures is common, and en bloc resection without disruption of the tumor is critical. The high propensity for multiple local recurrences in patients with parathyroid carcinoma is thought to be due to inadequate initial resection or the seeding of tumor cells during prior surgery. These deposits may vary in size and location. With the help of the gamma probe, the surgeon can be directed to residual areas of gamma emission, as well as limit the degree of scar tissue that must be manipulated.³⁷

28.2.9 Contraindications

Few contraindications exist for radioguided parathyroidectomy. Due to concerns of possible fetal exposure, pregnant patients are not candidates for this approach.³⁸ Additionally, patients felt to have dose limitations for technetium-99 m sestamibi cannot undergo this procedure. An additional relative contraindication is recent diagnostic imaging with technetium-99 m sestamibi because it may take more than 3 days to completely flush this from the system before another dose can be administered for surgery. Conversely, prolonged delay between injection and the procedure will diminish the utility of the gamma probe during the procedure.³⁹

28.3 Day of Surgery

28.3.1 Preparation of the Patient

The morning of surgery the patient will undergo an injection via a peripheral intravenous catheter of technetium-99 m sestamibi. Dosing protocols vary greatly, ranging from 1 to 25 mCi being administered.^{6,17,19,40} Lower-dose protocols require much shorter time intervals between injection and operation, whereas doses closer to the 25 mCi amount allow for both diagnostic imaging as well as a longer time frame before surgery.^{19,40} The authors favor a midrange dose of 10 mCi for adult patients injected roughly 90 minutes prior to surgery.⁶ No nuclear imaging is obtained the day of surgery. Again, it is critical to stress the importance of coordination within the health system to ensure timely injection. By routine use of this technique, all parties involved are familiar with the process, making delays or disruptions less likely.

28.3.2 In the Operating Room

The patient is placed on the operating room table in a supine, modified beach chair position. Because the level of radiation emitted from the patient is both low and rapidly deteriorates with distance, no particular safety precautions are necessary for the operating room personnel.^{41,42} Patient, surgeon, and anesthesia preference can determine the type of anesthesia performed, although this procedure can be safely done with local anesthesia, local with monitored anesthesia, or general anesthesia with a laryngeal mask airway or endotracheal tube.^{40,43} An ultrasound for localization confirmation and incision planning can be performed by the surgeon at this time.

Equipment necessary for radioguided parathyroid surgery is often already on hand in the operating room because the same



Fig. 28.1 Collimated gamma probe and base unit (Neoprobe 2000 Gamma Detection System, by Ethicon Endo-Surgery Breast Care).

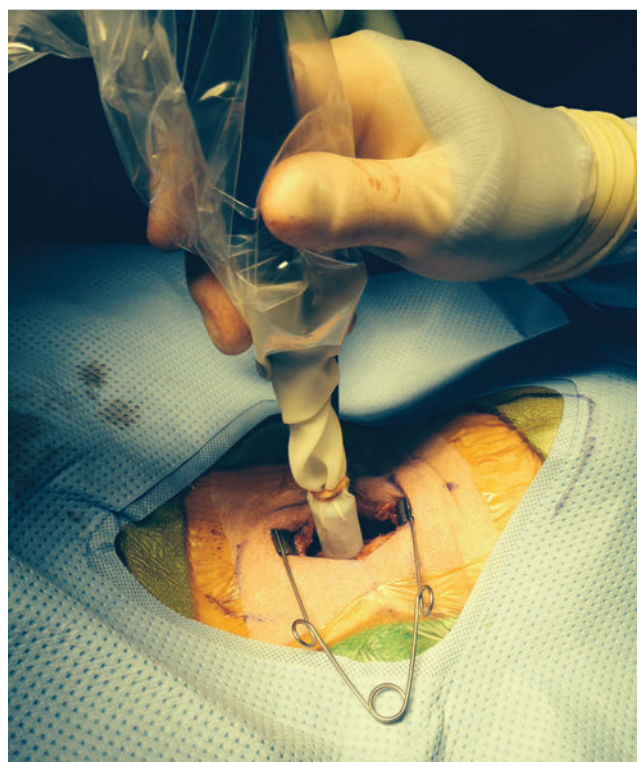


Fig. 28.3 In vivo measurements within the wound.

device used for sentinel lymph node biopsies for breast and melanoma cases can be programmed for parathyroidectomy. We use an 11 mm collimated gamma probe (Neoprobe 2000 Gamma Detection System, by Ethicon Endo-Surgery Breast Care) (► Fig. 28.1). A sterile covering for the gamma probe permits its use throughout the procedure within the operative field.



Fig. 28.2 Measuring background counts over the thyroid isthmus.

The probe is held over the thyroid isthmus to obtain a measurement of background emission (► Fig. 28.2). Alternative sites to establish background counts include the shoulder opposite the injection arm and the ear. In patients without clear localization prior to surgery, quick measurements can be obtained in the bilateral upper and lower neck. Areas of increased counts convey to the surgeon the location of enlarged glands.⁸

Incision and dissection is carried out to identify the enlarged gland(s). As needed, the probe can be inserted into the wound to confirm the direction and depth necessary for dissection, particularly for ectopic glands (► Fig. 28.3). Tissues considered suspicious for parathyroid adenomas can be assessed for in vivo radioactivity prior to resection.³⁸ Once a gland is excised, ex vivo counts are obtained, and a percentage of background is calculated (► Fig. 28.4 and ► Fig. 28.5). Note that the excised tissue is placed directly on the tip of the probe and held away from the patient to minimize any emission detected from the patient. Tissue noted to emit counts that are at least 20% of the initial background measurement are consistent with parathyroid tissue, whereas adipose tissue, lymph nodes, scar, and thyroid will be within single digits.^{8,39}

Although surgeons performing routine bilateral exploration with radioguidance may omit the use of additional intraoperative adjuncts (i.e., intraoperative parathyroid hormone monitoring), the authors feel strongly that patients undergoing a directed or focused procedure must have additional confirmation to ensure resection of all hyperfunctioning tissue and minimize the risk of persistent disease.^{38,40,44,45} Once the hyperfunctional gland has been excised it is the authors' practice to obtain 5-, 10-, and 15-minute postexcisional measurements of IOPH, in addition to a preincision baseline. Our institutional criterion for cure is based on a variation of the Miami criterion, a 50% decline from baseline at any time point.^{38,46}

Although awaiting return of IOPH values, the incision is injected with a long-acting local anesthetic and is closed. Once confirmation via IOPH levels that no additional exploration is required, the patient is awakened and taken to recovery.

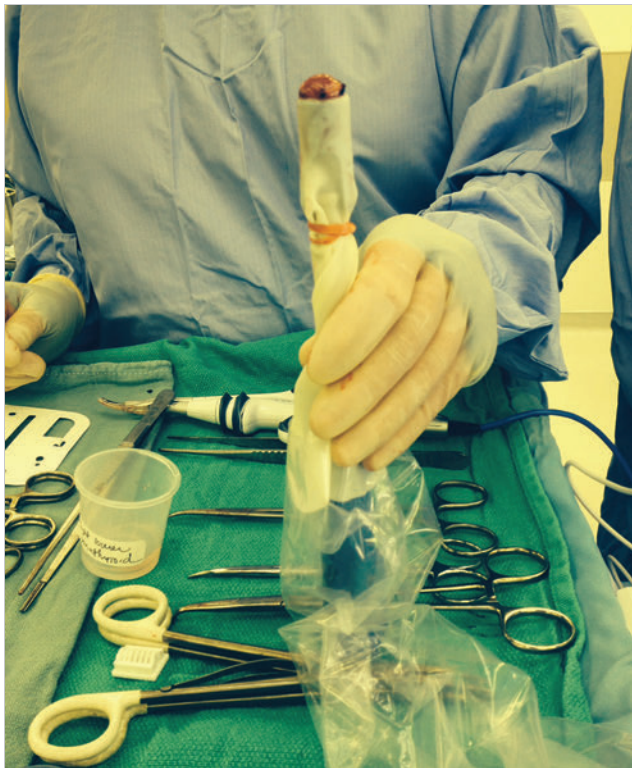


Fig. 28.4 Excised specimen placed on the tip of the gamma probe to obtain ex vivo counts.

28.4 Pearls and Pitfalls

Because the probe simply measures the emitted gamma rays from the direction of the tip, the surgeon must be cognizant of the angulation of the tip when it is used within the surgical wound. Increased background emissions from the salivary glands, carotid arteries, heart, and liver can all lead to false-positive readings. This is of particular importance when one is taking in vivo readings of the thymus and searching for an upper mediastinal adenoma from a cervical incision. Additionally, the thyroid tissue can have inconsistent uptake in nodular disease. To optimize reliability of the in vivo count, the surgeon must measure counts on the targeted tissue from various different angles. In addition to the system-related issues discussed earlier, the surgeon also must have familiarity with the technique that only consistent use can provide in order to ensure dependable results.

Because the levels of technetium-99 m sestamibi are dependent on a differential uptake of the isotope within the tissues as well as clearance from the body as time passes, timing of the injection and surgery is critical. Based on our dosing protocol, an operative window of 45 to 90 minutes is ideal. With larger doses of mCi given too close to surgery, not enough of a differential within the tissues may exist to direct dissection. If too much time has elapsed between injection and surgery, counts may be too weak to provide useful information.

As mentioned, the equipment required for gamma detection is also used for breast cancer and melanoma cases. This requires operating room coordination to ensure enough equipment is



Fig. 28.5 Base unit displaying ratio of target (ex vivo) count over initial background count. In this instance the excised gland measured 117% (220/188), well above the 20% rule diagnostic for parathyroid tissue.

available for all, or that cases are not scheduled to overlap if limited machines are available.

The dosing protocols for radioguided parathyroidectomy are safe for the patient and operative team alike.^{41,42} However, centers performing extremely high volumes of this procedure may elect to cover the patient with a lead blanket to minimize the cumulative exposure over time to the operating room staff.⁴⁰

28.5 Postoperative Care

Once meeting criteria, the patient is generally discharged home from the recovery room. Patients are advised to use topical ice packs to the anterior neck to minimize pain and any postoperative swelling.⁴⁷ Pain control is achieved with the use of oral analgesics. Patients are kept on oral calcium with or without vitamin D supplementation, with explicit counseling on the symptoms of hypocalcemia and instructions to take additional doses should any of those symptoms occur. At the postoperative visit, serum calcium and PTH levels are drawn to document resolution of hypercalcemia and PTH elevation, to indicate patients with persistent disease, and to predict the clinical course for patients experiencing profound hypocalcemic symptoms. Additional calcium and PTH measurements are obtained at 6 months after surgery to document cure.

28.6 Conclusion

Radioguided parathyroidectomy is a helpful tool for any parathyroid surgeon. It can be applied to nearly any and all patients or procedure types. As with any operation, it is only with practice and repetition that optimal results can be expected. In an era of several intraoperative adjuncts and variation in the availability of these aids, the more options surgeons can employ, the more likely they can adapt to any operating environment.

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29 Reoperative Parathyroid Surgery

David J. Terris and William S. Duke

29.1 Introduction

Parathyroid surgery has evolved dramatically over the past decade, principally as a result of the introduction of key technologies such as the sestamibi scan,¹ high-resolution ultrasound,² and the rapid intraoperative parathyroid hormone assay.³ Collectively, these advances have facilitated a minimally invasive targeted approach to removing diseased parathyroid glands. This has prompted outpatient management for these cases,⁴ an approach that would have been considered reckless in the early 1990s.

Commensurate with this change in surgical approach there has been a proliferation in surgeons who now feel capable of pursuing parathyroid surgery, despite in some cases limited training, and even more limited volumes. It is speculated that the increasingly straightforward approach to the management of these patients has attracted attention from surgeons who otherwise would probably have deferred to more expert surgeons. The result has been a new phenotype of parathyroid surgery failure, in which a very limited exploration is performed, with a failure to correct hypercalcemia.

Although single-gland surgery can be highly successful, failures regularly occur, with a variety of causes. As with many surgical and nonsurgical conditions, prevention is often the best medicine. With this in mind, we propose a systematic approach to the patient who has suffered a failed parathyroid exploration, along with strategies to minimize failure at the primary operation.

29.2 Confirm the Diagnosis

When asked to assess the patient who has undergone a failed parathyroid exploration, the first responsibility is to confirm the diagnosis. In rare cases, the surgery may have been ineffective because the patient was suffering from familial hypocalciuric hypercalcemia (FHH) or a multiple endocrine neoplasia syndrome. Other errors in diagnosis may be as simple as vitamin D deficiency with secondary hyperparathyroidism confused for primary disease.

The evaluation of the patient with failed primary parathyroid surgery of course begins with a thorough history and a careful physical examination (with a laryngeal exam to confirm normal movement of the vocal cords). The most important assessment, however, is a biochemical profile, in which simultaneous calcium and parathyroid hormone levels are obtained. Both the total calcium and the ionized calcium should be assessed to identify marginal cases of primary hyperparathyroidism. Renal function should also be evaluated by means of a serum phosphorous level and both a creatinine level and a glomerular filtration rate. In equivocal cases a thiazide diuretic challenge may be revealing. Mildly diminished renal function may be responsible for persistently elevated parathyroid hormone levels following curative parathyroid surgery.⁵

A 24-hour urine collection (with a sufficient volume of urine) can help identify patients who have FHH and who will not

benefit from surgical intervention. In these cases the family history is of particular importance. The inclusion of the 24-hour urine calcium level as a threshold for recommending surgery in asymptomatic hyperparathyroidism has been restored in the most recent version of the international guidelines.⁶ Furthermore, a reduced fractional excretion of calcium (calcium/creatinine clearance <0.01) is a relatively definitive determinant of patients with FHH.

Although patients with parathyroid disease are often managed principally by the surgeon or a primary care physician, if there is any question about the diagnosis, especially in patients who failed previous surgery, consultation with an endocrinologist (preferably one who specializes in bone disease) should be sought.

29.3 Understand the Reason for Failure

It is helpful to understand the reason why a previous exploration failed. To make this determination, previous records and imaging should be obtained if possible. The original imaging, and in particular the sestamibi scan, as well as the reports from the imaging, may shed light on the thought process of the prior surgeon.

In addition to imaging, the most objective element of information will be represented by the pathology report from the prior exploration. This should be assessed in conjunction with the operative note. A carefully dictated operative note may provide important clues as to both the reason for failure and the location of an unidentified parathyroid adenoma. When repeat imaging is performed (as it virtually always is) the findings should be compared to those of the original imaging (► Fig. 29.1).

There may be multiple reasons for a failed exploration. Of course, an ectopically located gland is commonly presumed, and the mediastinum may harbor such a missed gland (► Fig. 29.2). However, large-scale studies have demonstrated that the missed gland is most often in a eutopic location (► Fig. 29.3).^{7,8} These cases may reflect inexperience on the part of the surgeon or anatomical factors that make exploration more challenging (obesity, presence of thyroiditis, scar tissue from a different operation, such as anterior cervical disk surgery, etc.). When the missed gland remains in the cervical field despite a seemingly thorough exploration, and especially when planar imaging suggests an inferior adenoma, experience has proven that an overly descended superior gland in a parasophageal location is often the cause (► Fig. 29.4).

29.4 Repeat Imaging

In the patient with persistent hyperparathyroidism, repeat imaging is almost always necessary. Generally, this begins with the usual first-line imaging of high-resolution ultrasound by an experienced ultrasonographer and sestamibi scanning at a

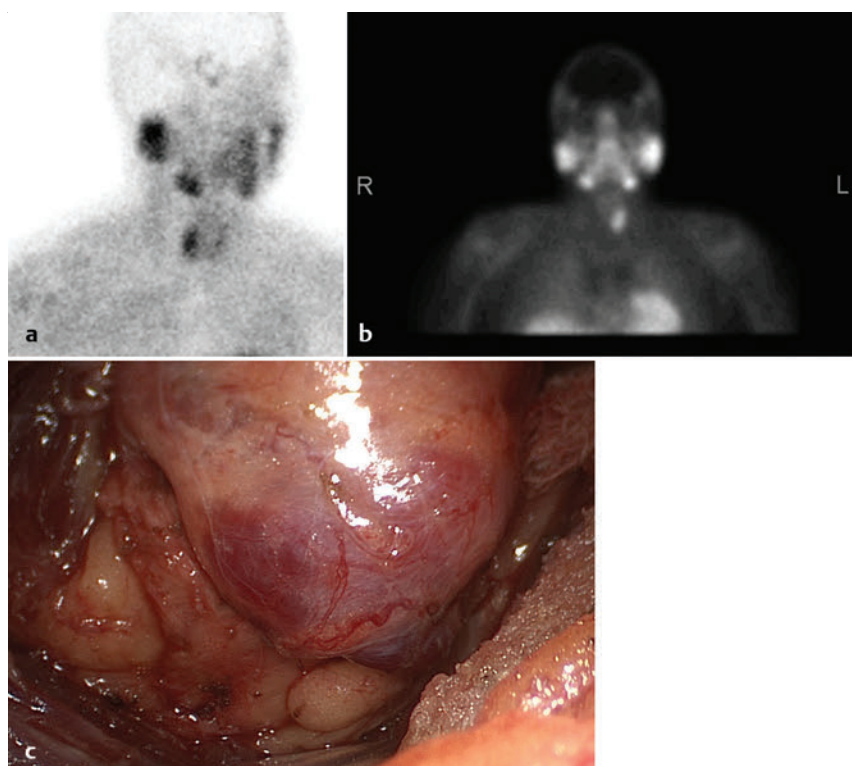


Fig. 29.1 In addition to obtaining the operative note and the pathology report from a failed parathyroidectomy, review of the previous imaging can be revealing. (a) This patient underwent a unilateral right exploration at an outside institution on the basis of the original sestamibi scan, with removal of a single normal parathyroid. A thyroid lobectomy was done and an oncocytic adenoma was diagnosed on final pathology. No intraoperative PTH testing was done, and the patient suffered from persistent hypercalcemia. (b) Repeat imaging revealed an obvious left inferior adenoma. (c) The adenoma was removed at subsequent surgery.

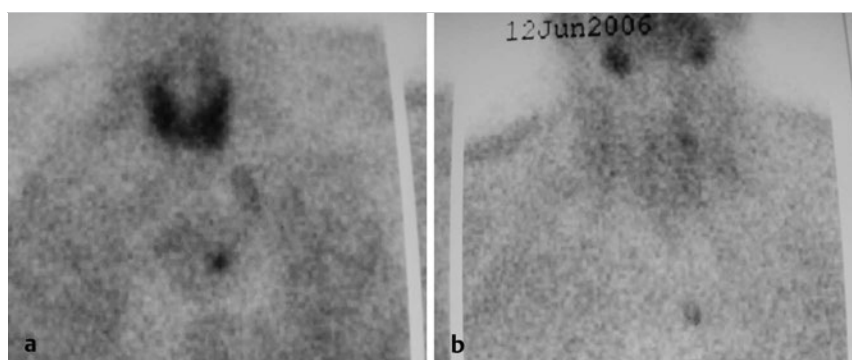


Fig. 29.2 Glands missed at primary surgery may be ectopic, and when they are the mediastinum is often the location for these adenomas. A patient with renal hyperparathyroidism had a four-gland exploration, but only three glands were identified. (a) The first imaging he had done was subsequent to the failed primary surgery, and the sestamibi scan revealed a left mediastinal hyperplastic gland, early phase, and (b) delayed phase. This gland was retrieved using a trans-cervical approach with reoperative surgery.

high-volume center (the yield is considerably better at institutions that perform > 30 sestamibi scans/y⁹). Some investigators advocate that at least two co-localizing studies are necessary before contemplating reoperative surgery.¹⁰

If the ultrasound or sestamibi scan is negative or equivocal, additional imaging may be considered. Historically, magnetic resonance imaging (MRI) or computed tomography (CT) was often pursued. More recently, the group at MD Anderson Cancer Center has described a novel and robust sequencing of a CT scan, dubbed a four-dimensional (4D)-CT (in which time is the fourth dimension).¹¹ Although this exposes the patient to a considerable amount of radiation, a number of authors have found this modality to be reliable, especially in the reoperative setting.¹²

Invasive localization techniques are also available, but not without substantial risks. Selective venous sampling was described as early as the 1970s,¹³ and more recently has been combined with the rapid parathyroid hormone (PTH) assay to identify a gradient that may reveal the location of an adenoma.¹⁴ Angiography has also been described as a method of identifying

a tumor “blush” suggestive of an adenoma.¹⁵ Angiography has the added advantage of providing a means for devascularizing the adenoma with embolization. There have been reports of patient stroke and even death with these invasive studies, so they should be reserved for only rare circumstances.

Finally, there are nonradiological physiological adjuncts that may help to localize or at least lateralize the location of a missing adenoma. Bilateral internal jugular venous sampling for the PTH level can demonstrate the side of the adenoma by virtue of a 5 or 10% gradient. This may be done preoperatively¹⁶ or intraoperatively.¹⁷ If a lesion is visualized either by ultrasound or intraoperatively, a washout of a needle aspirate may be sent for a PTH level. The result of this assessment is essentially binary; a lymph node, thyroid nodule, or other nonparathyroid tissue will have a level of <20. Parathyroid tissue will have a level > 2,000 or 3,000. It is important to note that this type of aspirate should not be done in primary or otherwise routine cases because there is a risk of disrupting the histology and creating a clinical and pathological appearance that mimics parathyroid carcinoma.

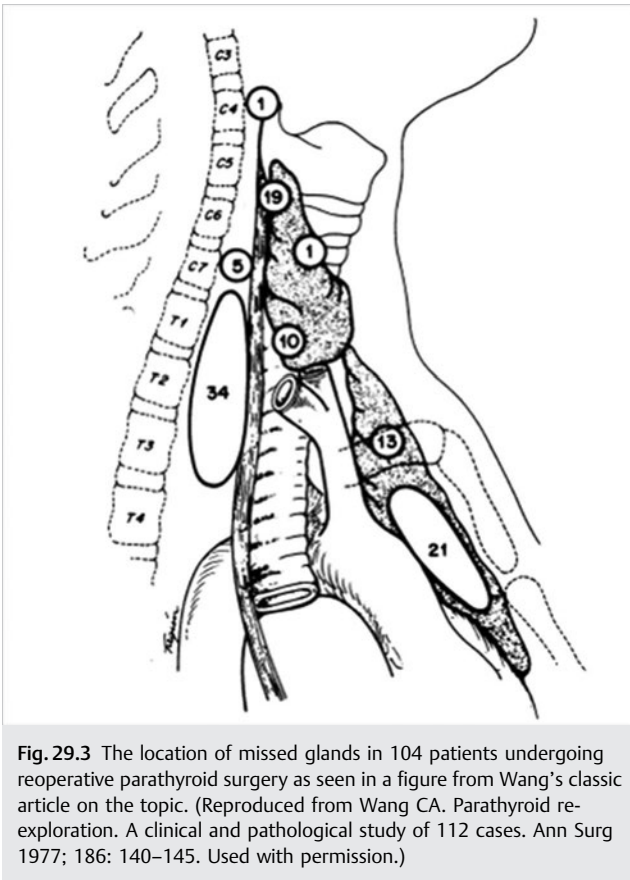


Fig. 29.3 The location of missed glands in 104 patients undergoing reoperative parathyroid surgery as seen in a figure from Wang's classic article on the topic. (Reproduced from Wang CA. Parathyroid re-exploration. A clinical and pathological study of 112 cases. *Ann Surg* 1977; 186: 140–145. Used with permission.)

29.5 Embryology and Common Locations for Ectopy

It is important to be familiar with embryology as it relates to the parathyroid glands. The superior parathyroid glands are associated with the fourth branchial arch, whereas the inferior parathyroid glands are associated with the third branchial arch and the thymus. Because the inferior glands travel a greater distance they are substantially more variable in location than the superior glands and are more likely to be ectopic. They may be undescended, and therefore located in the submandibular triangle or just superior to the superior vascular pedicle of the thyroid glands. They are commonly located in the thyrothymic ligament, or even in the thymus proper. They may be located anywhere along the carotid sheath. Importantly they remain ventral to the recurrent laryngeal nerve regardless of the inferior/superior positioning (► Fig. 29.5).

The superior glands by contrast remain dorsal to the recurrent laryngeal nerve, even when they are ectopic in their location. They may be overly descended and in a paraesophageal or retroesophageal location, or even further inferior in the posterior mediastinum. They may also be relatively undescended and therefore retropharyngeal. Either the superior or inferior glands may also be intrathyroidal, which occurs about 1% of the time (► Fig. 29.6).¹⁸

Patients with renal hyperparathyroidism pose a particular challenge in that they are much more likely to harbor ectopic glands. In addition, they not uncommonly have supernumerary glands. It is likely that these represent activation of parathyroid

rests in the thymus that are known to occur. This rate of ectopy, which approaches 40%, is one reason why imaging, especially a sestamibi scan, is appropriate in this patient population despite historical dogma to the contrary.¹⁹

29.6 Surgical Considerations

A deliberate approach should be taken when contemplating reoperative parathyroid surgery. Assuming the diagnosis has been confirmed, the reasons for previous failure have been determined, and localization has been obtained, the surgeon should be moderately to highly confident of the adenoma's location before recommending reoperation. Necessarily, the threshold for pursuing surgery is higher because reoperative procedures carry a greater risk of complications, and scar tissue from the prior exploration will substantially impact the ability to accomplish a thorough dissection. Therefore mild cases in which imaging is unrevealing may be observed.

The quadrant and the specific location of the anticipated adenoma will impact the surgical planning. In addition, the extent of the prior exploration will be an important factor, particularly if a thyroidectomy (unilateral or bilateral) has been accomplished. A ventral approach is certain to require dissection through scar tissue. For this reason, and particularly for a superior adenoma or a paraesophageal lesion, a lateral approach (even if using a centrally located incision) may be advisable. This implies approaching the thyroid compartment from between the sternothyroid and the sternohyoid muscles, or lateral to the sternohyoid just medial to the carotid sheath. This is sometimes called a “back door” approach (► Fig. 29.7) and may also be useful for papillary thyroid cancer lymph node recurrences in the central compartment.

Because of the risk to the recurrent laryngeal nerve, nerve monitoring is advisable in reoperative surgery. As in primary explorations, identification of the recurrent nerve is not mandatory; however, if extended dissection is required it may be helpful to know the location of the nerve to allow a more aggressive dissection. We prefer a hybrid system of nerve monitoring (► Fig. 29.8) that uses the Nerve Integrity Monitor (Medtronic, Inc.) interface with a nondisposable stimulating device (Nerveana, Neurovision, Inc.).

The use of intraoperative PTH testing is helpful in two important dimensions. Not only does it function to assure that no residual hyperfunctional tissue remains after removal of the adenoma (as with primary surgery; ► Fig. 29.9) but it serves an additional important role in helping to mitigate against permanent hypoparathyroidism. Decisions regarding reimplantation of normal or even mildly abnormal parathyroid tissue may be governed by the level to which the PTH assay drops. The authors use the Future Diagnostics assay, which is performed as a point-of-care assay in the operating room and is accomplished with a turnaround of approximately 8 minutes.²⁰

As mentioned under the section on imaging, intraoperative physiological adjuncts may prove to be useful. Aspiration of tissue and assay of the needle washout can be done intraoperatively to distinguish parathyroid tissue from nonparathyroid tissue, and is faster than frozen sections.²¹ The internal jugular veins can be sampled bilaterally, and a differential between the two sides may indicate the likely side of the adenoma. Finally, immediate preoperative ultrasound (► Fig. 29.10) and

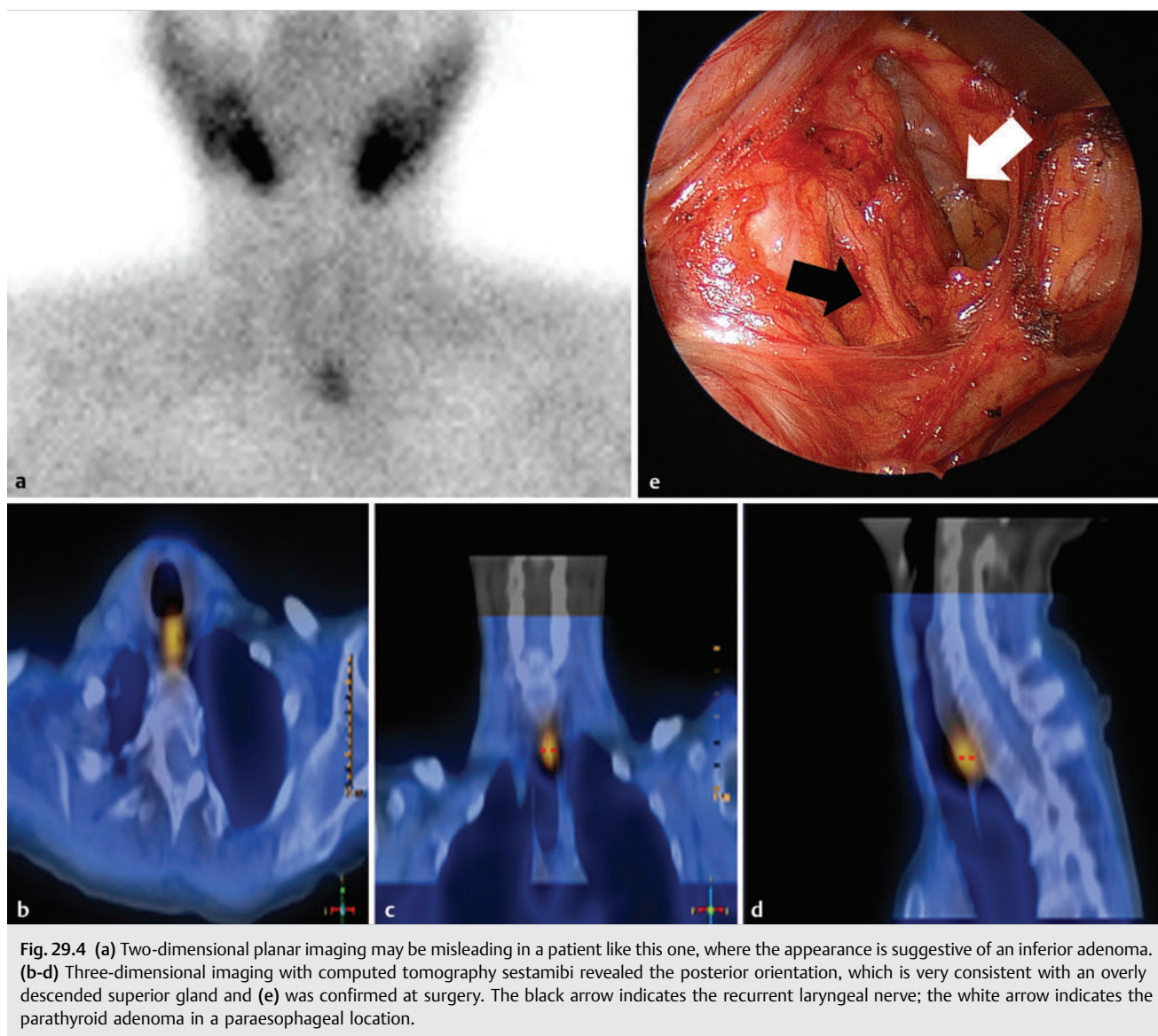


Fig. 29.4 (a) Two-dimensional planar imaging may be misleading in a patient like this one, where the appearance is suggestive of an inferior adenoma. (b-d) Three-dimensional imaging with computed tomography sestamibi revealed the posterior orientation, which is very consistent with an overly descended superior gland and (e) was confirmed at surgery. The black arrow indicates the recurrent laryngeal nerve; the white arrow indicates the parathyroid adenoma in a paraesophageal location.

occasionally intraoperative ultrasound can be used for verification purposes and to further localize an adenoma.

If the offending gland or glands cannot be identified in their expected location(s), the surgeon will need to decide if it is in the patient's best interest to proceed with a full, systematic exploration of all potential ectopic locations or if it is more prudent to terminate the procedure without causing further tissue disruption and potential morbidity. An empirical thyroid lobectomy should not be performed because it has a very low yield and will render future explorations more challenging.

29.7 Postoperative Management

It is well known that the risk of complications is substantially higher in patients undergoing reoperative parathyroidectomy compared with primary surgery. Both recurrent nerve injury and hypocalcemia occur at a higher rate in the reoperative setting.²²

The principal value of laryngeal nerve monitoring is the reduced likelihood of bilateral nerve dysfunction, which can occasionally necessitate a surgical airway. Although identification of the recurrent laryngeal nerve can be challenging, the stimulation of the vagus nerve, which is more proximal in the laryngeal nerve pathway, allows verification of electrophysiological nerve integrity on one side before contemplating surgery on the other side and may be useful.

Particularly when one or more parathyroid glands are removed at the previous operation, successful reoperative parathyroid surgery may in some circumstances render a patient hypoparathyroid, at least temporarily. When this circumstance is anticipated, we recommend early initiation of calcitriol in addition to our usual 3-week calcium supplementation regimen, which is used even in the primary surgery setting and for bilateral thyroid surgery.²³

Although most patients undergoing reoperative parathyroid surgery can be managed on an outpatient basis, as with patients undergoing primary surgery this should be pursued cautiously. Any type of renal parathyroid surgery, whether it is

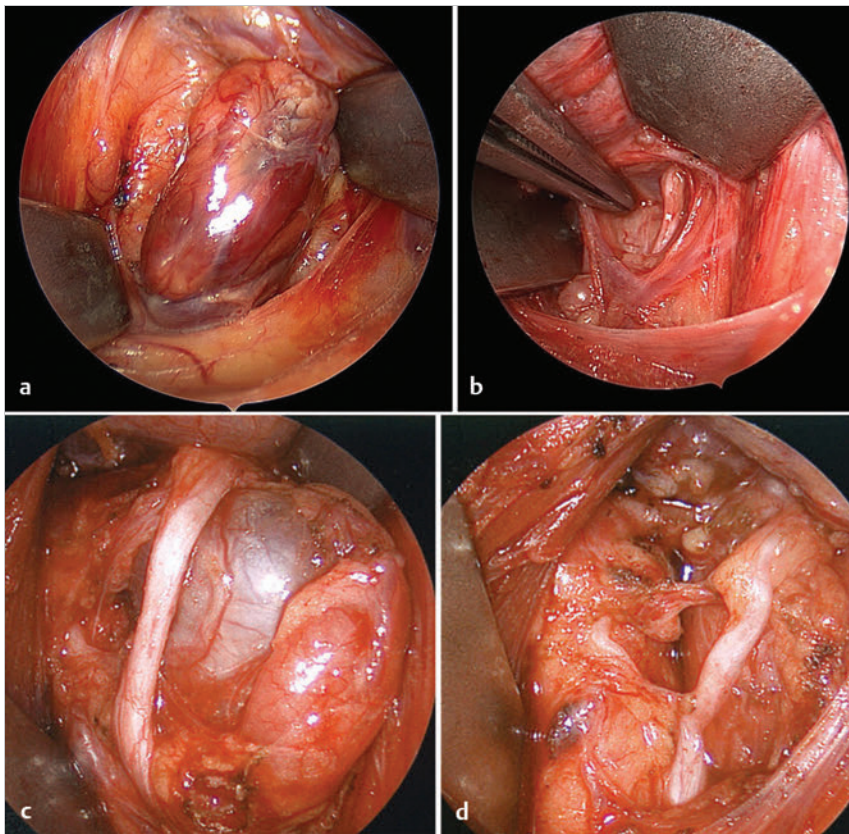


Fig. 29.5 The parathyroid glands have a consistent relationship to the recurrent laryngeal nerve. (a) An inferior adenoma will be ventral to the nerve, which is seen after removal of (b) the overlying adenoma. (c) Superior adenomas are deep to the nerve, which in this case is somewhat displaced over the top of the nerve. (d) After removal, the nerve is restored to its anatomical location.

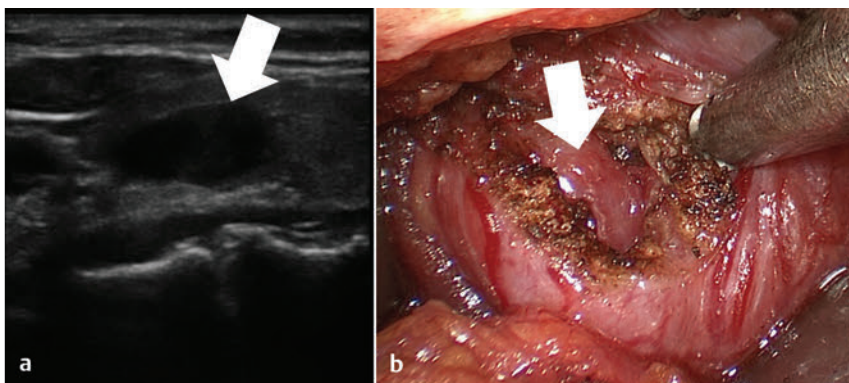


Fig. 29.6 (a) Intrathyroidal parathyroid adenomas may be suspected preoperatively on the basis of ultrasound appearance or computed tomography sestamibi findings. (b) The adenoma may be retrieved by performing a thyroidotomy (without the need for removing the lobe). The white arrow indicates the parathyroid adenoma.

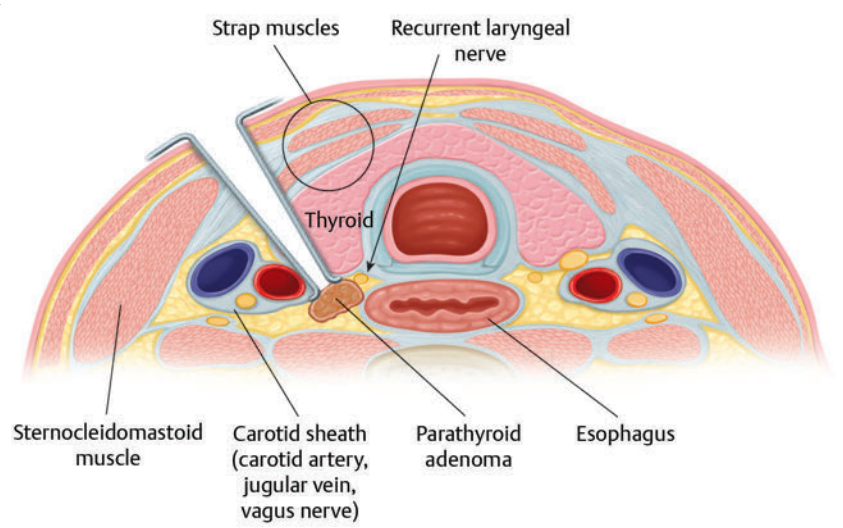


Fig. 29.7 When pursuing reoperative surgery after a ventral approach, scar tissue may be avoided by approaching the thyroid compartment from lateral to the strap muscles (and medial to the carotid sheath).

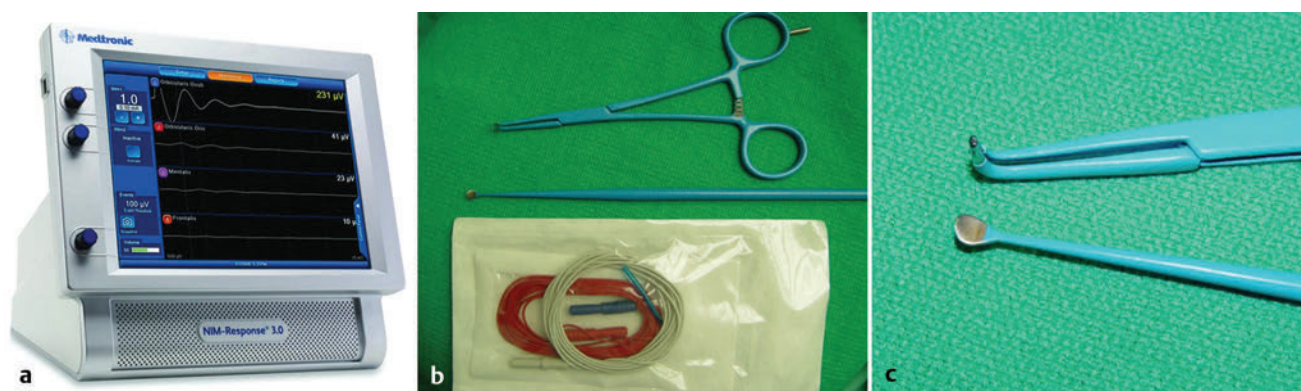


Fig. 29.8 (a) The authors have evolved to using a hybrid nerve monitoring system that exploits the superior user interface of the Medtronic Nerve Integrity Monitoring System, along with nondisposable instruments crafted by Neurovision Medical Products. We prefer an elevator and right-angle clamp (b,c).

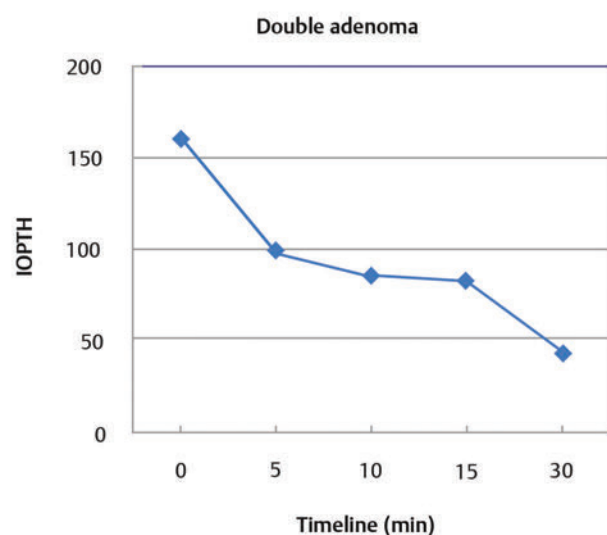


Fig. 29.9 The intraoperative parathyroid hormone (IOPTH) assay can be instrumental in reducing failure due to a missed double adenoma. The degradation pattern often reflects a reduction in PTH level after excision of the first adenoma, but with a failure to reach the normal range until the second adenoma is excised.

primary or reoperative, will require overnight hospitalization, often for several days.

29.8 Outcomes and Future Directions

Patients undergoing reoperative parathyroid surgery are not only at higher risk for complications, they may anticipate a lower chance of surgical success. Nevertheless, in expert hands and especially with positive localizing studies the success rate may approach 85 or 90%. Although cryopreservation has been advocated in the past, with the advent of the rapid intraoperative PTH assay, and considering the expense and logistics associated with storing frozen tissue coupled with the poor long-term



Fig. 29.10 It is helpful to repeat cervical ultrasound after the patient is anesthetized and positioned properly on the operating table.

viability of cryopreserved parathyroid tissue, this approach has largely been abandoned.

Promising investigation in the area of recombinant parathyroid hormone holds the possibility of replacement therapy for either postthyroidectomy or postparathyroidectomy patients in whom there is no viable parathyroid tissue remaining.²⁴ Intraoperative identification of parathyroid tissue is also the subject of intense research, and application of novel techniques may represent another important advance.²⁵ As with the last decade, it is likely that technology will provide the fulcrum for additional incremental improvements in the care of the patient with hyperparathyroidism in the near future.

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Part 6

Special Topics

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30 Complications of Thyroid and Parathyroid Surgery

Michele N. Minuto and Emanuela Varaldo

30.1 Introduction

The history of thyroid surgery is a perfect example of how surgery evolved between the 19th and 20th centuries. In the mid-19th century, thyroid surgery was legally banned by the French Academy of Medicine and was also discouraged by many surgeons from different countries because of its appalling results. In 1850, perioperative mortality following thyroid surgery was 40%.^{1,2} The use of ether, antiseptics, and effective instruments for hemostasis led to a significant improvement in the results of thyroid surgery and heralded its “modern era.” Thanks to iconic surgeons, such as Kocher, Billroth, Halsted, Mayo, Crile, and Lahey, the decrease in mortality steered discussion toward issues of specific “morbidity” related to this surgery.

By 1909, when Kocher was awarded the Nobel Prize, mortality from thyroid surgery had decreased to <1%. As a result, long-term outcomes could be properly evaluated. Further, comparisons could be made between the results obtained by Kocher and those of other surgeons, such as Billroth. According to Halsted, who visited both Bern and Vienna, Kocher's patients suffered postoperatively from a condition that was described as “cachexia strumipriva,” whereas Billroth's patients developed a condition similar to tetany. Both of these postoperative complications were considered serious. Complications resulting from damage to the recurrent laryngeal nerve (RLN), which had been known since the 16th century, led Billroth, Kocher, and Joll to describe a technique called “no see, no harm.” The premise was that a low incidence of injury to the RLN could be achieved by not exposing the nerve during surgery. However, this proved not to be true. Later, in 1938, based on Bier's descriptions,³ Lahey reported that routine exposure of the RLN resulted in an injury rate of only 0.3%.⁴

During the 20th century, a greater understanding of the factors that led to complications resulted in “minor” technical upgrades that yielded excellent results. These benefits are still evident today. Nevertheless, despite every technical improvement and effort to use sound surgical techniques, complications associated with all surgical procedures are inescapable, even if they are extremely rare.

Within this context, morbidity can be divided into two main groups: (1) the generic surgical complications that are common to every surgical procedure and mainly involve postoperative bleeding, infections, deep venous thrombosis, and the cosmetic issues related the site incision; and (2) surgical complications that are specific to thyroid and parathyroid surgery, such as recurrent and superior laryngeal nerve injury and hypoparathyroidism. This chapter primarily discusses specific causes of morbidity following thyroid and parathyroid surgery, with some attention devoted to the more peculiar aspects of the general complications.

30.2 General Complications

30.2.1 Bleeding

The most dreaded complication following thyroid and parathyroid surgery is the possibility of life-threatening bleeding.

Postoperative bleeding has been well described since the dawn of this operation, and, in 1866, Samuel L. Gross memorably described its horrific nature.⁵ Although at the beginning of the 20th century, postoperative bleeding (along with infection) was the main cause of mortality, today it is a rare complication.⁶ The actual incidence of postoperative bleeding, which occurs more after thyroidectomy than parathyroidectomy, is difficult to assess because of the diversity of findings reported in the literature. The reported incidence of postoperative bleeding requiring surgical intervention ranges from 0.3 to 4.2%.^{7,8,9,10} It is commonly accepted that the true incidence is <1%. Apart from meticulous hemostasis during the surgery, there is no evidence that there is any effective strategy that can identify patients who have a higher risk of bleeding or that can prevent its occurrence following surgery.^{7,11} Therefore, neither the use of hemostatic devices,^{12,13,14} agents,¹⁵ or drains¹⁶ have been shown to be effective in lowering the incidence of bleeding or the necessity for reoperation.

In conclusion, a certain rate of bleeding is unavoidable and this, in fact, is the main objection to the practice of outpatient thyroid and parathyroid surgery, which should be limited to carefully selected patients. Even though most bleeding occurs within the first 6 to 8 hours, a longer observation period is warranted because delayed bleeding has been reported.^{7,10,11,17} Clinically, the acute onset of neck swelling or compressive symptoms (dyspnea and dysphonia) warrants strict evaluation and immediate treatment. From a strategic point of view, the algorithm for the management of bleeding complications is well standardized. The key points entail securing the airway and reoperation in clinically severe or even doubtful cases.

30.2.2 Infection

Infection is an extremely rare complication following thyroid and parathyroid surgery, with most series reporting an incidence well under 1%.^{8,18} Therefore, the administration of prophylactic antibiotics does not appear to be necessary for all patients undergoing surgery (even if this strategy varies considerably among different centers), and should be indicated only in selected patients who are at a higher risk of developing infections.

30.2.3 Deep Venous Thrombosis

Patients undergoing thyroid and parathyroid surgery are generally mobile in the immediate postoperative period, with many centers performing the surgery on an outpatient basis. Consequently, the incidence of deep venous thrombosis results mainly from anecdotal reports. Because the potential consequences of a bleeding complication are significantly greater in thyroid and parathyroid surgery than in other types of procedures, medical prophylaxis of deep venous thrombosis is generally considered unsafe and unnecessary. However, chemical prophylaxis may be appropriate in certain carefully selected high-risk patients.¹⁹

30.2.4 Poor Cosmetic Outcomes

In a population with a significant percentage of female patients, a good cosmetic outcome is essential when surgery is performed in such an exposed anatomical location as the anterior neck. Because cosmesis is a central issue in the overall outcome of this surgery, the possible formation of a keloid scar should be adequately discussed with the patient before surgery, together with the other morbidity-related issues. There are general principles that must be strictly followed when performing an incision on the neck that might reduce the risk of keloid formation.

First the location of the incision needs to be adequately planned, keeping in mind that, in the supine position, the scar is always lower than expected after surgery. The incision line should therefore be marked with the patient standing in the upright position while simultaneously correcting for the distortions caused by a bulky thyroid, with the aim of obtaining a symmetrical result. Traditionally, the incision should be placed on a skin crease, at an average distance of two fingerbreadths from the sternal notch (depending on the patient's anatomy), and its length should be tailored on the size of the gland to be removed. It is worth noting that the incision can be significantly smaller than the size of the gland, because the manipulation and the devascularization of the gland will decrease its size, allowing for safe extraction. This fact has been taken to the extreme in minimally invasive techniques.^{20,21} Nevertheless, the incision should not be so small that the skin edges are traumatized by excessive stretching from retractors or that the risk of undesired necrosis is increased from using energy instruments in a narrow space. In obvious or suspected cases of traumatized edges, adequate resection of the margins followed by reconstruction at the end of the procedure is highly suggested, as described by Terris and colleagues.²²

Another significant factor leading to a poorer cosmetic outcome is the creation of a wide skin flap when entering the thyroid bed. Avoiding or limiting this dissection eliminates dead space under the skin where fluid might accumulate, and might therefore be helpful in obtaining a good cosmetic result.

The skin closure can be performed using several different techniques and materials. There is no large, prospective, randomized study that clearly demonstrates the superiority of any one method. Every material (monofilament, staples, or cyanoacrylate) and every technique (stitches or intradermic sutures) has its own pros and cons. Therefore, the choice of which method to adopt depends on the surgeon's personal preference.

A few words should also be devoted to the placement of the drains, which do nothing to prevent postoperative bleeding (see earlier). Drains can be responsible for cosmetic impairments if incorrectly placed. The correct positions are generally considered those that are separate from but in line horizontally with the main incision. This technique makes the drain incision less noticeable and often leads to healing without a visible scar. Placing the drain beneath the incision line or, worse, inferiorly and medially, is not suggested, because the risk of a keloid scar is higher in this location and the incision is less likely to be hidden. Lastly, the placement of a drain in the middle of the incision is discouraged because it can create a widened scar at its point of entry.

30.3 Specific Complications

30.3.1 Recurrent Laryngeal Nerve Injury

Recurrent laryngeal nerve injury is the most universally known complication following thyroid and parathyroid surgery and has been described since the first reports of patients undergoing thyroid surgery who survived the operation. It is also the most obvious complication that seriously impacts the patient's quality of life due to its immediate impairment of vocal cord functioning, ventilation, or swallowing.

Even though the incidence of RLN injury is frequently reported to be approximately 1%, the actual rate is far greater for several reasons:

- The lowest incidences reported in the literature are derived from studies with a limited number of patients. These studies do not have the statistical power to arrive at definitive conclusions about the true incidence of such a rare event.
- These same studies are generally performed with aims other than evaluating morbidity. Therefore, the incidence of RLN injury, although correctly reported, cannot be considered significant.
- Even though an incidence of RLN injury of approximately 1% may be achievable when dealing with benign thyroid or parathyroid disease, the studies that focus only on these disorders are uncommon. Thyroid surgery performed for malignant disease will invariably have a worse injury rate.
- The results are often reported without the contribution of a routine pre- and postoperative laryngoscopic evaluation, and thus rely only on the patient's postoperative symptoms for diagnosis. Because it is well described that damage to the RLN can exist in the presence of a remarkably normal voice, the real incidence of injuries cannot be adequately assessed in the absence of postoperative laryngoscopy. In a series that was not limited to patients who had undergone previous neck surgery, it was shown that asymptomatic paralysis of the vocal cords is present in as high as 1.8% of patients preoperatively.²³

Taken together, these observations place the reported incidence of RLN injury between 0.3% as described by Bergamaschi et al²⁴ and 6.6% as reported by Echternach et al.²³ Although it is reasonable to assume that the true incidence lies somewhere between these two extremes, to our knowledge, no study has included a large enough sample size (arguably consisting on more than 1,000 nerves-at-risk) to allow a definitive conclusion. The incidence of transient and permanent RLN injury in studies with a significant amount of nerves-at-risk is summarized in ► Table 30.1.^{8,23,24,25,26,27,28,29,30,31}

A detailed analysis of these studies reveals that, once the extreme results are eliminated, the incidence of RLN injury is quite similar across all experienced groups. Further, a reasonable rate can be placed at less than 1% during thyroidectomies for benign disease, and approximately 2% for patients undergoing surgery for malignant disease. Regarding the latter, it is interesting that a huge multicenter Italian study by Rosato and colleagues⁸ found that the incidence of paralysis increased with the more aggressive tumors, reaching a high of 16.5% in patients with anaplastic thyroid cancer, followed by 5.4% in those with medullary thyroid cancer and finally 1.4% in patients

Table 30.1 Summary of recurrent laryngeal nerve (RLN) morbidity rates in thyroidectomy, as found in studies with significant numbers of nerves at risk/patients

Study	Nerves at risk	Surgical indication	Recurrent laryngeal nerve injury		Study/country
			Transient	Permanent	
Rosato et al, 2004 ⁸	14,934 patients	Benign and malignant disease	3.4	1.4	Multicenter, Italy
Thomusch et al, 2000 ²⁵	13,436	Benign disease	2.1	1.1	Multicenter, Germany
Bergamaschi et al, 1998 ²⁴	2,010	Benign disease	2.9	0.3	Single center, France
Echternach et al, 2009 ²³	1,365	Benign and malignant disease	6.6		Single center, Germany
Efremidou et al, 2009 ²⁶	1,864	Benign disease	0.2	1.3	Single center, Greece
Lefevre et al, 2007 ²⁷	685 patients	Recurrent disease / completion thyroidectomy	2.6	1.5	Single center, France
Steurer et al, 2002 ²⁸	1,080	Benign/malignant / hyperparathyroidism	3.4/7.2/2.5	0.3/1.2/0	Single center, Austria
Chiang et al, 2005 ²⁹	704	Benign and malignant disease	5.1	0.9	Single center, Taiwan
Toniato et al, 2008 ³⁰	1,008	Malignant disease	2.2		Single center, Italy
Lo et al, 2000 ³¹	787	Benign and malignant disease	3.3	0.9	Single center, China

with papillary thyroid cancer. Given the rarity of both medullary and anaplastic thyroid cancer, this result could only have been obtained with confidence based on the large sample size of approximately 15,000 patients. Further, these results confirm that the more aggressive the surgery the higher the rate of iatrogenic injuries.

Reoperation for either benign or malignant disease represents another preoperative factor that significantly impacts the rate of RLN injuries. One multicenter German study also showed lobectomy as a potential higher risk factor, though this observation is difficult to justify.²⁵ Other factors that have been traditionally associated with higher rates of RLN injuries, such as surgery performed for Graves' disease, substernal goiter, or thyroiditis, have not been proven to increase this morbidity in well-designed studies. The risk factors associated with a higher risk of RLN injury are summarized in ► Table 30.2.^{8,27,31,32,33,34}

Preoperatively, patients should be made aware that their risk of RLN injury in most cases is approximately 1% and that the risk of injury increases with malignant or recurrent thyroid disease. Conversely, the incidence of RLN injury is negligible in those patients undergoing parathyroid surgery.²⁸

From a pathophysiological point of view, the precise mechanisms that lead to injury of the RLN are still unclear, except for those extremely rare situations where the nerve is purposely or accidentally sectioned. In these circumstances, suturing the transected nerve is indicated, a strategy that has been described since the first years of modern thyroid surgery. Though suturing the nerve rarely leads to a full recovery of vocal cord motility, it at least allows the affected cord to maintain some bulk and better prepares the patient for voice therapy.³⁵

Most commonly, paralysis of the vocal cord occurs without transection of the nerve. In these cases, the damage may have resulted from excessive manipulation of the nerve, trauma from several causes (such as prolonged compression or other mechanical injuries), excessive dissection causing devascularization, thermal injuries from electrocautery or other energy instruments, or local inflammation. When a nerve is not transected, vocal cord motility generally recovers after anti-inflammatory therapy with steroids, some cycles of voice therapy, or even spontaneously, though the time to recovery may range from a few hours to 6 months. Postoperative paralysis of the vocal cords is considered temporary when present in the first 6 months after surgery and should be labeled as permanent if it persists beyond that time frame.

Other rare situations that might be responsible for unexpected vocal cord paralysis from RLN injury include the lack of recognition of the nerve during the thyroidectomy (possibly due to an earlier transection), transection of a laryngeal motor branch mistaken for an esophageal branch (laryngeal motor branches are not necessarily the largest ones, though they are generally those most anterior and closest to the thyroid gland),³⁶ and the presence of a rare anatomical anomaly, such as a nonrecurrent variant in patients with an arteria lusoria (aberrant right subclavian artery),³⁷ which is present in 0.5 to 1% of the population. In the latter case, if the variant is not properly recognized, the aberrant nerve can be transected in the early phases of the operation. Unfortunately, even though there are now costly preoperative techniques that can correctly identify arteria lusoria,³⁸ these are not routinely performed for patients undergoing thyroid or parathyroid surgery.

Table 30.2 Risk factors significantly associated with higher rates of recurrent laryngeal nerve injury during thyroidectomy in studies with significant numbers of patients or nerves at risk

Study	Nerves at risk/patients at Risk	Risk factor(s)
Dralle H et al, 2004 ³²	29,998	Recurrent benign/malignant disease, thyroidectomy for cancer, lobectomy
Rosato L et al, 2004 ⁸	14,934 patients	Malignant disease: anaplastic > medullary > papillary/follicular
Erbil Y et al, 2007 ³³	3,250 patients	"Extended" thyroidectomy
Lefevre et al, 2007 ²⁷	685 patients	Recurrent disease and completion thyroidectomy
Loh et al, 2000 ³¹	787	Malignant disease and recurrent substernal goiters
Shindo et al, 2010 ³⁴	512	Lymph node dissection

Intraoperative nerve monitoring can be used during thyroidectomy and parathyroidectomy and is particularly useful in identifying the RLN. Though this technology might help to identify how damage to the nerve occurs, several studies have failed to show that monitoring has a significant impact on the rate of RLN injuries.³⁹

Clinically, patients suffering from an RLN injury generally display symptoms that are primarily related to the position of the paralyzed vocal cord, which can be either medial or lateral. Overall, the voice is generally hoarse, though it may sound normal to inexperienced ears. Along with the patients themselves, however, experienced thyroid surgeons can generally perceive even minimal voice changes. The voice changes can also be described as "breathiness," which is often a more appropriate term because it better reflects the weakness of the voice. This weakness results from the relative incompetence of the glottis during phonation caused by the lateral position of the cord so that the airflow is not effectively modulated in a symmetrical fashion to the opposite cord. The extent of the voice impairment is generally directly correlated with the degree of lateral displacement. When the cord is in the medial position, dysphonia may be less pronounced, but patients may have respiratory compromise due to a significant reduction in the caliber of the airway. This compromise is generally more apparent in situations of high respiratory demand, such as physical exertion.

In addition to the voice alterations, patients with RLN injuries may also have impairment of their swallowing ability, reflecting the damage to the sensory branches that run lateral to the motor branches and innervate the esophagus. The patients may also complain of dysphagia when the motor branches are left intact and the thinner sensory branches are not recognized and are inadvertently injured during surgery. Impaired glottic closure coupled with loss of sensation can lead to aspiration.

In conclusion, patients with RLN injury generally present with different symptoms according to the severity and the position of the paralyzed cord. These include variable degrees of voice impairment, dysphagia, respiratory distress, and, in the long run, a higher rate of respiratory infections. If a postoperative stroboscopy is not routinely performed after surgery, the presence of these symptoms warrants appropriate diagnosis and treatment.

30.3.2 Bilateral Recurrent Laryngeal Nerve Injury

When a total thyroidectomy is planned, the patient should be informed during the consenting process of the rare possibility

of bilateral RLN paralysis. Although these cases are mostly anecdotal, they are a part of almost every surgeon's experience and represent emergencies that require urgent treatment. In these cases, the airway should be secured by either reintubation or tracheotomy if the patient displays acute respiratory obstruction (in cases where both cords are medialized). If, after extubation, the patient is able to tolerate the degree of airway obstruction, continuous monitoring of oxygenation should be performed and intravenous steroids given. When the O₂ saturation has normalized and is stable, the patient can undergo further evaluation and treatment. In all other cases, a temporary tracheotomy should be performed and later removed after adequate motility of at least one vocal cord is confirmed.

Current Italian guidelines⁴⁰ recommend reintubation for 24 hours immediately following the diagnosis of bilateral paralysis of the vocal cords. A second attempt at extubation should be carried out the day after surgery following treatment with steroids. If the acute obstruction is still present then a second extubation is attempted 48 hours after surgery. If, after instituting these steps, the patient still fails to maintain an adequate respiratory status, tracheotomy is indicated.

30.3.3 Superior Laryngeal Nerve Injury

Postoperative rates of superior laryngeal nerve (SLN) injury during thyroidectomy range from 0 to 28% (► Table 30.3).^{41,42,43} This wide range essentially results from the same reasons previously described for the incidence of RLN damage. The SLN originates within the nodose ganglion of the vagus. Approximately 1.5 cm below the jugular foramen it divides into two branches: the internal branch, supplying the sensory innervation to vocal folds and supraglottic larynx, and the external branch (EBSLN), which provides motor innervation to the cricothyroid muscle. The EBSLN courses along the inferior pharyngeal constrictor muscle in close proximity to the branches of the superior thyroid artery. It then curves anteriorly and medially and approaches the larynx within the sternothyroid-laryngeal triangle after which it divides in two branches, one entering the pars recta and the second at the pars obliqua of the cricothyroid heads.

The EBSLN motor fibers to the cricothyroid muscle cause it to tilt the thyroid cartilage, tensing the vocal cords. This action affects the characteristic timbre of one's voice. Injury to the nerve changes the quality, projection and production of high-pitched sounds. In these cases, patients typically complain of voice fatigue, problems reaching high-pitched sounds, increased work of phonation, and dysphagia.

Table 30.3 Visualization and morbidity rates for the superior laryngeal nerve during thyroid surgery in studies with a significant number of patients

Author	No. patients	Visualization rate (%)	Morbidity rate (%)	Study
Bellantone R et al, 2001 ⁴¹	289	89 (when searched for) vs. 0	0 vs. 0	Prospective, randomized
Jonas et al, 2000 ⁴²	108	37.5	0	Prospective
Hurtado-Lopez et al, 2005 ⁴³	100	78 (when searched for) vs. 0	8 vs. 20	Prospective, randomized

Table 30.4 Incidence of postoperative hypoparathyroidism after thyroidectomy, as reported in studies with a significant number of patients

Author	Patients	Surgical indication	Hypoparathyroidism (%)		Study/country
			Transient	Permanent	
Rosato et al, 2004 ⁸	14,934	Benign and malignant disease	8.3	1.7	Multicenter, Italy
Thomusch et al, 2000. ²⁵	7,266	Benign disease	6.4	1.5	Multicenter, Germany
Bergamaschi et al, 1998 ²⁴	1,163	Benign disease	20	4	Single center, France
Efremidou et al, 2009 ²⁶	932	Benign disease	7.3	0.3	Single center, Greece
Lefevre et al, 2007 ²⁷	685	Recurrent disease / completion thyroidectomy	5	2.5	Single center, France
Toniato et al, 2008. ³¹	504	Malignant disease		6.3	Single center, Italy

The close relationship between the EBSLN and the superior thyroid vessels puts it at risk of damage during transection of the superior pole of the thyroid, particularly in the presence of its more caudal variants. Different classification schemes have been proposed that aim to describe landmarks that would make it easier to identify the EBSLN during surgery. The most commonly used systems include Cernea's, which categorizes the EBSLN variations according to the distance separating the nerve from the vessels of the superior pole of the thyroid, and Friedman's, which describes the relationship between the nerve and the inferior constrictor muscle (see Chapter 2).^{44,45,46} Despite all surgical effort, a significant percentage of patients have cephalic variants of the EBSLN that cannot be identified during thyroidectomy without unnecessarily extending the surgical dissection. As a result, some thyroid surgeons recommend routine identification of the EBSLN, whereas others do not. Those who support routine identification do so based on studies that have reported a lower incidence of injury when the nerve is identified.^{41,43} To this purpose, the use of intraoperative nerve monitoring has been described to identify the EBSLN, with some series reporting successful results.^{47,48}

Methods have been proposed to aid intraoperative identification and avoid injury of the EBSLN.^{42,46,47,48,49} Careful blunt dissection and gentle traction of the superior thyroid pole in a lateral and caudal direction is performed to obtain good exposure of the superior vascular pedicle. Selective ligation of the vessels of the upper pole as close to the thyroid pole as possible is recommended. Later, to prevent iatrogenic heat injuries, care must be taken to avoid indiscriminate use of monopolar electrosurgical or energy-based devices for sealing vessels.

EBSLN injury can be confirmed postoperatively only through a videostroboscopy in conjunction with electromyography of

the cricothyroid muscle. Both of these evaluations are operator dependent and can create a significant amount of discomfort for the patient. For these reasons, these tests are indicated only in suspicious cases and are not routinely performed. This may in fact provide a partial explanation as to why EBSLN injuries are underestimated. In the presence of a documented EBSLN injury, specific speech therapy and voice rehabilitation are recommended because these interventions may lead to successful remission.^{50,51}

Because the superior and inferior parathyroids and the EBSLN are not anatomically in close proximity, this injury has never been described during parathyroid surgery.

30.3.4 Postoperative Hypoparathyroidism

Hypoparathyroidism and postoperative hypocalcemia are the most common complications after thyroidectomy, with a reported incidence between 0.3 and 20%,^{8,24,25,26,27,30} as shown in ► Table 30.4. Because postoperative evaluation of serum calcium is routinely performed, hypoparathyroidism can be classified in "biochemical" (in the presence of asymptomatic hypocalcemia) or "clinical" (e.g., when patients display symptoms of hypocalcemia, such as mild perioral and/or distal acral paresthesias, muscle pain, carpopedal spasm, tetany, and/or laryngospasm), with symptoms usually manifesting 24 to 48 hours after surgery. Hypoparathyroidism is defined as permanent when the hypocalcemia lasts more than 6 to 12 months after surgery and is considered transient in all other cases.

Permanent hypoparathyroidism presents a significant burden for the patient because of the need for lifelong calcium and vitamin D supplementation and the associated increased risk of

developing calcification of the basal ganglia and cataracts. Permanent hypoparathyroidism also increases health care costs through prolonged hospitalizations and long-term health care visits and blood tests. For these reasons, significant effort has been made to define possible risk factors for hypoparathyroidism and develop surgical strategies to preserve parathyroid function.⁵²

The degree of hypoparathyroidism is directly linked to technical factors, such as excessive manipulation (i.e., temporary “stunning” of the glands), devascularization, or inadvertent removal of the glands. Identifying and preserving as much functional parathyroid tissue in situ as possible is essential to reduce the risk of hypoparathyroidism.^{53,54,55} For this reason, a thorough knowledge of parathyroid anatomy (especially the normal and ectopic locations in addition to the blood supply) is critical in thyroid surgery.

The superior parathyroid glands often lie in the posterior aspect of the superior thyroid pole. Their blood supply generally comes from branches of the inferior thyroid artery, from the superior thyroid artery (less frequently), from an anastomotic loop between the superior and inferior thyroid artery, or from the thyroid gland. Their position is generally less variable because of the limited embryological course they follow. Conversely, the position of the inferior parathyroid glands is more variable because of their wider embryological course. They can be found anywhere near the lateral, anterolateral, or posterior aspects of the lower pole of the thyroid. Less commonly, they can be found within the thymus remnant. Their blood supply is derived from branches of the inferior thyroid artery or directly from the thyroid gland.

Once identified, each parathyroid should be meticulously preserved by avoiding excessive dissection and preserving its blood supply by individually ligating the multiple branches of the inferior thyroid artery as close as possible to the thyroid gland capsule. If a surface parathyroid hematoma develops, the parathyroid capsule should be sliced to avoid parathyroid capsule edema.^{54,55}

When the viability of a parathyroid gland is questionable, or in cases of accidental avulsion, autotransplantation in the sternocleidomastoid muscle is suggested. This should be performed after the gland is cut into thin slices (1–2 mm wide) and possibly after intraoperative histological confirmation of parathyroid tissue has been obtained. Following this strategy, despite a potential rise in the incidence of temporary hypoparathyroidism, the rate of permanent hypoparathyroidism can drop to 0%.^{56,57,58,59}

Other factors linked to the development of hypoparathyroidism are related to surgical procedures (e.g., the extent of thyroid resection, bilateral central neck lymph node dissection, and reoperative thyroid surgery),^{55,58,60} the indications for surgery (e.g., Graves' disease), or patient characteristics (e.g., female sex, younger age, and preoperative parathyroid hormone [PTH], calcium, phosphate, magnesium, and vitamin D levels).^{52,61,62,63}

To maximize the chances of a safe and early discharge from the hospital, different protocols have been developed to identify patients at high risk of developing hypocalcemia who should be treated with calcium and vitamin D. Some authors recommend a PTH evaluation 24 hours after thyroid surgery.^{64,65,66} Others suggest that serum calcium levels should be checked 6 hours after surgery and 1 day postoperatively.⁶⁷ Still others advocate

checking ionized calcium on postoperative days 1 and 2,⁶⁸ or both PTH and serum calcium levels on postoperative day 1.⁶⁹ No single protocol has been shown to be more advantageous for the early identification of hypoparathyroid patients.

Different medical centers use different regimens to treat postoperative hypocalcemia. Although there is no consensus, some basic principles should be followed. Hypocalcemia should always be medically treated. Calcium carbonate (1–2 g/d) should be administered orally when the patient is asymptomatic and intravenously in the presence of symptoms. Furthermore, in selected cases, the administration of the biologically active form of vitamin D (calcitriol) can be added to calcium therapy at a dose of 0.25 to 1 µg/d to maximize calcium absorption.

In patients at increased risk for developing hypocalcemia, prophylactic treatment with oral calcium, and later with vitamin D supplementation, has been proposed as a preventive measure. Though this regimen has shown promising results, clear advantages have not been demonstrated in large prospective, randomized trials. Because inhibition of PTH secretion from the residual parathyroid tissue is a theoretical side effect of this prophylactic regimen, this protocol is not universally followed.^{70,71}

30.4 Conclusion

The procedural and technological advances used in thyroid and parathyroid surgery have grown exponentially since the pioneering days at the beginning of the 20th century. Although these advances are now associated with a lower incidence of poor outcomes, greater safety, and improved morbidity, complications following these procedures have not completely disappeared. As with any surgical endeavor, the minimal but significant rate of morbidity that still persists is not likely to be eliminated completely. Surgeons must, therefore, have a clear understanding of the risks of these procedures, mechanisms to minimize their occurrence, and the ability to recognize and rapidly manage complications when they do inevitably arise.

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31 Intraoperative Nerve Monitoring

Dipti Kamani, Rahul Modi, and Gregory W. Randolph

31.1 Introduction

Galen, in the second century, identified and named the recurrent laryngeal nerve (RLN). The anatomical drawings of the RLN distribution were provided much later, in the 16th century by Vesalius.¹ In 1938, Lahey introduced routine dissection and demonstration of the RLN during thyroid surgery.² Prior to this, some researchers believed that the RLN was extremely sensitive and dissection for identification of the RLN led to injury to the nerve, but it has since been proven that identification and dissection of the RLN is well tolerated. Although RLN identification is the gold standard for prevention of RLN injury, intraoperative nerve monitoring (IONM) is a useful adjunct and extension to visual identification, adding a new functional dynamic during thyroid, parathyroid, and neck base surgery. This chapter reviews the principles and application of RLN monitoring techniques, the utility of IONM, and new advancements in the technique. The fundamental philosophy of neural monitoring is that a visually identified, surgically preserved, and structurally intact nerve may not necessarily function normally. A visually intact nerve may not reveal occult stretch or thermal injury. Several recent studies have established that satisfactory electromyographic (EMG) activity at the completion of surgery carries a high negative predictive value (NPV) of >95% for nerve injury.^{3,4,5}

Current studies suggest a majority of general and head and neck surgeons use neural monitoring in their thyroid surgeries in both the United States and Germany. Interestingly, IONM is found to be more commonly used by experienced surgeons in higher-volume head and neck endocrine surgery units. There is increasing organizational support for neural monitoring; German Practice Guidelines and the International Neural Monitoring Study Group suggest that IONM should be considered for all surgeries of the thyroid gland.^{6,7} The American Academy of Otolaryngology–Head and Neck Surgery (AAOHN) published their Clinical Practice Guidelines in 2013, outlining 12 key action evidence-based statements created by a panel of otolaryngologists, laryngologists, anesthesiologists, general surgeons, medical endocrinologists, nursing representatives, patient advocacy representatives, and clinical practice guidelines experts representing the American Academy of Otolaryngology, the American Thyroid Association, the American Association of Endocrine Surgery, the American Head and Neck Society, and the American Medical Association.⁸ They recommend IONM as an option for patients undergoing thyroid surgery, owing to established application of IONM in reducing intraoperative RLN identification time, in reducing temporary vocal cord paralysis (VCP) rates, and in evading bilateral VCP by prognostication of postoperative vocal cord function.

The American Thyroid Association Surgical Affairs Committee recently published consensus statements (on outpatient thyroid surgery and on optimal surgical management of goiters) that support neural monitoring as a tool to confirm intact neural function at the end of surgery, which in turn may impact on discharge planning.^{9,10} Additionally, American Head and Neck

Society (AHNS) guidelines for the management of invasive thyroid cancer proposes that IONM delivers important intraoperative and postoperative functional information impacting the timing of contralateral surgery, and recommends IONM for all cases of thyroid cancer.¹¹

31.2 Reported Incidence of Iatrogenic Recurrent Laryngeal Nerve Injury

The literature reports permanent RLN paralysis rates in expert hands in the 1 to 2% range.¹² However, the rates of RLN paralysis after thyroidectomy in many studies are likely underestimated because most intraoperative RLN injuries are not readily recognized by the surgeons, surgical units with unfavorable data are less likely to report their findings, and not all patients undergo postoperative laryngeal examination.¹³ The Scandinavian Quality Register states that RLN paralysis rate doubles when postoperative laryngeal exams are performed routinely in all patients.¹⁴ Preoperative and postoperative laryngeal examinations are necessary in all patients in order to appreciate the true rate of RLN injury. A recent review of 27 articles that analyzed more than 25,000 thyroidectomy patients found the average postoperative VCP rate was 9.8%.¹⁵ Unilateral VCP can lead to voice changes sufficient to alter vocation, especially in professional voice users, and may be accompanied by dysphagia and aspiration.¹⁶ Bilateral VCP may result in tracheotomy. The factors associated with an increased risk of RLN injury include lack of intraoperative RLN identification, an inexperienced surgeon, surgery for cancer, extensive bilateral surgery, revision surgery, and surgery associated with greater blood loss.

31.3 Preoperative and Postoperative Laryngeal Exam in All Patients

Knowledge of preoperative and postoperative glottic function greatly impacts RLN monitoring as well as surgical management. A preoperative laryngeal exam can detect vocal cord paralysis in the absence of associated symptoms, suggest invasive disease, impact intraoperative management of an invaded nerve, avoid wrongful accusation of postoperative paralysis, and provide a basis to compare postoperative vocal cord function. A postoperative laryngeal exam is necessary; it represents the only precise outcome measure for postoperative RLN function, because voice changes and vocal cord paralysis can occur independently.¹⁷ It allows comprehensive interpretation of intraoperative neural monitoring electrophysiological parameters and also allows for postoperative patient safety and planning of contralateral surgery. The AAOHNS voice guidelines provides recommendations for preoperative and postoperative voice

assessment.⁸ Routine preoperative and postoperative laryngeal exam at the time of thyroidectomy is currently recommended by the British Association of Endocrine and Thyroid Surgeons, the German Association of Endocrine Surgery, and the International Neural Monitoring Study Group.^{6,7,18} The American Thyroid Association Anaplastic Cancer Guidelines recommend preoperative laryngeal examination, as do the American Thyroid Association Goiter Surgery Guidelines.¹⁰ The American Head and Neck Society Invasive Thyroid Cancer Guidelines and National Comprehensive Cancer Network (NCCN) both recommend a preoperative laryngeal exam in all thyroid cancer patients.¹⁹ Preoperative vocal cord exam findings, intraoperative nerve stimulability, and nerve invasion have a very fascinating relationship.

31.4 Application of Intraoperative Neural Monitoring

Although the utility of IONM in reducing the incidence of postoperative VCP has not proven to be statistically significant when comparing results from surgeries with and without IONM, the use of IONM definitely shows a trend toward reduction in postoperative VCP. There are many underlying reasons for this observation, the most important being the need for a large number of surgeries to achieve adequate statistical power. Other confounding factors relate to monitoring techniques and equipment. Nonetheless, many individual studies have established that IONM decreases temporary and permanent vocal cord palsy rates in thyroid surgeries, especially in cases of retrosternal goiters, revision surgeries, and surgeries for thyroid cancer.²⁰ A study by Dralle has shown that there is a significant decline in the rate of VCP when low-volume surgeons apply IONM during thyroid surgeries.²¹

Benefits of IONM can be categorized as follows:

1. Neural mapping
2. Insight into pathological states of the RLN
3. Prognostication of neural function as it relates to intraoperative injury

These benefits are realized when the electrical and functional dynamic information provided by IONM are applied to complement visual nerve identification. Neural monitoring requires a completely bloodless field, has a learning curve, and also entails some added cost. The added cost provides valuable additional information that helps a surgeon in nerve identification, in making decisions regarding intraoperative nerve management, and in foretelling postoperative expectations.

31.4.1 Neural Mapping

In the paratracheal region, linear stimulation by a neural monitor probe with 2 mA stimulation current may be employed to map out the entire path of the nerve electronically prior to its visualization. This neural map can serve as a guide in directing subsequent dissection and visualization of the nerve in this region. This leads to limited, well-focused dissection with the added benefit of reducing operative time by optimizing the surgical dissection needed for nerve visualization.

Neural mapping can be particularly helpful in revision surgeries where scar tissue can impose difficulty in nerve identification and in cases presenting with distorted anatomy, for example, large goiters and invasion by malignancy.

31.4.2 Insight into Pathological States of the Recurrent Laryngeal Nerve

Surgical management of the invaded nerve can be impacted by intraoperative electromyographic (EMG) activity (► Fig. 31.1).²² When electrophysiological stimulation of an invaded nerve reveals significant residual EMG activity in the setting of preoperative VCP, the surgeon becomes cognizant of the functional consequences of resection of such a nerve, including additional dysphagia and aspiration to some extent. Such functional information is valuable and cannot be achieved by visual identification of the nerve alone.

31.4.3 Prognostication of Neural Function as It Relates to Intraoperative Injury

Intraoperative neural monitoring of the RLN is extremely helpful in neural mapping, neural identification, and understanding pathological states of the nerve. However, its most important application arises from its ability to intraoperatively predict postoperative neural function. In the absence of neural monitoring, visual inspection of the nerve is the only available method to determine functionality of the nerve. A nerve injured by blunt trauma or stretching may remain visually intact, but in such cases structural integrity does not translate into normal postoperative function. Current data in the literature reveal that only approximately 10% of all injured nerves are correctly identified by visual inspection.^{14,23,24} Contrary to this, IONM data in the literature suggest that EMG testing of the vagus–RLN system after thyroid surgery is a highly precise neural function test and has negative predictive value of more than 95%.^{3,4,5,25,26,27,28}

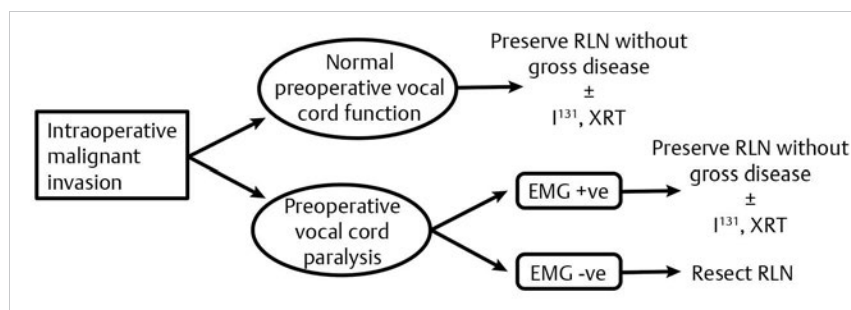


Fig. 31.1 Intraoperative management of invaded nerves based on preoperative vocal cord function and electromyographic (EMG) information. EMG +ve, EMG positive; EMG -ve, EMG negative; RLN, recurrent laryngeal nerve; XRT, radiation therapy.

However, positive predictive value is lower and can be quite variable and is related to how presumptive loss of signal is evaluated with respect to equipment troubleshooting. Universal and accurate definition of loss of signal and a better knowledge of normative neural monitoring parameters will greatly augment the prognostic function of IONM.^{7,19,29}

Once a loss of signal resulting from definite neural injury is established, retrograde testing of the affected RLN, initiated at the laryngeal entry point and continued proximally, can be performed to identify the injured nerve segment. This presents many therapeutic as well as learning opportunities for the surgeon. The concept of postponing the surgery on the opposite side in the setting of neural signal loss represents the greatest extension of the neural prognostication ability of IONM. The loss of signal is further explored in the following section.

31.5 Intraoperative Nerve Monitoring Standards

Differences exist in the application of IONM across multiple centers. This variation may arise secondary to the use of different electrodes, techniques, and output methods leading to mixed and incomparable results. This heterogeneity may subsequently limit the overall utility and uniform applicability of the IONM technology in ensuring enhanced patient safety.

Also, the most common inaccuracies in IONM occur due to incorrect tube placement, tube size errors, or setup-related problems.³⁰ Keeping this in mind, the International Nerve Monitoring Study Group has developed certain guidelines to standardize nerve monitoring. Major domains reviewed in these guidelines include placement of endotracheal tubes (recording electrodes), equipment setup, and problem solving during neural monitoring.⁷

31.5.1 Intraoperative Nerve Monitoring Technique

A basic setup of the neural monitoring equipment is shown in ► Fig. 31.2. The most preferred neural monitoring equipment is an endotracheal tube–based system that includes a visual graphic documentation of the EMG waveform elicited from thyroarytenoid muscle activity. Either needle-based electrodes or surface electrodes may be used. Prefabricated endotracheal tubes with paired stainless steel electrodes exposed at the level of the glottis or a standard tube with thin electrodes placed over the tube with adhesive pads can be used. Additional electrodes to record posterior cricoarytenoid (PCA) muscle twitch are also available, however, they add very little to the sensitivity to the system.^{31,32}

31.5.2 The Setup

Adherence to a standard setup algorithm reduces the occurrence of intraoperative problems related to IONM. It is important to keep the electrocautery unit more than 10 feet away from the neural monitoring unit to avoid electrical interference. Ground electrodes are adhered to the shoulder or the sternum area. Poor grounding can cause a noisy baseline, making it difficult to interpret the EMG data. After the equipment is set up,

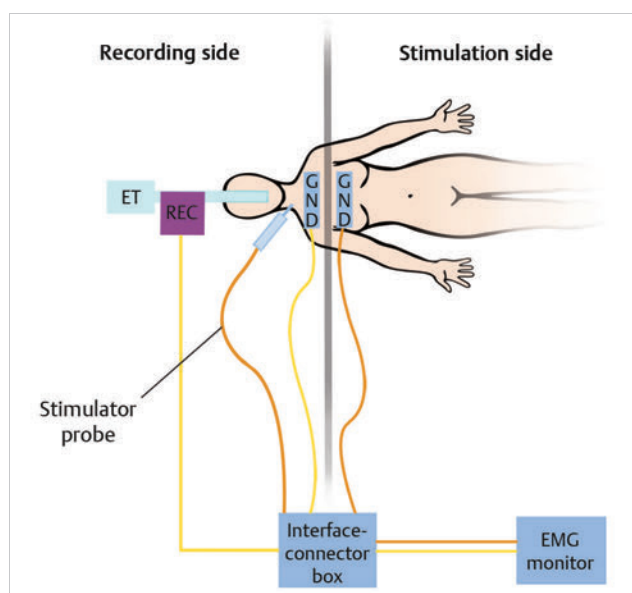


Fig. 31.2 Basic monitoring equipment setup. EMG, electromyographic; ET, endotracheal tube; REC, recording electrodes; GND, ground electrodes.

care is taken to ensure that the recording side and the stimulation side of the circuitry are complete.

Similar to any other task in the operating room, IONM requires teamwork. The major participants are the surgeon, the anesthesiologist, and the monitoring technician. As a key member of the team, the anesthesiologist should understand that there are some special considerations for administering anesthesia during IONM. It has been shown that use of muscle relaxants during anesthesia may attenuate EMG response and make it difficult to perform quantitative analysis during IONM.^{7,33} Thus preservation of spontaneous muscular activity is important, and use of long-acting muscle relaxants or paralytic agents should be avoided. Use of short-acting muscle relaxants is acceptable at the time of induction. The endotracheal tube should be inserted without the use of any lubricant jelly or any other coating. Excessive salivation may also obscure the EMG signals; thus it is recommended to use suction and possibly a drying agent. It is critical that the electrodes should abut the vocal cords, hence selection of the largest tube possible for intubation is important. It is prudent also to check proper placement of the tube once it is secured because this is the first and foremost step in ensuring optimum monitoring setup. Because tube displacement of up to 6 cm can occur during final positioning of the patient, especially with neck extension, it is imperative that tube placement checks be performed once the patient is in the final position.³⁴ The method commonly used by our group, which has proven to be consistently reliable, is the presence of respiratory variations. Respiratory variations are small waveforms with amplitudes between 30 and 70 μ V, which cause coarsening of the baseline EMG (► Fig. 31.3), and are seen during a small window of time when the effect of the muscle relaxant given at the time of induction wears off and the patient is in a lighter plane of anesthesia just before the patient starts to move spontaneously or “buck.” In the absence of respiratory variation, a repeat direct laryngoscopy, preferably by the

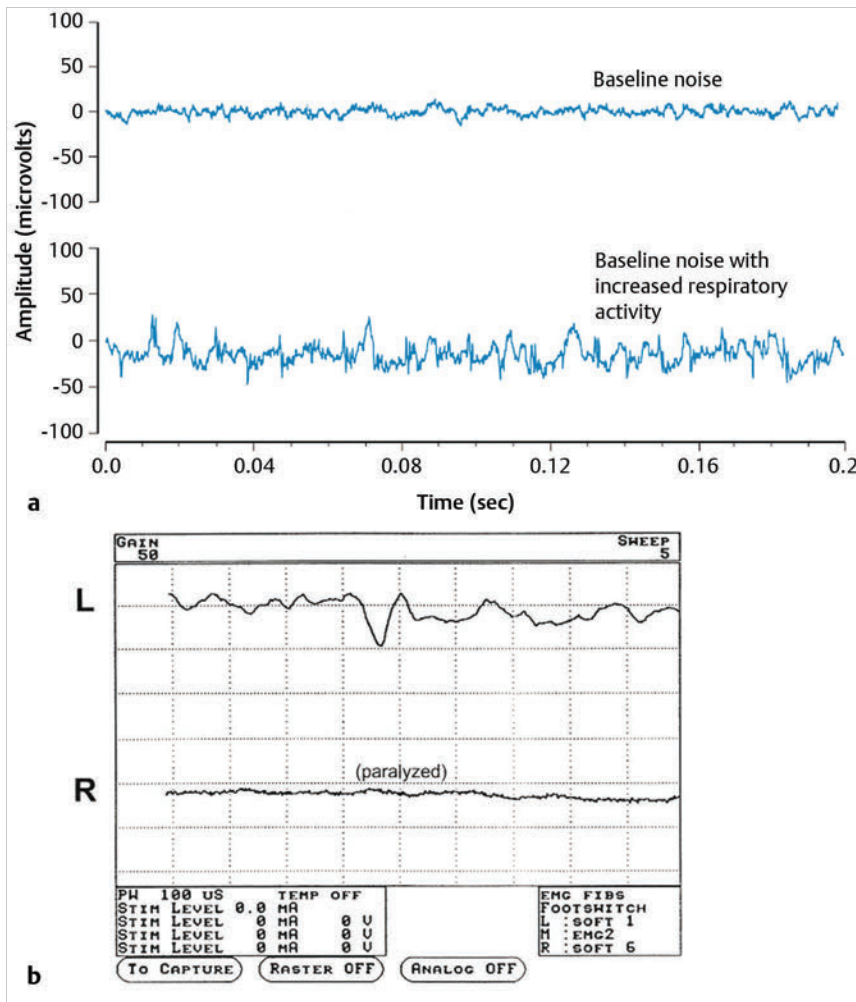


Fig. 31.3 Respiratory variation waveforms. (a) Upper line—baseline noise, typically between 10 and 20 μV . Lower line—coarsening of the baseline with respiratory variation (occurring in the 30- to 70- μV range when the patient is on the brink of bucking in the early anesthetic period). (b) Left and right baseline tracings in a patient. The left vocal cord demonstrates normal respiratory variation. The right vocal cord is electrically silent (patient had known right vocal cord paralysis from past surgery).

surgeon, to confirm tube placement is recommended. A recently published study by our unit found that identification of respiratory variation was possible in 91% of patients, whereas the remaining 9% required a repeat laryngoscopy.³⁵ It was also found that the presence of respiratory variations independently predicted a good intraoperatively evoked vagus and RLN response, obviating a need for a repeat laryngoscopy in these patients. At final positioning, the impedance of the electrodes should be less than 5 Ω , and the imbalance between the two sides should be < 1 Ω . A higher impedance imbalance may suggest inappropriate tube placement requiring repositioning, whereas if the overall impedance is high then the ground electrodes should be assessed or replaced.

Once the setup is complete, it is important to set the monitor event threshold at 100 μV and the stimulator probe to a pulsatile output of 4/s. At the initiation of surgery, the stimulation of strap muscles resulting in a gross muscle twitch can be performed to confirm the absence of paralytic agents as well as an intact stimulatory pathway.

Predissection intraoperative suprathreshold vagal nerve stimulation confirms a functional system and allows acceptance of a negative stimulation as true negative. For each patient, essential data pertaining to IONM include a preoperative laryngeal exam, an initial intraoperative suprathreshold vagal nerve stimulation, an initial intraoperative RLN stimulation and

also a similar set of events recorded at the end of the surgery, followed by a postoperative laryngeal exam. The aforementioned essential elements can be summarized by noting L1, R1, V1, and R2, V2, and L2.^{36,37} A suprathreshold current of 2 mA is useful for neural mapping; once the RLN has been visualized the current can be reduced to 1 mA for further testing and end of surgery prognostication. Evoked waveforms for the human RLN or vagus nerve are commonly biphasic or triphasic. The amplitude of a monitoring waveform, as defined in the International Guidelines, is the vertical height of the apex of the positive initial waveform deflection to the lowest point in the net subsequent opposite polarity phase of the waveform.⁷ Caragianu et al found that no statistically significant difference exists between the amplitude when the nerve is stimulated by suprathreshold levels at 1 or 2 mA.³⁸ Normative values were thus defined at 1 mA. An amplitude of > 250 μV was found to be highly predictive of a functioning RLN. The study also revealed that, regardless of the variations, a clinically useful normative range can be established and used for surgical decision making (► Fig. 31.4).³⁸ Latency is not defined consistently in the IONM literature. The International Monitoring Group defines latency as the time from the stimulation spike to the first evoked waveform peak.⁷ Latencies recorded during intraoperative monitoring are distinctive and can differentiate artifacts from stimulated neural structures and can also distinguish the RLN,

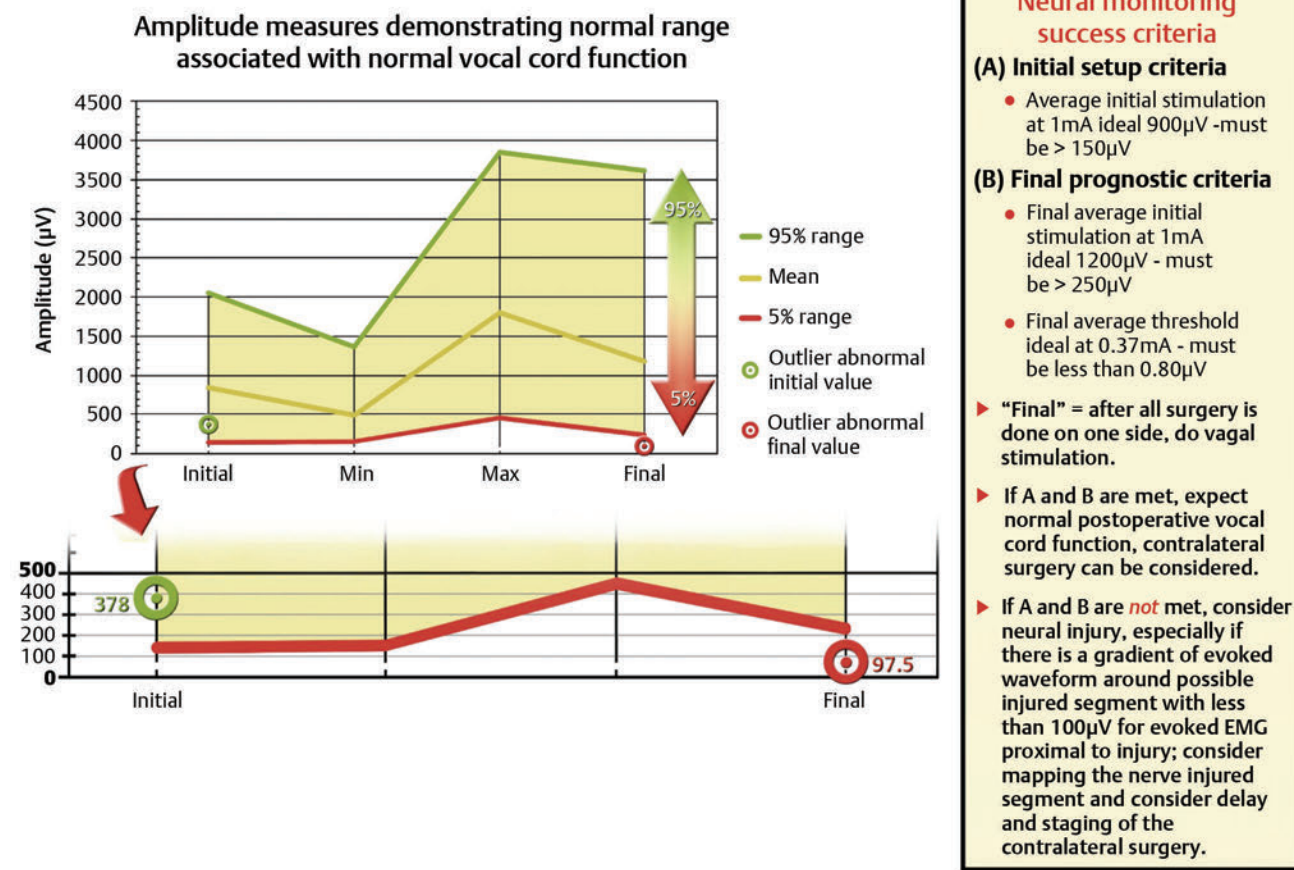


Fig. 31.4 Amplitude measures demonstrating normal range associated with normal glottic function.³⁸

superior laryngeal nerve, and vagus nerve, including the left from the right vagus nerve. Threshold is defined as the stimulation current that first starts to trigger minimal EMG activity. Our unit has described normative EMG data and graphical waveforms generated from the RLN, SLN, and left and right vagus nerves (► Fig. 31.5).³⁹

Repetitive stimulation of the RLN at levels of 1 and 2 mA has been reported to be extremely safe, and no unfavorable effects have been reported.³⁸ IONM has been safely employed in children and adults, assuming proper patient isolation and grounding.⁷

31.5.3 Interpretation of Loss of Signal during Intraoperative Nerve Monitoring

Loss of signal (LOS) during IONM could be encountered due to various reasons (► Fig. 31.6). A surgeon should first rule out equipment- or setup-related LOS before considering true LOS. As soon as LOS is encountered, assessment of the laryngeal twitch response to ipsilateral and contralateral vagal stimulation should be performed to evaluate the integrity of the IONM setup. The presence of a laryngeal twitch establishes that the stimulating side of the equipment is functioning adequately. Recording side equipment issues most commonly arise from improper tube positioning, which should be adjusted if found.

Other issues related to adequacy of current and use of paralytic agents should also be considered. An event must satisfy three conditions to be labeled as true LOS:

1. Presence of a satisfactory EMG (amplitude > 100 µV) prior to the event
2. No or low response (i.e., ≤ 100 µV) with stimulation at 1 to 2 mA in a dry field
3. Absence of laryngeal twitch and/or glottis twitch on ipsilateral vagal stimulation

A true LOS should prompt the surgeon to identify the site of injury. It provides the opportunity to treat the nerve injury if possible. This may also impact the surgical plan and may lead to postponement of surgery on the contralateral side.

31.5.4 Passive EMG Activity during Intraoperative Nerve Monitoring

Any passive EMG activity occurring frequently signifies mechanical nerve injury or cautery stress and should prompt urgent evaluation of the surgical maneuvers being performed at the time. Several researchers have reported that such bursts of passive activity correlate with some degree of nerve injury.^{40,41,42} However, their relationship to frank vocal cord paralysis is not yet established.

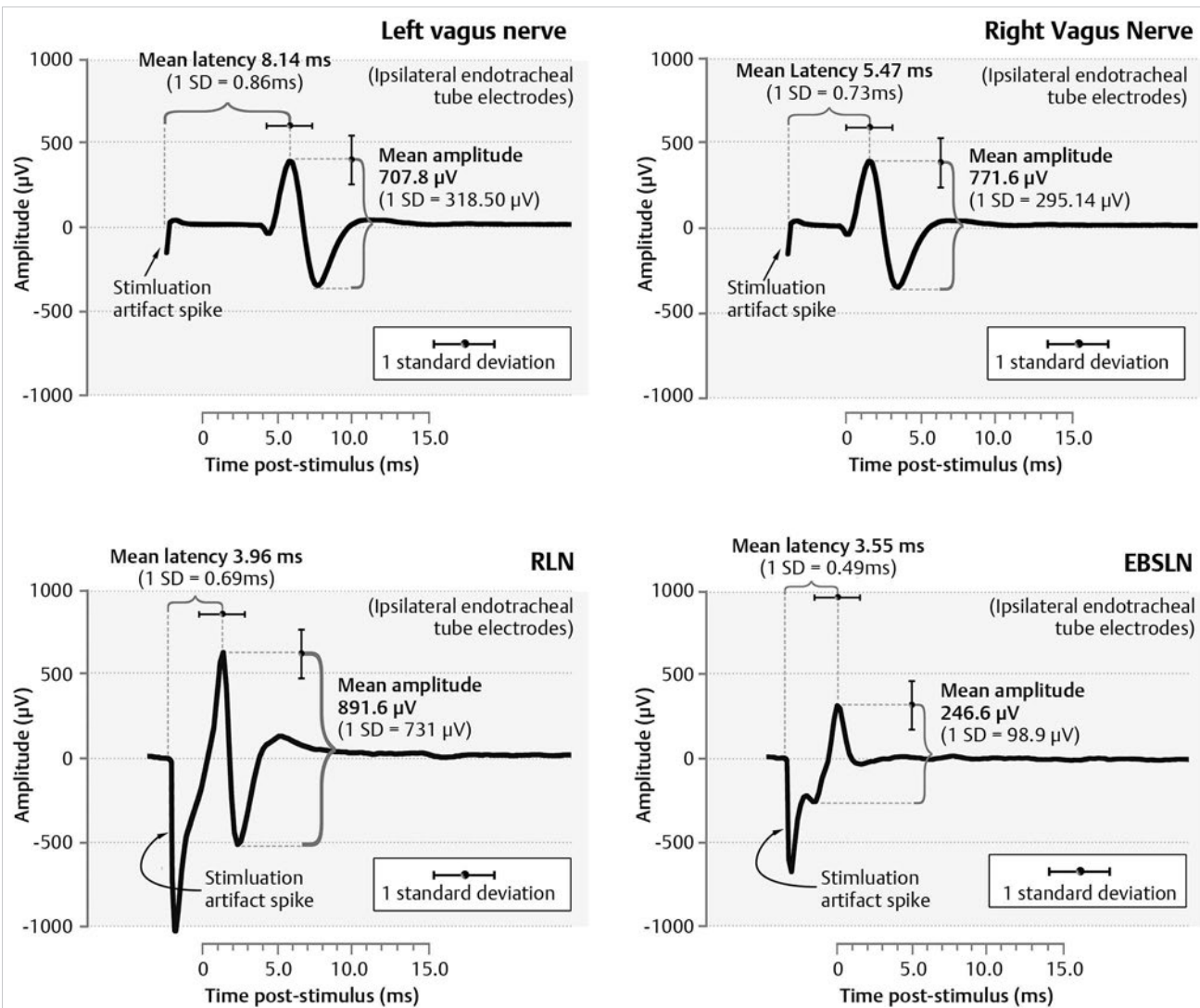


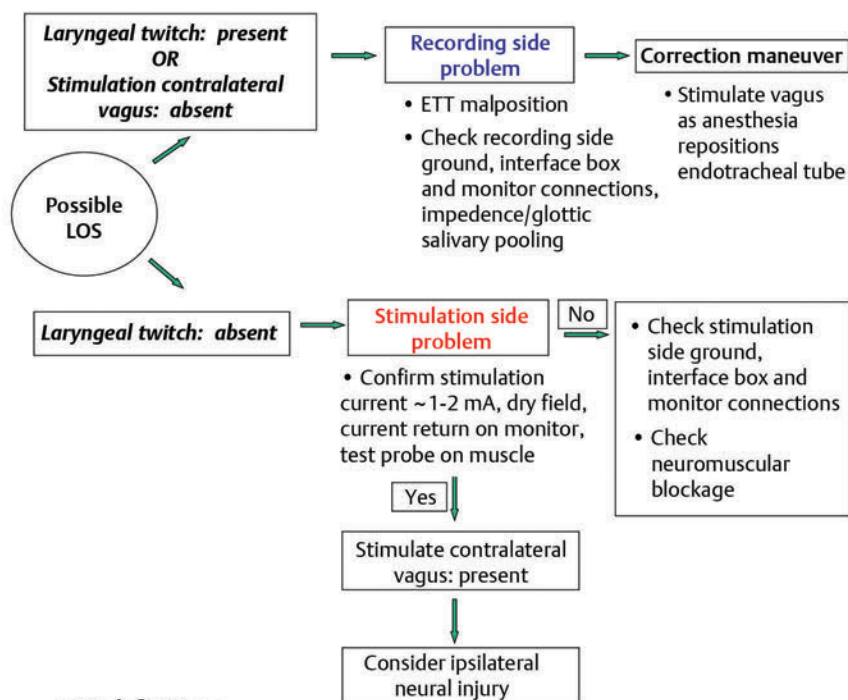
Fig. 31.5 Ipsilateral endotracheal electrode recordings of electromyographic waveforms for the left and right vagus nerve, pooled recurrent laryngeal nerve (RLN), and pooled external branch of the superior laryngeal nerve (EBSLN) illustrating normative waveform morphology, latency, and amplitude.

31.6 New Horizons in Intraoperative Nerve Monitoring

31.6.1 Continuous Vagal Monitoring and Neural Injury Prevention

One of the biggest drawbacks of the existing IONM format is that it permits only intermittent stimulation and evaluation of the functional integrity of the RLN. Although IONM is immensely useful in resolving certain surgical dilemmas, the nerve remains at risk for injury in between stimulations.^{21,26} This could possibly explain the suggestion that, in its present format, IONM may have a limited ability to prevent neural injury.^{21,24,27,43} An ideal IONM format would be the one that provides real-time EMG data that can alert the surgeon before permanent or irreversible neural damage sets in. Early studies have shown that continuous IONM (CIONM) with a vagal nerve electrode can provide this information and is not associated with significant neural, cardiac, pulmonary, or gastrointestinal vagal side effects.^{43,44,45,46}

It is important, however, that the accepted format differentiates true events from electrical artifacts. Combining reduction in amplitude with increase in latency, our group has defined mild and severe combined events (mCEs and sCEs) (► Table 31.1). Our study demonstrated that mCEs and isolated amplitude or latency changes were not associated with VCP, whereas an sCE signified a typically reversible electrophysiological change when the related surgical maneuver was aborted, otherwise it could lead to LOS (which characteristically is much less reversible) and to postoperative VCP. Thus CIONM allows the surgeons to instigate corrective action to preserve nerve function by aborting maneuvers that lead to adverse EMG changes.⁴⁷ Modification of a surgical maneuver when such an event occurs can prevent development of a complete LOS and subsequent VCP. It is evident that IONM overall is more useful for preventing impending neural damage secondary to a stretch or compression injury than an inadvertent transection of the nerve by the surgeon.⁴⁷

Intraoperative LOS evaluation standard**LOS definition:**

- 1 - EMG change from initial satisfactory EMG
- 2 - No or low response (i.e. 100 μ V or less) with stimulation @ 1-2 mA, dry field
- 3 - No laryngeal twitch and/or observed glottic twitch

With LOS:

- 1 - Map lesion and determine type I (segmental) or type II (global) injury
- 2 - Consider contralateral surgery timing

Fig. 31.6 Intraoperative loss of signal (LOS) evaluation standard. EMG, electromyographic; ETT, endotracheal tube.

31.6.2 Superior Laryngeal Nerve Monitoring

Recently published guidelines on SLN monitoring by the International Neural Monitoring Study Group have highlighted the fact that neural monitoring of the SLN is associated with higher rates of nerve identification than are possible with visual identification alone.⁴⁸ The laryngeal head of the sternothyroid serves as a useful landmark for identification of the external branch of the superior laryngeal nerve (EBSLN). A twitch in the cricothyroid muscle seen on stimulation is currently the most accurate measure of nerve localization. A specially designed electrode array incorporated on an endotracheal tube can also record EMG activity from the glottis in 100% of patients.⁴⁹ For a detailed discussion on the technique and utility of SLN monitoring the reader is requested to refer to the guidelines published by the International Monitoring Group.⁴⁸

31.6.3 Neural Monitoring and Staged Thyroidectomy in Thyroid Cancer Surgery: an Emerging Concept

Bilateral nodal metastases in thyroid cancers are frequently encountered and require extensive surgery, typically carrying a

higher risk of complications, with bilateral RLN paralysis being one of the most feared complications.

Staging of surgery may offset some of these complications, especially those that are temporary in nature. RLN with neuropraxia may recover between the two stages of surgery, eliminating the risk of bilateral VCP. Similarly, parathyroid glands may recover functionally in the intervening period. The benefits of staging bilateral radical neck dissection have been documented earlier. It was Frazzelli in 1961 who proposed a planned staging of surgeries where sacrifice of bilateral internal jugular veins was anticipated.⁵⁰ Dunhill in 1912 and Lahey in 1936 recommended staged surgery for severe toxic goiter and severe hyperthyroidism, respectively.^{51,52}

Evidence suggesting the utility of LOS as a decision-making tool during surgery is slowly accumulating. Integration of LOS in surgical decision making with regard to proceeding with bilateral thyroidectomy or staging the opposite-side surgery can greatly influence the postoperative bilateral VCP rate. Goretski et al have reported that the incidence of bilateral VCP drops to zero from 17% in bilateral surgery when LOS is incorporated in the surgical strategy.⁵³

Our unit routinely offers staged surgery to patients with extensive thyroid malignancy with bilateral nodal disease. In our unpublished series of patients presenting with advanced thyroid cancer undergoing planned staged surgery, the

Table 31.1 Mild and severe combined events suggestive of nerve injury

Event type	Criteria
Mild combined event (mCE)	Amplitude decrease of >50 to 70% with a concordant latency increase of 5 to 10%.
Severe combined event (sCE)	Amplitude decrease of >70% with a concordant latency increase of >10%

permanent RLN paralysis rate was zero and the permanent hypoparathyroidism rate was 3.3%. Postoperatively thyroglobulin was undetectable in 90% and averaged 0.8 ng/mL in 3-year follow-up. Dralle et al found that 94% of surgeons in Germany would stage a total thyroidectomy if they encountered an LOS during the surgery.⁵⁴ This is especially true for centers with a higher caseload. However, a detailed preoperative consent process is imperative when staged surgery is being contemplated as a possibility.⁵⁵

31.6.4 Intraoperative Identification of a Nonrecurrent Laryngeal Nerve

The nonrecurrent laryngeal nerve (NRLN) is an anatomical variant of the RLN that has no functional impact but increases the susceptibility to intraoperative injury by a surgeon unaware of its presence. A right NRLN is reported to account for 0.5 to 1% of all RLNs and a left NRLN accounts for only 0.04%.^{56,57} Our series on NRLN monitoring recommends an electrophysiological algorithm where the presence of a positive EMG response to proximal stimulation of the vagus at the superior border of the thyroid cartilage and the absence of an EMG response to distal stimulation of the vagus below the inferior border of the fourth tracheal ring reliably identify a NRLN.⁵⁸ Currently, because no dependable technique of preoperative recognition or exclusion of NRLN is available, the aforementioned electrophysiological algorithm reliably alerts a surgeon to the presence of an NRLN prior to the dissection in the related cervical region. This vagal stimulation technique for NRLN identification is supported by Brauckhoff et al.⁵⁹ In these cases the right NRLN behaves similarly to a normal right RLN in terms of amplitude, threshold, and latency. Some workers have suggested that a latency of <3.5 ms strongly suggests NRLN.⁶⁰ However, further studies are warranted before it is considered as a definitive indication of a NRLN.

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32 Office-Based Ultrasonography

David L. Steward and Russell B. Smith

32.1 Introduction

Office-based ultrasound (US) has gained popularity over the last decade. Most would agree that incorporation of this technology into a clinical practice provides advantages to both the patient as well as the physician. For the patient, it can significantly streamline medical care. For example, a patient with a thyroid nodule can be seen for a clinical evaluation by the physician and also undergo the necessary diagnostic imaging as well as US-guided biopsy for cytological diagnosis in a single office encounter. For the physician, performing real-time US maximizes the diagnostic yield from the imaging study. There is little doubt that physicians who perform the US obtain exponentially more information from the study than those who view only static images obtained by another. Beyond that, the physician is able to couple their inherent knowledge of the disease with the findings of the history and physical exam to perform a comprehensive diagnostic US tailored to the disease process and ultimately optimize patient care. But there are costs that must be considered as one contemplates adding office-based US to a clinical practice. These costs extend beyond the monetary considerations of purchasing the equipment; they also include the investment of time and effort to complete the appropriate training as well as determining how to include additional procedures into an already busy clinic schedule. In the end, most will find the benefits of office-based US far exceed the costs and will feel that it is an invaluable part of providing care to patients.

32.2 Technique of Performing Office-Based Ultrasound

There are some physics principles that must be understood as one starts performing office-based US. The first principle involves the relationship between sound wave frequency and the depth of penetration of a sound wave into tissues. The depth of penetration is inversely proportional to the frequency of the sound wave. Hence, lower-frequency sound waves have deeper penetration, whereas higher-frequency sound waves have more superficial penetration. Given that the vast majority of neck pathology is relatively superficial (<4 cm), one can use a high-frequency transducer (≥ 10 MHz) for neck US. The ability to use higher-frequency sound waves for neck US leads to a second principle, that the use of higher-frequency sound waves for imaging results in better axial and lateral resolution. Therefore, the images obtained during neck US are of extremely high quality and allow very small abnormalities to be clearly defined.

In general, the neck is a readily accessible area to evaluate with US. As the neck evaluation extends inferiorly and superiorly, some limitations are encountered due to the presence of the sternoclavicular and mandibular bony anatomy, respectively. The vast majority of imaging is completed in B mode (gray scale) scanning, but a working knowledge of color Doppler and power Doppler is necessary to complete a thorough evaluation. The high-frequency linear transducers used for neck

US are typically 4 to 6 cm wide and approximately 1 cm in thickness. Lead zirconate titanate crystals are located in the end of the transducer. When these crystals are stimulated by electricity, sound waves are generated and subsequently emitted into the tissue. Conversely, when the sound waves return from the tissue, compression of the crystals generate an electrical current that ultimately creates the US image. This phenomenon is known as the piezoelectric effect. The crystals in the transducer alternate between generating and receiving sound, and at any given time the majority of the crystals in the transducer are receiving sound waves that have been reflected back from the tissue. The width of the US image that is generated by this process is essentially the same width as the transducer, but the thickness of the area being imaged is much thinner than the transducer (~ 1 mm thick). Hence the image generated during neck US can be thought of as being roughly the shape of a credit card. This has obvious implications when one is performing US-guided needle biopsies.

The room configuration for office-based US will generally position the machine to the patient's right side (► Fig. 32.1). This allows the physician to use the right hand (dominant hand) to hold the transducer during the exam while the left hand manages the knobs and keys on the US machine. For someone who is left-hand dominant, this configuration may be switched. The US transducer is held between the thumb and first two fingers near the skin interface, which then allows the ring and/or little finger to brace on the patient for stability (► Fig. 32.2). For the most part, the probe is maintained in a perpendicular orientation to the skin, but subtle angulations can be used to image behind structures, such as the larynx, trachea, mandible, sternum, and clavicle. An adequate amount of gel is required to bridge the interface between the transducer and the skin. If there is not enough gel present the sound waves will not be transmitted to the tissue. If a poor image is being obtained the angulation of the transducer needs to be adjusted so that the



Fig. 32.1 Room configuration for office-based ultrasound. The exam chair should allow the patient to be examined in a sitting or supine position. The ultrasound unit is on the patient's right and a Mayo stand is useful to hold the supplies used during a needle biopsy.



Fig. 32.2 Holding the ultrasound transducer. The transducer is held between the thumb and first fingers to allow the other digits to extend and stabilize the transducer during the exam.

footplate sits against the neck skin along its entire width (► Fig. 32.3).

A systematic approach to neck evaluation should be consistently utilized when performing neck US. This approach should include both the central and lateral neck compartments and be extended to other areas such as the parotid or posterior neck as necessary. Given that the majority of neck US is performed for thyroid and parathyroid disease, the evaluation usually starts inferiorly and centrally and then extends laterally and superiorly. The majority of imaging is performed in a transverse plan, but longitudinal or oblique imaging may occasionally be necessary. Any pathology that is identified requires a three-dimensional assessment to define the size of a lesion.

For central neck imaging, the entire compartment from carotid artery to carotid artery should be evaluated. Frequently, this cannot be accomplished with a single pass of the transducer. Typically, one will position the transducer on the neck such that the carotid sheath is on one side of the image and at least half the trachea occupies the other side of the image. This is completed for both sides of the central neck (► Fig. 32.4). As the exam extends to the lateral neck to assess for lymphadenopathy, one will position the transducer on the neck so that the carotid sheath is on one side of the image and the remainder of the transducer spans the node-containing area of the neck (► Fig. 32.5). This allows levels II through IV to be evaluated with a single pass of the transducer. Additional transverse passes more posteriorly allow level V to be examined. For the vast majority of thyroid and parathyroid disease, evaluation of level I adds little additional information. But for pathology such as a thyroglossal duct cyst, level I imaging is necessary to fully evaluate the mass.

Documentation of the US examination is an important aspect of office-based US and often includes both a text report and image in the medical record. As pathology is encountered there are two methods to record the findings, and in some situations both methods may be used. The first method is to capture a static image of a representative part of the pathology. This image can then be labeled, measured, and then incorporated into the medical record. The second method of recording is to complete a cine loop of the area of interest. This loop can be from 3 to 10 seconds in length depending upon the size,

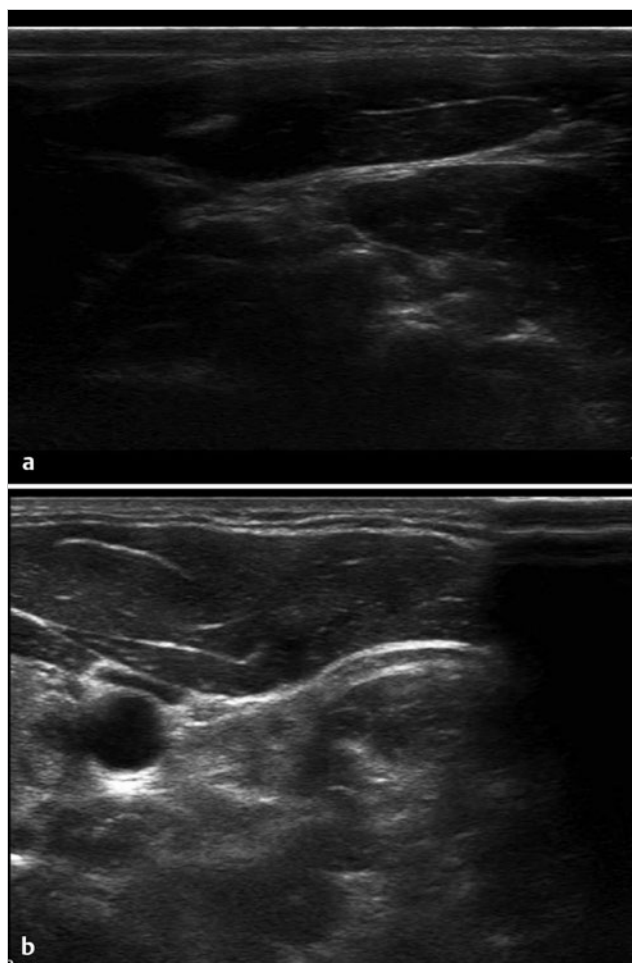


Fig. 32.3 Poor image quality during ultrasound. (a) Appearance of image when there is inadequate gel on the patient's neck. (b) Appearance of image when the transducer is not fully contacting neck skin. The right side of the transducer is off the skin.

location, and number of findings that need to be documented. This approach will not allow for as detailed labeling or measuring of a mass, but can be an important adjunct to the static image.

32.3 Thyroid Ultrasound

Office-based US provides a thorough evaluation of a variety of pathologies that affect the thyroid gland. Compared to computed tomography (CT) and magnetic resonance imaging (MRI), US is the most detailed imaging modality for assessing thyroid disease. The appearance of a normal thyroid gland is homogeneous and has an intermediate gray scale appearance and is considered an isoechoic structure of the neck. A diffuse heterogeneous appearance of the thyroid gland is associated with a wide variety of inflammatory conditions, with Graves' disease and Hashimoto's thyroiditis being the two most common entities (► Fig. 32.6). With Graves' disease, the gland tends to be slightly enlarged, with a diffuse hypoechoic appearance and intensely increased vascularity on Doppler evaluation, especially when not controlled medically. In patients with suspected Graves' disease, US not only assists in excluding other etiologies

of thyrotoxicosis but also assesses for coexisting nodular disease, which has a higher risk of malignancy in this population.¹ With Hashimoto's thyroiditis, the gland may be enlarged, normal sized, or even atrophied after long-standing disease. The gland has a splotchy hypoechoic appearance when compared to

Graves' disease. In addition, the gland will have variable vascularity, with a more recent onset of disease having increased vascularity and a more long-standing disease having limited to no vascularity. Nodular variants of Hashimoto's disease are frequently encountered and may have a single or multiple

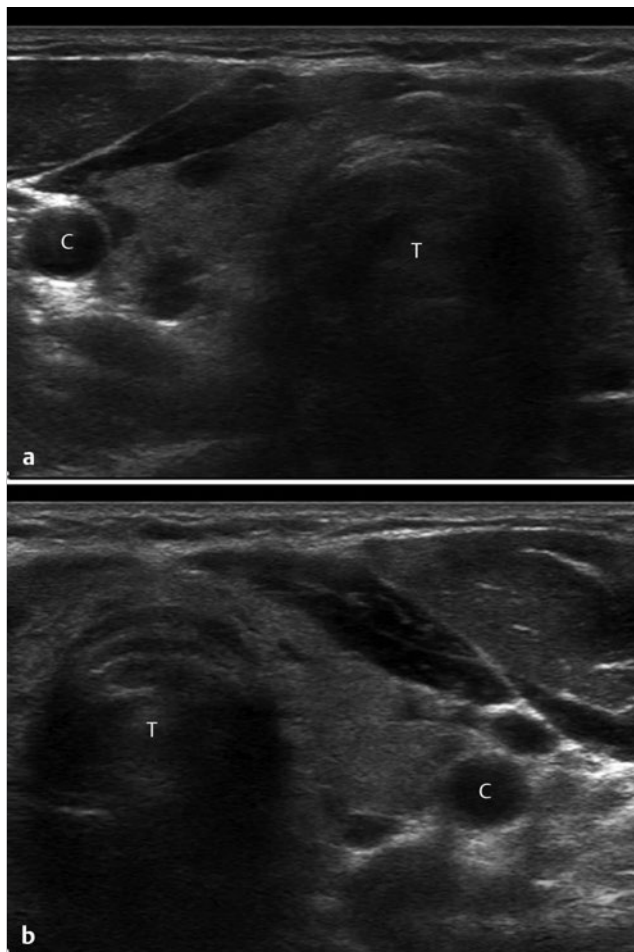


Fig. 32.4 Evaluation of the central neck. (a) Representative ultrasound (US) image of the right central neck evaluation with the trachea (T) on the right and the carotid artery (C) on the left. (b) Representative US image of the left central neck evaluation with the trachea (T) on the left and the carotid artery (C) on the right.

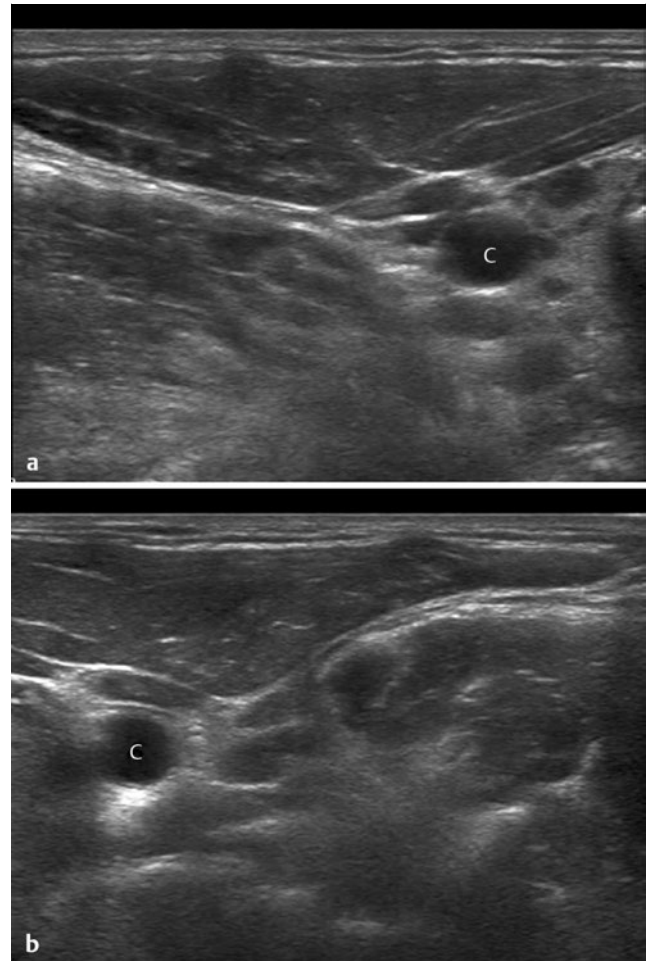


Fig. 32.5 Evaluation of the lateral neck. (a) Representative ultrasound (US) image of the right lateral neck evaluation with the carotid artery (C) on the right side of the image. (b) Representative US image of the left lateral neck evaluation with the carotid artery (C) on the left side of the image.

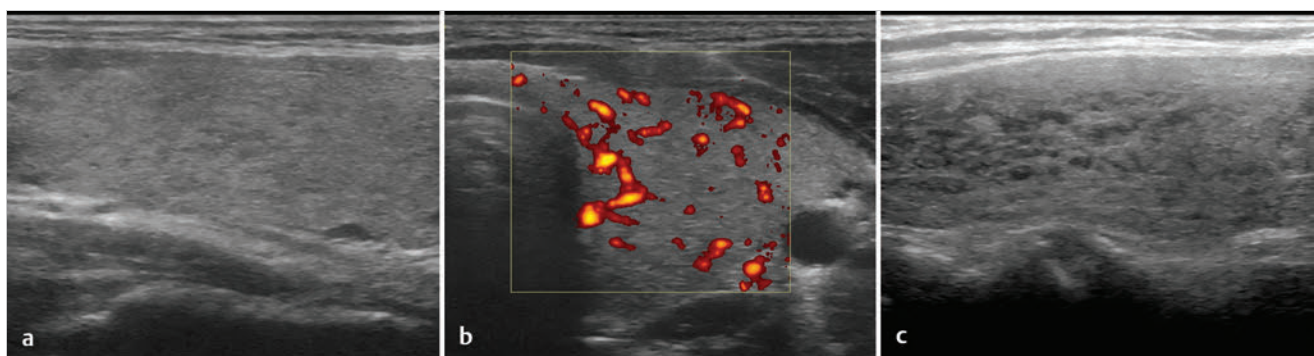


Fig. 32.6 Typical heterogeneous sonographic appearance of autoimmune thyroid disease. (a) Graves' disease, left-sided longitudinal plane in gray scale/B mode. (b) Graves' disease, transverse plane with power Doppler showing increased vascularity. (c) Hashimoto's thyroiditis, left-sided longitudinal plane in gray scale/B mode.

Table 32.1 Sonographic characteristics of a thyroid nodule

Benign characteristics	Malignant characteristics
Isoechoic	Hypoechoic
Simple cyst	Solid/complex mass
Spongiform	Irregular border
Smooth well-defined border	Extrathyroidal extension of nodule
Presence of a halo around nodule	Diffuse/central vascularity
Peripheral vascularity	Taller than wide axial size
Wider than tall axial size	Microcalcifications
Macrocalcifications	Associated suspicious lymph nodes

nodules that demonstrate a wide variety of sonographic characteristics.²

Documentation of a thyroid gland exam should include the three-dimensional size of both thyroid lobes as well as any nodular disease of the gland. Nodular disease of the thyroid gland can be accurately sized and defined by use of both B mode scanning and Doppler evaluation. In patients with goiter that contains numerous nodules, it is not always practical to measure every nodule. In this situation, the largest and most worrisome nodules should be recorded and measured. In addition to the size of a nodule, there are a number of sonographic features of a thyroid nodule that can be described (► Table 32.1). Several of these features can be suggestive of malignancy and assist the physician in determining the need for biopsy.³ Sonographic pattern is more important than nodule size when evaluating the likelihood of malignancy, with an accuracy of about 80%.⁴ Simple colloid cysts and spongiform or mixed cystic/solid colloid nodules are nearly always benign, whereas hypoechoic nodules with irregular borders and microcalcifications are almost always malignant. Solid isoechoic or hyperechoic nodules without suspicious features are sonographically indeterminate and often cytologically indeterminate, consistent with possible follicular neoplasm. The revised American Thyroid Association Guidelines for Thyroid Nodules describes which nodules benefit from biopsy based on size and sonographic appearance.⁵

32.4 Parathyroid Ultrasound

Preoperative parathyroid localization is effectively performed with office-based US but is technically more challenging than thyroid imaging. The typical sonographic appearance of a parathyroid adenoma is a smooth ellipsoid or crescent-shaped hypoechoic mass, which may have a well-defined vascular pedicle on Doppler evaluation. The mass is typically located on the posterior surface of the thyroid gland for a superior adenoma and near the inferior pole of the thyroid gland for an inferior adenoma (► Fig. 32.7 and ► Fig. 32.8).

Differentiating a superior from inferior parathyroid adenoma sonographically can be difficult, especially when the superior gland is located inferiorly. In general, a superior adenoma is located deep to the coronal plane of the recurrent laryngeal nerve, whereas an inferior adenoma is superficial to this plane. One can use the posterior surface of the carotid artery as a

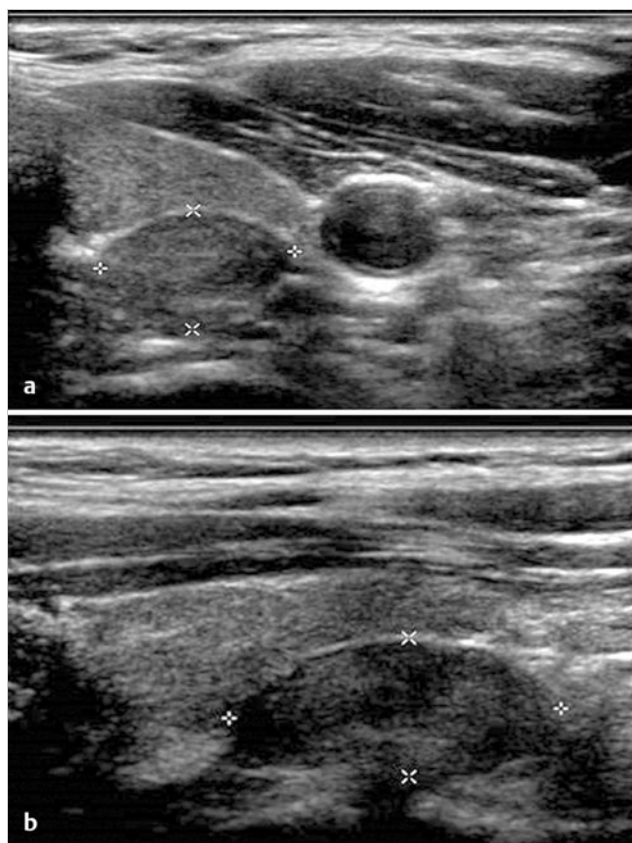


Fig. 32.7 Location of the left superior parathyroid adenoma. (a) Axial image showing a left adenoma posterior to the thyroid lobe. (b) Longitudinal image showing a left adenoma posterior to the thyroid lobe.

surrogate marker for the coronal plane of the recurrent laryngeal nerve on transverse imaging to help define the gland that is affected. This information can be very helpful intraoperatively, especially if performing a minimally invasive surgery. This emphasizes the benefits of surgeons having office-based US at their disposal.

If an adenoma is not identified in the typical locations when performing US for localization, one should evaluate for possible ectopic locations. The most common locations for an ectopic adenoma include the carotid sheath, the retroesophageal space, the thymus, the anterior and superior mediastinum, and the thyroid. Special positioning of the patient and the transducer may be necessary to assess for adenomas in these locations. To improve superior mediastinal imaging, the patient should be positioned with a hyperextended neck, and the probe should be used transversely at the sternoclavicular area while the probe is angled to image inferiorly. This allows imaging down to the innominate and subclavian vasculature and identification of a superior mediastinal adenoma. To improve imaging behind the upper aerodigestive tract along the prevertebral fascia, longitudinal imaging allows one to angulate the probe toward the space. Additionally, increasing the far field time gain compensation and use of a lower-frequency transducer can improve visualization in this area. If localization is still not successful despite these techniques, one may have to consider cross-sectional imaging using CT.⁶

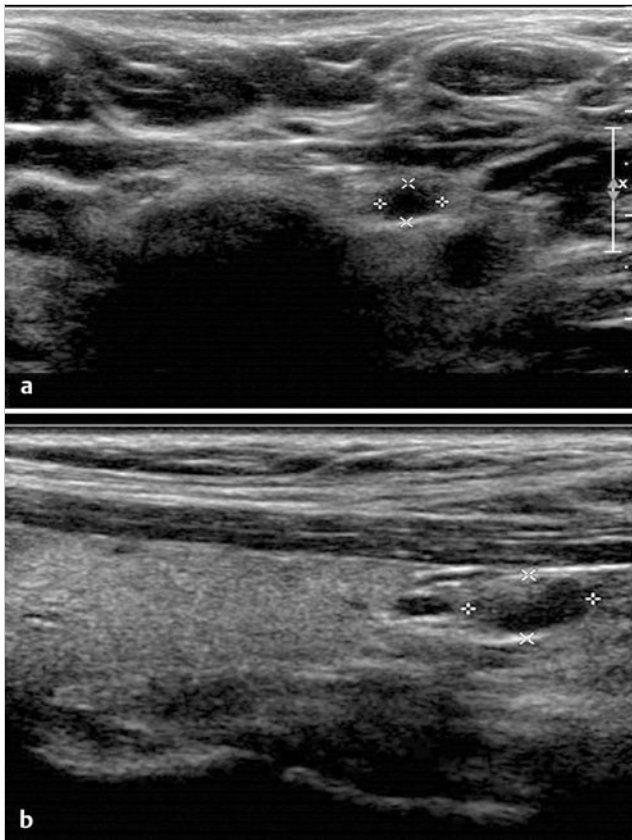


Fig. 32.8 Location of the left inferior parathyroid adenoma. (a) Axial image showing a small left adenoma inferior to the thyroid lobe in a paratracheal location. (b) Longitudinal image showing a small left adenoma inferior and in the same plane as the thyroid lobe.

While performing neck US for preoperative parathyroid localization, incidental thyroid nodularity will frequently be detected. Although the majority of these nodules will be benign, thyroid cancers will be encountered. Preoperative identification allows for US-guided biopsy to be performed prior to parathyroid exploration. This has been shown to reduce unnecessary thyroid surgery at the time of parathyroidectomy as well as allow appropriate thyroidectomy and node dissection to be performed in cases of concomitant thyroid malignancy.⁷ On rare occasions, medullary thyroid cancer will occur simultaneously with parathyroid disease. In this scenario, it is important to screen for hereditary syndromes such as multiple endocrine neoplasia type 2A (MEN2A) and complete biochemical screening to rule out pheochromocytoma prior to parathyroidectomy, thyroidectomy, and neck dissection.

32.5 Lymph Node Ultrasound

For patients with nodular disease of the thyroid, the neck US will often include an evaluation of the cervical lymph nodes. Lymph node evaluation by US is technically more challenging than evaluation of the thyroid gland. Head and neck surgeons have an advantage over their endocrine colleagues with their intimate knowledge of lymphatic drainage patterns and complex anatomy of the neck. Unlike the thyroid gland, which has a

consistent location in the neck and distinct boundaries with the adjacent muscles and upper aerodigestive tract, lymph nodes are smaller, more variable in location, and frequently interspersed among multiple blood vessels making them less distinct on imaging. There are a host of characteristics that can be used to distinguish benign from pathological cervical lymph nodes.⁸ The following are some characteristics of benign cervical lymph nodes:

- Small size
 - Less than 1.5 cm in level I to II
 - Less than 1 cm in Level III to V
- Oval shape
- Smooth well-defined borders
- Homogeneous hypoechoic mass with a hyperechoic hilum
- Blood flow limited to hilum on Doppler evaluation

The following are some characteristics of pathological cervical lymph nodes:

- Larger size
 - Greater than 1.5 cm in level I to II
 - Greater than 1 cm in level III to V
- Round shape
- Irregular borders
- Heterogeneous mass with central areas of anechoic signal
- Diffuse blood flow on Doppler evaluation
- Clustering of multiple nodes
- Microcalcifications (for papillary thyroid cancer)

It should be noted that none of these characteristics are absolute signs of malignancy, and findings such as larger size or absence of a hyperechoic hilum can occur with benign lymph nodes.⁹

A systematic approach is used for lymph node assessment so that metastatic disease is not overlooked and left unaddressed during initial surgery for thyroid cancer. Evaluation of level VI is best completed as a part of the thyroid gland evaluation. Central compartment lymph nodes involved with thyroid cancer typically are identified posterior or inferior to the thyroid gland. The evaluation of the central compartment should be to a depth that the hyperechoic signal of the vertebral bodies is seen. It should also extend laterally to evaluate the retrocarotid region and inferiorly to the innominate artery to assess for superior mediastinal metastases. Lymph nodes posterior to the common carotid artery likely represent metastasis along the inferior thyroid artery. A comprehensive lateral neck evaluation should also be completed. The largest normal lateral nodes usually appear on the posterior aspect of the submandibular gland (level I) and are rarely involved in thyroid cancer. In contrast, lymph nodes identified in levels II, III, IV, and VI should be carefully evaluated for features of malignancy. Lymph nodes indenting the jugular vein are also highly suspicious. Level V is imaged last and is the most difficult to examine but rarely demonstrates nodal metastasis without involvement in levels II, III, or IV.

As a part of surveillance for thyroid cancer, neck US is often performed every 6 to 12 months for the first 3 years after initial treatment for thyroid cancer, especially if there is biochemical evidence of disease.⁵ Lymph node evaluation during surveillance is critical because the majority of recurrences involve the cervical lymph nodes. Especially for patients with a detectable

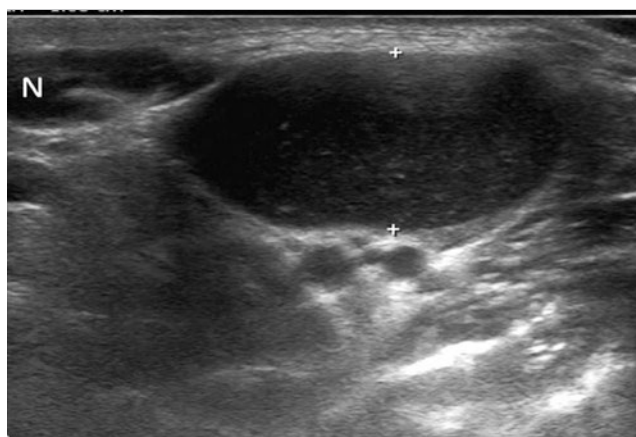


Fig. 32.9 Ultrasonographic appearance of a branchial cleft cyst. The mass is a simple cystic lesion with posterior enhancement. There is a small benign lymph node (N) with a well visualized hilum adjacent to the cyst on left.

thyroglobulin (Tg), neck US can often identify subcentimeter nodal metastases. However, in low-risk cases with an initial undetectable TSH-stimulated Tg, negative antithyroglobulin antibodies, and negative neck ultrasound, basal Tg and less frequent US surveillance may be sufficient.

32.6 Ultrasound for Nonendocrine Neck Pathology

When performing office-based US to evaluate thyroid and parathyroid disease, one should consider that coincidental secondary pathology may be encountered. Conversely, primary sonographic evaluation of neck masses and salivary gland disease can often be very helpful in diagnosis. There are a wide variety of benign and malignant diseases that may be detected during neck US. Commonly encountered benign entities include subcutaneous lesions, such as epidermal and sebaceous cysts as well as adnexal tumors. More deeply located benign lesions include lipomas, thyroglossal duct cysts, branchial cleft cysts, neural lesions, and salivary gland tumors. Based on shape and location, most of these entities are easily distinguished from one another. A branchial cleft cyst can be one of the most confusing lesions of the neck, and frequently metastatic cervical adenopathy is misdiagnosed as a branchial cleft cyst (► Fig. 32.9). Branchial cleft cysts are distinguished as solitary cystic structures without irregularly thickened areas along the cyst wall. The mass can have variable internal echogenicity, but posterior enhancement is commonly seen.¹⁰ Most importantly, it should be recognized that not all pathological adenopathy is related to thyroid cancer. Although the presence of microcalcifications is almost exclusively associated with papillary thyroid cancer, there are significant similarities in the sonographic appearance of metastatic adenopathy from a multitude of primary sites.¹¹ Conversely, pathological lymphadenopathy associated with lymphoma usually has a distinctly different appearance relative to metastatic disease. The lymph nodes tend to be hypoechoic with intranodal reticulations, but rarely will central necrosis be seen (► Fig. 32.10).¹¹

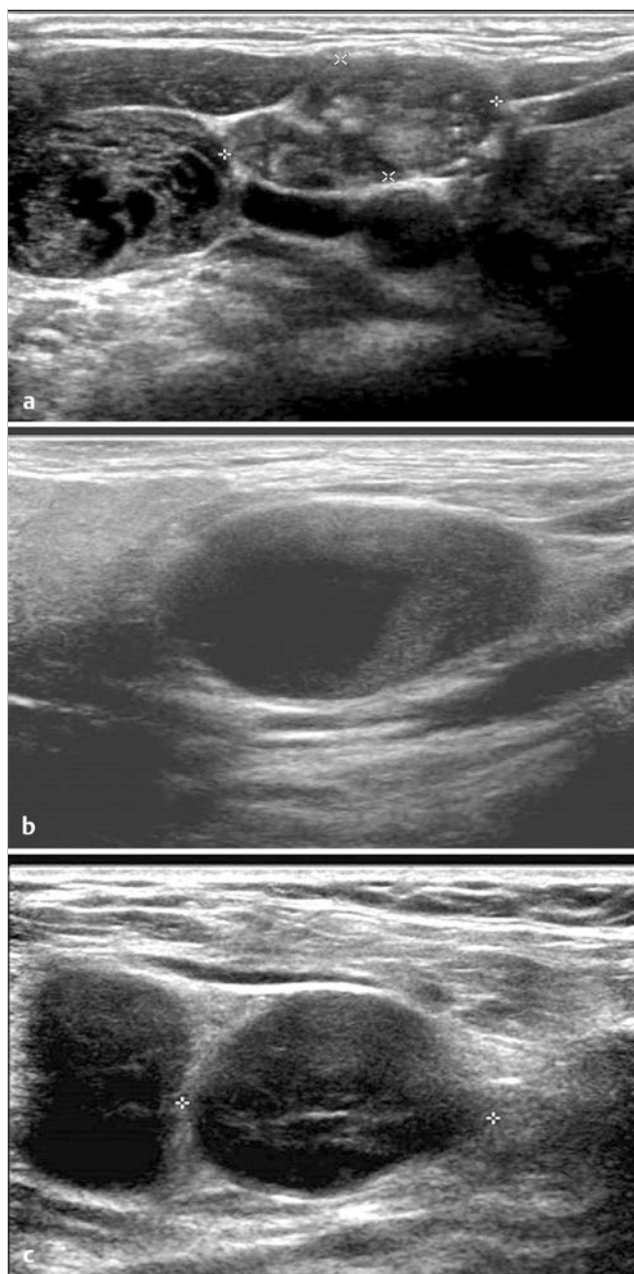


Fig. 32.10 Pathological lymphadenopathy. (a) Papillary thyroid carcinoma with characteristic microcalcifications. (b) Squamous cell carcinoma has a similar appearance but does not contain microcalcifications. A combination of isoechoic solid areas as well as necrotic hypoechoic areas are seen. (c) Lymphoma is much less likely to have cystic degeneration; and is usually a solid homogeneous enlarged node with a round shape, intranodal reticulations, and loss of the fatty hilum.

32.7 Ultrasound-Guided Procedures

The most commonly performed office-based US procedure is fine-needle aspiration biopsy (FNAB) of a thyroid nodule. Although palpation-guided FNAB of thyroid nodules is possible in some situations, the use of US guidance will reduce the non-diagnostic biopsy rate by ensuring that the solid component of

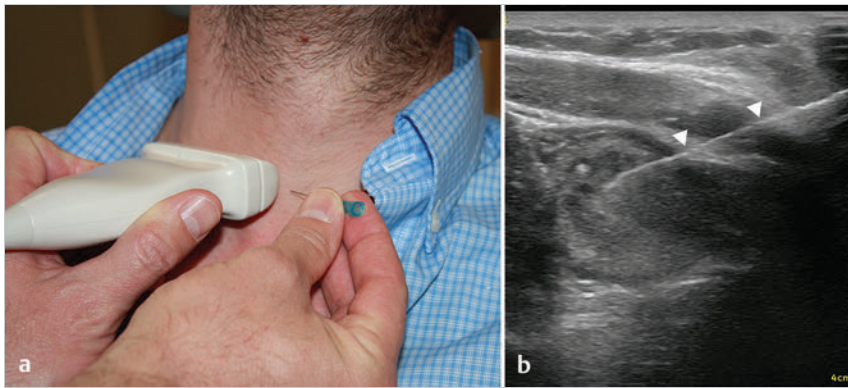


Fig. 32.11 Long-axis technique for fine-needle aspiration biopsy. (a) The needle is being inserted parallel to the long axis of the transducer. (b) The appearance of the needle (arrowheads) during biopsy of a mass.

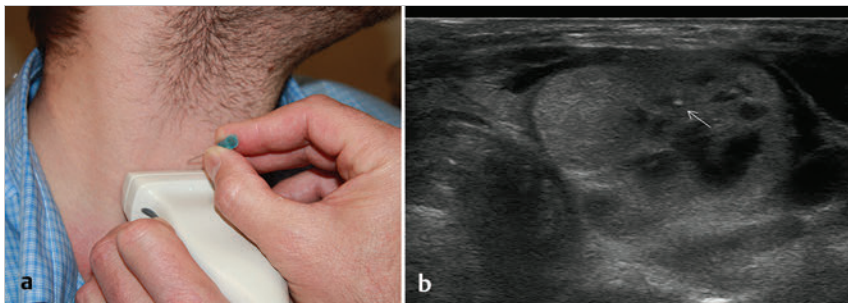


Fig. 32.12 Short-axis technique for fine-needle aspiration biopsy. (a) The needle is being inserted perpendicular to the long axis of the transducer. (b) The appearance of the needle during biopsy of a mass (arrow delineates needle tip).

a mass is sampled during the procedure.¹² Similarly, using US guidance for FNAB of a neck mass suspected of metastatic disease will improve the success of the procedure given that these masses will frequently have central necrosis. In contrast, US-guided biopsy for parathyroid disease is rarely necessary (unless there is suspicion of an intrathyroidal parathyroid adenoma), does not differentiate an adenoma from a carcinoma, and may result in fibrosis, which can make subsequent excision more challenging. Other US-guided procedures that may be necessary in a thyroid and parathyroid practice include drainage of fluid collections following neck surgery as well as ethanol ablation of recurrent neck disease.

A number of supplies are necessary to perform office-based US-guided FNAB. Most biopsies are completed with either a 22-gauge or 25-gauge 1.5 in needle. Two to three separate needle samples are obtained from each mass being biopsied. As the biopsy is being performed, aspiration with approximately 1 mL of negative pressure can be applied via a syringe. It is important to apply negative pressure only after the needle tip is confirmed to be in the mass. Similarly, the negative pressure must be released prior to removing the needle from the mass. Biopsies can also be completed using the capillary sampling technique (no negative pressure). The advantages to this approach include less pain and a lower likelihood of a bloody aspirate. In some instances, both approaches are used when sampling a mass. After each aspirate has been obtained, it must be immediately placed on the slide and smeared so that the specimen does not clot in the needle. In addition to the slide preparation, part of the aspirate should be placed in a liquid preparatory medium for cell block. In cases where thyroid cytomolecular or gene expression classifier testing is considered, a portion of the specimen should be placed in the appropriate RNase. If lymphoma is suspected, one will need to submit the specimen in

a Roswell Park Memorial Institute (RPMI) medium for flow cytometry.

There are two different approaches to performing US-guided FNAB, the long-axis technique and the short-axis technique. In the long-axis technique, the needle is inserted parallel to the long axis of the transducer. With this approach, the entire course of the needle is seen and the tip clearly visualized as it enters the mass (► Fig. 32.11). In the short-axis technique, the needle is inserted perpendicular to the long axis of the transducer. For the short-axis technique, only the tip of the needle is seen within the mass as the plane of the needle intersects the plane of the transducer (► Fig. 32.12). Keeping the bevel of the needle toward the US transducer will increase the echogenicity of the needle, which can be especially helpful when using either technique to ensure the tip is in the target.

The approach to needle biopsy of thyroid nodules and lymph nodes are similar and the cytological preparation is the most critical aspect of the procedure. Lymph node biopsies can potentially be more challenging for a multitude of reasons. First, the lymph nodes tend to be more intimately associated with neck vasculature compared to thyroid nodules, making direct access to the mass more difficult. In addition, the lymph nodes tend to be slightly smaller and move more readily in the neck compared to a thyroid nodule as one attempts to pass the needle into the mass. In some instances, additional testing beyond cytology may be warranted when performing a biopsy on a lymph node suspected to be recurrent well-differentiated thyroid cancer. Thyroglobulin washings can be included as part of the lymph node biopsy and if there is a high level of Tg detected in the washing, metastatic disease is confirmed.¹³ Simultaneous serum Tg testing is recommended to avoid a false-positive result related to blood contamination of the lymph node biopsy.

Table 32.2 Example of annual reimbursement for office-based ultrasound

Procedure	Medicare reimbursement	Annual procedure volume (46 weeks)	Revenue
Low-volume ultrasound (US) practice Assuming on average two diagnostic ultrasound (US) and one US-guided biopsy per week for 46 weeks			
76536	\$116.70	92	\$10,736.40
76942/10022	\$61.21 + \$142.83 = \$204.04	46	\$9,385.84
			= \$20,122.24
High-volume US practice Assuming on average five diagnostic US and two US-guided biopsies per week for 46 weeks			
76536	\$116.70	230	\$26,841.00
76942/10022	\$61.21 + \$142.83 = \$204.04	92	\$18,771.68
			= \$45,612.68

The indications for parathyroid biopsy are few, but include confirmation of a suspected intrathyroidal adenoma and confirmation of recurrent disease localization in patients that have undergone multiple previous operations. Although Tg washings are only occasionally necessary when performing lymph node biopsies, one should always perform washings for parathyroid hormone (PTH) during biopsy of a suspected parathyroid mass.¹⁴ With suspected parathyroid disease, cytology should also be performed, but there are significant limitations in being able to distinguish thyroid epithelium from parathyroid epithelium. When performing a biopsy for Tg or PTH washings, the needle aspirate should be flushed with 1 mL of saline. These procedures should be discussed with the pathology department before sending these specimens for processing because this is typically not within their standard biopsy protocol.

32.8 Financial Considerations in Office-Based Ultrasound

A significant financial investment is required to incorporate office-based US into a clinical practice. A variety of US units are available for performing office-based US. These can be more traditional console units, but smaller, high-quality laptop versions are also available. If one is considering sharing a unit with other medical specialties, the number of transducers required to meet the clinical needs is increased. Good-quality units can range from \$25,000 to as much as \$100,000 depending on the number of features and transducers that are included. If one plans to limit the use to the head and neck region, a single high-frequency linear-array transducer can meet the vast majority of clinical scenarios. Some will choose to purchase a second smaller linear transducer that may be used for US-guided biopsy procedures.

There are three Current Procedural Terminology (CPT) codes that are used for office-based US. The CPT code for diagnostic neck US is 76536. When US-guided FNA is performed, two separate CPT codes should be used: 76942 and 10022. The first represents the use of US for needle placement and the second for performing the FNA with US guidance. This combination of codes is repeated for each nodule, node, or mass biopsied, but

not for each needle pass into the same lesion. The following is an example of correct coding for a clinic encounter that incorporates office-based US. A patient is seen in the clinic for evaluation of palpable thyroid nodule and a diagnostic US is performed confirming bilateral dominant nodules. In addition, US-guided FNA is performed of a nodule in each lobe with four needle passes through each. For this encounter in addition to the Evaluation and Management code, one would bill 76536 for the diagnostic US as well as 76942/10022 × 2 for bilateral US-guided FNAs.

The 2015 Medicare physician reimbursement for each of these CPTs is as follows: 76536—\$116.70, 76942—\$61.21, and 10022—\$142.83.¹⁵ As an estimate of the procedure volume required to cover the cost of an office-based US machine, 100 diagnostic US CPT procedure codes billed annually would cover a \$30,000 machine in about 3 years. If one also performs US-guided biopsy as a part of the clinical practice, one can easily generate revenue to cover the investment for an office US machine (► Table 32.2).

32.9 Competency in Office-Based Ultrasound

Over the last decade, there has been a rapid increase in the number of thyroid and parathyroid surgeons and endocrinologists that perform office-based US as a part of their practice. These physicians who initially embraced the technology had an obligation to ensure their competency to perform an adequate US exam of the head and neck region. This process was not standardized but typically involved (1) completing a US course that included hands-on training, (2) working with a mentor, potentially not of the same specialty, to promote additional skills development, and (3) performing US exams on patients without billing for the procedure and then sending the patient to a radiology department to have a confirmatory US to ensure accuracy of the exam. This process could take anywhere from 6 to 12 months depending on the volume of exams performed. Once this process had been completed, the physician would independently perform and bill for head and neck US exams. In addition, physicians would need to work with the hospital to

obtain privileges to perform US as a part of their practice, if hospital based.

Currently, there are enough thyroid and parathyroid surgeons and endocrinologists in most academic centers performing office-based US to give residents and fellows a robust US experience as a part of their training. This experience definitely facilitates the process of developing competency with head and neck US. However, the surgical resident and fellow experience with office-based US is not recorded in a standardized fashion, as are surgical cases. Trainees are encouraged to independently record their experience with head and neck US so they have supporting documentation as they seek clinical privileges in the future.

A limited number of options exists for US courses with hands-on training. The American College of Surgeons offers a thyroid and parathyroid hands-on course as a part of the annual clinical congress. Additionally, an exported course with expanded head and neck content is held annually at the American Academy of Otolaryngology–Head and Neck Surgery meeting. Finally, exported US courses are held as a component of multiple academic institutions' CME programs throughout the year in the United States. The American Association of Clinical Endocrinologists (AACE) offers an ultrasound course as a part of their meetings, which is also exported to the American Thyroid Association annual meeting. Completion of any of these ultrasound courses results in receiving a certificate to recognize a physician's participation in the educational event, but these courses do not ensure one's competency in performing head and neck US.

There are currently two accreditation processes for thyroid and parathyroid US. Both of these processes are through the American Institute of Ultrasound in Medicine (AIUM). The first process is the Endocrine Certification in Neck Ultrasound that is associated with the AACE.¹⁶ Endocrinologists, otolaryngologists/head and neck surgeons, endocrine surgeons, radiologists, and cytopathologists are eligible to participate in this accreditation process. A new second accreditation process will be available starting in 2015 through the AIUM.¹⁷ This is a broader process encompassing Head and Neck Ultrasound. Otolaryngologists/head and neck surgeons, general surgeons, and radiologists are eligible to participate. Both of these pathways require passing a certification examination, submitting cases for central review, ongoing continuing education, and recertification after 3 years.

32.10 Conclusion

Office-based US has gained significant popularity for physicians that care for patients with thyroid and parathyroid diseases. Although there are cost considerations for incorporating this technology into a clinical practice, it is financially feasible and there are significant advantages to both the patient and the physician. The technical aspects of performing office-based US

are relatively straightforward, and developing a systematic approach to performing and documenting the exam is critical for success. Overall, those that decide to pursue office-based US will find it a valuable component of providing patient care.

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33 Outpatient Endocrine Surgery

Michael C. Singer and David J. Terris

33.1 Introduction

Over the past 15 years the practice of thyroid and parathyroid surgery has changed significantly. Technological and surgical innovations have fostered advances such as the minimally invasive thyroidectomy and focused parathyroidectomy. The postoperative care of these patients has also been transformed. Traditionally, all patients undergoing thyroidectomy or parathyroidectomy were admitted after surgery. Parathyroid surgery is now routinely performed on an outpatient basis. However, despite the numerous benefits provided by ambulatory thyroid surgery it is only routinely performed at select institutions in the United States. This chapter reviews the benefits of ambulatory endocrine surgery, discusses the optimal approach to its implementation, and focuses on specific techniques to facilitate its performance.

33.2 Ambulatory Surgery

Outpatient or ambulatory surgery is defined as any surgery that does not require postoperative overnight observation or admission. A 23-hour observation period, which has become popular in the United States, is not considered ambulatory care. Rather, ambulatory patients are typically observed for 2 to 4 hours in the postanesthesia care unit or same-day surgery center and then are discharged home.

In the early 1980s, due to increasing concerns over expanding health care costs, several financial incentives were implemented through Medicare, which promoted the performance of outpatient surgery. These enticements for institutions and physicians, which were subsequently adopted by private insurers, led to a dramatic shift toward an ambulatory approach for many procedures that previously were performed on an inpatient basis. In 1983 only 380,000 outpatient procedures were performed in the United States. By 1996 this had increased to 31.5 million, and by 2006 up to 53.3 million ambulatory procedures were completed.

Although initially adopted due to financial concerns, same-day discharge following surgery is now widely viewed by patients as an advantage, allowing them to avoid the potential risks of inpatient care and to recuperate in the comfort of their home.

33.3 Thyroid and Parathyroid Surgery

33.3.1 Parathyroid Surgery

Historically, all patients undergoing parathyroidectomy were hospitalized after surgery. However, mirroring overall surgical trends, many of these patients in the United States are now managed on an ambulatory basis.¹ This approach has been shown to be safe in patients with primary hyperparathyroidism.^{2,3} This is in contrast to patients with renal hyperparathyroidism, who can experience severe hypocalcemia (as well as

other electrolyte imbalances) after surgery and consequently are most appropriately managed on an inpatient basis.

33.3.2 Thyroid Surgery

A recent American Thyroid Association statement on outpatient thyroidectomy discusses this practice in depth and documents many of the concerns surrounding it.⁴ Unlike ambulatory parathyroidectomy, the practice of outpatient thyroid surgery is much more controversial. Therefore, the balance of this chapter focuses on this practice.

The first report of outpatient thyroidectomy was published in 1986 by Steckler.⁵ Lo Gerfo and colleagues further explored its safety and promoted its adoption in the early 1990s.⁶ These initial series examining the possibility of outpatient management were limited to patients undergoing hemi- and subtotal thyroidectomies. Although ambulatory hemithyroidectomy is increasingly practiced in the United States, an extensive shift toward routine same-day discharge, particularly after total or completion surgery, has not occurred. This is despite a number of large series demonstrating both its feasibility and its safety.^{7,8,9,10}

33.4 Benefits of Ambulatory Surgery

Studies have consistently shown that performing thyroid surgery on an ambulatory basis provides cost savings. The precise reduction in cost per patient is debatable; however, several studies have indicated that an ambulatory approach may result in savings of up to \$2,500 per patient.^{11,12} Although initially spurred by financial considerations, ambulatory thyroid surgery provides a host of potential benefits to patients. As a result many patients will opt for this approach if offered.

Although the presumption is that inpatient care provides a greater degree of safety than an ambulatory approach, hospitalization is not without its risks. Inpatient care raises the possibility of a host of nosocomial infections that otherwise are unlikely. An additional concern with inpatient care is the occurrence of medical errors. Although the care of a patient after thyroid surgery is relatively straightforward the potential exists for significant medical errors and injuries to occur. Both of these risks are reduced by ambulatory care.

Another significant advantage of ambulatory surgery is the ability for patients to recover in a more comfortable setting. Many patients appreciate the opportunity to receive care from family and friends at home rather than in the noisy, disruptive atmosphere of a hospital.

33.5 General Principles of Ambulatory Surgery

Above all else, ambulatory endocrine surgery must equal or exceed the safety profile of the inpatient approach. Although

Table 33.1 Potential contraindications to outpatient thyroidectomy

Clinical	Social	Procedural
Uncompensated cardiac or respiratory disease	Excessive distance from skilled facility	Massive goiter
Dialysis for renal failure	Living alone with no person to accompany	Extensive substernal goiter
Anticoagulant or antiplatelet therapy	Lack of transportation	Locally advanced cancer
Seizure disorder	Patient preference	Challenging hemostasis
Anxiety disorder	Communication barriers	Difficult thyroidectomy with Hashimoto's thyroiditis or Graves' disease
Obstructive sleep apnea		
Hearing loss		
Visual impairment		
Mental impairment		
Pregnancy		

Source: Terris et al.¹³

specific techniques can be employed to minimize the risks of certain complications, several general principles should guide the implementation of an ambulatory thyroid program.

33.5.1 Patient Selection

With ambulatory endocrine surgery, as with any surgery, careful patient selection is critical to achieving successful outcomes. The most fundamental considerations relate to a patient's overall health and ability to tolerate anesthesia. Major medical comorbidities may preclude the option of outpatient surgery. The following are some criteria for the eligibility for outpatient thyroidectomy¹³:

- No major comorbidities or ASA IV (American Society of Anesthesiologists Physical Status Classification System, ASA IV: "A patient with severe systemic disease that is a constant threat to life")
- Provision and understanding of preoperative education
- Team approach to education and clinical care
- Primary caregiver willing and available
- Social setting conducive to postoperative management
- Proximity to skilled facility

Importantly, advanced age should, not on its own, be considered a contraindication for ambulatory care. Instead, the individual patient's overall medical status should guide the patient's eligibility.

Beyond medical concerns the type of surgery scheduled can be used to help guide decisions about the suitability of same-day discharge. Some surgeons will not offer ambulatory care to patients who they feel are at greater risk of postoperative complications, such as those with substernal goiters or Graves' disease or those requiring central neck dissections. However, with increasing experience with ambulatory thyroidectomy a surgeon may become less restrictive with these limitations. For example, in the authors' practices, only the performance of a lateral neck dissection automatically mandates admission after surgery.

Several social factors should also be considered when assessing a patient for possible outpatient thyroid surgery. These include the ability of the patient and the care provider to understand and follow the postoperative instructions. Logistically, patients should have relatively prompt access to a medical facility. A final element of patient selection is a patient's motivation to proceed with outpatient care. Patients voicing concerns about the prospect of being discharged should be considered for inpatient management (► Table 33.1).¹³

33.5.2 Established Program

Optimizing outcomes with ambulatory thyroid surgery is most readily achieved in the context of an established program. This allows a team approach to patient management, including the surgeon, anesthesiologist, and nursing staff. Postanesthesia care unit nurses play a particularly important role in an ambulatory model as they can potentially identify early signs of evolving issues prior to a patient's discharge. Additionally, they help determine that a patient's pain and nausea are adequately controlled for safe release. As part of an ambulatory program, patients should be provided with thorough and easily understood written (as well as oral) instructions. Lastly, providing reliable contact information to knowledgeable staff assures that patients can easily have their questions answered and complications quickly triaged.

33.5.3 Patient Education

A systematic approach to ambulatory thyroid surgery dovetails with the educational component needed for these patients. With all members of the care team providing a consistent message patients are more likely to absorb the information relayed to them. From the time of the initial consultation the implications of an ambulatory approach should be discussed with the patient and caregivers. Importantly, they must understand the risks associated with outpatient thyroid surgery and be able to identify the signs and symptoms of potential complications.

Additionally, the instructions for care of the patient following discharge should be reviewed until clearly understood.

33.6 Specific Risks

In addition to the general risks of any ambulatory surgery, outpatient thyroid surgery has several specific complications that can arise. Concerns about the airway, the development of an expanding hematoma, and the possibility of hypocalcemia all are cited by those resistant to ambulatory thyroidectomy. Although these risks do exist, specific techniques can be used to reduce their incidence and mitigate the impact if they do occur.

33.6.1 Airway

Temporary or permanent injury of the recurrent laryngeal nerve (RLN) can occur in any thyroid surgery. Given the possible associated risks in regard to airway compromise it is ideal to be aware of the function of the larynx prior to discharge.

Bilateral vocal cord paralysis is the most feared airway complication after thyroidectomy because it may cause severe distress, stridor, and obstruction. Although the risk of bilateral vocal cord paralysis can be all but eliminated with the use of laryngeal nerve monitoring, it does still occur. This complication is usually recognized soon after extubation due to the severity of the symptoms. These patients are not eligible for same-day discharge because they need close observation and sometimes require reintubation.

Although less dramatic, a unilateral vocal cord paralysis can cause mild airway distress, difficulty swallowing, and patient discomfort. Although not an absolute contraindication to same-day discharge, patients with a unilateral vocal cord paralysis should be properly assessed prior to discharge. Importantly, the RLN may not exhibit immediate postoperative function despite normal anatomical integrity at the end of a surgery. It is therefore best to test the function of the nerve and not just rely on visual judgment. There are several approaches to assessing the function of the RLN after dissection. One approach is laryngeal nerve monitoring. This is most commonly performed with the use of an electromyographic endotracheal tube attached to a nerve monitor. Loss of signal after dissection can reliably be used to determine the postoperative function of the vocal cord. The laryngeal nerve twitch response is an alternative test of laryngeal function that can be used and does not require a nerve monitor or specialized equipment. A second approach to assess nerve function, which can be used in addition to or in place of nerve monitoring, is postoperative laryngoscopy performed in the recovery room. This provides the most accurate evaluation of vocal cord function.

Of note, after removal of large goiters concern has existed over possible airway obstruction secondary to tracheomalacia. Although large goiters can cause compression of the trachea while in situ it does not appear that this ever leads to a flaccid tracheal segment after removal. When the gland is removed during surgery, a compressed trachea often immediately regains its normal structure. Stridor present after thyroidectomy probably is not due to malacia but rather to vocal cord paralysis. Removal of large goiters is therefore not a contraindication to ambulatory thyroid surgery.

33.6.2 Hematoma

The risk of hematoma formation is one of the primary objections to ambulatory thyroid surgery. Although small fluid collections occur frequently, hematomas of clinical significance occur in <1% of patients undergoing thyroidectomy.

It is only the potential to cause airway compromise that makes hematomas dangerous. The development of a limited hematoma is of little clinical concern. Airway obstruction does not result from direct compression of the cartilaginous structures of the larynx and trachea. Rather, a progressively expanding hematoma locked within the tight confines of the central neck compartment exerts pressure on the surrounding soft tissue. This pressure eventually can exceed that of the lymphatic and venous drainage of the larynx. This obstruction results in watery edema and swelling of the supraglottis and glottis, eventually causing airway compromise. Postoperative admission theoretically allows the majority of these cases (most hematomas occur within 24 hours of surgery) to be recognized and managed promptly.

Beyond inpatient observation, surgeons have tried to prevent significant hematomas by using drains (whether active or passive). Many surgeons would also place a pressure dressing on or around the wound in an effort to limit the expansion of any collection. However, neither drain placement nor dressings have been shown to reduce the risk of hematoma formation.^{14,15,16} Given this, the use of drains and specialized dressings is unnecessary. Although select patients, such as those with a clotting disorder or end-stage renal disease, may benefit from drain placement, the vast majority of patients do not, which greatly simplifies their outpatient management. For surgeons reluctant to forgo the use of drains, ambulatory surgery is still an option because patients can be discharged with a drain and follow-up as an outpatient for removal.

Although the authors routinely use advanced energy devices for vessel sealing and place a hemostatic agent in the wound at the end of surgery, there are no data to show that these reduce the rate of hematoma formation. A “deep extubation” (extubation while the patient is still deeply anesthetized) minimizes coughing and bucking after surgery. This may reduce the risk of bleeding by preventing large increases in blood pressure. Most important for preventing clinically significant hematomas, however, is careful hemostasis during surgery and thorough assessment of the field prior to closure to assure it is dry.

As already above, the development of a hematoma is concerning only if it causes airway obstruction. Therefore, the focus should be on mitigating the impact of the rare, clinically significant hematoma (rather than small and indolent fluid collections). Understanding the mechanism of airway obstruction has led to a widely adopted technique change involving reapproximation of the strap muscles. In order to cause lymphatic and venous outflow obstruction a hematoma must apply pressure in the deeper areas of the neck. A more superficial hematoma may cause subcutaneous swelling and ecchymosis but is less likely to cause airway obstruction. Strap muscles are reapproximated in the midline after central neck compartment surgery to prevent the “cobra deformity,” as well as to avoid the skin from possibly scarring down directly onto the trachea after surgery. Both of these deformities are challenging to remedy if they occur. Surgeons have reapproximated the strap muscles in

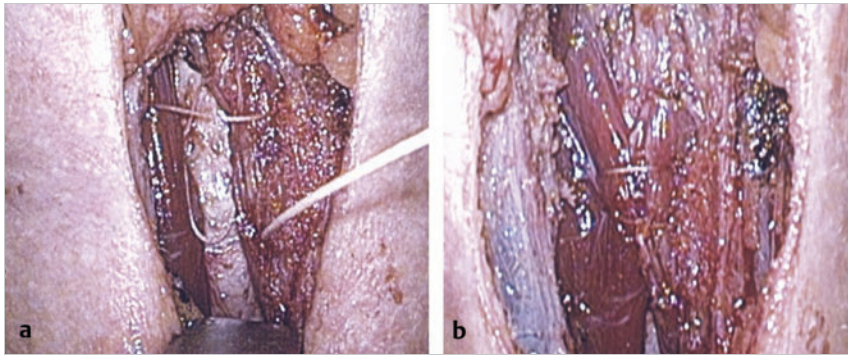


Fig. 33.1 (a,b) Single-point closure, the safest technique for reapproximation of the strap muscles, is demonstrated. (From Terris.¹⁶ Used with permission.)

the midline using multiple simple stitches or a running stitch from inferior to superior. However, if that approach is used and a hematoma occurs it may be locked in the deep spaces of the neck. Consequently, some surgeons advocate single-point fixation of the strap muscles in the midline with one figure-of-eight stitch (► Fig. 33.1)¹⁶ This approach accomplishes the goals of muscle reapproximation but it also allows egress of blood to the more superficial aspects of the wound. Consequently, if patients do develop a hematoma they present with a subcutaneous swelling instead of dysphagia and dyspnea (► Fig. 33.2).

Although these techniques can help reduce the incidence of clinically relevant hematomas they do still sometimes occur. As a result, education of patients and their caregivers regarding the signs and symptoms of hematomas is a critical component of safe ambulatory thyroid surgery.

33.6.3 Hypocalcemia

Despite meticulous management of the parathyroid glands during surgery a significant percentage of patients (up to 25%) undergoing total or completion thyroidectomy experience transient postoperative hypoparathyroidism and consequent hypocalcemia. Traditionally, one of the primary purposes of admission after thyroidectomy was monitoring for possible hypocalcemia. Close observation, with both frequent laboratory tests and physical examinations, was typically maintained for 48 to 72 hours after surgery (the nadir for hypocalcemia typically occurs during this time period). If hypocalcemia developed patients would then be supplemented as needed.

Although relatively common, hypocalcemia has been shown to be readily treatable with oral supplementation. Furthermore, as hypocalcemia worsens patients experience a predictable pattern of symptoms that signal the need for therapy (perioral and fingertip paresthesias followed by muscle cramping). These factors have allowed two alternative approaches to the management of hypocalcemia to become popularized: routine prophylactic supplementation and PTH-based selective supplementation. Both options allay concerns over hypocalcemia and permit patients to be discharged after thyroidectomy.

With universal supplementation all patients at risk of developing hypocalcemia are started on calcium supplementation after surgery.¹⁷ Different regimens have been described but they are all premised on the fact that those patients who do not need supplementation are put at little additional risk because the excess calcium is excreted in the urine. This allows the patients who do require supplementation to be effectively treated without risk to the remaining patients. Studies have



Fig. 33.2 Using single-point reapproximation of the strap muscles allows any potential hematoma to collect in the subcutaneous space. This avoids the potential danger of developing a compressive hematoma.

shown that, after surgery, patients can be started on 1,000 mg of calcium carbonate three times daily. Few become symptomatic and far fewer still require postoperative admission for severe hypocalcemia. One concern expressed by some surgeons is the possibility of hypercalcemia with supplementation. This is only a risk in patients taking calcitriol in addition to calcium. As a result, most surgeons using routine supplementation limit their regimens to calcium alone.

The alternative approach used for calcium management in the context of ambulatory thyroid surgery is selective calcium supplementation.¹⁷ In these patients, postoperative blood tests determine which patients are most at risk of developing hypocalcemia. Some surgeons use these levels to dictate appropriateness for ambulatory care. However, most commonly these levels are employed to establish which patients should be started on supplementation (and with what regimen). A number of groups have described using a PTH-based selective supplementation approach.^{18,19} A PTH level drawn in the recovery

room (most commonly 1 to 2 h after surgery) designates patients to one of three discharge pathways: no supplementation, supplementation with calcium, or supplementation with calcium and calcitriol. Regardless of the precise timing or regimen this selective approach has been shown to be safe and effective.

With calcium management, as with all elements of ambulatory thyroid surgery, education of patients and their caregivers is critical. Patients should clearly understand the supplementation regimen prescribed and be able to reliably follow it. Also, they should be instructed in the symptomatic presentation of hypocalcemia and what steps to take if those symptoms occur.

33.7 Conclusion

Ambulatory thyroid and parathyroid surgery provides patients with a wide array of benefits. Although outpatient parathyroidectomy has been widely adopted, surgeons have been more reluctant to take this approach with thyroidectomy. However, a systematic approach combined with careful patient selection and ample education permits the vast majority of thyroid surgery patients to be managed safely on an outpatient basis.

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