

ORAL CANCER

From Prevention to Intervention



Peter Thomson

Oral Cancer

Oral Cancer:

From Prevention to Intervention

By

Peter Thomson

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PREFACE

It is often said that, 'prevention is better than cure'. Whilst the origins of this popular proverb remain obscure, it is an undeniable and simple truism based upon common sense and ultimately life experience. In essence, prevention literally means stopping something happening and it is clearly far better to stop 'something bad' from happening than having to deal with the resultant consequences. Perhaps there is no better example of 'something bad' happening to someone than development of a life threatening disease such as cancer in which prevention can be effective and relatively economical, whilst cure may not only be elusive but also expensive in terms of financial and emotional costs. Cancer is the term colloquially applied to all malignant disease, although strictly speaking actually refers to those invasive and metastasizing tumours that arise from disturbed cell growth and replication within the ubiquitous epithelial lining tissues of the body.

Oral cancer, principally squamous cell carcinoma (SCC), thus arises from the specialized stratified squamous epithelium that, together with its underlying lamina propria of fibro-vascular connective tissue, forms the functional lining mucosa of the mouth, which is of course a significant entry-point into the upper aero-digestive tract and thereby the body itself. Often, though not exclusively, the consequence of over-use of tobacco and alcohol, resultant tumours present as non-healing erosive or ulcerative lesions that subsequently progress to invasive and ultimately painful growths. Established oral cancer is one of the commonest head and neck malignancies, and is a lethal and deforming disease due to local tissue invasion, oral and facial destruction, metastasis to cervical lymph nodes and widespread blood-borne dissemination to the lungs and the liver. Worldwide, it is estimated to be the 6th most common cancer with 5-year survival rates of only 50%, much worse than other more common and better known cancers such as breast or colon. Indeed, annual mortality rates are predicted to rise from around 370,000 to over 600,000 by 2030, raising the genuine spectre of a global epidemic. Individual patient prognosis is compromised by late presentation of advanced and aggressive disease which is sadly all too common in contemporary clinical practice and even initially successful treatment, often a combination of extensive surgical resection and debilitating chemo-radiotherapy, may be

complicated by recurrence or new, multi-focal disease extending throughout the upper aero-digestive tract as a result of widespread epithelial changes; a phenomenon described as ‘field cancerization’.

Immediately prior to invasive SCC development, however, earlier epithelial disorganisation and dysmaturation changes can be identified microscopically and delineated by pathologists into increasingly severe grades of ‘epithelial dysplasia’, thus representing an increased risk of cancer development. Importantly, such changes may be clinically recognizable during conventional oral examination and characterized as mucosal abnormalities, most commonly leukoplakia (a mucosal white patch), and termed potentially malignant disorders (PMD). Whilst all PMD share an increased risk of cancer development compared to ‘apparently normal’ mucosa, not all will inevitably transform, thus creating a challenging management dilemma for clinicians and patients alike.

Is there, therefore, an opportunity for prevention, early diagnosis and low-morbidity therapeutic intervention during this clinically identifiable ‘oral pre-cancer window’ that might ‘stop the oral cancer clock’ and help reduce the long-term risk of malignant transformation? This is an essential question, and forms the fundamental theme of the book you are about to read.

It is important to stress at this juncture that I have not attempted a systematic review of the global oral cancer literature, nor have I undertaken a meta-analysis of treatment intervention. Although of undoubted scientific validity and interest, such a work would be difficult to read and would not serve the particular purpose of this book, which is to guide the reader through a more personalised journey documenting a clinically orientated research programme undertaken by the author, in an attempt to improve both knowledge and understanding of the natural history of oral cancer. Nonetheless, detailed references will be provided in each chapter for those wishing to pursue their studies further.

Perhaps to explain this approach more fully, I should refer the interested reader to the preface of a previously published work on oral pre-cancer, in which I first detailed an approach to the diagnosis and management of PMD and described the genesis of my interest in studying this most intriguing and beguiling of disorders¹. Nearly 40 years has passed since, as an undergraduate dental student, I first attended specialist oral surgery and oral medicine clinics at a well-known dental teaching hospital in North-West England. It was here that I was introduced to the fascinating and

confusing array of oral mucosal lesions deemed to be PMD and discovered their varied aetiologies, histopathological and clinical diagnoses and, perhaps most significantly of all, their devastating potential to transform to life-threatening cancers.

My early interest and enthusiasm was tempered, unfortunately, by the gradual realisation that my clinical teachers, many of whom were senior clinicians and professors of international repute, were unable to determine the individual risk of patients undergoing carcinogenesis. Nor could they offer reliable prognoses for disease progression or, apparently, any appropriate treatment intervention. Worst of all was to encounter those unfortunate individuals who, despite regular clinic attendance for examination and reassurance, subsequently went on to develop oral cancer.

As I commenced my clinical training in hospital dentistry and then medical undergraduate studies, followed by a period of scientific research in epithelial biology, before specialising as an oral and maxillofacial surgeon I learned a great deal more about the devastating consequences, both in terms of morbidity and mortality, of oral cavity cancer. The personal inspiration to try to combat this pernicious oral disease was born. Could rationalizing oral diagnostic technique and developing an efficacious interventional management protocol improve treatment outcomes for patients? The reader, I hope, will have the opportunity to judge.

Like most clinicians, I owe enormous personal debt to my clinical teachers and surgical trainers through the years, but I particularly wish to acknowledge and thank my patients for their stoicism and loyalty and especially the trust they have bestowed on me as their advisor and surgeon. It is for them, and future patients like them, that this book is dedicated.

Peter Thomson

Hong Kong

2018

Reference

1. Thomson PJ. Oral Precancer. Diagnosis and management of potentially malignant disorders. Chichester: Wiley-Blackwell; 2012. ISBN 978-1-4433-3574-3.

PART ONE

PROBLEMS

'a situation regarded as harmful and needing to be dealt with...'

CHAPTER ONE

A PERSONAL JOURNEY

'...the act of travelling from one place to another...over a long period...'

I do hope that the reader will, at the outset, indulge me with some brief reflection on my personal academic and professional journey. As already alluded to in the Preface, I trust that this will help to place much of what is to follow in perspective and clarify the precise development of many of the hypotheses, theoretical arguments and treatment philosophies described in the subsequent chapters of this book.

Even today, as I rapidly approach my 60th year, I remain unable to explain exactly why, from an early age, I always wanted to be a dentist. Strange in many ways because, like many people growing up in the 1960's, I did not particularly look forward to attending as a dental patient or undergoing treatment at my local practice, despite the consummate skill and consideration I always received. Perhaps it was, indeed, the evident professionalism of my own dentist that catalysed my personal interest and enthusiasm for considering dentistry as a career. To be able to offer specialist knowledge and advice, and provide skilled practical help to people in need was I think what attracted me most about practising as a dentist; it still does to this day.

In 1978, therefore, I was pleased to commence undergraduate studies in the Turner Dental School at the Victoria University of Manchester. Lasting four years and one term in those days, the course was demanding, time consuming and highly rewarding all in equal measures. Gaining both knowledge and practical operative skills, I qualified BDS (Honours) in December 1982 and became a registered practitioner with the General Dental Council; Figure 1.1. During my studies, I particularly enjoyed pathology and medical and surgical subjects, although I never held any particular aspiration to work as a medical practitioner. In my senior student years, as discussed in the Preface, I developed an especial interest in the study of oral cancer and potentially malignant disorders (PMD) and realised that the specialty of oral surgery, particularly in an academic

environment, combined the subjects that interested me most in a particularly challenging and proactive manner. Somewhat ironically for me, 1982 was also the year that oral surgery formally transformed into oral & maxillofacial surgery in the UK, thereby undertaking a broader range of head and neck surgery and appropriately now requiring both dental and medical qualifications for specialist training.

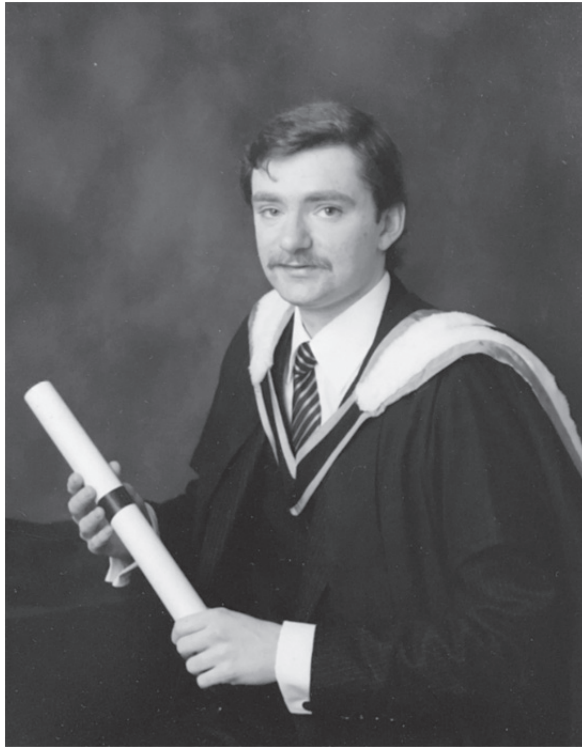


Figure 1.1: The author, graduating BDS from Manchester University, December 1982.

The die was therefore well and truly cast for me. Whilst undertaking my first job as a dentist working as a dental hospital house officer at Manchester in 1983, I applied and was accepted to study medicine at the University of Newcastle upon Tyne, ultimately qualifying MBBS and becoming a medical practitioner in 1988. To be candid, I found medical studies as an undergraduate far less demanding than dentistry, the latter of course requiring significant clinical and practical skill acquisition in

addition to knowledge retention, and I was fortunate to have time, primarily during evenings, weekends and university holidays, to practise part-time as a general dental practitioner in a busy and well-regarded practice within a small mining town in County Durham. Looking back at those happy and fulfilling years, it is impossible to over-emphasize how much experience I truly gained and how much I learned about clinical dental practice; quite simply, invaluable 'real-world' experience for the would-be specialist.

In 1989, after pre-registration medical jobs in Newcastle, I was offered a post as a junior lecturer in oral & maxillofacial surgery back at my alma mater in Manchester. This was the start of my clinical academic career and an exciting time, as I joined a successful and expanding academic surgical department. During this time, I sat the required training examinations gaining Fellowships in Dental Surgery from the Royal College of Surgeons of England and Ireland in 1990 and, following a period of general surgical training, a Fellowship in Surgery from the Edinburgh College in 1992. I was enrolled as a higher trainee and was fortunate to work with a number of outstanding and skilled oral & maxillofacial surgeons; as time went on, it was clear that oral cancer and head & neck oncology was becoming the focus of my clinical training.

A senior colleague in the department at the time, and one far more gifted than I, introduced me to research opportunities at the Paterson Institute for Cancer Research at the Christie Hospital in Manchester. Here I discovered the fascinating science of epithelial cell kinetics and was welcomed as a novice to laboratory research by renowned cell biologists. How they ever tolerated my disruptive, part-time forays into oral carcinogenesis research I will never know, but these astonishingly generous scientists supported and guided me to complete both MSc¹ and PhD² research degrees in epithelial biology; I owe them an enormous debt, hence their appearance and recognition, albeit far too briefly, in this book!

In 1996 I had completed my surgical specialty training and, quite unexpectedly and without forewarning, was invited to apply for the newly re-established Chair in Oral & Maxillofacial Surgery in the School of Dentistry at Newcastle University. Although I was only 36 years old, and it genuinely felt premature, I was nonetheless interviewed and appointed to the post. With the prescribed remit of re-invigorating the academic department and developing oral cancer research and teaching, I returned to Newcastle in August of that year as Professor of Oral & Maxillofacial Surgery.

High rates of oral cancer have always existed in Northern England, unfortunately, with the general health of some 280,000 people living in the city of Newcastle upon Tyne worse than average for many parameters documented in England, including reduced life expectancy, high levels of adult smoking and smoking-related deaths, and significant rates of alcohol-related disease and hospital admission. Whilst an average of 70 new cases of oral cancer occurred each year in the region³, no data existed at all to document the incidence or prevalence of PMD. In an attempt to improve both knowledge and patient management, I established a dedicated PMD clinical service based within the Newcastle Dental Hospital and the Maxillofacial Unit at the Royal Victoria Infirmary. From rather inauspicious beginnings, we were ultimately managing around 1200 patient attendances each year comprising new patient referrals of suspicious oral lesions, forwarded from both primary care practitioners and specialist hospital colleagues, together with the longer-term follow-up of previously diagnosed and treated cases.

A specific interventional management protocol was developed for these patients, based firmly upon those early dental student observations, concentrating upon the recognition of patients with PMD, the early diagnosis and characterization of disease, the removal or ablation of 'high risk' 'pre-cancer' mucosal lesions by CO₂ laser (a technique I was first introduced to in Manchester) and structured patient follow-up and surveillance⁴; much of this will be examined and discussed in detail later in the book.

Looking back, the ensuing 20 years literally flew by as my colleagues and I worked hard to build effective clinical, teaching and research capabilities for our specialty of oral & maxillofacial surgery. It was hard work, not always without professional opposition to our desire to grow and develop, but steady progress continued, students were taught, research papers published and patients increasingly treated to the highest standards we could achieve.

In 1999, following a merger of adjacent NHS hospital trusts, a particularly important and welcome development was the formation of the Northern Head & Neck Cancer Unit. Based at Newcastle's Freeman Hospital, a functioning and truly innovative, multi-disciplinary head & neck cancer service was developed and delivered for the first time with surgeons from different specialities combining their expertise, and with oncologists and patient supportive services fully coordinated to centralise and prioritise exemplary patient care. This, of course, has now become the model for

cancer centres throughout the UK and indeed globally to improve diagnosis and management for patients; but Newcastle was one of the first!

Working ‘hand in glove’ with colleagues, we continued to integrate services for patients to build the best specialist oncology centre we could in Newcastle. Research in our discipline continued to prosper too; with an increase in academic and clinical staff came more publications, new postgraduate students and an expanding profile of research income. My own work continued in a concerted attempt to improve the overall efficacy of diagnosis and management for PMD and, in particular, the early identification and treatment of oral SCC.

In 2002, we had the opportunity to join a major, Europe-wide epidemiological study to stratify risk assessment for oral cancer development, especially in relation to lifestyle habits, dietary factors and occupation. Following appropriate ethics committee approval, we recruited 73 Newcastle oral cancer patients and 112 controls into the Alcohol Related Cancers and Genetic susceptibility in Europe (ARCAGE) study. Ultimately, this project examined data of 2304 head and neck cancer cases and 2227 controls from 15 centres in 11 European countries, adding significantly to our understanding of the epidemiology and aetiology of oral cancer⁵. After some years of continuing and productive research, we then became part of the even larger International Head and Neck Cancer Epidemiology (INHANCE) consortium, which together collated data from 14,520 head and neck cancer cases and 22,737 controls⁶. These were indeed exciting times, with ‘big data’ sets to analyse, providing outstanding opportunities to advance our knowledge of oral carcinogenesis; many of the resulting publications from these research collaborations are referenced throughout this book. I am delighted to report that this work is still on-going as I write!

In 2009, I was honoured to be appointed Hunterian Professor at the Royal College of Surgeons of England, followed in 2011 by a King James IV Professorship at the Royal College of Surgeons in Edinburgh in recognition of my research and clinical work in oral oncology and the advancement of surgical care, respectively. In 2012, I edited and published my book on PMD management, which I hope the reader will find a suitable and complementary companion volume to this work⁷, and in 2014 gained a higher doctorate (DDSc) from Manchester University for my collected published works on oral cancer research⁸. This was followed in 2016 by an MD thesis from the University of Bath detailing the results of

interventional management of PMD over a 20-year period⁹; we will carefully examine these substantive data in a later chapter.

In 2014, after a very rewarding but personally exhausting 4-year stint as Clinical Director of the Dental Hospital, I took sabbatical leave from Newcastle and spent a term as Visiting Professor at the National University of Singapore, which enjoyably and quite spectacularly expanded my global view of dental education, training and research. Shortly afterwards, I was invited to consider becoming the new Head of School at a dental teaching institute in Australia. Although extremely tempting, both the local university and I ultimately decided that this was not the right time or place for me; looking back now, I realise that was probably a wise decision.

The Asia-Pacific experience did, however, significantly alter my outlook on my professional life to date and, after nearly 20 years in Newcastle, I realised it was time to seriously consider some change and professional renewal. I had, after all, developed, staffed and led a modern and innovative clinical academic department, mentored young colleagues to develop their clinical, research and managerial skills, and worked hard to ensure full integration of clinical services with teaching and research. I really felt that, in order to develop my own skills further, I needed a new professional challenge.

In April 2016, therefore, when an opportunity arose I took a leap of faith and joined the University of Queensland's School of Dentistry in Brisbane as Professor of Oral & Maxillofacial Surgery and Academic Clinical Director; an exciting move tinged, of course, with some sadness as I left many colleagues, friends and patients behind in the UK. The newly commissioned Oral Health Centre, located at the University's Herston campus, possessed the most modern dental facilities I have ever seen and it was an absolute pleasure to teach and practice there. Within a year, I was asked to take on the new role of Oral Health Alliance Director to lead the conjoint delivery of oral health services and teaching between the University of Queensland and Metro North Hospitals and Health Service, the local provider of public health services¹⁰. This became a fascinating project as we essentially deconstructed the existing University-led clinical service to reconfigure a new public oral health service; I wonder how similar it must have been during the launch of the NHS in the UK some 70 years beforehand!

And finally...to the present day when, after a receiving an enticing offer but facing a very difficult decision making period, I left Brisbane in September 2017 having accepted the post of Clinical Professor and Head of Oral & Maxillofacial Surgery at the University of Hong Kong's Faculty of Dentistry¹¹. At the time of writing the World's number one ranked dental school for three consecutive years, I hope that the extraordinary vibrant academic environment here and personal interaction with outstanding colleagues will help me to refine and consolidate my on-going research work in oral oncology; we begin again!¹².

Quite a journey then from the Turner Dental School in Manchester 40 years ago, especially when summarised, edited and fast-tracked over 4 pages or so of text, but in reality just the background scene setting for the detailed story about to unfold.



Figure 1.2: Hong Kong, March 2018

References

1. Thomson PJ. An investigation into the effects of growth factors on oral epithelium. MSc Thesis, University of Manchester. 1993.
2. Thomson PJ. An investigation into oral epithelial cell activity and the pathogenesis of squamous cell carcinoma. PhD Thesis, University of Manchester. 1997.
3. O'Hanlon S, Forster DP, Lowry RJ. Oral cancer in the North-East of England: incidence, mortality trends and the link with material deprivation. *Community Dentistry & Oral Epidemiology* 1997 25: 371-376.
4. Thomson PJ, Wylie J. Interventional laser surgery: an effective surgical and diagnostic tool in oral precancer management. *International Journal of Oral & Maxillofacial Surgery* 2002 31:145-153.
5. Macfarlane TV, Macfarlane GJ, Oliver RJ, Benhamou S, Bouchardy C, Ahrens W, Pohlabein H, Laggiou P, Laggiou A, Castellsagu X, Agudo A, Merletti F, Richiardi L, Kjaerheim K, Slamova A, Schejbalova M, Canova C, Simonato L, Talamini R, Barzan L, Conway DI, McKinney PA, Znaor A, Lowry RJ, Thomson PJ, Healy CM, McCartan BE, Marron M, Hashibe M, Brennan P. The aetiology of upper aerodigestive tract cancers among young adults in Europe: The ARCAGE study. *Cancer Causes Control* 2010 21: 2213-2221.
6. Chuang S-C, Jenab M, Heck J, Bosetti C, Talamini R, Matsuo K, Castellsague X, Franceschi S, Herrero R, Winn D, LaVecchia C, Morgenstern H, Zhang Z-F, Levi F, Dal Maso L, Kelsey K, McClean M, Vaughan T, Lazarus P, Muscat J, Ramroth H, Chen C, Schwartz S, Eluf-Neto J, Hayes R, Purdue M, Boccia S, Cadoni G, Zaridze D, Koifman S, Curado M, Ahrens W, Benhamou S, Matos E, Laggiou P, Szeszenia-Dabrowska N, A Olshan A, Fernandez L, Menezes A, Agudo A, Dault A, Merletti F, Macfarlane GJ, Kjaerheim K, Mates D, Holcatova I, Schantz S, Yu G-P, Simonato L, Brenner H, Mueller H, Conway D, Thomson PJ, Fabianova E, Znaor A, Rudnai P, Healy CM, Ferro G, Brennan P, Boffetta P, Hashibe M. Diet and the risk of head and neck cancer: a pooled analysis in the INHANCE consortium. *Cancer Causes Control* 2012 23: 69-88.
7. Thomson PJ. Oral Precancer. Diagnosis and management of potentially malignant disorders. Chichester: Wiley-Blackwell; 2012. ISBN 978-1-4433-3574-3.
8. Thomson PJ. Science, Surgery and Surveillance - Studies and Scientific Writings on the Pathogenesis of Oral Squamous Cell

- Carcinoma and the Interventional Management of Potentially Malignant Disorders. DSc Thesis, University of Manchester. 2014.
9. Thomson PJ. An investigation into the efficacy of interventional therapy for oral potentially malignant disorders. MD Thesis, University of Bath. 2016.
 10. Thomson PJ. Building an Alliance: A new future for academic dentistry 'Down Under'? *Faculty Dental Journal* 2017 8: 122-127.
 11. Thomson PJ. Oral & Maxillofacial Surgery: A View from the East. *Faculty Dental Journal* 2018 9: 70-73.
 12. Thomson PJ, Su R, Choi S-W. Oral cancer in Hong Kong: identifying and managing the 'high-risk' population. *Faculty Dental Journal* 2018 9: 116-121.

CHAPTER TWO

ORAL CANCER

‘...know your enemy...’

Introduction

Perhaps somewhat ironically, in view of the title, this is not actually a book about oral cancer. On the contrary, it is very much a manuscript dedicated to the prevention of cancer by the early diagnosis of pre-cancerous or pre-malignant change and the development of effective, minimally invasive interventional strategies to halt the progress of oral carcinogenesis. Nonetheless, if we are to be truly successful in our battles with this pernicious and lethal disease I think it is very important at this juncture that we take time to try to understand more fully the true nature of our enemy.

What is Cancer?

It is estimated that one in three people will develop cancer at some point in their life; quite a sobering statistic. To address the titular question, cancer is essentially a genetic disorder resulting from accumulation of multiple mutations in cellular DNA, particularly those resulting in cell immortality and the loss of response to normal growth control mechanisms. Originally termed ‘cancer’ due to the microscopically observed ‘crab-like’ projections of abnormal epithelium invading subjacent connective tissue, malignant tumour formation involves a complex, multi-stage disruption to the processes of cell proliferation, differentiation and development¹.

An established tumour is thus an abnormal, uncoordinated tissue growth that persists in an excessive manner after the initiating stimuli have ceased. Tumour initiation and then progression may result from damage caused by extraneous physical, chemical or biological agents which are termed carcinogens, or unpredictably by spontaneous mutation. Uncontrolled growth facilitates local tissue invasion and destruction, including direct

involvement of adjacent nerves, blood vessels and lymphatics. Loss of cell adhesion leads to metastasis and widespread organ involvement by tumour seeding. A battle for nutritional resource, and ultimately biological survival, ensues between tumour and host. In the absence of effective treatment intervention, the host becomes progressively weakened by the ever increasing tumour mass, giving rise to classical clinical signs of malignancy including cachexia, anaemia and muscle wasting, before progressing to organ failure and death.

In recent years, somatic stem cells, the adult tissue equivalent of their embryonic counterparts, have been postulated as the primary target cell in carcinogenesis. Such activated 'cancer stem cells' may be responsible not only for tumour growth, but also for the development of metastases, treatment resistance and ultimately recurrent disease².

Whilst tumours arising from accessible epithelial surfaces such as skin and oral mucosa may be readily observed upon clinical examination, others arising in deeper body structures may require endoscopic examination or advanced imaging with techniques such as CT or MR scanning. Once identified, biopsy and histopathological grading is essential for the diagnostic process³.

Cancer treatment involves one or quite often a combination of the following aggressive treatment modalities: surgery, radiotherapy and chemotherapy. These are increasingly combined in specific regimes, devised and prescribed in multi-disciplinary specialist cancer clinics, in an attempt to improve efficacy. Conventional surgery requires access techniques at operation to facilitate full tumour visualisation and resection with a margin of adjacent normal tissue in anticipation of local invasion, and excision of draining lymph nodes to address metastatic spread. The application of ionising radiation as localised radiotherapy to the primary tumour site is performed to preferentially destroy rapidly proliferating tumour tissue, albeit at the expense of damaging normal tissue, or following surgery to 'sterilise' the operative field of residual tumour cells. Chemotherapy offers similar effect, targeting actively dividing cells to eliminate tumours whilst allowing normal cells to repair, but is administered as systemic treatment. Newer techniques now utilise combined chemo-radiotherapy in an attempt to enhance the sensitivity of tumour cells to radiation³.

Post-treatment morbidity in cancer patients can be extensive owing to the toxic effects of chemotherapy on bone marrow, surgical deformity and

scarring, and long-term local tissue damage from ionising radiation. In general, the earlier a tumour is diagnosed and treated, the better the outcome. Individual patient prognosis is highly dependent on the type of cancer, stage of disease and the effectiveness of treatment. Unfortunately, despite significant advances in diagnosis and management, many patients with malignant disease will eventually die from progression of their primary tumours or from uncontrolled and widespread metastatic disease. Increasingly it is recognised that individual host/tumour relationships are probably unique and highly patient-specific; these realizations may well inform future cancer treatment strategies.

Improvements in patient survival will depend on more effective and earlier detection of potentially malignant disease states and, undoubtedly, future developments in cancer treatment must focus more on prevention, earliest possible diagnosis and more personalised treatment based upon genetic profiling and development of more effective anti-cancer drugs³.

Oral Cancer

Oral squamous cell carcinoma (SCC) arises from the mucosal lining of the mouth, accounts for over 95% of all oral cancer cases and is not only one of the most frequent head and neck malignancies, but is also one of the commonest cancers to affect males worldwide. It presents clinically as non-healing ulcerative lesions due to epithelial destruction and subsequently irregular, raised, invasive and ultimately painful tumour masses due to continued growth. Many of these features are clearly illustrated in Figure 2.1 which shows SCC arising from the floor of mouth and ventral tongue mucosa, a particularly common site of tumour origin in Western and European populations. Induration, or hardness, is common in SCC owing to extensive keratin production and is a characteristic finding on palpation of tumours clinically, as is fixation due to invasion into the immediately underlying tissues. Established SCC is thus a lethal and deforming disease due to local invasion, oral and facial destruction, metastasis to cervical lymph nodes and widespread blood-borne tumour dissemination particularly affecting the lungs and the liver^{4,5}.

Whilst other forms of oral cancer are recognized, including minor salivary gland tumours, lymphoma, melanoma and metastases from other body sites, these are all relatively rare in comparison. It is also increasingly recognised that oral cavity cancer should be clearly distinguished from

oro-pharyngeal malignancy, in which aetiology, clinical presentation and treatment vary significantly.

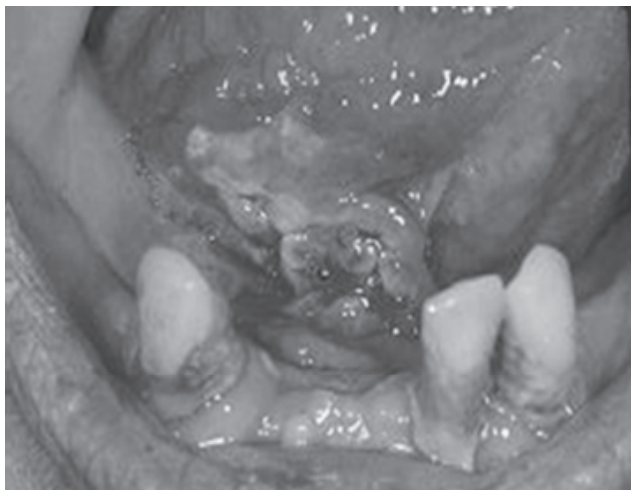


Figure 2.1: Irregular and ulcerated oral SCC arising from the floor of mouth and adjacent ventral tongue tissue, invading underlying musculature

Worldwide, oral cancer is estimated to be the 6th most common cancer with 5-year survival rates around 50% and a prognosis significantly compromised by advanced disease and late presentation, which are common features in contemporary clinical practice^{6,7}. In the UK 8,302 new cases of oral cancer were diagnosed in 2017, a 49% increase over the preceding 10 years, with 2,722 deaths reported (The State of Mouth Cancer UK Report 2018/2019, Oral Health Foundation). There has thus been a significant rise in incidence, particularly affecting young and female patients, and researchers predict a mouth cancer ‘epidemic’ will occur during the 21st Century⁷⁻⁹.

Pathologically, SCC is classified as well, moderately or poorly differentiated dependent upon how closely the tumour resembles normal oral epithelium. Although somewhat subjective in nature, studies have suggested that poorly differentiated tumours are likely to have the worst prognoses. Other histological features used to determine the aggressiveness of individual oral SCCs include the pattern and depth of connective tissue invasion and the presence or absence of perineural, lymphatic and vascular involvement¹.

Whilst the number of patients suffering uncontrolled oral cancer at primary sites in the head and neck has fallen over the last 30 years, due to improved management techniques, primarily by combining treatment modalities of surgery and chemo-radiotherapy, many will die as a result of metastatic disease, and up to a quarter of patients will experience multiple cancer development in the upper aerodigestive tract either synchronously or metachronously^{5,10}.

The presentation of multiple lesions in an individual patient is a manifestation of widespread epithelial instability, which is a hallmark of head and neck squamous cell carcinoma, classically referred to as 'field change' cancerization¹¹. This was the term first introduced by Slaughter et al¹² who proposed that oral cancers develop in multifocal areas of 'pre-cancer change'. The risk of multiple, primary cancer development is probably highest in younger patients, perhaps reflecting an inherent genetic susceptibility, and in those who are continually exposed to carcinogenic influence^{7,13}.

Aetiological factors responsible for malignant transformation of oral squamous epithelium most commonly involve the excessive consumption of tobacco products, alcohol misuse and betel quid. The latter is a complex mixture containing areca nut, with or without tobacco, that is wrapped in betel leaf and held or chewed in the mouth particularly associated with SCC development on the buccal mucosa in South Asian populations^{14,15}. Globally, 25% of oral cancers have been attributed to tobacco use, either by smoking or various non-smoking or tobacco chewing habits, with an association that appears highly dose-dependent. Tobacco smoke contains over 300 known carcinogens, such as the aromatic hydrocarbon benzopyrene and tobacco-specific nitrosamines, generated especially when tobacco burns, and probably to a lesser extent by smokeless tobacco, which then dissolve in saliva with high carcinogenic potency. In smokers, the risk of oral cancer has been shown to increase markedly for smoking durations greater than 20 years, a daily cigarette consumption in excess of 20, and an enhanced addiction to tobacco use^{15,16}.

Around 7 to 19% of oral cancer cases have been linked with regular alcohol consumption which also seems to increase risk in a dose-dependent manner, such that individuals consuming 4 to 5 drinks daily show a 2 to 3 times higher risk than non-drinkers¹⁷. Alcohol is metabolised in the body to the known carcinogen acetaldehyde, resulting in DNA damage within oral epithelial cells. Whilst there is no doubt that oral cancer risk increases further amongst alcohol drinkers who also smoke,

possibly due to increased mucosal absorption of exogenous carcinogens, uncertainty still remains regarding the true significance of alcohol in people who have never smoked^{16,18}.

A further complication is that many people who smoke and drink do not develop cancer whilst other studies have observed that, equally, many oral cancer patients have never been overexposed to tobacco or alcohol, so it is likely that other risk factors are involved¹⁹. Genetic predisposition to DNA mutation in oral epithelium, poor diet and nutrition, ageing, an impaired immune response, low socioeconomic status, short stature, manual occupations, poor oral health and infections have all been implicated, but evidence of their precise role in carcinogenesis remains obtuse and is still evolving^{1,20,21}. Petti¹⁶, for example, reported that 10 to 15% of oral cancer cases may be attributed to diets low in fresh fruit and vegetable intake, but again the specific interaction between putative anti-carcinogenic properties of the diet versus heavy smoking and alcohol drinking remains unclear.

daSilva et al²² also emphasized the close interrelationships that exist between the principal aetiological agents of oral cancer: lifestyle habits (tobacco exposure and alcohol consumption), dietary factors, occupation, socioeconomic status, exposure to external agents and genetic susceptibility. It is, I believe, reasonable to consider that the causative agents implicated in oral SCC development will be similarly influential during PMD initiation, although the evidence supporting this is less robust.

Although a significant role for human papillomavirus (HPV) infection (especially subtype 16) has been suggested during oral carcinogenesis, and indeed HPV is now considered an important contemporary risk factor, this seems uniquely associated with a rise in oropharyngeal, tonsil and tongue base cancer affecting younger patients and often presenting with extensive cervical lymph node metastases and a postulated sexually transmitted aetiology. Thus, as alluded to earlier, HPV associated head and neck cancer probably represents a distinct disease entity, with the precise role of HPV in classic, tobacco-related intra-oral cancer still remaining obscure^{4,5,23,24}.

Oral Carcinogenesis and Epithelial Dysplasia

Carcinogenesis is, unquestionably, a highly complex process. A 'progression model' proposed for oral carcinogenesis suggests that, following genetic mutation and irreversible genotypic damage, various

phenotypic epithelial tissue disorganisation and dysmaturation changes occur which, if allowed to progress, ultimately lead to invasive carcinoma^{1,25}; this is outlined in diagram form in Figure 2.2. Fundamental to this process are alterations in genes regulating cell division, cell cycle progression and DNA synthesis and repair. Promotion of oncogenes, inactivation of tumour suppressor genes and alteration of growth factor activity all lead to abnormal regulation of cell proliferation, which is a fundamental hallmark of carcinogenesis; proposed mechanisms and markers involved in carcinogenesis are listed in Table 2.1. The sequential order in which mutations arise is almost certainly less important than their cumulative number and, whilst accumulation of abnormalities may occur by random mischance, they are more commonly caused by environmental carcinogens, especially the synergistic effects of tobacco and alcohol¹.

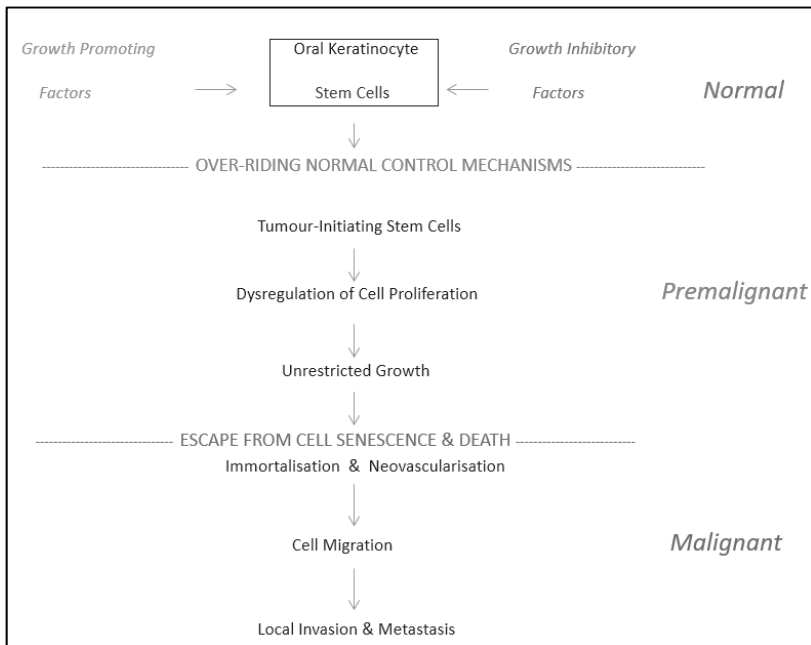


Figure 2.2: Principal Steps in Oral Carcinogenesis¹

Table 2.1: Mechanisms and Markers Active during Oral Carcinogenesis¹

Mechanism	Marker
Oncogenes	Epidermal Growth Factor / Receptor Transforming Growth Factor α Transcription Factor-Activating Proteins Cyclins and Cyclin-dependent Kinases
Tumour Suppressor Genes	p53 Retinoblastoma Protein
Genetic Abnormalities	DNA Aneuploidy and Allelic Instability Chromosome Loss of Heterozygosity 3p 9p 13q 17p Mitochondrial Mutation
Cell Cycle Disruption	Cell Proliferation Cell Differentiation Cytokeratins Apoptosis BcL-2 Survivin
Loss of Cell Adhesion	Annexins Syndecans Integrins Basement membrane Components
Angiogenesis	Vascular Endothelial Growth Factor Nitric Oxide Synthase 2
Immortalisation	Telomerase p16
Viruses	HPV
Prostaglandin Synthesis	COX-2 Enzyme

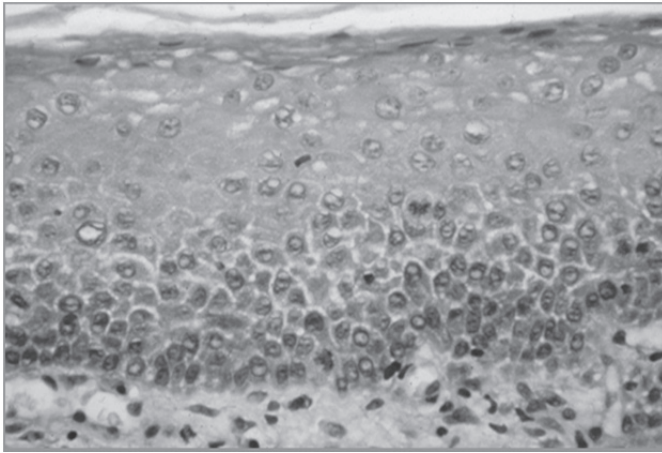
Whilst molecular oncology has undoubtedly advanced our understanding of carcinogenesis, it is unfortunate that few studies have helped elucidate the natural history of PMD, and none of the biomarkers studied to date have been of use in clinical practice. We thus rely upon the recognition of phenotypic changes within oral mucosa, seen histopathologically as epithelial dysplasia, that varying presence of cellular atypia and structural tissue dysmaturation that characterises PMD. Oral epithelial dysplasia is thus an expression of a tissue maturation and cellular proliferation disorder, and is an important histopathological entity that delineates morphological changes affecting both individual epithelial cells (which take on a more ‘primitive’ appearance with variable size, shape and mitotic activity) and the overall integrity of epithelial structure (which

loses its normal maturation and stratification); these features are summarized in Table 2.2^{1,26}.

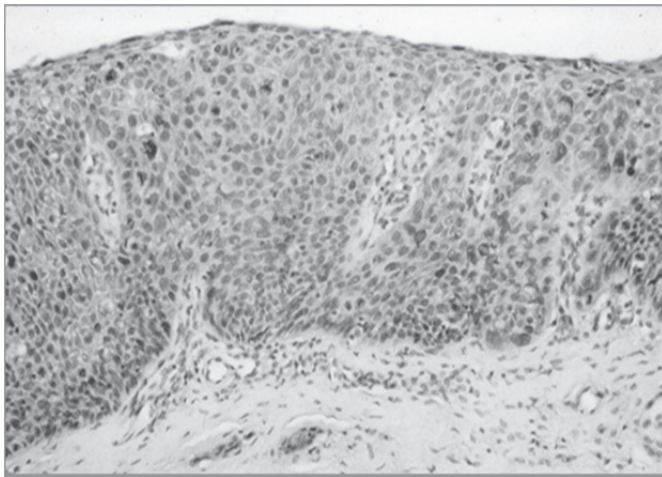
In clinical practice, an assessment of the degree of dysplastic change in a tissue is made following incision biopsy and microscopic classification into mild, moderate or severe categories, according to the tissue thickness occupied by the atypical epithelium. Carcinoma-in-Situ (CiS) is regarded as the most severe form of epithelial dysplasia and is characterised by full-thickness cytological and architectural disturbance^{1,26,27}. As epithelial proliferative units and oral keratinocyte stem cell activity are postulated to lie within the basal and supra-basal layers, it is not surprising that the initial changes of mild dysplasia are first recognised within the basal third of the oral epithelium, ultimately progressing through the higher epithelial layers as severity increases¹.

Table 2.2: Histopathological Features of Dysplasia in PMD

<i>Cytology</i>	<i>Tissue Architecture</i>
Variation in Nuclear Size (Anisonucleosis) Variation in Nuclear Shape (Pleomorphism) Variation in Cell Size (Anisocytosis) Variation in Cell Shape (Pleomorphism) Increased Nuclear to Cytoplasmic Ratio Increased Nuclear Size Atypical Mitotic Figures Increased Number & Size of Nucleoli Hyperchromasia	Irregular Epithelial Stratification Loss of Polarity of Basal Cells Drop-shaped Rete Ridges Increased Number of Mitotic Figures Abnormally Superficial Mitoses Premature Keratinisation in Single Cells (Dyskeratosis) Keratin Pearls within Rete Ridges



A



B

Figure 2.3: Microscopic appearance of (A) mild dysplasia affecting only the basal third of oral epithelium and (B) full-thickness change commensurate with severe dysplasia.

The more severe the dysplasia, the higher the risk of malignant change, although there is a strong subjective element in dysplasia grading and both biopsy sampling error and change in severity over time may confound the accuracy of diagnosis^{1,26,27}. Ultimately, through loss of cell adhesion, increased cellular motility and local invasion, the underlying lamina propria is breached and immortalised cancer cells penetrate through into the underlying connective tissue: the hallmark of an invasive SCC.

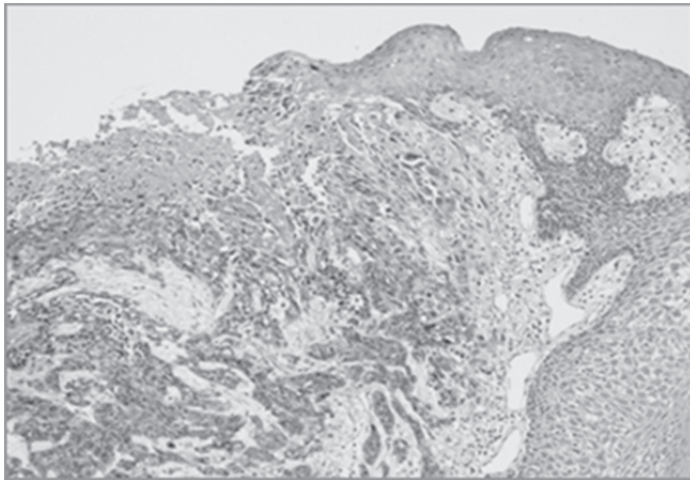


Figure 2.4: Microscopic appearance of oral SCC invading underlying connective tissue, arising from adjacent dysplastic oral epithelium.

Concerns have been raised recently regarding the use of current terminology in oral cancer diagnosis and the potential lack of agreement between pathologists regarding the importance of individual histopathological features for dysplasia grading in particular²⁸. It is also recognised that there is an overall lack of reproducibility and a poor predictive ability in current grading systems. Dost et al²⁹, for example, have specifically criticised current dysplasia grading systems citing their imprecision, low reproducibility and lack of inter- and intra-observer agreement during the diagnostic process. The use of epithelial dysplasia assessment to predict malignant transformation thus remains problematic because both the overall grading system and the individual features to be characterised are poorly defined²⁸. As a result, a binary dysplasia classification, distinguishing between lesions at ‘low’ or ‘high risk’ of cancer progression has been proposed to try to improve objectivity but,

despite appealing to clinicians attempting to rationalize treatment intervention, it has not yet found routine application in clinical practice²⁶.

An additional and important observation specific to PMD diagnosis is the realization that even in the absence of epithelial dysplasia some oral mucosal lesions may still transform to cancer. This has been noted, in particular, for isolated mucosal lesions exhibiting lichenoid inflammatory features³⁰. In addition, early-stage proliferative verrucous leukoplakia, an aggressive multi-focal potentially malignant disorder, with a known high risk of malignancy, shares a number of histopathological features similar to lichenoid mucositis such as hyperkeratosis, sub-epithelial lymphocytic infiltration, basal cell degeneration, and apoptosis, often without the classic features of dysplasia, rendering the diagnostic process complex³¹. We will return to explore many of these issues more fully later in the book.

Oral epithelial dysplasia grading, however, remains the ‘reference’ investigation in patient management and is one of the few clinically applicable predictors of risk for malignant transformation. Similarly, as the association between oral malignancy and the presence of dysplasia remains significant, early intervention to remove pre-cancerous dysplastic tissue prior to invasive change appears a logical treatment approach. Dost et al²⁹ recently proposed definitive treatment for all oral mucosal lesions exhibiting dysplasia, irrespective of severity. It is indeed this specific concept that forms the basis for the interventional clinical work presented and analysed in subsequent chapters of this book.

Contemporary Oral Cancer Patient Management

Whilst it is not particularly the remit of this chapter to detail treatment protocols for individual oral cancers, it is important to outline the basic principles governing contemporary management; these are therefore listed in Table 2.3. The ramifications consequent upon diagnosis and treatment of established oral cancer will also, I hope, clearly demonstrate the over-riding importance of prevention and early intervention during the process of carcinogenesis.

Table 2.3: Principles of Oral Cancer Management

- | |
|---|
| <ol style="list-style-type: none">1. Thorough evaluation of the patient and disease status2. Tumour diagnosis, classification and staging of disease3. Comprehensive treatment planning4. Coordination of therapeutic modalities5. Post-treatment reconstruction and rehabilitation6. Psychological and social support |
|---|

As a locally invasive and metastasizing tumour, oral SCC has devastating effects on both patient morbidity and mortality, and its management presents considerable challenges. As introduced in Chapter 1, patients require access to multi-disciplinary head and neck oncology clinics, staffed by surgical, oncological, dental, nursing and physiotherapy specialists, for comprehensive care throughout their assessment, treatment and long-term follow-up. The optimal treatment aim is elimination of the primary tumour and any neck node metastases, whilst attempting at all times to minimise patient morbidity^{32,33}.

Oral SCC management requires an initial and thorough evaluation of the disease status of the patient, including careful consideration of their general medical background and accurate recognition of co-morbidities such as cardio-respiratory disease; the latter often significant in patients with long-term tobacco and alcohol misuse. Detailed physical examination, biopsy of the primary tumour to confirm diagnosis and histopathological type, formal examination under anaesthesia to facilitate inspection, palpation and measurement (particularly for large, posteriorly-sited tumours) and evaluation of cervical lymph node involvement are usually required. Diagnostic imaging utilising CT and MR scanning provides confirmatory and detailed assessment of tumour size and position, local tissue invasion, lymph node involvement and identification of systemic tumour spread³³.

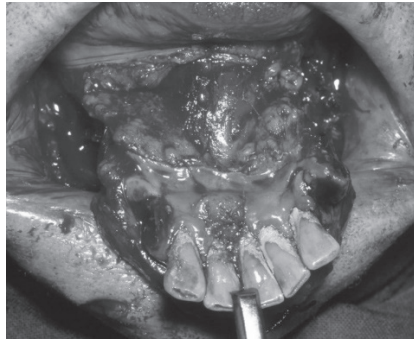
Evaluation facilitates classification of cancers according to the size of the primary tumour (T), extent of lymph node involvement (N) and the presence of distant metastases (M). Using this internationally recognised TNM system, it is then possible to formally stage the severity of each patient's disease on a scale of I to IV, with stage IV most advanced and extensive. Staging informs treatment planning and prognostic assessment, as well as providing meaningful reference for data analysis between different treatment centres³³.

Following case discussion within the multi-disciplinary team and between patients and their relatives, a fundamental decision is required whether curative or palliative treatment is appropriate. Whilst curative treatment is focused upon disease elimination, palliative care is designed to prolong symptom-free life, recognising that the disease is unlikely to be completely eradicated. In head and neck cancer, palliative management may require quite extensive treatment at the primary tumour site to establish local disease control.

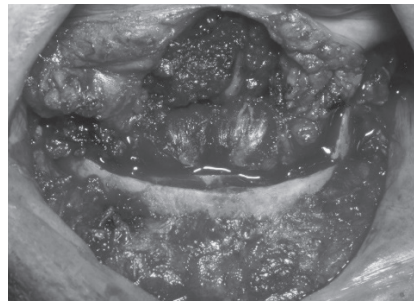
As outlined earlier in this chapter, modern treatment protocols for cancer are based upon coordinated regimes utilising surgery, radiotherapy and chemotherapy. The general health, age, life expectancy and wishes of the patient must all be carefully balanced in finalising individual patient treatments^{3,33}.

Surgery requires appropriate access to expose and then completely excise oral tumours ensuring that all tissue margins are free from disease; this may necessitate loss of important functional units such as the lips, tongue or underlying mandibular or maxillary bone. This is usefully illustrated in Figure 2.5, in which a substantial surgical defect is created consequent upon resection of a relatively small anterior mandibular SCC arising on the gingiva. Loss of oro-facial form and function, even following excision of Stage I tumours, can thus be extensive.

Surgery does, however, offer the ability to perform in-continuity neck dissection to remove cervical lymph nodes containing metastatic disease and allows immediate reconstruction using free tissue flap transfer and microvascular anastomosis; a significant advance in surgical practice. Post-operative adjuvant radiotherapy is often administered, especially for advanced stage disease or aggressive tumours with close or involved resection margins. Longer-term, rehabilitation of oral function is increasingly facilitated using osseo-integrated dental implants to support specifically designed dental prostheses³³. Figure 2.6 illustrates the approach to surgical excision, flap reconstruction and implant-borne prosthetic rehabilitation of the SCC case originally shown in Figure 2.1.



A



B



C

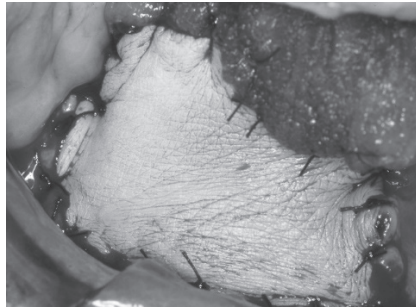
Figure 2.5: Intra-Oral SCC Resection demonstrating (A) excision specimen containing mandibular gingiva SCC, (B) extensive surgical defect involving loss of mandibular alveolus, labial sulcus and floor of mouth and (C) reconstruction with locally-based naso-labial skin flaps



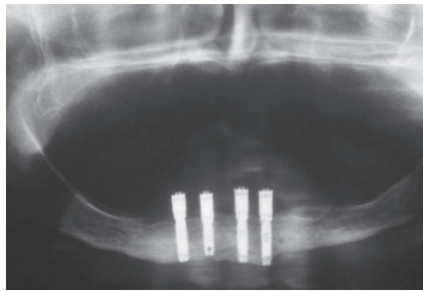
A



B



C



D



E

Figure 2.6: Surgical Management of Oral SCC illustrating (A) neck dissection, (B) in-continuity SCC and neck dissection excision specimen, (C) forearm flap reconstruction of oral defect, (D) osseointegrated implants in-situ and (E) rehabilitation with implant-borne dental prostheses

If pre-existing co-morbidity precludes patients undergoing long or complex surgical procedures, radiotherapy may be utilised as primary treatment. Ionising radiation, of course, produces both immediate morbidity such as oral mucositis (due to direct damage to the delicate mucosa lining), xerostomia (following salivary gland destruction), destructive radiation caries, as well as long-term problems affecting the bone such as osteoradionecrosis; many of these treatment consequences are shown in Figure 2.7.

Modern radiotherapy techniques increasingly utilise computerised planning to intensify external beam radiation to tumour tissue, whilst attempting to minimise doses to surrounding vital structures and thus reduce the incidence of these considerable morbidities; these are often referred to as intensity-modulated radiation therapies (IMRT)^{3,33}.

Chemotherapy also produces damaging effects on normal tissues, although these are more widespread and systemic in nature and include nausea, vomiting, alopecia and bone marrow suppression. Chemotherapy agents are often combined with radiotherapy as chemo-radiation to increase the sensitivity of oral SCC to radiation damage³.

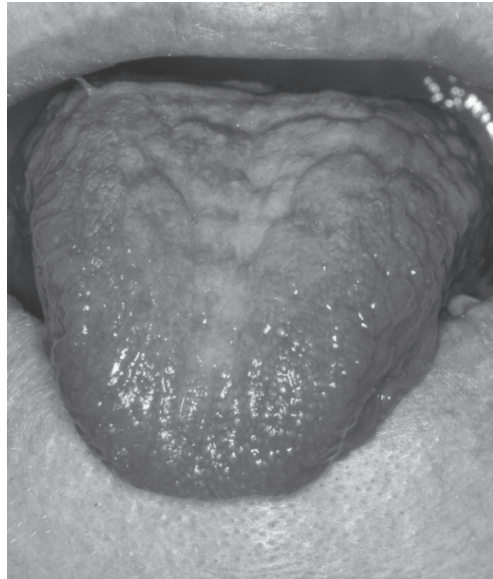
The on-going dental care of oncology patients is vitally important to their overall welfare, especially when head and neck radiotherapy is administered. Careful pre-treatment dental assessment and effective preventive care and oral hygiene are essential to preserve oral health and well-being throughout treatment³².

Accompanying the patient through their treatment journey, psychological and social support are mandatory for successful therapeutic outcomes. Increasingly, attention to quality of life for head and neck cancer patients has been the focus of research and development in modern health care.

Despite significant refinements in all the above technologies, and undoubted improvement in loco-regional disease control, survival rates for oral SCC have changed little over the past 30 years. Persistent or recurrent SCC is a major problem, and often challenging to manage in anatomical regions previously operated upon or following radiotherapy treatment. A greater number of patients now die from distant metastatic disease or from the emergence of second or even third primary tumours in the upper aero-digestive tract.



A



B



C



D

Figure 2.7: Radiotherapy Morbidity illustrating (A) immediate mucositis affecting buccal mucosa, (B) significant xerostomia leading to (C) extensive, destructive radiation caries and (D) osteoradionecrosis of dead, infected mandibular bone

It is unlikely that modifying conventional treatments will improve clinical outcome further, and new and innovative approaches to earlier intervention are thus required. Improvements in oral SCC therapy require effective public health measures to target high-risk population groups, and a wider introduction of effective preventive therapies at much earlier disease stages³⁴.

References

1. Thomson PJ. Oral Carcinogenesis. In: PJ Thomson (ed) Oral Precancer – Diagnosis and Management of Potentially Malignant Disorders. Chichester: Wiley-Blackwell; 2012. p31-47. ISBN 978-1-4433-3574-3.
2. Jones KB, Klein OD. Oral epithelial stem cells in tissue maintenance and disease: the first steps in a long journey. *International Journal of Oral Science*. 2013 5: 121-129.
3. Robinson CM, Thomson PJ. In: Greenwood M (ed) *Essentials of Human Disease in Dentistry* (2nd Edition). Chichester: Wiley-Blackwell; 2018. p251-264. ISBN 978-1-119-25184-2.
4. Mehanna H, Paleri V, West CML, Nutting C. Head and neck cancer – Part 1: Epidemiology, presentation, and prevention. *British Medical Journal* 2010 341: 663-666.
5. Mehanna H, West CML, Nutting C, Paleri V. Head and neck cancer – Part 2: Treatment and prognostic factors. *British Medical Journal* 2010 341: 721-725.
6. Conway DI, Petticrew M, Marlborough H, Berthiller J, Hashibe M, Macpherson LMD. Socioeconomic inequalities and oral cancer risk: A systematic review and meta-analysis of case-control studies. *International Journal of Cancer* 2008 122: 2811-2819.
7. Warnakulasuriya S. Global epidemiology of oral and oropharyngeal cancer. *Oral Oncology* 2009 45: 309-316.
8. Warnakulasuriya S. Causes of oral cancer – an appraisal of controversies. *British Dental Journal* 2010 207: 471-475.
9. Kalavrezos N, Bhandari R. Current trends and future perspectives in the surgical management of oral cancer. *Oral Oncology* 2010 46: 429-432.
10. Shah JP, Gil Z. Current concepts in management of oral cancer – Surgery. *Oral Oncology* 2009 45: 394-401.
11. Dakubo GD, Jakupciak JP, Birch-Machin MA, Parr RL. Clinical implications and utility of field cancerization. *Cancer Cell International* 2007 doi:10.1186/1475-2867-7-2.

12. Slaughter DP, Southwick HW, Smejkal W (1953). Field cancerization in oral stratified squamous epithelium: clinical implications of multicentric origin. *Cancer* 6: 963-968.
13. Hamadah O, Goodson ML, Thomson PJ. Clinicopathological behaviour of multiple oral dysplastic lesions compared with that of single lesions. *British Journal of Oral & Maxillofacial Surgery* 2010 48: 503-506.
14. Anantharaman D, Marron M, Laggiou P, E Samoli E, Ahrens W, Pohlabein H, Slamova A, Schejbalova M, Merletti F, Richiardi L, Kjaerheim K, Castellsague X, Agudo A, Talamini R, Barzan L, Macfarlane T, Tickle M, Simonato L, Canova C, Conway D, McKinney P, Thomson PJ, Znaor A, Healy C, McCartan B, Hashibe M, Brennan P, Macfarlane G. Population attributable risk of tobacco and alcohol for upper aerodigestive tract cancer. *Oral Oncology* 2011 47: 725-731.
15. Lee Y-C, Zugna D, Richiardi L, Merletti F, Marron M, Ahrens W, Pohlabein H, Laggiou P, Trichopoulos D, Agudo A, Castellsague X, Betka J, Holcatova I, Kjaerheim K, Macfarlane GJ, Macfarlane TV, Talamini R, Barzan L, Canova C, Simonato L, Conway DI, McKinney PA, Thomson PJ, Znaor A, Healy CM, McCartan BE, Boffetta P, Brennan P, Hashibe M. Smoking addiction and the risk of upper-aerodigestive-tract cancer in a multicenter case-control study. *International Journal of Cancer* 2013 133: 2688-2695.
16. Petti S. Lifestyle risk factors for oral cancer. *Oral Oncology* 2009 45: 340-350.
17. Marron M, Boffetta P, Moller H, Ahrens W, Pohlabein H, Benhamou S, Bouchardy C, Laggiou P, Laggiou A, Slamova A, Schejbalova M, Merletti F, Richiardi L, Kjaerheim K, Agudo A, Castellsague X, Macfarlane T, Macfarlane G, Talamini R, Barzan L, Canova C, Simonato L, Biggs A-M, Thomson PJ, Conway D, McKinney P, Znaor A, Healy C, McCartan B, Brennan P, Hashibe M. Risk of upper aerodigestive tract cancer and type of alcoholic beverage: a European multicentre case-control study. *European Journal of Epidemiology* 2012 27: 499-517.
18. Hashibe M, Brennan P, Benhamou S, Castellsague X, Chen C, Curado MP, DalMaso L, Daudt AW, Fabianova E, Wunsch-Filho V, Franceschi S, Hayes RB, Herrero R, Koifman S, LaVecchia C, Lazarus P, Levi F, Mates D, Matos E, Menezes A, Muscat J, Eluf-Neto J, Olshan AF, Rudnai P, Schwartz SM, Smith E, Sturgis EM, Szeszenia-Dabrowska N, Talamini R, Wei Q, Winn DM, Zaridze D, Zatonski W, Zhang Z-F, Berthiller J, Boffetta P. Alcohol drinking in

- never users of tobacco, cigarette smoking in never drinkers, and the risk of head and neck cancer: pooled analysis in the International Head and Neck Cancer Epidemiology Consortium. *Journal of the National Cancer Institute* 2007 99: 777-789.
19. Macfarlane TV, Macfarlane GJ, Oliver RJ, Benhamou S, Bouchardy C, Ahrens W, Pohlman H, Laggiou P, Laggiou A, Castellsagu X, Agudo A, Merletti F, Richiardi L, Kjaerheim K, Slamova A, Schejbalova M, Canova C, Simonato L, Talamini R, Barzan L, Conway DI, McKinney PA, Znaor A, Lowry RJ, Thomson PJ, Healy CM, McCartan BE, Marron M, Hashibe M, Brennan P. The aetiology of upper aerodigestive tract cancers among young adults in Europe: The ARCAGE study. *Cancer Causes Control* 2010 21: 2213-2221.
 20. Thomson PJ. Managing oral potentially malignant disorders: A question of risk. *Faculty Dental Journal* 2015 6: 186-191.
 21. Diajil AR, Thomson PJ. Risk factors of oral cancer and potentially malignant disorders (PMDs) – Developing a high / low risk profiling system. *Journal of Baghdad College of Dentistry* 2016 28: 63-72.
 22. daSilva SD, Ferlito A, Takes RP, Brakenhoff RH, Valentin MD, Woolgar JA, Bradford CR, Rodrigo JP, Rinaldo A, Hier MP, Kowalski LP. Advances and applications of oral cancer basic research. *Oral Oncology* 2011 47: 783-791.
 23. Syrjanen S, von Bultzingslowen I, Aliko A, Arduino P, Campisi G, Challacombe S, Ficarra G, Flaitz C, Zhou HM, Maeda H, Miller C, Jontell M (2011). Human papillomavirus in oral carcinoma and oral potentially malignant disorders: a systematic review. *Oral Diseases* 17 (Suppl 1) : 58-72.
 24. Anantharaman D, Gheit T, Waterboer T, Abedi-Ardekani B, Carreira C, McKay-Chopin S, Gaborieau V, Marron M, Laggiou P, Ahrens W, Holcatova I, Merletti F, Kjaerheim K, Talamini R, Simonato L, Castellsague X, Macfarlane T, Biggs A-M, Thakker N, Znaor A, Thomson PJ, Canova C, Conway D, Healy C, Tommasino M, Pawlita M, P Brennan P. Human papillomavirus infections and upper aero-digestive tract cancers: the ARCAGE study. *Journal of the National Cancer Institute* 2013 105 : 536-545.
 25. Califano J, van der Riet P, Westra W, Nawroz H, Clayman G, Piantadosi S, Corio R, Lee D, Greenberg B, Koch W, Sidransky D. Genetic progression model for head and neck cancer: implications for field cancerization. *Cancer Research* 1996 56: 2488-2492.
 26. Sloan P. Pathological aspects of oral precancer. In P J Thomson (Ed) *Oral Precancer – Diagnosis and Management of Potentially*

- Malignant Disorders. Wiley-Blackwell 2012. p93-106. ISBN 978-1-4443-3574-3.
27. Speight PM. Update on oral epithelial dysplasia and progression to cancer. *Head and Neck Pathology* 2007 1: 61-66.
 28. Tilakaratne WM, Sherriff M, Morgan PR, Odell EW. Grading oral epithelial dysplasia: analysis of individual features. *Journal of Oral Pathology & Medicine* 2011 40: 533-540.
 29. Dost F, LeCao K, Ford PJ, Ades C, Farah CS. Malignant transformation of oral epithelial dysplasia: a real world evaluation of histopathologic grading. *Oral Surg Oral Med Oral Pathol Oral Radiol* 2014 117: 343-352.
 30. Goodson ML, Sloan P, Robinson CM, Cocks K, Thomson PJ. Oral Precursor Lesions and Malignant Transformation – Who, Where, What and When? *British Journal of Oral & Maxillofacial Surgery* 2015 53: 831-835.
 31. Thomson PJ, Goodson ML, Smith DR. Potentially Malignant Disorders Revisited – The Lichenoid Lesion/Proliferative Verrucous Leukoplakia Conundrum. *Journal of Oral Pathology & Medicine* 2018 47: 557-565.
 32. Thomson PJ, Greenwood M, Meechan JG. General medicine and surgery for dental practitioners. Part 6 – cancer, radiotherapy and chemotherapy. *British Dental journal* 2010 209: 65-69.
 33. Thomson PJ. Tumours of the mouth and the management of oral cancer. In UJ Moore (ed) *Principles of Oral & Maxillofacial Surgery* (6th edition). Chichester: Wiley-Blackwell 2011 ISBN 978-1-4051-9998-8.
 34. Thomson PJ. Potentially Malignant Disorders – The Case for Intervention. *Journal of Oral Pathology & Medicine* 2017 46: 883-887.

CHAPTER THREE

POTENTIALLY MALIGNANT DISORDERS

‘...in which there is an increased risk of cancer development...’

Introduction

It has been recognized for many years that a spectrum of distinct, chronic oral mucosal abnormalities, now conventionally referred to as potentially malignant disorders (PMD) and which accompany dysplastic pre-invasive cancer change, may be identified clinically and characterized, albeit somewhat non-specifically, during oral examination. There is, therefore, potential for both early diagnosis and therapeutic intervention during this clinically identifiable ‘oral pre-cancer window’¹.

Terminology has varied through the years, with lesions variously described as ‘precancerous’ or ‘pre-malignant’, or even ‘potentially pre-malignant’ or more recently ‘potentially pre-malignant oral epithelial lesions’ but I suspect PMD, the World Health Organisation recommended term from 2007, is most relevant. PMD are therefore defined as recognizable oral mucosal diseases that share a significantly increased risk of squamous carcinoma development compared with apparently normal mucosa. This term usefully encompasses both localized lesions and more generalized conditions and, whilst emphasizing that not all will inevitably transform into cancer, also recognizes the widespread, often multi-focal nature of such disease within the entire upper aerodigestive tract²⁻⁴.

The list of mucosal diseases considered potentially malignant includes classically described entities such as leukoplakia, erythroplakia, erythroleukoplakia and more recently recognised disorders such as progressive, multi-focal proliferative verrucous leukoplakia, as well as widespread conditions such as immunodeficiency, oral submucous fibrosis, chronic hyperplastic candidosis, and perhaps more controversially oral lichenoid lesions^{5,6}.

Estimates of the prevalence of oral potentially malignant disorders suggest an overall figure of between 2 to 3% worldwide, but these data may not be entirely reliable due to differences in diagnostic terminology and methodology in many studies, and the presence of significant variation between global regions. A particularly high prevalence, for example, has been reported for Asia, in contrast to lower rates seen in Europe and North America; further research in to the incidence and aetiology in different populations would clearly be beneficial. The vast majority of PMD lesions appear clinically as leukoplakias, and usually present on the floor of the mouth, ventro-lateral tongue and buccal mucosa, although this may also vary with the use of different tobacco products and habits. Whilst previously seen as a disorder of older, male patients, increasing evidence suggests that a much younger population is now at risk⁷.

The concept that these disorders represent a recognizable potentially malignant state has arisen following a number of salient clinico-pathological observations including the observed transformation of precursor lesions into invasive cancers during patient follow up, the recognition that leukoplakic or erythroplakic lesions often co-exist with oral squamous cell carcinoma and the realization that numerous histopathological and biomolecular tissue changes are common to both cancers and their potentially malignant counterparts⁸.

The identification of PMD in an individual patient does not mean, however, that an inevitable malignant transformation will take place. Many oral lesions do not progress over time, whilst others may resolve or regress spontaneously and it remains impossible in clinical practice to reliably predict the behaviour of any individual lesion or patient. Nonetheless, affected patients remain at increased risk of squamous carcinoma development, estimated overall at around 12%^{4,9}.

Attempts have been made to stratify 'high' and 'low' risk factors for potentially malignant disease development¹⁰, but the ability to quantify risk for individual patients remains frustratingly elusive in contemporary practice. By synthesizing data from a number of publications summarizing risk factor research, however, a 'high risk' profile for oral carcinogenesis may be postulated: such patients are likely to misuse tobacco and alcohol, exhibiting a strong addiction to smoking and persistent high alcohol consumption¹¹, together with a diet low in fruit and vegetables, and with poor oral hygiene and irregular dental care². Most commonly, the patient will be a male of shorter-stature, low socioeconomic status and low educational attainment experiencing periods of material deprivation or long-

term unemployment or primarily engaged in manual occupations such as bricklaying and painting¹². In contrast, patients' age, general medical status and human papillomavirus exposure have all been shown to be less helpful in predicting disease status and risk¹². We will, however, discuss the concept of risk and analyse these data in some detail in the next chapter.

Clinical Presentation

Although PMD are classically distinguished as either localized mucosal lesions or widespread multi-focal disorders, it is much more likely that they actually represent a continuum of 'pre-cancer' disease that can affect the whole upper aero-digestive tract in susceptible patients^{5,6}. A persistent and specific clinical management problem remains the early identification of symptomless mucosal changes in an 'at risk' population that rarely, if ever, attends for regular oral and dental examination⁵.

Leukoplakia

Oral leukoplakia is the commonest clinical presentation, often described as a white patch that cannot be wiped from the mucosal surface and which cannot be attributed to any other identifiable pathophysiological cause, and usually accounts for between 60 to 70% of all PMD, with an overall prevalence rate ranging between 1 to 5%. The increased keratin production characteristic of leukoplakia enhances tissue hydration by saliva thus producing the white appearance observed clinically. Essentially a descriptive term, the formal WHO definition of leukoplakia reads: 'white plaques of questionable risk, having excluded other known diseases or disorders that carry no increased risk for cancer'. Primarily seen in middle-aged or elderly patients between fifth and seventh decades, leukoplakia is six times more common in smokers than non-smokers with lesion site largely determined by the nature of the tobacco habit. Thus, cigarette smoking in Western populations is primarily associated with ventro-lateral tongue and floor of mouth disease, whilst buccal lesions are often predominant in South-East Asia due to the effects of tobacco chewing or use of betel quid products⁵.

Homogeneous leukoplakia appears flat and uniformly white, presenting as faint patches or thicker lesions resembling a coating of paint. On other occasions, whilst remaining uniform, they may exhibit a rippled appearance, similar to the ebbing tide seen at the sea shore. In contrast, non-homogeneous lesions are irregular or nodular in appearance. Mixed

patches of homogenous and non-homogenous lesions are also seen, often presenting as widespread buccal mucosa lesions⁵.

Proliferative Verrucous Leukoplakia (PVL) is a more recently recognized and important PMD sub-category which are slow growing and progressive, appearing as expanding, fissured, exophytic and warty-looking white patches, characterized by multifocal presentation, resistance to treatment and especially high rates of malignant transformation (70 to 100%), often in the absence of identifiable dysplastic features on previous biopsy. PVL most frequently presents on gingiva, alveolar and buccal mucosa, typically arising in females in their sixth or seventh decades. The precise aetiology is obscure and, unlike other forms of leukoplakia, there is no strong association with tobacco and alcohol use. PVL diagnosis is based upon clinical appearance together with tissue architectural disturbances seen histopathologically. These features vary depending upon the stage of the disease: initial hyperkeratosis is followed by verrucous hyperplastic change leading to verrucous carcinoma and subsequent development of invasive SCC. An intense lymphocytic infiltrate may also be observed in PVL lesions obscuring the basement membrane and epithelial-connective tissue interface leading to diagnostic confusion with oral lichenoid lesions. Clinical signs suggesting transformation to malignancy include rapid growth of the verrucous patch, appearance of red or erosive areas and induration^{5,6}.

Figures 3.1 to 3.4 illustrate the varying clinical appearances of leukoplakia that may be seen within the oral cavity.

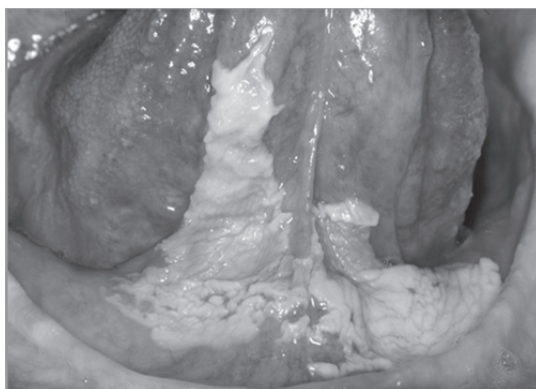


Figure 3.1: Thick homogenous leukoplakia on the floor of mouth and ventral tongue, including an 'ebbing tide' pattern seen on the patient's left side.



Figure 3.2: Irregular, non-homogenous leukoplakia extending widely across the buccal mucosa, with a faint appearance posteriorly.

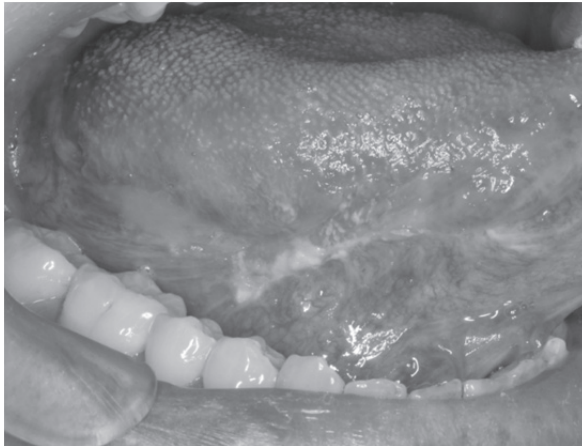


Figure 3.3: Localized band of non-homogenous leukoplakia presenting on the lateral tongue.



Figure 3.4: Proliferative Verrucous Leukoplakia (PVL) arising on maxillary gingiva.

Erythroplakia

Erythroplakia appears less commonly than leukoplakia and is a bright or fiery red, velvety patch, usually with a smooth, depressed or granular surface, well-defined from surrounding normal looking mucosa. Unlike leukoplakia, erythroplakic lesions are usually symptomatic, so that patients become aware of their presence reporting mucosal sensitivity and soreness. Prevalence erythroplakia varies between 0.02 to 0.83%, mainly affecting middle-aged and elderly patients with no specific gender preference. Alcohol, smoking and candida infections are recognized aetiological factors. Lesions are usually solitary and, although any site may be affected, the floor of mouth is particularly commonly involved; Figure 3.5. Histopathologically, lesions show atrophic epithelium, hence the red colouration visible clinically, and usually exhibit severe dysplasia or carcinoma-in-situ. In some cases, micro-invasive or early invasive SCC may already be present. As a result, most erythroplakias ultimately undergo malignant transformation and are regarded as high risk lesions⁵.

Erythroleukoplakia

This lesion, which is a combination often of nodular leukoplakia on a background of erythroplakic change (sometimes referred to as ‘speckled leukoplakia’) is also less common than leukoplakia. Although it may arise

at any site in the oral cavity, it is particularly common at the labial commissures associated with chronic candida infection. Erythroleukoplakias are also high risk lesions and have a much greater tendency to develop malignancy than homogeneous leukoplakia⁵.

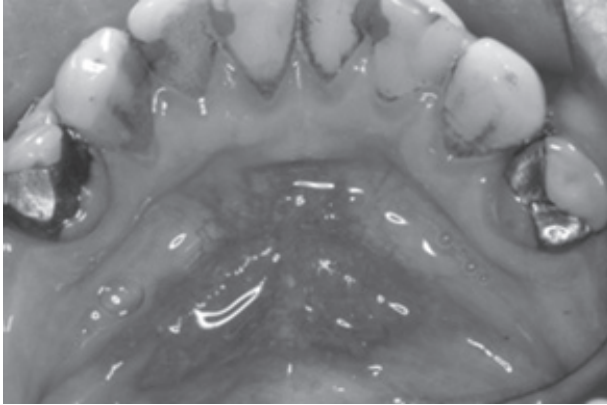


Figure 3.5: Erythroplakia presenting on the floor of the mouth.

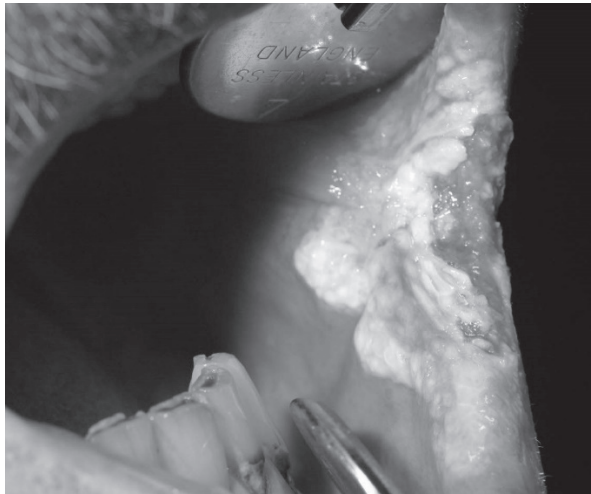


Figure 3.6: Erythroleukoplakia (speckled leukoplakia) arising at the labial commissure.

Multiple Lesion Disease

Whilst most patients exhibit single lesion disease, an important sub-group, affecting 3 to 24% of PMD cases, present with multiple lesions. Extensive areas of mucosa can thus exhibit dysplastic change due to field cancerization; within molecularly altered 'pre-neoplastic fields' multiple oral lesions thus develop, both synchronously and metachronously. Whether multiple lesion disease truly represents a distinct presentation in patients more susceptible to genetic damage, or is due to disease evolution over time remains to be seen².

However, a number of distinct clinico-pathological differences between single and multiple lesion patients have certainly been observed. Whilst single lesions are observed primarily on floor of mouth, ventro-lateral tongue and gingiva sites, multiple lesions are more prevalent on the buccal mucosa, are more likely to persist and to undergo malignant transformation, perhaps reflecting more widespread mucosal instability. The strongest risk factors for multiple lesion development appear to be tobacco chewing, regular alcohol consumption and diets low in fruit and vegetables.

Multi-focal or widespread PMD should probably be regarded as a marker for increased cancer risk not just within the oral cavity but throughout the entire upper aero-digestive tract. Strategies for managing multiple lesion disease are thus much more challenging than that required for single lesions and involve 'field mapping biopsies', regular and careful clinic review and targeted interventional laser surgery^{2-4,16}.

Premalignant Conditions

Whilst the majority of PMD appear as discrete leukoplakia, other more generalized conditions also predispose to oral SCC development. It is instructive to briefly review some of these interesting disorders, as they appear to share a number of consistent aetiological factors including anaemia, infection, chronic inflammation, tobacco use and altered immune function. These may all be highly pertinent in designing future preventive strategies.

Probably the commonest premalignant condition seen is immunosuppression, which may be due to congenital immunodeficiency or more frequently following prolonged use of immunosuppressive therapy. Whilst a resultant leukoplakia may arise at any intra-oral site, the

labial mucosa and commissures are especially affected; there is also a notable increased risk of facial skin cancer. Multiple lesions are common, with often quite rapid progression to SCC.

Controversy has long-persisted regarding the malignant potential of the inflammatory mucocutaneous disorder lichen planus. Multifactorial in origin, including genetic and autoimmune aetiologies, histology shows extensive lymphocyte accumulation immediately subjacent to keratinized, acanthotic or atrophic oral epithelium. Hyperkeratosis produces white mucosal striae, plaques or nodules, whilst epithelial atrophy leads to redness, erosion or frank ulceration. Although buccal mucosa is most frequently and symmetrically involved, dorso-lateral tongue, gingiva, palate and lips may all be affected. Overall, the risk of malignant transformation is less than 1% but atrophic and erosive forms may be at greater risk due to reduced mucosal protection to carcinogens. The area affected may also be relevant, with extensive mucosal disease at risk of 'field cancerization'. A diagnostic dilemma involves oral lichenoid lesions or reactions which, although clinically indistinguishable from lichen planus are usually solitary and idiopathic in origin, or triggered by hypersensitivity reactions to drug therapy, amalgam restorations or graft versus host disease; a clinical example of an isolated lichenoid lesion is shown in Figure 3.7. Incisional biopsy of lichenoid lesions for histopathological assessment and exclusion of epithelial dysplasia or SCC is advised. The term 'lichenoid dysplasia' has been used to describe lymphocytic infiltrates beneath dysplastic epithelium, with anecdotal reports suggesting high malignancy risk, but no consistently supportive data exist. Although impossible to predict malignant potential for individual lichenoid lesions, those arising from ventro-lateral tongue mucosa may be especially at risk. It is possible that varying lichenoid disorders form part of a disease progression continuum. Regardless of lichenoid appearance, histological confirmation of dysplasia is considered most significant and such lesions regarded as primarily dysplastic and 'high risk'; it may be that intense inflammatory cell infiltrates in sub-epithelial tissue represent an enhanced immune response to antigenically disturbed dysplastic epithelium.



Figure 3.7: Isolated oral lichenoid lesion arising on buccal mucosa.

Oral Submucous Fibrosis is a chronic disorder found predominantly in Southeast Asia, whereby fibrosis and hyalinization in the lamina propria of oral mucosa results in loss of vascularity, mucosal pallor and atrophy of overlying epithelium. The mucosa is leathery in texture and vertical fibrous bands arise within the cheeks and faucial pillars leading eventually to trismus. Later, there may be distortion of the uvula and woody change to both buccal mucosa and tongue. The principal cause is betel quid use, areca nut mixed with slaked lime and wrapped in vine leaf, held for prolonged periods in the mouth. Teeth are stained red-brown by dye extracted from the nut by lime and, at the site of quid placement, there may be erythema, erythroplakia or leukoplakia. Atrophic epithelium is predisposed to SCC development, with a malignant transformation rate of approximately 0.5%. In the presence of demonstrable epithelial dysplasia, however, much higher malignant transformation rates ranging between 1.9 to 9.13% are reported.

Sideropaenic dysphagia (Plummer-Vinson syndrome) is a rarer condition, usually in middle-aged females, comprising glossitis, dysphagia (due to proximal oesophageal web formation) and iron deficiency anaemia. Although primarily associated with post-cricoid carcinoma, the disorder also gives rise to dysplastic lesions in atrophic oral mucosa.

Discoid lupus erythematosus (DLE) is a chronic autoimmune condition, again primarily in females, in which scaly red patches on facial skin appear symmetrically distributed in a butterfly pattern across the nose and cheeks. Intra-oral lesions arise on buccal mucosa as discoid erythema or ulceration surrounded by white keratotic borders, which resemble lichenoid lesions or erythroplakia; malignant transformation is seen at both buccal and labial mucosa sites.

Chronic hyperplastic candidosis presents as a dense, opaque and nodular leukoplakia often triangular in shape and symmetrically positioned at the labial commissures. Particularly common in heavy smokers, tobacco may be the principal aetiological agent. Histologically, areas of hyperkeratosis may alternate with patches of atrophic epithelium giving rise to speckled erythroleukoplakia; this appearance is shown in Figure 3.6. Candidal hyphae invade parakeratin at right angles reaching the prickle cell layer. Reactive cellular atypia may be reversed by antifungal therapy but, if not, progression to epithelial dysplasia occurs. Regardless of whether a primary dysplastic leukoplakia secondarily infected by candida, or an initial infection with secondary dysplasia due to carcinogens such as nitrosamines or acetaldehydes generated by candida/tobacco interaction, there is undoubtedly a high risk of malignant change, especially for patients who continue to smoke.

Very rarely, patients with tertiary syphilis present with widespread feint leukoplakia particularly involving the dorsum of the tongue and exhibit a high risk of malignant transformation. Although the precise aetiology of syphilitic leukoplakia is unclear, it is probably due to epithelial atrophy and a chronically impaired immune surveillance system.

‘High Risk’ Appearance and Malignant Transformation

Although the ‘natural history’ of PMD is inconsistent with no definitive or consistently reliable features to accurately predict SCC risk, a number of comments can be made based upon observational studies. In general, older patients, females, and non-smokers (the latter perhaps indicating inherent disease predisposition) all appear at greater risk. PMD of large size, those of long duration, those arising in the floor of mouth, ventro-lateral tongue, retromolar and soft palate/faucial regions are also more likely to develop SCC, whilst erythroplakia and erythroleukoplakia are at higher risk than leukoplakia. Non-homogeneous or nodular leukoplakia may also exhibit greater risk than homogeneous counterparts. PMD undergoing rapid increase in size, appearance of reddened areas, erosions or ulcerations, or

onset of induration and fixation are all highly suspicious signs of SCC arising in precursor lesions and should raise concern. An early invasive SCC arising from a lateral tongue mucosal lesion is pictured in Figure 3.8. All of the above descriptors, however, are likely to be part of a continuum of clinical appearances that merge together, rendering an individual examination and assessment difficult^{4,5,7}.



Figure 3.8 SCC presenting on the lateral tongue as a painful, non-healing erosive plaque.

Early Disease Recognition

In order to improve patient survival and reduce the morbidity following oral cancer diagnosis, it seems logical for oral clinicians to utilize the ‘oral pre-cancer window’ to identify potentially malignant change at the earliest possible stage and to then consider intervention to halt the disease process¹³. In addition to the professional uncertainties surrounding diagnosis and management of potentially malignant disease there is also,

unfortunately, considerable public ignorance regarding oral cancer and the patient population most 'at risk' is known to rarely attend for oral examination or regular dental care¹⁴.

General population screening programmes for oral cancer have been recognized to be fundamentally flawed as health care interventions for similar reasons. However, a more pragmatic approach may be to specifically identify and then target individual patient groups deemed to be at 'high risk' of developing cancer. Thus, focused oral cancer screening, specific health care information and treatment interventions should all target the 'at risk' populations¹⁵; this is an important practical application of the treatment intervention discussed later in this book.

The ultimate and fundamental clinical management goal is, of course, the prevention of cancer, and we shall examine approaches to oral cancer prevention in more detail in Chapter 4. Suffice to say that all classic tiers of preventive medicine may be applicable: primary to avoid disease development by eliminating principal risks factors and promoting protective behaviour, secondary to detect premalignant or early malignant disease at a stage when intervention leads to cure or reduced morbidity and mortality, and tertiary to reduce risks of disease recurrence or further disease¹⁶.

An interesting but alternative viewpoint was proposed by Esserman et al¹⁷ who emphasized potential danger in over-diagnosis and over-treatment of 'indolent lesions of epithelial origin', defined as clinically recognizable lesions never likely to proceed to invasive or metastatic cancer. Whilst this may have validity in general screening programmes, for some breast or prostate intraepithelial neoplasms for example, the reality remains that oral SCC is a particularly lethal and progressive disease and far too many patients present with advanced, locally invasive, and ultimately incurable metastasizing disease.

Previously available scientific literature has struggled to resolve the fundamental question whether early diagnosis and treatment of oral potentially malignant disorders will actually prevent the development of invasive cancer. It is not, however, an unreasonable hypothesis and as such has provided the direct stimulus and catalyst for the clinical research work presented in later chapters of this book.

Current Problems in Diagnosis and Management

Whilst the clinical recognition of an oral mucosal abnormality may be relatively straightforward, the precise diagnosis ascribed to an individual PMD patient can be demanding, requiring detailed coordination of specific clinical and pathological data. Problems in both diagnosis, particularly in terms of early disease recognition, and in delivering efficacious PMD treatment in contemporary clinical practice are thus recognized and are summarized in Table 3.1¹⁶.

Table 3.1: Problems Associated with Diagnosis and Management of PMD

Diagnostic Dilemmas	Clinical Management Issues
Confused terminology Non-specific diagnoses Lack of diagnostic consistency Clinical behaviour of lesions unpredictable Disease progression variable Poorly defined clinical outcomes Unpredictable risk of malignancy	Treatment aims are unclear No agreed treatment protocols No relevant randomised controlled trials Clinical outcome data vary Medical management is unsuccessful

Diagnostic dilemmas principally relate to confused and inconsistent use of terminology, both clinical and pathological descriptors; this has compounded our apparent lack of understanding of the natural history of PMD and the subsequent risk of malignant transformation. Similarly, patient management has suffered from ill-defined treatment aims and poor agreement over treatment protocols and clinical outcome data. Many published papers in the literature are anecdotal, observational and retrospective in nature with no defined patient cohorts, heterogeneous lesions treated, and uncoordinated management and follow-up regimes.

The lack of relevant clinical trials in PMD management has also posed a significant challenge in rationalizing contemporary clinical practice. High-quality randomised trials are, of course, important in ensuring effective comparison of treatment methods by limiting bias and confounding influences and remain fundamental to establishing meaningful systematic review evidence.

In clinical practice, however, the condition of ‘potential malignancy’ is a difficult concept to define so it is perhaps unsurprising that proposed treatment interventions appear non-specific often with poorly-specified

goals and no clear end-points; the few clinical trials reported in the literature have concentrated on medical therapies and suffer from small patient numbers and short study durations which question the ultimate significance of their results. It is also unhelpful that none of the studies have ever demonstrated long-term lesion resolution, reduction in disease incidence or prevention of malignant transformation, although most authors agree that prevention of malignancy is clearly the main priority^{16,18}.

Despite the theoretical advantage of a chemo-preventive strategy, especially topical therapies to readily accessible oral mucosa, no successful medical intervention has yet been established for PMD¹⁹. Effective treatment is thus more likely to be based upon the surgical excision of identifiable precursor lesions and the eradication of the visible manifestations of dysplastic mucosal fields²⁰. Whilst there is little controversy in the literature regarding the need for intervention in severely dysplastic lesions (which probably possess the greatest risk of malignancy) opinion remains divided over the use of clinical observation versus treatment for lesions exhibiting mild to moderate dysplasia²¹.

Brennan et al²² stated, somewhat unhelpfully perhaps, that due to a lack of randomized controlled trials, no evidence-based recommendations could be provided for either surgical or non-surgical treatment interventions for oral dysplastic lesions. In the absence of evidence-based treatment protocols or meaningful randomized controlled patient intervention trials, therefore, longitudinal patient cohort studies and clinical outcome data presented as an integral part of this book offer a unique opportunity to study a coordinated diagnostic and interventional management strategy for potentially malignant disorders. We will also return to discuss further aspects of both diagnosis and management in detail in Chapters 5 and 6.

Determining the Objectives of PMD Treatment

Significant variation in PMD management protocols have existed for many years and, today, there is still only limited consensus on appropriate treatment. Controversy has surrounded all aspects of diagnosis, detection and treatment. It is, however, pertinent at this juncture to define a number of salient management goals in treating PMD; these are listed in Table 1.4 and briefly discussed in the following pages¹⁶.

Table 3.2: Management Goals in Treating PMD

Accurate and Definitive Diagnosis
Prediction of Clinical Behaviour
Early Recognition of Malignancy
Removal of Dysplastic Mucosa
Prevention of Recurrent or Further Dysplastic Lesions
Prevention of Malignant Transformation
Patient Acceptance and Minimal Morbidity
Cost Effectiveness

Accurate and Definitive Diagnosis

Accurate diagnosis is, of course, fundamental to all clinical management strategies, but the use of incision biopsies to characterise oral mucosa disease is unlikely to represent the true nature of dysplastic mucosal lesions, particularly for large and widespread disorders^{23,24}. Specifically, there exists a risk of ‘under-diagnosis’ when excised PMD lesions are compared histopathologically to their initial incision biopsies; this may affect up to 30% of cases^{25,26}. It is thus recognised that complete excision and histological examination of the entire clinical lesion may be necessary to establish accurate dysplasia grading and definitive diagnosis²⁷.

Prediction of Clinical Behaviour

The ability to predict the clinical behaviour of individual oral mucosal lesions, in particular identifying those PMD most at risk of SCC development, would certainly help facilitate objective patient treatment planning. To date, unfortunately, such accurate prediction remains elusive in contemporary clinical practice⁷.

Early Recognition of Malignancy

Similar to the observations above regarding incision versus excision biopsy, total surgical excision of PMD may well facilitate both early recognition of and subsequent treatment of cancer. Indeed, it has been reported that between 7 to 12% of excised PMD lesions have actually exhibited SCC on histopathological examination, despite being undetected by immediately preceding incision biopsies²⁵.

Removal of Dysplastic Mucosa

By definition, PMD are mucosal conditions only and do not require the aggressive treatment necessary for removal or destruction of invasive SCC. It would seem sensible, therefore, to consider early intervention to remove dysplastic mucosa at such a 'pre-invasive' stage. Whilst surgical treatment has become increasingly recommended^{20,27,28}, questions remain whether surgical excision can reduce the risk of PMD recurrence or malignant transformation²⁹. In general, the type and method of surgical intervention is rarely specifically defined, although PMD have been treated by conventional scalpel excision, cutting diathermy, CO₂ laser surgery and photodynamic therapy.

Prevention of Recurrent or Further Dysplastic Lesions

An important, and fairly consistent observation, is that the incidence of post-treatment recurrence or the development of further PMD appears to increase with the length of patient follow up. Non-homogeneous lesions, PVL, involvement of large mucosal areas, more severe dysplasia and origin at floor of mouth and ventral tongue sites are all thought to predispose to persistent disease development^{12,16}.

Prevention of Malignant Transformation

The risk of malignant transformation for PMD remains unpredictable, varying widely between 0.13 to 36.4%⁴. Mehanna et al²⁰ reviewed 14 studies reporting on 992 PMD patients and calculated an overall transformation rate of 12%. A fundamental hypothesis of this book, and probably the most significant reason for actively treating PMD, is that surgical excision of dysplastic lesions should reduce the ultimate risk of malignancy. Unfortunately, current evidence is inconclusive. Some studies have observed a 5 to 6% transformation rate in patients whose lesions were excised, compared with 15% when no treatment was given^{20,30}. Others, however, have compared SCC incidence in both treated and untreated leucoplakia, and observed little difference in outcome³¹. Perhaps of most significance was a 25% transformation rate reported in a UK dysplasia clinic in which, despite long term patient follow up, there appeared to be no coordinated interventional protocol³². Lodi & Porter²⁹ postulated that PMD natural history may be independent of treatment intervention, and that a 'subgroup' of lesions may be destined for SCC

development irrespective of treatment intervention, although this does seem a rather negative perspective.

Patient Acceptance and Minimal Morbidity

For interventional treatment to become the PMD management of choice, it is important that there is good patient acceptability and that post-operative morbidity remains low.

Cost Effectiveness

In considering aspects of health economics in relation to PMD management, details of treatment efficiency, cost and value for money will require attention, particularly in comparison to the likely extensive healthcare costs associated with oncology treatment. There are virtually no data in the literature to support or refute the concept that early, minimal intervention to attempt secondary or tertiary prevention of oral SCC in an 'at risk' population is cost-effective, but it is not an unreasonable hypothesis and an integral component of the hypothesis driving the clinical research work described in this book.

In subsequent chapters, we will return to review in detail these eight fundamental management goals in an attempt to determine whether our proposed interventional strategies are truly successful in achieving the aims and objectives of an effective PMD treatment protocol.

Conclusions

PMD are chronic mucosal lesions that are identified by clinical examination and confirmed by histopathological assessment to have an increased risk of developing into an oral SCC. Most commonly appearing as leukoplakia, often arising on the floor of mouth and ventro-lateral tongue and exhibiting microscopic features of epithelial dysplasia, it nevertheless remains difficult if not impossible for clinicians to predict the risk for individual PMD lesions to transform to invasive cancer. In the next chapter of this book, we will turn our attention to that vital and fundamental question of risk.

References

1. Thomson PJ. Introduction. In: PJ Thomson (ed) Oral Precancer – Diagnosis and Management of Potentially Malignant Disorders. Wiley-Blackwell; 2012. p1-12. ISBN 978-1-4443-3574-3.
2. Hamadah O, Goodson ML, Thomson PJ. Clinicopathological behaviour of multiple oral dysplastic lesions compared with that of single lesions. *British Journal of Oral & Maxillofacial Surgery* 2010 48: 503-506.
3. Thomson PJ. Oral Carcinogenesis. In: PJ Thomson (ed) Oral Precancer – Diagnosis and Management of Potentially Malignant Disorders. Chichester: Wiley-Blackwell; 2012. p31-47. ISBN 978-1-4433-3574-3.
4. Thomson PJ. Malignant Transformation and Oral Cancer Development. In: PJ Thomson (ed) Oral Precancer – Diagnosis and Management of Potentially Malignant Disorders. Wiley-Blackwell; 2012. p156-169. ISBN 978-1-4443-3574-3.
5. Thomson PJ, Goodson ML. Clinical Presentation of Oral Precancer. In: PJ Thomson (ed) Oral Precancer – Diagnosis and Management of Potentially Malignant Disorders. Wiley-Blackwell; 2012. p48-74. ISBN 978-1-4443-3574-3.
6. Thomson PJ, Goodson ML, Smith DR. Potentially Malignant Disorders Revisited – The Lichenoid Lesion/Proliferative Verrucous Leukoplakia Conundrum. *Journal of Oral Pathology & Medicine* 2018 47: 557-565.
7. Napier SS, Speight PM. Natural history of potentially malignant oral lesions and conditions: an overview of the literature. *Journal of Oral Pathology & Medicine* 2008 37: 1-10.
8. Warnakulasuriya S, Johnson NW, van der Waal I. Nomenclature and classification of potentially malignant disorders of the oral mucosa. *Journal of Oral Pathology & Medicine* 2007 36: 575-580.
9. Warnakulasuriya S (2009). Global epidemiology of oral and oropharyngeal cancer. *Oral Oncology* 2009 45: 309-316.
10. Diajil AR, Thomson PJ. Risk factors of oral cancer and potentially malignant disorders (PMDs) – Developing a high / low risk profiling system. *Journal of Baghdad College of Dentistry* 2016 28: 63-72.
11. Goodson ML, Hamadah O, Thomson PJ. The role of alcohol in oral precancer: observations from a North-East England population. *British Journal of Oral & Maxillofacial Surgery* 2010 48: 507-510.
12. Thomson PJ. Managing oral potentially malignant disorders: A question of risk. *Faculty Dental Journal* 2015 6: 186-191.

13. Thomson PJ. Science, surgery, and surveillance: stopping the clock in oral cancer. Research Report 2010-2012, Royal College of Surgeons of Edinburgh 2012 p96-99.
14. Scott SE, Grunfeld EA, Auyeung V, McGurk M. Barriers and triggers to seeking help for potentially malignant oral symptoms: implications for interventions. *Journal of Public Health Dentistry* 2009 69: 34-40.
15. Williams M, Bethea J. Patient awareness of oral cancer health advice in a dental access centre: a mixed methods study. *British Dental Journal* 2011 210: E9.
16. Thomson PJ. Management of Oral Precancer. In: PJ Thomson (ed) *Oral Precancer – Diagnosis and Management of Potentially Malignant Disorders*. Wiley-Blackwell; 2012. p107-137 ISBN 978-1-4443-3574-3.
17. Esserman LJ, Thompson IM, Reid B. Overdiagnosis and overtreatment in cancer. An opportunity for improvement. *Journal of the American Medical Association* 2013. 310: 797-798.
18. Ribeiro AS, Salles PR, daSilva TA, Mesquita RA. A review of the nonsurgical treatment of oral leukoplakia. *International Journal of Dentistry* 2010 doi:10.1155/2010/186018.
19. Dionne KR, Warnakulasuriya S, Zain RB, Cheong SC. Potentially malignant disorders of the oral cavity: current practice and future directions in the clinic and laboratory. *International Journal of Cancer* 2015 136: 503-515.
20. Mehanna HM, Rattay T, Smith J, McConkey CC. Treatment and follow-up of oral dysplasia – a systematic review and meta-analysis. *Head & Neck* 2009 31: 1600-1609.
21. Thomson PJ, McCaul J, Ridout F, Hutchison I. To treat...or not to treat? Clinician views on oral potentially malignant disorder management. *British Journal of Oral & Maxillofacial Surgery* 2015 53: 1027-1031.
22. Brennan M, Migliorati CA, Lockhart PB, Wray D, Al-Hasimi I, Axell T. Management of oral epithelial dysplasia: a review. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2007 103 (suppl 1): s19.e1-s19.e12.
23. Cox G, Alcock C, Corbridge R. Treatment of oral cancer. Biopsy under local anaesthetic is inadequate. *British Medical Journal* 1999 319: 706.
24. Goodson ML, Kumar A, Thomson PJ (2011). Oral precancer excision is required for definitive diagnosis: incisional vs. excisional

- biopsies in oral leukoplakia management. *Oral Oncology* 2011 47 S128-129.
25. Holmstrup P, Vedtofte P, Reibel J, Stoltze K. Oral premalignant lesions: is a biopsy reliable? *Journal of Oral Pathology & Medicine* 2007 36: 262-266.
 26. Lee J-J, Hung H-C, Cheng S-J, Chiang C-P, Liu B-Y, Yu C-H, Jeng J-H, Chang H-H, Kok S-H. Factors associated with underdiagnosis from incisional biopsy of oral leukoplakic lesions. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2007 104: 217-225.
 27. van der Waal I. Potentially malignant disorders of the oral and oropharyngeal mucosa; terminology, classification and present concepts of management. *Oral Oncology* 2009 45: 317-323.
 28. Dost F, LeCao K, Ford PJ, Ades C, Farah CS. Malignant transformation of oral epithelial dysplasia: a real world evaluation of histopathologic grading. *Oral Surg Oral Med Oral Pathol Oral Radiol* 2014 117: 343-352.
 29. Lodi G, Porter S. Management of potentially malignant disorders: evidence and critique. *Journal of Oral Pathology & Medicine* 2008 37: 63-69.
 30. Lumerman H, Freedman P, Kerpel S. Oral epithelial dysplasia and the development of invasive squamous cell carcinoma. *Oral Surg Oral Med Oral Pathol* 1995 79: 321-329.
 31. Schepman KP, van der Meij EH, Smeele LE, van der Waal I. Malignant transformation of oral leukoplakia: a follow-up study of a hospital-based population of 166 patients with oral leukoplakia from The Netherlands. *Oral Oncology* 1998 34: 270-275.
 32. Ho MW, Risk JM, Woolgar JA, Field EA, Field JK, Steele JC, Rajlawat BP, Triantafyllou A, Rogers SN, Lowe D, Shaw RJ. The clinical determinants of malignant transformation in oral epithelial dysplasia. *Oral Oncology* 2012 48: 969-976.

CHAPTER FOUR

A QUESTION OF RISK

‘...the potential to lose something of value, such as health...’

Introduction

There are, unfortunately, many dilemmas that face clinicians planning treatment for PMD patients, and many of these have been outlined and discussed in Chapter 3. In essence, an oral disease process that is characterised as ‘potentially malignant’, which is neither entirely benign nor frankly malignant, is a very difficult concept for both clinicians and their affected patients to fully comprehend and accept. The inability to predict the individual behaviour of oral mucosal lesions and, in particular, the difficulty in quantifying malignant transformation risk combine to render objective treatment planning for patients extremely difficult.

Whilst the clinical recognition of an oral mucosal abnormality may be relatively straightforward, the precise diagnosis ascribed to an individual PMD patient can be highly demanding, requiring detailed coordination of specific clinical and pathological data together with a fundamental attempt to distinguish ‘high risk’ from ‘low risk’ cases. Figure 4.1 illustrates a typical clinical presentation and management dilemma; the question the clinician must try to answer is what is the risk of SCC development for this patient?

As a general principle, decisions regarding treatment for any clinical disorder require recognition of the potential seriousness of the disease, the absolute risk for any individual patient to develop that disease and to what extent the risk can actually be reduced by treatment. It is also pertinent to consider any potential risks or side effects of the treatment itself and, indeed, as alluded to in the previous chapter the cost-effectiveness of such intervention.

Whilst contemporary clinical practice struggles to predict individual PMD lesion behaviour, quantify risk for malignant transformation or objectively plan treatment intervention, recognising and addressing the uncertainty and unpredictability inherent in PMD may offer a strategy to objectify treatment protocols.

In this chapter, therefore, we will explore the fundamental question of risk as it relates to both initial diagnosis and then subsequent management of PMD. We will also consider whether this complicated concept of risk can be made more understandable to patients. To begin with, it is perhaps useful to examine the specific concepts underlying risk, uncertainty, and unpredictability.



Figure 4.1: Irregular, non-homogeneous leukoplakia affecting the edentulous mandibular alveolar ridge, floor of mouth and postero-lateral tongue. What is the risk of SCC development for this patient?

Risk

Whilst the implication underpinning risk is the potential to lose normal health status, it is perhaps more accurate to define risk as the probability of an adverse clinical event developing over time based upon a detailed quantification of active risk factors. Accurate risk evaluation is thus crucial in nature and fundamental to successful PMD management, and yet remains persistently obscure and highly variable in contemporary clinical

practice. Risk stratification for malignant transformation relies on currently available clinical and histopathological assessments of suspicious oral mucosal lesions, but is frustratingly limited in practice by its highly subjective nature¹⁻⁴.

Uncertainty

Uncertainty is predominant in situations where there is either imperfect or unknown information. If uncertainty can ultimately be expressed or quantified in terms of risk, it is possible to utilize a risk estimate as the basis for rational decision making and informed patient consent. Unfortunately, limited information and poor understanding of the natural history of PMD is reflected in our inability to communicate accurately to patients the precise nature of their presenting complaint and, perhaps most frustratingly of all, their likely clinical outcomes. Such inherent uncertainty during illness is likely to contribute to negative patient experiences³. We will explore many of these issues in more detail in Chapter 10.

Unpredictability

It remains difficult to foresee or predict individual patient outcomes in contemporary PMD management, which contributes significantly to overall unpredictability and is a dilemma that many patients find hard to accept, especially in the absence of clinically applicable bio-molecular markers to guide treatment decisions. The ability to predict disease development in individual patients, however, remains a fundamental and desirable principle intimately linked to the very act of prevention itself.

Whilst it has been recognized for some time that older patients, female gender, individuals who have never used tobacco and those with extensive oral lesions arising particularly at ventro-lateral tongue and floor of mouth sites appear statistically to be most at risk of SCC development, these observations are actually of little practical help in advising individual patients³. This has proved a persistent problem throughout approaches to PMD management: is, for example, the young female, non-smoker with a mildly dysplastic tongue leukoplakia at greater or less risk than an elderly male smoker with moderately dysplastic leukoplakia presenting on the floor of mouth and ventral tongue? The author, unquestionably, prioritizes the former patient, in view of the presupposed inherently unstable and unpredictable nature of dysplastic oral mucosa in the absence of known

risk factor exposure, but this is, of course, highly anecdotal and based purely upon personal clinical experience.

Risk Factors

What, therefore, is the overall significance of risk factors? A risk factor is defined as an attribute, underlying characteristic, variable or exposure that increases the likelihood of disease development in an individual, and includes factors acting as both initiators and promoters of disease. It is important, of course, to distinguish between a correlation and a proven causation when considering the influence of individual risk factors, although this may be far from clear-cut in practice.

Whilst the aetiology of oral cancer has been discussed in previous chapters, daSilva et al⁵ usefully emphasized that a very close interrelationship exists between many of the principal aetiological agents: lifestyle habits (tobacco exposure and alcohol consumption), dietary factors, occupation, socioeconomic status, exposure to external agents and genetic susceptibility. Although our ability to manage risk factors in PMD has been poorly established in clinical practice, concentration of patients and clinical expertise in specialist services may offer new and pragmatic opportunities for both knowledge development and the delivery of more effective interventional strategies.

Tobacco and Alcohol Use

Associations between tobacco use (both smoked and smokeless) and oral SCC development have long been established. In a previous study, we attempted to characterize smoking habits in a cohort of Newcastle patients treated for PMD; unsurprisingly, perhaps, all 27 patients were smokers at initial presentation and despite attempts to stop, smoking remained a considerable problem for the majority following laser treatment. In specific relation to quitting smoking, the availability of specialist non-smoking programmes were seen to be integral to secondary care PMD services if long term smoking cessation was to be effective in reducing further disease incidence. Indeed, we found the presence of a dedicated smoking cessation adviser, as part of the PMD clinic team, invaluable in achieving long term results for patients trying to stop⁶. Other workers have also noted a statistically significant risk of disease recurrence or progression in patients who continue to smoke following PMD surgery^{7,8}.

Over use of alcohol is linked with oral SCC development, and it would appear it is the overall amount consumed over time rather than the number of drinks per day or the type of alcoholic beverage consumed that is most important. The reliability of patient reported data remains an important issue, however, and inevitably patients' simultaneous use of alcohol and potential dietary and nutritional deficiencies confound the ability to stratify individual risk factors. Jaber⁹ re-emphasized the important synergistic effects of combined tobacco smoking and alcohol drinking and noted that individuals who smoke more than 20 cigarettes per day and consume more than 100g of alcohol per day have an increased risk of developing PMD, although also noted that in non-smokers, consumption of alcohol alone was not a significant predictor of PMD. In a pooled analysis of 15 case control studies, including 10,244 head and neck cancer patients, alcohol consumption in never smokers was found to be associated with an increased risk of oral and oropharynx carcinogenesis but only at very high levels of drinking¹⁰.

We therefore examined the specific role of alcohol use as an independent risk factor in 54 Newcastle patients with PMD. Whilst all patients smoked 10 to 20 cigarettes per day, we found that a high alcohol intake (greater than 28 units per week) was associated with both increased severity of dysplasia at presentation and recurrent PMD following laser surgery. We also noted that raised mean corpuscular volume (MCV) measurements of alcohol-related red blood cell macrocytosis were reliable and objective markers of alcohol intake and corresponded with both patient reported intake and increased dysplasia seen in mucosal lesions¹¹.

In order to explore such issues more comprehensively, 73 Newcastle oral cancer patients and 112 controls were enrolled in much wider multi-centre, Europe-wide epidemiological studies to stratify risk assessment for cancer development, especially in relation to lifestyle habits, dietary factors and occupation. Aspects of these Alcohol Related Cancers and Genetic susceptibility in Europe (ARCAGE) and the International Head and Neck Cancer Epidemiology (INHANCE) consortium studies pertinent to risk factor behaviour have contributed significant observational and epidemiological data to the contemporaneous literature, especially the increased cancer risk proportionate to alcohol consumption and smoking addiction¹²⁻¹⁶. Of particular interest, however, was the observation that only 60% of ARCAGE oral cancer cases were thought to be caused by tobacco and/or alcohol use, emphasizing the importance of identifying other, unknown risk factors during oral carcinogenesis.

Indeed, whilst PMD patients who continue to smoke and drink are at increased risk of recurrent or further disease post-treatment, we have also observed that patients who were life-time non-smokers and non-drinkers ultimately had the poorest disease-free outcomes 5-years post-laser surgery, emphasizing the significance of pre-existing and widespread mucosal genetic abnormalities in such patients^{17,18}. Ho et al¹⁹ confirmed this observation by noting a high risk of malignant transformation in non-smoking PMD patients, postulating an inherited predisposition to cancer and advising aggressive treatment, although did not actually specify what the nature of such treatment might be.

Jaber⁹ similarly commented upon the presentation of oral dysplastic lesions in non-smoking, non-alcohol consuming patients, which comprised 37 out of a total of 456 PMD patients in a United Arab Emirates study. These lesions more commonly occurred in women, exhibited mild dysplasia and showed a predilection for tongue and buccal mucosa sites. A trend for increased risk of second dysplastic lesions and a higher malignant transformation rate was seen in this non-smoking and non-alcohol drinking group. It is now increasingly recognized that non-smoking and non-alcohol drinking patients, often elderly females, may develop oral SCC and are likely to exhibit significantly worse disease-specific mortality. Whether this is solely related to the ageing process and the lifetime accumulation of genetic mutations in oral mucosa remains to be seen²⁰.

Dietary Factors

Defining the true role of dietary factors in oral carcinogenesis is inevitably complicated by the numerous interactions between tobacco smoking, alcohol use and varying cultural and social influences. Indeed, the assessment of dietary information has long been a source of conceptual and methodological concern in epidemiological studies. It is recognized, however, that consumption of fresh fruit and vegetables and other micronutrients may inhibit the development of PMD. Micronutrients such as vitamins A, B₁₂, C, E, beta-carotene, folate, iron, zinc and selenium may protect oral epithelium from carcinogenic influence by antioxidant activity, modulation of carcinogen metabolism, inhibition of cell proliferation and enhancement of immune function²¹⁻²³. Consumption of fresh vegetables, fruit, olive oil and tea all appear to be associated with a reduced risk of upper aerodigestive tract cancer, whilst highest cancer risk

is seen with diets low in fruit and vegetables and high red meat consumption^{23,24}.

In Newcastle, we examined the influence of various risk factors in the development of PMD, by comparing clinico-pathological data from 18 multiple lesion patients with 78 single lesion patients, and noted that multifocal lesions were most commonly seen in patients consuming low intakes of fruit and vegetables (defined as less than 3 portions per day)²⁵.

Socioeconomic Status

In a specific study of 100 Newcastle oral cancer patients, we developed an index to specifically measure material deprivation. A significant trend was seen for cancer patients to come from the most deprived populations compared with their age and sex-matched controls, with 60% demonstrating periods of long-term unemployment; inevitably, of course, such observations suffer from the confounding effects of over-use of tobacco and alcohol²⁶. Low socioeconomic status, however, has been significantly associated with a high risk of oral cancer development worldwide, albeit in complex interrelationships with other risk factor behaviours²⁷.

Whilst no direct evidence of occupational risk for women is seen, case history analyses confirm that socioeconomic inequality, in terms of educational attainment, occupation, social class and unemployment, pose an increased cancer risk in male patients; construction workers and occupations involving bricklaying and painting appear particularly linked to the presence of oral SCC²⁸.

There are very few studies in the literature that have specifically investigated occupational risk factors and PMD, but it is reasonable to assume that the same aetiological agents implicated in SCC development are involved. Hashibe et al¹⁰ analysed education, occupation, income and socioeconomic status in Kerala in India for over one thousand PMD patients and nearly 50,000 controls. Whilst these data may not be wholly applicable to European populations, higher socioeconomic status appeared protective against PMD development, and was clearly related to lower smoking and alcohol habits, good nutritional intake, diets high in fruit and vegetables, better living environments, greater access to health care and improved psychosocial support.

Profiling of Risk

Risk Factors

Clearly, not all risk factors should be considered to be of equal significance. In an attempt to delineate high and low risk factors for oral carcinogenesis and PMD development, we reviewed 300 papers published over a 30-year period and stratified the evidence for oral cancer risk as sufficient or limited in extent. Overall, 8 factors were considered to be high-risk, unsurprisingly these included tobacco, alcohol and betel quid misuse as the most significant, with a further 6 lower risk, such as poor oral health, low socio-economic status and HPV infection, because in these latter cases the linking evidence to oral carcinogenesis appeared either inconsistent or controversial. All these factors are ranked, in descending order of their calculated significance, in Table 4.1²⁹.

Table 4.1: High and Low Risk Factors in Oral Carcinogenesis

High Risk
1. Tobacco Use
2. Alcohol Consumption
3. Use of Betel Quid
4. Use of Cannabis
5. Inherent Susceptibility & Genetic Factors
6. Advanced Age
7. Influence of Dietary Factors
8. Immunodeficiency
Low Risk
1. Poor Oral Health & Hygiene
2. Low Socio-economic Status
3. Human Papilloma Virus (HPV) Infection
4. Candida albicans Infection
5. Use of Alcohol-Containing Mouthwash
6. Diabetes Mellitus

Table 4.2: PMD Risk Factor Data Collection**Patient Demography**

Sex

Age

Occupation

Married / Divorced / Single

Medical History

1. General Medical Status

2. Immunodeficiency

3. Diabetes Mellitus

4. Anaemia

5. Infection – HPV / Candida

Risk Factors*Tobacco Smoking*

Current / Ex-Smoker / Non-Smoker

Number of Cigarettes per Day

History of Smoking (Years)

Use of Alcohol

Current / Ex-Drinker / Non-Drinker

Number of Units per Week

History of Alcohol Use (Years)

Diet

Prepared & Processed Food / Fresh Fruit & Vegetables

*Familial Cancer History*Father / Mother / 1st Relative / 2nd Relative*Oral Health*

Good / Poor Oral Hygiene

Mouth Wash Use & Type

Oral Prosthesis Wear

Epidemiological risk factors such as these, however, do not directly inform individual patient care. However, using such stratification, it was thus considered feasible to attempt the identification of high risk patients by attention to data collection regarding specific factors during medical history taking and clinical assessment of PMD patients, particularly within specialist clinic settings where such structured information collation could be encouraged and coordinated; Table 4.2²⁹.

Patient Profiling

It is unfortunate that our ability to quantify risk for individual patients remains somewhat elusive in contemporary practice but, in an additional attempt to profile patients most at risk of oral SCC development we synthesized additional data from a number of publications documenting both long-term PMD patient surveillance and risk factor research, to attempt

To delineate a patient profile those individuals most at risk of malignancy and/or resistant and progressive disease.

The 'high risk' patient will, unsurprisingly, misuse both tobacco and alcohol, exhibiting a strong addiction to smoking and persistent and regular, high alcohol consumption, together with a diet low in fruit and vegetables, and poor oral hygiene and irregular dental care. Most commonly, the patient will be a male of shorter-stature, low socioeconomic status and low educational attainment, experiencing periods of material deprivation or long-term unemployment or will have been primarily engaged in manual occupations such as bricklaying and painting. In contrast, patients' age, medical history or medication use and human papillomavirus exposure have all been shown to be much less helpful in predicting disease status and risk³.

Speight et al³⁰ recently proposed a low, medium or high risk stratification for presenting PMD patients, based upon the assessment of details obtained sequentially from individual patient histories, clinical examination data and histopathology diagnoses from biopsies, although this seems potentially distracting from the more important principle of specifically identifying 'high-risk' disease. It has always been a concern of this author exactly how one should interpret categories of 'moderate' or 'medium' risk.

Modification of Risk

There remains a surprising and concerning level of ignorance in the general population regarding oral cancer and its cause. An effective clinical management protocol must commence, therefore, with education of patients regarding the aetiology of PMD and SCC, and emphasize the importance of both recognising and then eliminating active risk factors. In the vast majority of cases, of course, this relates primarily to tobacco and

alcohol use, and it is disheartening how often patients fail to stop smoking or reduce their alcohol intake even following diagnosis and treatment of oral lesions^{6,11}.

Nicotine is the primary addictive substance in tobacco and, as it is probably not a carcinogen in itself, various nicotine replacement therapies have been advocated through the years in attempts to help smokers quit. Additional approaches to smoking cessation have included the use of electronic cigarettes or 'heat-not-burn' cigarettes, which are thought to contain lower levels of carcinogens, but whether these are truly safe for patients at risk of oral carcinogenesis remains to be seen.

In non-smoking patients and those with low alcohol consumption, the importance and relevance of other risk factors will require further careful elucidation. The type of risk factor requiring attention may include deficiencies in dietary intake of fresh fruit and vegetables, the possible influence of HPV infection and oral sexual behaviour, together with a number of background medical conditions, such as immunosuppression and diabetes mellitus, all of which may influence both PMD development and disease progression. Whilst it may not, ultimately, be possible to reduce the significance or alter the course of these disparate influences, it is certainly important to identify them and recognise their relevance to individual patient care pathways.

Conclusions

It remains difficult in contemporary practice to quantify the risk of malignant transformation or to predict clinical outcome. Indeed, correct risk evaluation is a formidable challenge for healthcare in general. However, integration of patient profiling to existing diagnostic and clinic surveillance protocols appears a pragmatic tool to aid in discrimination of 'high' and 'low' risk PMD cases. Further clinical application, ideally as part of a multi-centre trial, is necessary to determine a precise role for such profiling in contemporary practice. In later chapters, we will review both long-term treatment outcomes and SCC development in PMD patient cohorts to try to improve both our understanding of the natural history of disease and to aid the development of more objective risk stratification procedures to inform future interventional management strategies³¹.

References

1. Thomson PJ. Oral Carcinogenesis. In: PJ Thomson (ed) Oral Precancer – Diagnosis and Management of Potentially Malignant Disorders. Chichester: Wiley-Blackwell; 2012. p31-47.
2. Thomson PJ. Potentially Malignant Disorders – The Case for Intervention. *Journal of Oral Pathology & Medicine* 2017 46: 883-887.
3. Thomson PJ. Managing oral potentially malignant disorders: A question of risk. *Faculty Dental Journal* 2015 6: 186-191.
4. Field EA, McCarthy CE, Ho MW, Rajlawat BP, Holt D, Rogers SN, Triantafyllou A, Field JK, Shaw RJ. The management of oral epithelial dysplasia: The Liverpool algorithm. *Oral Oncology* 2015 51: 883-887.
5. daSilva SD, Ferlito A, Takes RP, Brakenhoff RH, Valentin MD, Woolgar JA, Bradford CR, Rodrigo JP, Rinaldo A, Hier MP, Kowalski LP. Advances and applications of oral cancer basic research. *Oral Oncology* 2011 47: 783-791.
6. Hamadah O, Hepburn S, Thomson PJ. Effects of active non-smoking programmes on smoking behaviour in oral precancer patients. *International Journal of Oral and Maxillofacial Surgery* 2007 36: 706-711.
7. Poate TW, Warnakulasuriya S. Effective management of smoking in an oral dysplasia clinic in London. *Oral Diseases* 2006 12: 22-26.
8. Vladimirov BS, Schiodt M. The effect of quitting smoking on the risk of unfavorable events after surgical treatment of oral potentially malignant lesions. *International Journal of Oral & Maxillofacial Surgery* 2009 38: 1188-1193.
9. Jaber MA. Oral epithelial dysplasia in non-users of tobacco and alcohol: an analysis of clinicopathological characteristics and treatment outcome. *J Oral Science* 2010 52: 13-21.
10. Hashibe M, Jacob BJ, Thomas G, Ramadas K, Mathew B, Sankaranarayanan R, Zhang ZF. Socioeconomic status, lifestyle factors and oral premalignant lesions. *Oral Oncology* 2003 39: 664-671.
11. Goodson ML, Hamadah O, Thomson PJ. The role of alcohol in oral precancer: observations from a North-East England population. *British Journal of Oral & Maxillofacial Surgery* 2010 48: 507-510.
12. Anantharaman D, Marron M, Lagiou P, E Samoli E, Ahrens W, Pohlabein H, Slamova A, Schejbalova M, Merletti F, Richiardi L, Kjaerheim K, Castellsague X, Agudo A, Talamini R, Barzan L,

- Macfarlane T, Tickle M, Simonato L, Canova C, Conway D, McKinney P, Thomson PJ, Znaor A, Healy C, McCartan B, Hashibe M, Brennan P, Macfarlane G. Population attributable risk of tobacco and alcohol for upper aerodigestive tract cancer. *Oral Oncology* 2011 47: 725-731.
13. Marron M, Boffetta P, Moller H, Ahrens W, Pohlabein H, Benhamou S, Bouchardy C, Laggiou P, Laggiou A, Slamova A, Schejbalova M, Merletti F, Richiardi L, Kjaerheim K, Agudo A, Castellsague X, Macfarlane T, Macfarlane G, Talamini R, Barzan L, Canova C, Simonato L, Biggs A-M, Thomson PJ, Conway D, McKinney P, Znaor A, Healy C, McCartan B, Brennan P, Hashibe M. Risk of upper aerodigestive tract cancer and type of alcoholic beverage: a European multicentre case-control study. *European Journal of Epidemiology* 2012 27: 499-517.
 14. Lee Y-C, Zugna D, Richiardi L, Merletti F, Marron M, Ahrens W, Pohlabein H, Laggiou P, Trichopoulos D, Agudo A, Castellsague X, Betka J, Holcatova I, Kjaerheim K, Macfarlane GJ, Macfarlane TV, Talamini R, Barzan L, Canova C, Simonato L, Conway DI, McKinney PA, Thomson PJ, Znaor A, Healy CM, McCartan BE, Boffetta P, Brennan P, Hashibe M. Smoking addiction and the risk of upper-aerodigestive-tract cancer in a multicenter case-control study. *International Journal of Cancer* 2013 133: 2688-2695.
 15. Berthiller J, Straif K, Agudo A, Ahrens W, Bezerra dos Santos A, Boccia S, Cadoni G, Canova C, Castellsague X, Chen C, Conway D, Curado MP, Dal Maso L, Daudt A, Fabianova E, Leticia F, Franceschi S, Fukuyama EE, Hayes RB, Healy C, Herrero R, Holcatova I, Kelsey K, Kjaerheil K, Koifman S, Laggiou P, La Vecchia C, Lazarus P, Levi F, Lissowska J, Macfarlane T, Mates D, McClean M, Menezes A, Merletti F, Morgenstern H, Muscat J, Olshan AF, Purdue M, Ramroth H, Rudnai P, Schwartz SM, Serraino D, Shangina O, Smith E, Sturgis EM, Szeszenia-Dabrowska N, Thomson PJ, Vaughan TL, Vilensky M, Wei Q, Winn DM, Wunsch-Filho V, Zhang Z-F, Znaor A, Ferro G, Brennan P, Boffetta P, Hashibe M, Lee Y-C. Low frequency of cigarette smoking and the risk of head and neck cancer in the INHANCE consortium pooled analysis. *International Journal of Epidemiology* 2016 45: 835-845.
 16. Anantharaman D, Miller D, Laggiou P, Ahrens W, Holcatova I, Merletti F, Simonato L, Macfarlane TV, Thomson PJ, Robinson CM, Conway DI, Healy CM, Westin U, Overvad K, Drogan D, Hallmans G, Laurell G, Peeters P, Agudo A, Larranaga N, Travis R, Trichopoulos D, Grioni S, Tumino R, Severi G, Panico S,

- Weiderpass E, Lund E, Gram I, Riboli E, Pawlita M, Waterboer T, Kreimer A, Johansson M, Brennan P. Combined effects of smoking and HPV 16 in oropharyngeal cancer. *International Journal of Epidemiology* 2016 45: 752-761.
17. Hamadah O, Thomson PJ. Factors affecting carbon dioxide laser treatment for oral precancer: A patient cohort study. *Lasers in Surgery and Medicine* 2009 41:17-25.
 18. Diajil AR, Robinson CM, Sloan P, Thomson PJ. Clinical outcome following oral potentially malignant disorder treatment: a 100 patient cohort study. *International Journal of Dentistry* 2013 <http://dx.doi.org/10.1155/2013/809248>.
 19. Ho MW, Risk JM, Woolgar JA, Field EA, Field JK, Steele JC, Rajlawat BP, Triantafyllou A, Rogers SN, Lowe D, Shaw RJ. The clinical determinants of malignant transformation in oral epithelial dysplasia. *Oral Oncology* 2012 48: 969-976.
 20. Koo K, Barrowman R, McCullough M, Iseli T, Wiesenfeld I. Non-smoking non-drinking elderly females: a clinically distinct subgroup of oral squamous cell carcinoma patients. *International Journal of Oral & Maxillofacial Surgery* 2013 42: 929-933.
 21. Gupta PC, Hebert JR, Bhonsle RB, Murti PR, Mehta H, Mehta FS. Influence of dietary factors on oral precancerous lesions in a population-based case-control study in Kerala, India. *Cancer* 1999 85: 1885-1893.
 22. Zain RB. Cultural and dietary risk factors of oral cancer and precancer – a brief overview. *Oral Oncology* 2001 37: 205-210.
 23. Edefonti V, Hashibe M, Ambrogi F, Parpinel M, Bravi F, Talamini R, Levi F, Yu G, Morgenstern H, Kelsey K, McClean M, Schantz S, Zhang Z, Chuang S, Boffetta P, LaVecchia C, Decarli A. Nutrient-based dietary patterns and the risk of head and neck cancer: a pooled analysis in the International Head and Neck Cancer Epidemiology consortium. *Annals of Oncology* 2011 doi:10.1093/annonc/mdr 548: 1-11.
 24. Chuang S-C, Jenab M, Heck J, Bosetti C, Talamini R, Matsuo K, Castellsague X, Franceschi S, Herrero R, Winn D, LaVecchia C, Morgenstern H, Zhang Z-F, Levi F, Dal Maso L, Kelsey K, McClean M, Vaughan T, Lazarus P, Muscat J, Ramroth H, Chen C, Schwartz S, Eluf-Neto J, Hayes R, Purdue M, Boccia S, Cadoni G, Zaridze D, Koifman S, Curado M, Ahrens W, Benhamou S, Matos E, Lagiou P, Szeszenia-Dabrowska N, A Olshan A, Fernandez L, Menezes A, Agudo A, Dault A, Merletti F, Macfarlane GJ, Kjaerheim K, Mates D, Holcatova I, Schantz S, Yu G-P, Simonato L,

- Brenner H, Mueller H, Conway D, Thomson PJ, Fabianova E, Znaor A, Rudnai P, Healy CM, Ferro G, Brennan P, Boffetta P, Hashibe M. Diet and the risk of head and neck cancer: a pooled analysis in the INHANCE consortium. *Cancer Causes Control* 2012 23: 69-88.
25. Hamadah O, Goodson ML, Thomson PJ. Clinicopathological behaviour of multiple oral dysplastic lesions compared with that of single lesions. *British Journal of Oral & Maxillofacial Surgery* 2010 48:503-506.
 26. Greenwood M, Thomson PJ, Lowry RJ, Steen IN. Oral cancer: material deprivation, unemployment and risk factor behaviour - an initial study. *International Journal of Oral & Maxillofacial Surgery* 2003 32: 74-77.
 27. Conway DI, Petticrew M, Marlborough H, Berthiller J, Hashibe M, Macpherson LMD. Socioeconomic inequalities and oral cancer risk: A systematic review and meta-analysis of case-control studies. *International Journal of Cancer* 2008 122: 2811-2819.
 28. Richiardi M, Corbin M, Marron M, Ahrens W, Pohlabein H, Lagiou P, Minaki P, Agudo A, Castellsague X, Slamova A, Schejbalova M, Kjaerhiem K, Barzan L, Talamini R, Macfarlane GJ, Macfarlane T, Canova C, Simonato L, Conway DI, McKinney P, Sneddon L, Thomson PJ, Znaor A, Healy C, McCartan B, Benhamou S, Bouchardy C, Hashibe M, Brennan P, Merletti F. Occupation and risk of upper aerodigestive tract cancer: The ARCAGE study. *International Journal of Cancer* 2012 130: 2397-2406.
 29. Diajil AR, Thomson PJ. Risk factors of oral cancer and potentially malignant disorders (PMD) – developing a high/low risk profiling system. *Journal of the Baghdad College of Dentistry* 2016 28: 63-72.
 30. Speight PM, Khurram SA, Kujan O. Oral potentially malignant disorders: risk of progression to malignancy. *Oral Surg Oral Med Oral Pathol Oral Radiol* 2018 125: 612-627.
 31. Conti AA, Conti A, Gensini GF. The concept of risk in medicine: historical and epistemological reflections. *Minerva Medicine* 2010 101: 59-62.

PART TWO

THEORIES

'a supposition or system of ideas intended to explain something'

CHAPTER FIVE

DIAGNOSIS

'...identification of the nature and cause...'

Introduction

Diagnosis may be defined as the identification of the nature of an illness or disorder by examination and analysis of the presenting signs and symptoms. It is assumed, not unreasonably, that early diagnosis of PMD is desirable. This is our first and most important theory therefore, and is based upon the fundamental hypothesis that once diagnosed, prompt intervention may halt the disease process and ultimately prevent SCC development. Controversy, of course, exists whether either of the aforementioned aims can realistically be achieved for every patient. However, as already illustrated, when the consequences of SCC development in the oral cavity can be so disastrous, efforts to improve prompt identification of PMD and earlier recognition of invasive SCC must both be encouraged.

In order to improve patient survival and reduce the morbidity following oral cancer diagnosis, it seems logical therefore for oral clinicians to utilize the 'oral pre-cancer window' to identify PMD at the earliest possible stage and to intervene to halt the disease process. It would also seem logical that the clinical responsibility for early identification of oral mucosal changes and the recognition of the potentially malignant nature of suspicious oral lesions should rest with dental practitioners. Unfortunately, however, in a relatively recent study involving primary care practitioners in Northern England, significant concerns were raised regarding lack of rigorous and systematic approaches amongst many dentists towards not only recognising suspicious oral signs and symptoms, but also detection and management of established PMD¹. Similar difficulties were also noted in relation to general dental practitioners' ability to identify early oral cancer cases, somewhat undermining conventional wisdom that dentists should screen patients for oral cancer at every routine check-up².

In addition to these professional uncertainties surrounding diagnosis and management of suspicious oral disease, there is also considerable public ignorance regarding oral cancer and its associated risk factors, and the patient population most 'at risk' is known to rarely attend for oral examination or regular dental care. General population screening programmes for oral cancer, defined as structured health care interventions to detect disease at latent or asymptomatic stages (and thereby interrupting disease progression or facilitating cure) are thus intrinsically and fundamentally flawed as effective health care interventions³.

It is recognised that patients who smoke and drink excessively and are thus most at risk of oral cancer are also likely to have poor diets, come from lower socioeconomic groups and will be the least likely to access medical services or to attend their dentist for regular oral examination. The problem therefore remains how to encourage such individuals to attend for clinical assessment, but in addition there are clearly important practical questions to address such as how, when and to whom they should actually present themselves for that examination.

Improving public awareness of oral cancer and PMD, with specific education of the 'at risk' population to alert them to potential signs and symptoms of early stage disease, together with a much greater emphasis on prevention, are significant priorities for oral health care. A robust and pragmatic approach may be to specifically identify individual patient groups deemed to be at 'high risk' of developing cancer. Targeted screening of individuals deemed 'high risk' provides opportunities for risk factor modification and prevention, whilst 'case finding' specifically applies diagnostic tests to a patient already presenting with abnormal signs or symptoms in order to establish a definite diagnosis. Taken together, these approaches are likely to be more useful as pragmatic tools during PMD diagnosis and in facilitating early and effective interventional strategies⁴.

The earliest possible, most accurate and definitive diagnoses are mandatory for timely and effective recognition of malignant change and to subsequently deliver optimal patient treatments. In this chapter, therefore, we will examine the critical role of diagnosis, and the potential utilization of diagnostic aids or adjuncts, in specific relation to the assessment of PMD and the early identification of oral SCC.

Clinical Diagnosis

Overall, the clinical diagnosis of PMD and/or early invasive SCC remains problematic due to the difficulty in attracting 'high risk' patients to attend for screening, the presence of many benign mucosal abnormalities which confound the diagnostic process, the varying clinical appearances of PMD and, of course, the realisation that potentially malignant tissue may exist unseen in clinically normal looking mucosa.

In practice, most PMD diagnoses are based on the recognition of suspicious looking lesions in presenting patients by an experienced clinician carrying out a careful and thorough mucosal inspection in good light during routine oral examination. It is clear, therefore, that all dental clinicians should be encouraged to improve the quality and reliability of their oral examinations. It is also recognised that clinicians should adhere to a regular routine and be methodical in inspecting every region of the oral cavity to avoid missing abnormalities⁵.

A pragmatic approach therefore commences with anterior floor of mouth and ventral tongue inspection, moving backwards bilaterally along lateral tongue surfaces examining both lingual mucosa and posterior floor of mouth. The patient then protrudes their tongue forwards as far as they can comfortably; subsequent manoeuvring of the tongue tip to right and left sides helps visualise the postero-lateral tongue and tongue base. Alternatively, the clinician may gently manipulate the tongue with a damp swab but this can be uncomfortable and many patients are intolerant, which can actually result in a poorer quality examination. Inspection of lingual mandibular gingiva and retromolar areas are facilitated by use of the dental mirror. By requesting the patient to say, 'Ah', direct visualisation of the faucial pillars, tonsils and soft palate is facilitated. Tongue depression with a spatula or mirror may improve the view, but some patients are highly intolerant of this manoeuvre. Hard palate and palatal gingiva are best seen by direct visual inspection, as is buccal mucosa which can usefully be examined in a bilateral manner commencing posteriorly at each pterygo-mandibular raphe and finishing by inspection of anterior labial commissures, upper and lower lip mucosa and the adjacent vermilion borders. Finally, the patient is asked to close the teeth together to facilitate examination of all labial and buccal gingival surfaces⁵.

When a particular mucosal lesion is identified, its location, size, morphology and surface characteristics should all be recorded. Lesions are

then gently palpated with gloved fingers which helps determine whether they are soft and mobile or of a more sinister nature appearing firm, indurated, fixed to underlying structures or friable and haemorrhagic. Leukoplakic lesions should be further assessed to see if they can be wiped away by careful use of a damp swab, in which case the diagnosis may be that of an acute pseudomembranous candidosis. Feint or inconsistent lesions may be much better defined following gentle application of a dry swab to remove overlying moisture on the mucosal surface.

It is important that clinical examination findings are recorded accurately and concisely. Some clinicians record the lesion diagrammatically, entering it on a mouth map, or by photography; the latter may be especially helpful in hospital practice where patients may not always be reviewed by the same clinician at each clinic visit. The clinician then assigns a provisional diagnostic term to the lesion and determines whether further investigations are required. Table 5.1 lists the investigative techniques which are commonly utilised in the assessment of newly presenting PMD patients.

Table 5.1: Investigation of the PMD Patient

Patient History - Identification of risk factors and/or predisposing conditions

Clinical Examination - Visual inspection of oral mucosa

Palpation and manipulation of mucosal lesion

Clinic Investigation - Oral swab for microbiology assessment

Blood Tests - Full Blood Count

Ferritin, B12, Folate

Urea & Electrolytes

Random Blood Glucose

Liver Function Tests

Photography

Incision Biopsy

In almost all cases, incision biopsy of the lesion will be performed to facilitate histopathological identification and assessment of existing tissue disorganisation and dysmaturation changes, and thus confirmation or refinement of the clinical diagnosis. It is important to select a specific site for biopsy which includes the most representative or clinically severe looking region, together with the lesion margin and adjacent normal looking tissue. Whilst incisional biopsies are vital diagnostic tests, they only provide a provisional result because they may not always be entirely representative of the evolving nature of PMD, particularly so in large mucosal lesions and for widespread pan-oral disorders⁵.

A specific diagnostic problem is posed by patients who present with multiple lesions or pan-oral disease. Such multi-focal disease may affect up to 24% of patients with oral cancer and visualisation of the true extent of the disease, particularly where there is extensive involvement of the posterior oral cavity and pharynx, can be extremely difficult. In these cases, it is useful to consider a more detailed examination under anaesthesia to facilitate a comprehensive inspection and multiple incisional biopsies from involved sites to effectively 'field map' the histopathological features throughout the oral cavity and oropharynx^{6,7}.

It has been estimated that up to 15% of the general population may display some form of mucosal abnormality, the vast majority of which are usually benign conditions. Unfortunately, clinical examination alone cannot always reliably discriminate between innocent lesions and potentially malignant ones. Similarly, normal looking oral mucosa may actually harbour molecular abnormalities or even frank histopathological change commensurate with a diagnosis of PMD in 'at risk' patients⁶⁻⁸.

Adjunctive Diagnostic Techniques

In view of the aforementioned difficulties and, as clinical examination alone appears restricted in its ability to further improve diagnostic accuracy, a number of diagnostic adjuncts have been developed in an attempt to identify PMD at the earliest possible stage. Adjunctive techniques may be used to identify the presence of abnormal mucosa in the oral cavity or to determine malignant transformation risk in previously recognised oral lesions. In clinical practice, there is significant overlap between these complementary objectives. Whilst none are likely to be used without, nor indeed to replace, visual examination they are all

designed to try to assist clinicians in recognising and characterising PMD changes in oral mucosa that may be invisible to the naked eye⁸⁻¹².

Table 5.2 summarises a number of proposed diagnostic aids for PMD detection. Many publications within this field have proved highly anecdotal, however, and it is probably within specialist clinical practice that such adjunctive technologies will prove most beneficial, because their use in primary care as unfocused, general mucosa screening tools cannot be recommended on the currently available scientific evidence.

Table 5.2: Diagnostic Adjuncts for PMD Detection

Vital Tissue Staining – Toluidine Blue

Lugol's Iodine

Light Based Detection – Chemiluminescence

Tissue Autofluorescence

Tissue Fluorescence Spectroscopy

Photodynamic Diagnosis

Optical Visualization

Exfoliative Cytology – Brush Biopsy & Liquid Based Cytology

Salivary Biomarkers – Saliva Composition

Analysis of Shed Oral Epithelial Cells

Vital Tissue Staining

Vital tissue staining techniques are based upon the principal that dysplastic or neoplastic tissue preferentially take up applied chemical dyes, resulting in staining and thus highlighting abnormal mucosa in contrast to

immediately adjacent normal tissue. These are usually simple and relatively inexpensive chairside tests, and yet clinical trials to assess their usefulness in practice have shown highly variable results, with very few studies for example directly comparing staining with definitive histopathological diagnoses^{4,12}.

One of the more widely used stains is *Toluidine Blue*, for many years an aid to visualisation of lesions on both cervical and oral mucosal surfaces. It is a metachromatic dye that binds preferentially to rapidly proliferating epithelium, and is thought to stain nucleic acids, leading to a retained blue discolouration in abnormal tissue. In the oral cavity, patients undertake a pre-stain oral rinse with 1% acetic acid solution and then gargle with toluidine blue followed by a post-stain rinse of acetic acid. Any persistent blue stain seen on mucosa is regarded as a positive result, which should be biopsied immediately or reviewed in 14 days-time, re-stained and then biopsied if persistent. In general, whilst toluidine blue may be reliable at detecting established SCC or severely dysplastic PMDs, it is less effective in detecting early change. Similarly, there is no evidence that staining identifies or predicts malignant transformation in mucosal abnormalities not already seen on visual examination, which is of course the principal objective of an effective diagnostic adjunct. Unfortunately, toluidine blue also stains benign, inflammatory or ulcerative lesions and is retained within tongue dorsum crevices, dental plaque deposits and on gingiva, all of which contribute to confusion in interpreting results, especially in the presence of equivocally or pale staining lesions. These observations, together with lack of evidence that it is effective as a screening technique in primary care and its time consuming application method have limited widespread use in clinical practice. Of most significance perhaps, are the results of an 8000 patient population community screening programme in Taiwan, in which no advantage of toluidine blue staining was seen compared with standard visual examination alone¹³.

An alternative technique utilises *Lugol's Iodine*, a solution of elemental iodine and potassium iodide in water, and stains glycogen in normal oral mucosa brown, but exposes dysplastic or neoplastic tissue as pale. Similar limitations apply to this technique as toluidine blue, with an additional disadvantage that its use is primarily restricted to non-keratinised mucosa¹⁴. Whilst other workers have trialled agents such as *Methylene Blue* and *Rose Bengal* staining, the precise role of vital staining remains unclear and there exists no evidence to support its efficacy in routine clinical practice and certainly not as a primary care screening tool. It may, however, have a limited role in specialist PMD clinics, particularly in the

assessment and follow-up of patients presenting with widespread or multifocal disease to help delineate the most appropriate biopsy sites^{4,12}.

Light Based Detection

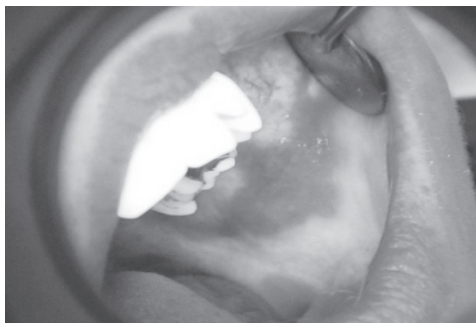
A number of light based detection systems have been developed as minimally invasive diagnostic visualization aids, based upon the different absorbance and reflectance profiles seen within dysplastic or neoplastic mucosa when oral mucosa is exposed to extrinsic light sources^{12,15}.

In *chemiluminescence*, tissue reflectance is utilized with devices such as ViziLite^R (Zila Pharmaceuticals, Phoenix, Az, USA) and MicroLux/DL^R (AdDent Inc, Danbury, CT, USA) used in conjunction with 1% acetic acid mouth rinse followed by direct visual examination with a blue-white light source. Acetic acid removes cellular debris and dehydrates cells facilitating visualization of cell nuclei. Displaying an increased nuclear to cytoplasmic ratio, dysplastic oral epithelial cells reflect diffuse, low level light and appear 'aceto-white' against a bluish normal mucosa background. Toluidine blue solution may be used in addition to mark out the 'aceto-white' lesions for biopsy once the light source is removed (ViziLite Plus^R). Unfortunately, whilst such systems may enhance the visibility of clinically identifiable lesions by improving sharpness and brightness, this hardly justifies the additional system costs. Similarly, they also fail to identify clinically undetectable lesions, have no predictive value in determining lesion behaviour, and do not discriminate between inflammatory, traumatic or PMD lesions. In addition, the presence of distracting visual highlights may unfortunately impair rather than enhance an oral examination⁴.

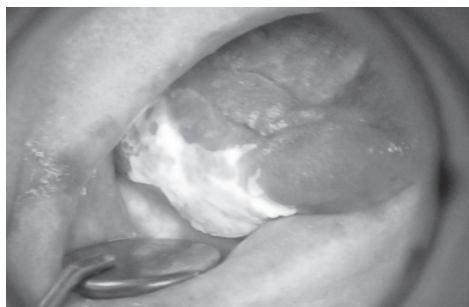
Alternatively, The VELscope^R (Visually Enhanced Lesion Scope; LED Dental Inc, White Rock, British Columbia, Canada) is a readily portable hand-held device facilitating direct visualization of the oral cavity, utilizing the principle of *autofluorescence*. In essence, following high-intensity light excitation, autofluorescence is produced by endogenous fluorophores such as tissue matrix molecules or intracellular collagen, elastin and keratin. In dysplastic tissue, increased cellular DNA, increasing epithelial thickness,



A



B



C

Figure 5.1: The VELscope[®] showing (A) hand-held device used in clinic (B) dark appearance of dysplastic buccal mucosa and (C) white hyperkeratotic lateral tongue leukoplakia

altered collagen content and increased vascularity alter the concentration of fluorophores and change the pattern of light scattering and absorption, attenuating excitation and resulting in visible colour change. The clinical application of the VELscope^R is illustrated in Figure 5.1. Under intense 400-460nm blue light excitation, normal mucosa emits a pale green autofluorescence when viewed through the hand-piece filter, whilst dysplastic or neoplastic tissue appears dark due to decreased fluorescence. Hyperkeratotic leukoplakic lesions often appear brilliantly white, however, irrespective of dysplastic change, whilst scars from previous biopsy or surgical sites may exhibit a dark appearance due to stromal neovascularization. Clearly, the non-specific nature of such change casts doubt over the reliability of the VELscope^R, although the technique may have a role in the refinement of examination during assessment and treatment of PMD in specialist practice¹⁶.

Tissue fluorescence spectroscopy is a technique in which a small optical fibre, producing different excitation wavelengths, is applied to oral mucosa and resulting spectra of reflected tissue fluorescence objectively analyzed by computer. The practical disadvantage is the small probe size, which limits its use to localized lesions, and it is only really of use once an abnormal lesion has been found on prior visual examination⁴.

In *photodynamic diagnosis*, a 5-aminolevulinic acid oral rinse stimulates intracellular accumulation of highly fluorescent protoporphyrin IX, particularly in dysplastic and malignant tissue, which is then excited by 405nm light exposure. Once again, such techniques are somewhat limited in both their effectiveness and general applicability^{4,12}.

Optical Visualization

A wide-range of emerging optical visualization and diagnostic technologies including Raman spectroscopy, elastic scattering and diffuse reflectance spectroscopy, narrow-band imaging, optical coherence tomography, and confocal laser or reflectance microscopy have all been applied to the analysis of oral dysplastic and neoplastic tissue but, disappointingly, rarely provide data as reliable or as informative as conventional diagnostic procedures¹².

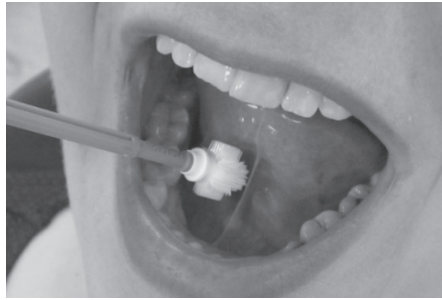
Exfoliative Cytology

Exfoliative cytology and subsequently cytodiagnosis refer to techniques whereby individual cells are loosened from their tissue of origin and then transferred to cytology slides, for microscopic analysis and interpretation. Whilst effective sampling of exfoliated oral epithelial cells for examination has previously proved unreliable, newer collection devices including a range of cytobrushes have been developed to facilitate full-thickness sampling of stratified epithelium. This is important because dysplastic change arises in basal epithelial layers, and cells may lose dysplastic characteristics as they mature during travel to superficial layers, with nuclei becoming less visible and increasing keratinisation rendering dysplasia grading less reliable⁴.

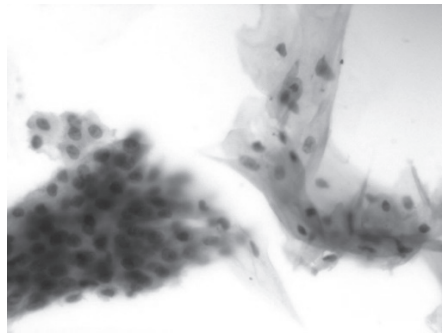
The Orcellex^R brush (Rovers Medical Devices BV., Oss, the Netherlands) was developed with a specially designed head comprising 5 segments of high-density fibres for optimal cell collection, storage and predictable release of cells from multiple layers of oral epithelium. In clinical practice, the brush head is firmly placed against the mucosa and rotated 10 times, then detached and transferred in BD SurePathTM ethanol-based preservative fluid for transfer to the laboratory. The use of liquid-based cytology (LBC), rather than conventional glass slide smears, improves cell distribution and produces thin-layer preparations ideal for cytological evaluation. The use of the Orcellex^R brush in harvesting cells from the floor of the mouth and the resultant cytological appearance are illustrated in Figure 5.2¹⁷.

As premalignant changes will occur at the molecular level before they are seen microscopically or clinically, additional biomolecular investigations including immunocytochemistry, HPV testing, DNA-ploidy, RNA and microRNA analyses of LBC samples may all contribute to a minimally invasive genetic screening approach for both detection and monitoring of PMD, especially following interventional treatment^{17,18}.

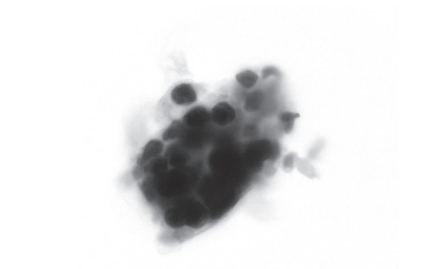
In a study analysing 310 PMD patients, the Orcellex^R brush technique was confirmed as an effective diagnostic adjunct, readily available in clinic, easy to use, minimally invasive and efficient in trans-epithelial cell collection. The brush design facilitated application to all oral sites and patient acceptance was high¹⁷.



A



B



C

Figure 5.2: Use of the Orcellex^R Brush (A) as applied during floor of mouth sampling, (B) Papanicolaou stained thin-layer LBC preparation showing dyskaryotic cells under microscopy (x40) and (C) high Ki67 labelling seen in severe dyskaryosis (x100).

Whilst cytological diagnoses of cellular atypia and mild, moderate or severe dyskaryosis correlate well with their dysplastic histopathological counterparts, direct comparison is not always feasible due to variations in cytology terminology and lack of epithelial-connective tissue structural hierarchy, which is of course essential for histopathological characterization, particularly in oral lichenoid lesions and for confirmation of invasive SCC^{4,17}.

It remains to be seen whether exfoliative cytology will truly develop from a research tool into a generally applicable diagnostic instrument. It may well have a significant adjunctive role, however, in the assessment and monitoring of PMD in a specialist clinic environment, especially for widespread mucosal abnormalities, multiple or persistent lesions and for non-compliant or irregular clinic attenders where repeat biopsies may be inconvenient, uncomfortable or impractical for patients.

Salivary Biomarkers

Measurement of potential biomarkers for PMD or SCC progression within saliva should theoretically provide rapid and non-invasive diagnostic adjunctive techniques. Unfortunately, to date, analyses remain experimental in nature only, and there is considerable risk of contamination from infective, inflammatory and extrinsic agents, all of which of course abound in the oral environment and may confound diagnostic accuracy¹².

Conclusions

In recent years, there has been a rapid development of diagnostic aids as potential screening or case finding tools, but none have been scientifically validated, clinical reporting of their use remains anecdotal, and there is no strong evidence to support the application of any one particular technique. It is perhaps quite telling that recent systematic reviews do not recommend adjunctive aids over the conventional approach of visual examination, scalpel biopsy and histopathological assessment, although there is recognition that cytological analysis does show promise as an additional technique to monitor suspicious mucosal lesions^{11,15}.

In order to improve patient morbidity and mortality from oral cancer, early detection and treatment of PMD remains an essential diagnostic prerequisite. Thorough and methodical visual examination of oral mucosa

by an experienced clinician, using sound clinical judgement, supplemented by targeted incisional biopsy for histopathological classification clearly remains the 'gold standard' for diagnosis. Dental clinicians should thus remain alert for signs of PMD and SCC in all patients when performing routine oral and dental examinations, especially so for patients who chronically over use tobacco and alcohol products¹⁹.

It is important, of course, to recognise the limitations of conventional diagnostic techniques, and it is indeed unfortunate that PMD demonstrate such heterogeneity in their clinical presentation, such that, even with a high index of suspicion, many lesions remain unrecognised or mistaken for benign conditions on examination. In the future, molecular and genetic profiling of potentially malignant tissue will undoubtedly supplement, and may ultimately exceed, existing clinical and histopathological assessments¹⁹⁻²¹.

A comprehensive clinical diagnosis of PMD requires more than ascribing terms and nomenclature to a particular oral lesion. A thorough diagnosis should, ideally, identify and categorise the patient and their lesion into either a 'high risk' or 'low risk' category for disease progression and malignant transformation, describe both the site and extent of mucosa involved and detail the provisional incisional biopsy histopathology report. Assessment of the potential for field change and multiple lesion disease should also be carried out and documented.

References

1. Brocklehurst PR, Baker SR, Speight PM. A qualitative study examining the experience of primary care dentists in the detection and management of potentially malignant lesions. 1. Factors influencing detection and the decision to refer. *BDJ* 2010 208: E3.
2. McGurk M, Scott SE. The reality of identifying early oral cancer in the general dental practice. *BDJ* 2010 208: 347-351.
3. Kujan O, Glennly A-M, Duxbury J, Thakker N, Sloan P. Evaluation of screening strategies for improving oral cancer mortality: a Cochrane systematic review. *Journal of Dental Education* 2005 69: 255-265.
4. Thomson PJ, Goodson ML. Diagnostic Methods. In: PJ Thomson (ed) *Oral Precancer – Diagnosis and Management of Potentially Malignant Disorders*. Chichester: Wiley-Blackwell; 2012. P75-92. ISBN 978-1-4433-3574-3.

5. Thomson PJ, Wylie J. Interventional laser surgery: an effective surgical and diagnostic tool in oral precancer management. *International Journal of Oral & Maxillofacial Surgery* 2002 31: 145-153.
6. Thomson PJ. Field change and oral cancer: new evidence for widespread carcinogenesis? *International Journal of Oral & Maxillofacial Surgery* 2002 31: 262-266.
7. Thomson PJ, Hamadah O. Cancerisation within the oral cavity: the use of 'field mapping biopsies' in clinical management. *Oral Oncology* 2007 43: 20-26.
8. Lingen MW, Kalmar JR, Karrison T, Speight PM. Critical evaluation of diagnostic aids for the detection of oral cancer. *Oral Oncology* 2008 44: 10-22.
9. Fedele S. Diagnostic aids in the screening of oral cancer. *Head & Neck Oncology* 2009 1: 5. doi: 10.1186/1758-3284-1-5.
10. Lingen MW, Abt E, Agrawal N, Chaturvedi AK, Cohen E, D'Souza G, Gurenlian J, Kalmar JR, Kerr AR, Lambert PM, Patton LL, Sollecito TP, Truelove E, Tampi MP, Urganhart O, Banfield L, Carrasco-Labra A. Evidence-based clinical practice guideline for the evaluation of potentially malignant disorders in the oral cavity. *JADA* 2017 148: 712-727.
11. Lingen MW, Tampi MP, Urganhart O, Abt E, Agrawal N, Chaturvedi AK, Cohen E, D'Souza G, Gurenlian J, Kalmar JR, Kerr AR, Lambert PM, Patton LL, Sollecito TP, Truelove E, Banfield L, Carrasco-Labra A. Adjuncts for the evaluation of potentially malignant disorders in the oral cavity. *JADA* 2017 148: 797-813.
12. Liu D, Zhao X, Zeng X, Dan H, Chen Q. Non-invasive techniques for detection and diagnosis of oral potentially malignant disorders. *Tohoku Journal of Experimental Medicine* 2016 238: 165-177.
13. Su WW, Yen AM, Chiu SY, Chen TH. A community-based RCT for oral cancer screening with toluidine blue. *Journal of Dental Research* 2010 89: 933-937.
14. Petruzzi M, Lucchese A, Baldoni E, Grassi FR, Serpico R. Use of Lugol's iodine in oral cancer diagnosis: an overview. *Oral Oncology* 2010 46: 811-813.
15. Macey R, Walsh T, Brocklehurst P, Kerr AR, Liu JL, Lingen MW, Ogden GR, Warnakulasuriya S, Scully C. Diagnostic tests for oral cancer and potentially malignant disorders in patients presenting with clinically evident lesions. *Cochrane Database of Systematic Reviews* 2015 5 CD010276.

16. Goodson ML, Thomson PJ. Tissue autofluorescence and the diagnosis and management of oral potentially malignant disorders. *Journal of Oral and Maxillofacial Surgery* 2014 Photon 117: 205-214.
17. Goodson ML, Smith DR, Thomson PJ. Efficacy of Oral Brush Biopsy in Potentially Malignant Disorder Management. *Journal of Oral Pathology & Medicine* 2017 46: 896-901.
18. Bremmer JF, Graveland AP, Brink A, Braakhuis BJ, Kuik DJ, Leemans CR, Bloemena E, van der Waal I, Brakenhoff RH. Screening for oral precancer with noninvasive genetic technology. *Cancer Prevention & Research* 2009 2: 128-133.
19. Richards D. Clinical recommendations for oral cancer screening. *Evidence-Based Dentistry* 2010 11:101-102.
20. Gillenwater A, Papadimitrakopoulou V, Richards-Kortum R. Oral premalignancy: new methods of detection and treatment. *Current Oncology Reports* 2006 8: 146-154.
21. Kao SY, Chu YW, Chen YW, Chang KW, Liu TY. Detection and screening of oral cancer and pre-cancerous lesions. *Journal of Chinese Medical Association* 2009 72: 227-233.

CHAPTER SIX

MANAGEMENT

'...communication, examination, evaluation, diagnosis, prognosis and intervention...'

Introduction

Having established a comprehensive PMD diagnosis for an individual patient, one of the principal difficulties in determining an appropriate management strategy is, quite frankly, the lack of available, properly agreed and defined treatment protocols. Treatments are rarely evidence based, unfortunately, but are instead strongly influenced by individual clinician preference and experience. There is a lack of clinically relevant randomised controlled trials, and most data come from uncoordinated, observational studies. As we have seen, the natural history of PMD remains poorly defined and unpredictable, so that uncertainty haunts all clinical management decisions. Specific problems inherent in the contemporary diagnosis and management of PMD were previously discussed in Chapter 3 and usefully summarized in Table 3.1¹.

As previously observed, Brennan et al² believed that, due to a lack of randomized controlled trials, no satisfactory evidence-based recommendations could be made for either surgical or non-surgical treatment interventions for dysplastic oral lesions. We therefore introduced and defined a number of salient management goals for PMD treatment, as initially reported in Chapter 3, but in addition during Chapter 5 recognised that, despite our best endeavours, precise and accurate diagnosis may be far from straightforward in clinical practice. However, our ability to identify early malignant change within individual oral mucosal lesions together with elimination of dysplastic tissue and prevention of further PMD disease are clearly the prerequisites for any successful treatment, and provide the basis for our hypotheses that an appropriate intervention can halt the process of carcinogenesis.

Perhaps the most fundamental dilemma in PMD management remains whether to observe patients or to intervene and offer them treatment. Whilst the reader should be in little doubt regarding the author's preference for an appropriate intervention, management has, for many years, been controversially polarised between surgical excision to remove identifiable mucosal lesions and more conservative medical or observational techniques. Although the definition of potential malignancy intuitively warrants some form of targeted management, rather than passive observation, the diverse range of treatment options quoted in the literature conspire to confound individual treatment decisions^{3,4}.

In this chapter, therefore, we will review and attempt a critique of the available treatment modalities for PMD. Table 6.1 lists the relevant approaches to treatment.

Table 6.1: Treatment Modalities for PMD Management

Risk Factor Identification and Elimination
Clinical Observation of Identified Mucosal Lesions
Medical Treatment
Surgical Excision

Risk Factor Identification and Elimination

As described in Chapter 4, risk factor education and identification in an individual patient ideally followed by their complete elimination provide the basis for all PMD management approaches. Whilst it is, of course, disappointing how often these strategies prove unsuccessful in the long-term, efforts to assist patients in understanding their personal cancer risk and empowering them to adjust risk factor behaviour may yet prove our most effective preventive intervention; indeed, such approaches are to be encouraged during all patient consultations¹.

Clinical Observation

Traditional clinical observation protocols, which comprise initial lesion recognition and diagnosis by incision biopsy, photography, routine oral inspection and patient monitoring, have often formed the mainstay of PMD management. Unfortunately, this has led in many cases to, effectively, passive observation of SCC development in a previously identified 'at risk' patient, which seems both self-defeating and highly inappropriate for a 21st Century patient-care pathway. A period of clinical

observation may, however, be very appropriate for patients with low grade dysplasia who stop smoking, who are prepared to address other relevant risk factor behaviour and are able to attend for regular clinical review. Whilst it is recognised that such PMD cases can improve and lesions regress following smoking cessation, it is important that this is carefully monitored. Failure of existing mucosal disease to resolve may mean that the patient has been unable to stop smoking or perhaps, more significantly, the identification of persistent PMD disease that represents significant and irreversible dysplastic change; it would be unwise to continue to merely observe such cases¹.

Medical Treatment

Numerous medical treatments and therapies have been proposed over many years in an attempt to facilitate management of PMD, including both local and systemic chemo-preventive agents. These medications, the most commonly utilised are summarised in Table 6.2, have included vitamins, carotenoids, chemotherapy drugs, anti-inflammatory and antimicrobial agents. Their proposed mode of actions have included anti-oxidant and anti-angiogenesis properties, together with targeted epithelial homeostasis and tissue repair mechanisms¹.

Table 6.2: Principal Medical Treatments Used in PMD Management

Vitamins A, C and E
Retinoids
Beta Carotene
Lycopene
Ketorolac
COX-2 Inhibitors
Bleomycin
Green Tea
Anti-Virals / Anti-Fungals
EGF Receptor Blockade
Curcumin

Systematic review of medical interventions for PMD have ultimately proven unhelpful in determining realistic management strategies and very few relevant randomised, controlled trials exist in the literature. It is also notable that little in the way of clinical benefit has ever been shown following medical treatment. There is no evidence, for example, of effective long-term clinical resolution of any mucosal abnormality, no

significant prevention of malignant transformation of existing lesions and no reduction at all in either disease incidence or recurrence compared with observation alone or indeed placebo treatment. Furthermore, many clinical trials have been undertaken on very small numbers of patients over short study durations, usually with cases followed up for only a few months rather than the several years post-treatment, which are so necessary to accurately characterise malignant transformation risk. Where clinical improvement was observed during the trial, lesions often worsened on cessation of therapy and, because no clear definitions of treatment goals or end-points were established, the overall significance of these treatments remains unclear⁵⁻⁷.

In addition, side effects have been described in many patients that actually interfered with compliance and prompted withdrawal from treatment; these included dermatitis, pruritus, skin discolouration, headaches, muscular pain, cardiovascular thrombosis and teratogenicity. Lee et al⁸ also reported a high, 31.4%, malignant transformation rate in oral leukoplakias that were treated with isotretinoin and/or β -carotene, emphasizing a truly significant limitation for medical therapy. Interestingly, only 2 to 4% of UK oral and maxillofacial surgeons reported that they would ever consider using chemo-preventive agents in PMD treatment, demonstrating I think the contemporary redundancy of such treatment^{9,10}.

Perhaps of even greater significance, however, is the realisation that all pre-medical treatment diagnoses rely entirely upon incisional biopsy diagnoses, which we now recognise as being provisional in nature only. As whole lesion examination is necessary for a definitive histopathological diagnosis, it is not unreasonable, therefore, to view medical treatments as fundamentally flawed therapies applied to diseased and abnormal mucosa in the absence of an accurate and reliable pathological diagnosis; a wholly unsatisfactory approach to modern clinical management^{1,11}.

Surgical Excision

A therapeutic approach that intervenes effectively to diagnose SCC at a 'pre-malignant' or early invasive phase and thereby also institutes curative treatment is surely to be embraced and encouraged. It is perhaps self-evident that only a surgical intervention will effectively remove localized areas of abnormal mucosa. PMD are, of course, mucosal conditions only and do not require the aggressive treatment modalities reported in Chapter

2 so necessary for removal and/or destruction of invasive OSCC, and are therefore obvious targets for interventional surgical management. Critics of surgery, however, correctly observe that no randomised controlled trials of surgical intervention have ever been carried out, particularly ones in which surgery is directly compared with a non-intervention arm. Nonetheless, surgery is often the clinicians' first choice for PMD management particularly when lesions exhibit high-grade dysplasia or there is suspicion of early cancer change. Table 6.3 lists the commonly available surgical approaches to PMD treatment¹.

Table 6.3: Surgical Approaches to PMD Management

Scalpel Excision
Cryotherapy
Laser Surgery
Photodynamic Therapy

Scalpel Excision

Surgical intervention by conventional scalpel excision and primary closure of small defects, or by mucosal or skin grafting techniques for large oral defects has rarely proved popular with clinicians or patients, primarily due to localised post-surgery scarring, contracture and deformity and the frequent failure of skin grafts to take reliably within the unforgiving oral environment. Although very small, isolated mucosal lesions may be excised in this way, this is rarely the manner in which PMD presents in practice. In particular, attempts to manage widespread or multi-focal PMD disease with such an approach is doomed to repeated failure and is simply not recommended¹.

Cryotherapy

Cryotherapy is a specialized technique involving the localized destruction of diseased tissue by the application of extreme cold, usually via liquid nitrogen. Although popular in the past for treating soft tissue oral lesions, it is nowadays less commonly used and it is not a recommended technique for either PMD or SCC treatment. Significant post-operative pain and swelling results from tissue damage following application of the cryoprobe, PMD are rarely if ever successfully or completely destroyed and, of course, no excision biopsy is undertaken to establish a definitive diagnosis. This, therefore, leaves partially treated dysplastic tissue, or even occult

SCC, in-situ that can then be ‘stimulated’ by a response to tissue damage that creates far more aggressive behaviour. Both high recurrence and increased malignant transformation rates have been reported following the use of cryotherapy which certainly appears to support these concerns^{1,5}.

Laser Surgery

Interventional therapies based upon laser surgery have thus evolved following the demonstrable failure of observational or medical therapies and the limitations of conventional surgery in treating oral cavity PMD. Laser, the acronym for ‘light amplification by stimulated emission of radiation’ delivers monochromatic, coherent waves of light energy to the target tissue via fibre-optic systems or alternatively a series of articulated arms and mirrors. A photo-thermal reaction occurs when laser light interacts with tissue; between 60 to 100°C coagulation produces tissue necrosis and/or facilitates localised haemostasis, whilst at 100°C and above vapourisation allows the surgeon to incise tissue, and to either resect or ablate lesions. The carbon dioxide (CO₂) laser is the author’s preferred modality to treat oral mucosal disease, because CO₂ generated laser light is within the mid-infrared range (10,600nm), close to the spectroscopic absorption peak for water, rendering successful interaction of all oral soft tissues with the laser beam. Figure 6.1 illustrates a typical example of a surgical laser¹.



Figure 6.1: CO₂ laser comprising hand-held delivery device connected to generation chamber via a series of articulated arms and mirrors

It is pertinent, at this point I think, to describe in some detail the technique of interventional laser surgery and the surgical procedure in clinical practice is usefully illustrated in Figure 6.2, which shows the excision of a PMD lesion arising on buccal mucosa. A hand-held delivery device, with a laser spot size of 1mm diameter, is used. As CO₂ laser light is invisible, a helium-neon aiming beam facilitates operator guidance to the target and an evacuation system removes smoke and debris from the surgical site. Single pulse laser mode is used to outline resection margins, which are situated at least 5mm outside the apparent clinical margins of the target lesion. Although excision margin placement is based upon subjective judgement by the operating surgeon, adjunctive visual examination techniques such as VELscope^R, have not proved helpful in influencing the intra-operative siting of resection margins or to significantly improve the achievement of disease-free resection margins¹. Pulse marks are connected using the laser in a continuous mode, deepening the incision to approximately 5mm in the sub-mucosal plane. Depth of excision is ultimately influenced by the anatomical site, less when involving thin floor of mouth tissue or resections overlying alveolar bone, and by the extent of known dysplasia; severe dysplastic lesions are resected where possible at a deeper level due to the risk of foci of micro-invasive or early invasive SCC co-existing. The whole specimen is then excised by undercutting at a constant depth. Following excision, the surgical bed and all peripheral margins are vapourised using a defocused laser beam to eliminate residual disease, facilitate haemostasis and to effectively extend the treatment field beyond the surgical excision zone. The excision specimen is sutured at one or two points to aid later tissue orientation, and is then placed in formal saline solution prior to forwarding to the pathology laboratory for histopathological analysis.

Clinically, there is little in the way of immediate post-operative pain, swelling or discomfort and patients may take clear fluids straight away, followed 2 hours later by a gradually increasing soft diet. Excised areas heal well by secondary intention, with a fibrinous cream coloured coagulum forming over the wound within the first few days followed by re-epithelialization from surrounding wound edges usually complete within 4 to 6 weeks. Due to the specific effects of laser vapourisation, a lack of mechanical trauma during surgery and the absence of wound suturing, scarring is usually minimal and excellent aesthetic and functional results ensue. Figure 6.3 documents post-laser surgery healing after excision of a PMD from lateral tongue mucosa.

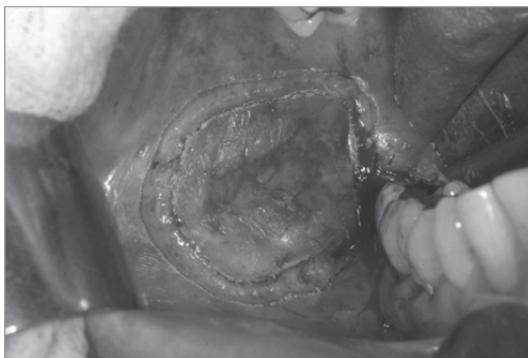
Whilst excision techniques are always preferred, there is a limited role for ablation therapy in which surface mucosa only is destroyed, to a varying depth selected by the surgeon and dependent upon the pathological lesion treated, using a defocused laser beam. Although tissue is not excised for histopathological examination and abnormal basal epithelium may be left in situ, ablation may be used to treat non-dysplastic or mildly dysplastic lesions on tightly bound down alveolar or gingival tissue, where excision can result in slow or non-healing mucosa with painful areas of denuded and ultimately de-vitalised alveolar bone¹. Figure 6.4 illustrates laser ablation destruction of a small patch of mildly dysplastic proliferative verrucous leukoplakia arising on the posterior maxillary gingiva.



A



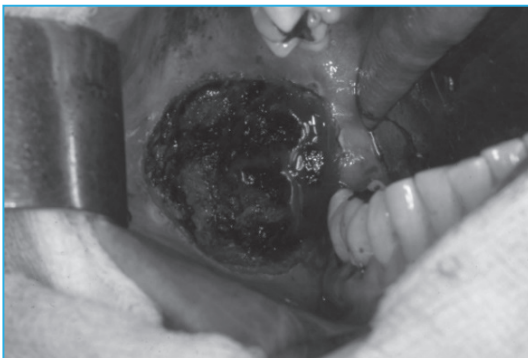
B



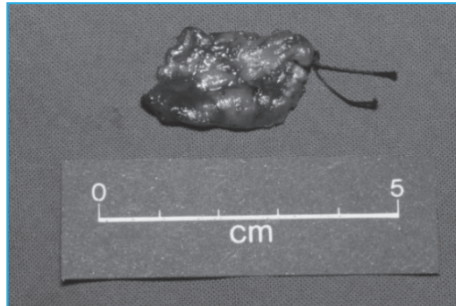
C



D



E



F

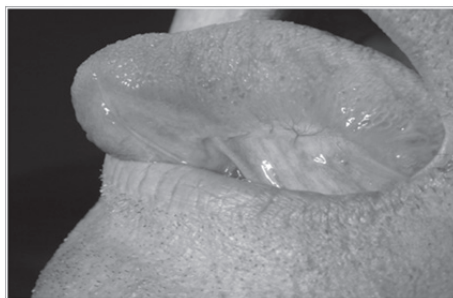
Figure 6.2: Laser Excision showing (A) buccal erythroleukoplakia which showed severe dysplasia on incision biopsy, (B) excision margin marked 5mm outside visible mucosal disease, (C) excision margin established, (D) dysplastic lesion resected at constant sub-mucosal level, (E) post-excision laser vapourisation of lesion margins and base to eliminate residual disease and facilitate haemostasis, and (F) excision specimen for histopathological assessment.



A



B



C

Figure 6.3: Healing Post-Laser Surgery (A) immediately following excision of dysplastic lateral tongue lesion, (B) 2 weeks post-surgery with creamy fibrinous exudate and pink, healthy granulation tissue, and (C) healing at 2 months with minimal scarring, good appearance and excellent functional mobility.



A



B

Figure 6.4: Laser Surgery Ablation (Gingiva) showing (A) the pre- and (B) the post-ablation appearance of posterior maxillary gingiva, following superficial destruction of a patch of mildly dysplastic proliferative verrucous leukoplakia.

The CO₂ laser thus offers precise mucosal lesion excision, full histopathological assessment of tissue specimens, minimal post-operative morbidity and, importantly, in the requirement for post-treatment follow-up helps facilitate a coordinated and structured patient surveillance strategy. Specific technical advantages of laser include a relatively bloodless surgical field, improved intra-operative accuracy, reduced post-operative pain and swelling, rapid mucosal re-epithelialization, limited scarring, reduction in damage to adjacent tissues, low complication rates and the ability to repeat treatment where necessary^{1,11}.

Although demonstrably effective, specific evidence is lacking, however, to confirm the efficacy of CO₂ laser surgery in reducing the risk of malignant transformation in treated PMD patients. Similarly, limited data are available to determine the length of patient follow up or the optimal time intervals between clinic appointments to monitor patients safely post-treatment.

Perhaps the biggest criticism of interventional laser surgery is the lack of evidence-based treatment protocols and meaningful randomized trials of treatment. In a small, comparative cohort study we therefore assessed the results of surgical intervention in 78 PMD patients deemed at 'high risk' of malignant transformation with observational management in 39 'low risk' cases and demonstrated that, whilst 64% of laser treated patients were disease free 3-years post-intervention, 77% of observed lesions persisted. Clearly limited in significance by its non-randomization, the study nonetheless helps support the efficacy of laser as a treatment intervention¹².

Other lasers in use for oral surgery include the neodymium:yttrium-aluminium-garnet (Nd:YAG) or the potassium-titanyl-phosphate (KTP) and a number of various argon and diode variants. There is little evidence to suggest that any one of these is more or less effective than another, and all have their advocates. The CO₂ laser, however, is probably the most utilised and studied in oral surgical practice.

Photodynamic therapy (PDT)

This is a specialised form of intervention, which relies on cellular destruction by a cold photochemical reaction following activation of a photosensitising drug, such as aminolevulinic acid or temoporfin, by low-power visible light. This technique has been advocated as a non-invasive PMD treatment although remains primarily a tool for palliative treatment of advanced head and neck SCC. A number of observational studies have reported variable success rates using PDT to treat oral leukoplakia, but with inconsistent reporting regarding recurrent disease and to date very limited, often only between 3 to 6 months, or in some cases actually no follow up data at all⁷.

Conclusions

The early diagnosis of oral cancer and the management of PMD are areas of contemporary clinical practice in which variability in decision-making and a lack of high-quality evidence has confounded treatment initiatives. The confusion that plagues the literature was well summarised by van der Waal¹³ who, on the one hand opinions that local lesion recurrence may be common following surgical treatment of leukoplakia and that neither intervention nor long term clinic follow-up is effective in reducing the risk of cancer development, whilst on the other hand importantly emphasizes that most PMD patients actually prefer treatment intervention, and has therefore decided to recommend surgical excision of localised, well-circumscribed oral mucosal lesions followed by long-term, specialist clinic follow-up.

Shiu & Chen¹⁴ attempted a systematic literature review to determine the effectiveness of treatment interventions for oral leukoplakia, but found such wide variation in diagnostic criteria, an extensive heterogeneity of proposed treatment methodologies and such disorganised patient compliance and follow-up data that they felt it was quite impossible to quantify their analyses in any meaningful way. Lodi et al⁵ previously stated that, whilst many quoted treatment interventions may be effective in initially resolving individual leukoplakic lesions, clinical relapse, adverse effects and limited evidence regarding prevention of malignant transformation limited the usefulness of current techniques. Wan et al¹⁵ observed that following successful primary therapy, local recurrence of leukoplakia and the development of new-site (or second primary)

leukoplakias accounted for the majority of unfavourable events experienced by patients.

Perhaps of greatest significance is the realization that, owing to the limited relevance of existing clinical trial data, systematic literature reviews and meta-analyses have repeatedly failed to answer the fundamental diagnostic and management dilemmas inherent in PMD treatment. Despite the negative observations and the limitations in evidence-based guidelines, a number of recommendations have been made for PMD treatment. In 2011, for example, ENT-UK (British Association of Otorhinolaryngology-Head & Neck Surgery) published multidisciplinary management guidelines for head and neck cancer which included advice upon targeted biopsy and histopathological assessment of potentially malignant lesions, advice for affected patients to reduce tobacco and alcohol use, surgical excision when lesion size and post-operative function allow, together with long term clinic surveillance. It is probably true that surgical excision of potentially malignant oral lesions should now be regarded as the preferred treatment modality in contemporary practice, although it remains important to confirm the overall efficacy of the technique^{1,16,17}.

Combining a defined surgical intervention with detailed patient profiling and active clinic surveillance, may thus provide a particularly well-coordinated and methodical clinical management protocol with the potential to stall or even halt the on-going process of oral carcinogenesis. It is probably of especial relevance for those patients who exhibit progressive PMD disease or for those deemed to be at 'high risk' of cancer development. One feature which is certainly agreed by contemporaneous authors, and is central to effective PMD management, is that regular patient follow up and repeated, detailed clinical examination remains mandatory for all PMD patients irrespective of the mode of proposed treatment^{1,4}.

References

1. Thomson PJ. Management of Oral Precancer. In: PJ Thomson (ed) Oral Precancer – Diagnosis and Management of Potentially Malignant Disorders. Chichester: Wiley-Blackwell; 2012. p107-137.
2. Brennan M, Migliorati CA, Lockhart PB, Wray D, Al-Hasimi I, Axell T. Management of oral epithelial dysplasia: a review. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2007 103 (suppl 1): s19.e1-s19.e12.

3. Carnelio S, Rodrigues GS, Shenoy R, Fernandes D. A brief review of common oral premalignant lesions with emphasis on their management and cancer prevention. *Indian Journal of Surgery* 2011 73: 256-261.
4. Mandal S, Agrawal R, Salgotra V, Kohli S. Management of potentially malignant disorders of oral cavity: role of medical therapies. *International Journal of Dental and Health Sciences* 2014 1: 187-193.
5. Lodi G, Sardella A, Bez C, Demarosi F, Carrassi A. Interventions for treating oral leukoplakia. *Cochrane Database of Systematic Reviews* 2006 Issue 4. DOI: 10.1002/14651858.CD001829.pub3.
6. Lodi G, Porter S. Management of potentially malignant disorders: evidence and critique. *Journal of Oral Pathology & Medicine* 2008 37 : 63-69.
7. Ribeiro AS, Salles PR, da Silva TA, Mesquita RA. A review of the nonsurgical treatment of oral leukoplakia. *International Journal of Dentistry* 2010 doi:10.1155/2010/186018.
8. Lee J-J, Hong WK, Hittelman WN, Mao L, Lotan R, Shin DM, Benner SE, Xu X-C, Lee JS, Papadimitrakopoulou, Geyer C, Perez C, Martin JW, El-Naggar AK, Lippman SM. Predicting cancer development in oral leukoplakia: ten years of translational research. *Clinical Cancer Research* 2000 6: 1702-1710.
9. Marley JJ, Cowan CG, LameyP-J, Linden GJ, Johnson NW, Warnakulasuriya KAAS. Management of potentially malignant oral mucosal lesions by consultant UK oral and maxillofacial surgeons. *British Journal of Oral & Maxillofacial Surgery* 1996 34: 28-36.
10. Kanatas AN, Fisher SE, Lowe D, Ong TK, Mitchell DA, Rogers SN. The configuration of clinics and the use of biopsy and photography in oral premalignancy: a survey of consultants of the British Association of Oral and Maxillofacial Surgeons. *British Journal of Oral & Maxillofacial Surgery* 2011 49: 99-105.
11. Thomson PJ, Wylie J. Interventional laser surgery: an effective surgical and diagnostic tool in oral precancer management. *International Journal of Oral & Maxillofacial Surgery* 2002 31: 145-153.
12. Thomson PJ, Goodson ML, Hamadah O. Cohort studies in oral precancer management: intervention vs. observation. *Oral Oncology* 2009 Suppl 3: 1 (116).
13. van der Waal I. Oral potentially malignant disorders: is malignant transformation predictable and preventable? *Med Oral Patol Oral Cir Bucal* 2014 19: e386-390.

14. Shiu MN, Chen TH. Intervention efficacy and malignant transformation to oral cancer among patients with leukoplakia. *Oncology Reports* 2003 10: 1683-1692.
15. Wan Y, Liang F, Nakasone T, Sunakawa H. Development of new leukoplakias and leukoplakia-associated second/multiple primary oral cancers: A case report and literature review. *Journal of Oral & Maxillofacial Surgery, Medicine & Pathology* 2014 26: 166-169.
16. van der Waal I. Potentially malignant disorders of the oral and oropharyngeal mucosa; terminology, classification and present concepts of management. *Oral Oncology* 2009 45: 317-323.
17. Gomes CC, Gomez RS. Oral leukoplakia: what is achieved by surgical treatment? *Annals of Oral & Maxillofacial Surgery* 2013 1: 9.

CHAPTER SEVEN

OUTCOMES

‘...the way something turns out...’

Introduction

Clinical outcome may be defined as a measurement of how patients feel, function or survive following disease recognition and treatment. Accurate, predictive assessment of PMD behaviour remains elusive in clinical practice and yet establishing and defining outcomes following treatment is fundamental to developing effective management protocols. Whilst the most significant and adverse clinical outcome for PMD is undoubtedly malignant transformation, available literature on outcome is confused in its use of terminology, varying types of dysplastic and non-dysplastic lesions studied, inconsistent treatment decisions and uncoordinated patient follow-up, with many published studies highly subjective and entirely retrospective in nature¹⁻³.

These observations render systematic review and meta-analysis extremely complicated, if not actually impossible. Mehanna et al⁴, for example, attempted a systematic review of 2837 PMD articles, ultimately rejecting the majority on non-eligibility grounds and analysing only 14 although these were also criticised for their inherent heterogeneity. Concentrating solely on malignant transformation, a mean transformation rate of 12.1% over a period of 4.3 years was calculated for dysplastic oral lesions. The risk for SCC development appeared greatest in high-grade dysplasia, but reduced for cases undergoing surgical excision⁴.

It is important to also note a consensus observation in contemporary literature that none of the perceived important and standard clinico-pathological factors routinely reported, including clinical appearance of individual lesions, anatomical site of origin, histopathological assessment, patient risk factor behaviour, age or gender help to accurately predict clinical outcome^{3,4}.

In the past, general observations regarding PMD outcome estimated that approximately 40% of dysplastic oral lesions change very little or progress only slightly over time, whilst 20% may regress spontaneously; a further 20% increase in size and extent, with the remaining 20% at risk of malignant progression. As overall estimates, based upon disparate population studies of both treated and non-treated lesions, these are not at all helpful in informing individual patient management decisions, although it is generally agreed that long-term follow-up for all PMD patients is essential^{1,4}.

Clinical outcome will also be influenced, if not actually determined, by the specific management applied to individual cases and the fundamental problem with PMD studies remains the lack of internationally accepted treatment guidelines, poor evidence base in the literature and the paucity of relevant prospective, randomised clinical trials comparing different management strategies.

In this short chapter, therefore, we will attempt to comprehensively define specific, identifiable clinical outcome categories that follow on from the diagnosis and treatment of PMD, and consider how these might then be utilised in meaningful analyses of patient treatment data.

Defining Clinical Outcomes

It is clearly important to define the parameters by which clinical outcome and evolution of PMD disease should be assessed. A list of terms and their definitions are thus summarised in Table 7.1; these are based upon the author's personal experience of documenting PMD patients' progress over many years post-intervention^{1,5,6}.

Disease Free Status (Clinical Resolution)

Disease Free (DF) Status or clinical resolution is the successful surgical removal or regression of a PMD resulting in clinically normal looking oral mucosa with no further PMD arising either at the site of previous disease or elsewhere within the oral cavity or oro-pharynx.

Table 7.1: Definitions of PMD Clinical Outcome

<i>Term</i>	<i>Definition</i>
Disease Free (Clinical Resolution)	Patient is clinically free of PMD
Persistent Disease	PMD persists clinically despite interventional treatment
Recurrent Disease (Same Site Recurrence)	PMD recurs at same-site following previous excision
Further Disease (New Site Recurrence)	New site development of PMD
Malignant Transformation	Oral SCC arising at the same-site as a clinically recognised precursor lesion
Oral Cancer Development	Oral SCC arising at a new- site distant from precursor lesions

Persistent Disease

Persistent Disease is the term used to describe PMD lesions which persist at the same-site following treatment. Thus, once post-operative healing has stabilised and despite whole lesion excision, there is evidence of residual PMD which can be seen and identified clinically. Such persistent lesions usually have an identical clinical appearance and often exhibit the same histopathological features as their original presenting lesion.

Recurrent Disease (Same Site Recurrence)

Recurrent Disease refers to PMD lesions which re-appear at the same-site following a treatment intervention which had, apparently, brought about clinical resolution for a period of time. Whilst precise timing varies, most recurrent lesions re-appear within 2-years of treatment. Such recurrent disease usually presents with the same clinical appearance, and is often associated with persistent use of tobacco and alcohol. As patients are under regular review careful clinical examination should identify such changes in mucosal appearance.^{7,8}

Further Disease (New Site Recurrence)

Further Disease is defined as the development of additional PMD lesions at new, distinct sites in the oral cavity which appear after successful treatment of pre-existing lesions. This is an important clinical

manifestation of field cancerization, which may not be directly related to known risk factor behaviour, and effectively demonstrates inherently unstable oral mucosa in a given patient.

Malignant Transformation

This refers to the same-site change of a previously identified PMD precursor lesion into an invasive SCC.

Oral Cancer Development

The term is used when patients with pre-existing or previously treated PMD subsequently develop invasive SCC at new intra-oral sites, distinct from their originally presenting lesions.

Distinction between these latter two malignant processes is fundamental because interventional treatment which excises individual PMD lesions may help to prevent malignant transformation at the site of the excised lesion, but oral cancer development at new sites remains a risk, especially in the presence of on-going risk factors. Whilst development of new-site SCC probably reflects the field change nature of PMD, the fact that patients remain under active surveillance and regular clinic follow up post-treatment should assist in the early identification of suspicious mucosal changes⁵.

It is important, therefore, to try to recognise clinical signs and elicit symptoms suggestive of SCC development at the earliest possible stage during patient follow up, and a high index of suspicion is essential to alert clinicians to malignant transformation. Changes suggestive of SCC development in a precursor mucosal lesion include enlargement, loss of homogeneity, redness, ulceration, induration and fixation. It remains a significant problem, however, that many patients are often unaware of such change until lesions reach an advanced stage⁵.

Patient Follow Up

In specific relation to PMD management, a coordinated and detailed follow up regime in which the clinician visualises and inspects the oral mucosa in detail should help to identify recurrent or further disease at the earliest possible stage, alongside the important opportunity to highlight the presence of early malignant change. Patient follow up is thus recognised as

fundamental and integral to comprehensive patient care, and the principle of active surveillance is as important as any other aspect of interventional treatment. Whilst it is difficult to be entirely prescriptive regarding the length of follow up or the time between clinic appointments, patients treated for high grade dysplasia and those who continue to smoke tobacco and drink alcohol almost certainly warrant a more rigorous follow up schedule⁶⁻⁸.

Conclusions

Accurate prediction of the behaviour of PMD remains a problem in modern clinical practice. Effective management strategies require robust predictive techniques to identify individual patients and lesions at risk of poor clinical outcome and, ultimately, SCC development. These issues are compounded by a lack of understanding of the natural history of PMD disease, confused terminology, limited agreement on therapeutic interventions and uncertainty regarding patient follow up. Defining the parameters by which outcome may be measured and the longitudinal study of patients undergoing treatment may offer realistic opportunities to increase our knowledge of both PMD and oral carcinogenesis.

References

1. Thomson PJ. Clinical Outcome. In: PJ Thomson (ed) Oral Precancer – Diagnosis and Management of Potentially Malignant Disorders. Wiley-Blackwell; 2012. p139-155. ISBN 978-1-4443-3574-3.
2. Holmstrup P, Vedtofte P, Reibel J, Stoltze K. Long-term treatment outcome of oral premalignant lesions. *Oral Oncology* 2006 42: 461-474.
3. Arduino PG, Surace A, Carbone M, Elia A, Massolini G, Gandolfo S, Brocchetto R. Outcome of oral dysplasia: a retrospective hospital-based study of 207 patients with a long follow up. *Journal of Oral Pathology & Medicine* 2009 38: 540-544.
4. Mehanna HM, Rattay T, Smith J, McConkey CC. Treatment and follow-up of oral dysplasia – a systematic review and meta-analysis. *Head & Neck* 2009 31: 1600-1609.
5. Thomson PJ. Malignant transformation and oral cancer development. In: PJ Thomson (ed) Oral Precancer – Diagnosis and Management of Potentially Malignant Disorders. Wiley-Blackwell; 2012. p156-169. ISBN 978-1-4443-3574-3.

6. Hamadah O, Thomson PJ. Factors affecting carbon dioxide laser treatment for oral precancer: a patient cohort study. *Lasers in Surgery & Medicine* 2009 41: 17-25.
7. Hamadah O, Hepburn S, Thomson PJ. Effects of active non-smoking programmes on smoking behaviour in oral precancer patients. *International Journal of Oral & Maxillofacial Surgery* 2007 36: 706-711.
8. Goodson ML, Hamadah O, Thomson PJ. The role of alcohol in oral precancer: observations from a North-East population. *British Journal of Oral & Maxillofacial Surgery* 2010 48: 507-510.

CHAPTER EIGHT

HYPOTHESES

‘...a proposed explanation based on limited evidence, a starting point for further investigation...’

Introduction

Having thus reviewed our current knowledge and explored theories regarding ways in which we might improve diagnostic techniques, rationalize approaches to management and better define subsequent clinical outcomes for PMD, it is pertinent at this juncture to consider the specific hypotheses that underpin the investigative work to be reported upon in Part Three of this book and indeed, define the overall aims and objectives of the work.

Strictly speaking, an aim is the specific result that a plan of action or set of objectives is intended to achieve, whilst a hypothesis is a proposed explanation for a particular identified phenomenon. For our purposes, however, it is more useful to expand these definitions to delineate a series of inter-related aims and objectives and define a number of hypotheses regarding the diagnosis and management of PMD and the early identification and treatment of oral SCC.

Accepting that our current knowledge base is only provisional in nature, and that it is primarily based upon many previous and incomplete observations, it becomes clear that a fuller and more detailed evaluation of carcinogenesis within the oral cavity is required. Any theory or hypothesis, of course, requires significant additional work by researchers in order to either confirm or disprove it, so that in the following chapters of this book we will review clinical research work carried out by the author with the intent of improving both our knowledge and our understanding of PMD.

Aims and Objectives

The over-arching aims of the work presented in this book are, in the absence of a robust and comprehensive evidence-base or indeed any formalised national or international PMD statistics, to improve our understanding of the natural history of PMD, to profile patient demography and clinico-pathological data obtained from patient cohorts presenting to a specialist PMD service within a university teaching hospital in Newcastle upon Tyne in Northern England, to document the clinical outcomes for such patients treated by an interventional management protocol, primarily CO₂ laser surgery, over a 20-year period, and to thereby attempt an overall assessment of the effectiveness of intervention during the state of 'pre-malignancy' and determine its influence on the on-going process of oral carcinogenesis.

A number of closely related and specific objectives, supporting these aims, may be determined as follows:

1. To improve our knowledge and understanding of oral epithelial cell biology and to characterize the extent and significance of disruption to cell proliferative activity during carcinogenesis,
2. To examine the significance of anatomical site effects and field change cancerization within the oral cavity,
3. To establish a better overall understanding of the natural history of PMD, and to develop tools to predict clinical behaviour and outcome,
4. To rationalize the diagnosis and interventional management of PMD and, by increasingly influencing contemporary clinical practice, reduce the burden of oral cancer disease,
5. To delineate and stratify risk for oral carcinogenesis both within population and patient cohort studies, thereby facilitating primary, secondary and tertiary preventive strategies.

Hypotheses

In specific support of the afore-mentioned aims and objectives, a number of hypotheses regarding the diagnosis and management of both PMD and early invasive SCC will need to be tested:

1. Assessment of conventional clinico-pathological features cannot adequately predict disease progression or clinical outcome for PMD,
2. Incision biopsy techniques are insufficient for definitive histopathological diagnosis, which will thus require excision of the entire mucosal lesion for microscopic examination,
3. Interventional CO₂ laser surgery is an effective tool facilitating both a more definitive diagnosis and a reliable and effective treatment for PMD and,
4. Active intervention during the 'pre-malignant' state halts the progress of oral carcinogenesis and thereby reduces the overall risk of SCC development.

Conclusions

In order to address the many long standing dilemmas and unanswered questions relating to early recognition of oral SCC and the particular roles that prevention and intervention play in the definitive management of PMD, a comprehensive review of the clinical research work carried out by the author in Newcastle will be presented through Chapters 9 to 12.

PART THREE

STUDIES

'systematic work undertaken to increase knowledge...'

CHAPTER NINE

DISCOVERIES

'...finding something previously unknown...'

Introduction

Normal growth and maintenance of oral mucosa requires that birth, differentiation and loss of epithelial cells are all regulated and coordinated. It is quite clear that a better understanding of the mechanisms that govern the transformation of normal oral mucosa firstly, into potentially malignant and then subsequently into malignant tissue remains fundamental to our attempts to improve diagnosis and rationalize early interventional management strategies for affected patients. As we have seen previously, the focus of such disruptive change is likely to arise within the oral epithelial stem cells. In general, oral epithelial cells are predominantly keratinocytes, and may be distinguished as basal, spinous, granular or cornified, dependent upon their structural position and appearance within the epithelium. Functionally, the progenitor compartment (basal and para-basal cells) is the site of cell division, whilst the maturation compartment (comprising spinous and granular cells) facilitates superficial cell migration and terminal cellular differentiation; the resultant superficial cornified compartment is composed of flattened keratinized squames, many of which exfoliate upon death. Epithelial proliferative units have been postulated, represented by epithelial ridges bounded by their connective tissue papillae on either side, which shelter the basal cells and thus effectively protect the self-renewing stem cells that lie within¹⁻⁴.

Building very much upon the work undertaken at the Paterson Institute at Manchester's Christie Hospital in the early 1990's, and introduced to the reader in Chapter 1, studies of the science of oral epithelial biology and cell kinetics became the focus and genesis of much of our early research work and thus our initial discoveries in Newcastle^{1,2}. In this chapter, therefore, we will explore in detail a number of these findings which I believe have helped to inform and advance not only our understanding of

oral carcinogenesis, but inspired more rationalized approaches to diagnosis and then treatment of diseases of the oral mucosa.

The Scientific Basis of Oral Carcinogenesis

Cell proliferation is justifiably considered as one of the most important mechanisms during carcinogenesis, and measurement of quantifiable proliferation indices have been used for some time now to assess malignant potential, tumour growth and prognosis. The identification of reliable markers of epithelial cell dysregulation and increased proliferation is an important goal in all spheres of clinical oncology.

The cell cycle is the normally ordered set of processes by which cells grow and divide; four phases are defined comprising gap 1 (G1), DNA synthesis (S), gap 2 (G2) and mitosis (M). Cell renewal occurs rapidly in oral epithelium, with an average cell cycle time between 2.5 to 3 days for human oral mucosa. Importantly, the cycle is governed by a complex series of molecular interactions and ‘checkpoints’ which ensure each step is completed without error, preventing significant DNA damage, before the next phase begins. Cycle progression is governed by a family of cyclin-dependent kinases (CDKs) which are activated by binding to cyclin proteins and inhibited by CDK inhibitors. Broadly speaking, passage through G1 into S-phase is regulated by cyclins D, E and A, whilst cyclin B1 controls the G2/M transition. Aberrantly expressed cyclins may lead to loss of cycle control and abnormal epithelial cell proliferation, which are fundamental steps in oral carcinogenesis³⁻⁷.

Experimental analysis of cell proliferation requires labelling of newly synthesized DNA with a detectable precursor molecule. The S-phase fraction may thus be quantified by such incorporation techniques by effectively counting the number of active cells in S at any given time. This may be done with tritiated thymidine (3HTdR), which is detected by autoradiographic examination, or via bromodeoxyuridine (BrdU), a halogenated thymidine analogue identified by monoclonal antibodies and immunohistochemistry. A technical modification utilizes a double labelling technique based upon sequential 3HTdR and BrdU S-phase labelling, which thereby introduces a temporal component to the labelling, and thus facilitates estimation of the duration of S phase and quantification of cell flux into and out of S; a very elegant technique indeed and devised by my colleagues at the Paterson Institute. In initial animal work, we then demonstrated not only a pronounced circadian rhythm in cell proliferation

in mouse tongue epithelium but also distorted epithelial cell proliferation (in terms of increased proliferative labelling indices and alterations in S-phase activity presumably affecting stem cell activity) under an experimental carcinogenic influence induced by excessive epidermal growth factor (EGF) administration^{4,5}.

Whilst a significant amount of data has been published to characterize cell proliferation within the oral cavity of laboratory animals, very few studies have reported on human oral epithelium, and most described inflamed gingiva. It seemed pertinent, therefore, to proceed to investigate human oral epithelial biology and attempt to characterize cell proliferative activity both in health and within PMD and SCC. Obtaining appropriate ethical committee approval and informed patient consent allowed us to collect redundant oral mucosa samples from patients in Manchester undergoing oral surgery procedures in a series of innovative cell kinetic studies. Importantly, we were able to determine that S-phase proliferative labelling indices in excised buccal mucosa and mandibular gingiva tissue samples, obtained from subjects between 09.00 and 16.00hrs and labelled via a modified *in vitro* 3HTdR and BrdU double labelling incubation technique, showed no significant time difference. We therefore concluded that human oral epithelium samples could be reliably studied during normal daily hours with no significant circadian influence on quantitative labelling. Whilst not showing a circadian variation, these oral samples nonetheless suggested that significant anatomical site differences in epithelial proliferative activity existed in the human oral cavity. There is, of course, marked heterogeneity of structure in various regions of the mouth, with a particular division into lining (which is non-keratinized and found on the lips, buccal mucosa, floor of mouth and ventro-lateral tongue) and masticatory (which is keratinized and found in the gingiva and palate). In this particular study, lining buccal mucosa demonstrated significantly higher labelling indices (11.7%) compared to the thicker, keratinized mandibular gingiva (8.5%); an illustrative photomicrograph of double labelled gingival tissue is shown in Figure 9.1⁶.



Figure 9.1: Photomicrograph of double-labelled human mandibular gingiva showing single BrdU labelled cells (brown), single 3HTdR labelled cells (black dots) and double labelled cells (brown + black dots) arising in the basal and parabasal layers (magnification x40).

Thus, the structure and function of oral mucosa varies significantly from site to site in the oral cavity, as indeed does the incidence of mucous membrane disease. It became important, therefore, to attempt to map out epithelial proliferative activity within the human oral cavity and to determine the extent of anatomical site (and presumed structural and functional) variability in cell activity. This was carried out by harvesting normal mucosa from 8 distinct anatomical sub-sites during surgical procedures and by measuring proliferation indices via 3HTdR and BrdU double labelling. Significantly increased cell proliferation was seen in the floor of mouth (12.1%) and ventrolateral tongue (10.1%), compared to lower proliferative active regions in thick keratinized or specialised mucosa such as the palatal mucosa (7.2%) and tongue dorsum (4.3%). Oral sites most prone to SCC and PMD development were thus objectively characterized for the first time to show inherently high proliferative states suggesting that an underlying predisposition to carcinogenesis may exist⁷. Figure 9.2 demonstrates the resultant topographical map of human oral epithelial cell activity.

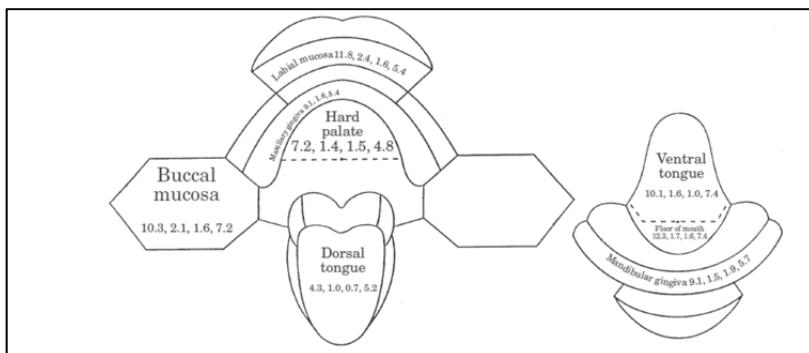


Figure 9.2: Topographical map of the oral cavity showing the anatomical site-specific: (1) labelling indices (%); (2) cell influx values (% per h); (3) cell efflux values (% per h); and (4) S phase durations (h).

It has often been postulated that the floor of the mouth, bounded by lateral and ventral aspects of the tongue and mandibular alveolus, acts as a 'horseshoe-shaped sump' into which soluble carcinogens from tobacco and alcohol may pool and then easily penetrate keratin-free mucosa and exert neoplastic change. However, the clear identification of pre-existing high proliferative activity within the mucosa of these regions may better explain such site-specific predilection. Indeed, it has long been believed that the cells most likely associated with pre-malignant change during carcinogenesis will be those possessing the highest proliferative activity. In a similar manner, the high activity recorded in buccal mucosa may also contribute to the high incidence of site-related smokeless tobacco and betel nut induced oral SCC⁷.

A unique feature of the sequential double labelling experiment is its ability to determine dynamic kinetic parameters such as cell influx to and efflux from S, and also the ability to calculate the overall duration of the S-phase. Whilst these laboratory techniques remain primarily research tools and are inevitably highly time-consuming and overly complex for routine diagnostic use, the data acquired for human oral epithelial cell activity remain unique in the literature. It is also of interest that floor of mouth and ventral tongue sites exhibited the longest S-phase durations (between 7.1 to 7.4 hours) potentially resulting in a prolonged exposure of vulnerable, replicating genetic material to extrinsic carcinogenic influence; these values were also prolonged for buccal mucosa sites (at 7.2 hours); Figure 9.2.

Despite the obvious clinical significance of distinct 'baseline' proliferative values in oral epithelia at different oral sites, very few other researchers have examined site specific variation in epithelial activity and most have studied diseased tissue. However, consistent findings that have appeared in the literature include increased proliferative activity seen in both oral dysplastic lesions and tumours with aggressive clinical behaviour, and this has been particularly noted for those that arise at ventro-lateral tongue and floor of mouth sites^{8,9}.

Our demonstration of quantifiable cell proliferation differences in normal oral mucosa, particularly the increased activity at high risk sites, prompted a further investigation in which 3HTdR and BrdU double labelling was again utilised to measure proliferative activity in excised abnormal oral mucosa, including both dysplastic pre-malignant and invasive malignant oral tissue. Six buccal mucosal leukoplakias showed a substantially higher mean labelling index of 14.5%, compared to the 10.2% seen in normal buccal mucosa, and 12 floor of mouth, ventral tongue and soft palate lesions showed a significant increase in proliferative activity of 2.2% for each worsening grade of dysplasia through mild dysplasia to carcinoma-in-situ. Similarly, when histopathological tumour differentiation was compared with double labelling indices for nine oral SCCs we observed a 12% increase in proliferative activity for each worsening grade of differentiation. Overall, a substantial overlap of labelling indices was seen ranging from 10.8 to 22.6% in dysplastic lesions and from 4.1 to 39.3% in SCC¹⁰.

Following similar ethical committee approval in Newcastle, we then carried out further comparisons of cell proliferative activity this time between single and multiple lesion PMD patients and found some notable differences. In this study cyclin A, cyclin B1 and Ki-67 proliferative labelling indices were determined immunohistochemically on paraffin-embedded tissue for 78 single excised dysplastic lesions, and also 54 dysplastic lesions excised from 18 multifocal lesion patients. In addition to the specific cyclin measurements, Ki-67 was assessed as an overall marker of cell proliferation; beginning its expression in S phase, Ki-67 rises through G2 peaking at mitosis. Interestingly, proliferative activity was noted to be much higher in single lesions with mean indices of 13.6%, 12.3% and 25.4%, compared with 11.3%, 10.6% and 20.7% in multiple lesions for cyclin A, B1 and Ki-67 labelling respectively. These differences between single and multiple labelling most probably reflected the higher incidence of severe dysplasia found in single lesion disease¹¹.

We will explore the significant clinico-pathological differences between single and multiple-lesion PMD disease in more detail later in this chapter.

Although research in oral epithelial kinetics has progressed relatively slowly since we first published our findings, it is undoubtedly time for further work to be done. Whilst recent oncology research has primarily focused upon molecular biology techniques, Pich et al¹² usefully re-emphasized that quantifiable cell proliferative changes are probably more likely to reflect the overall status of genetic damage in tissue compared with individual oncogene alterations and should be considered as possible prognostic indicators.

Prediction of Clinical Outcome

Whilst all the above studies have provided consistent information relating to increased cell proliferation in PMD they are primarily observational, cross-sectional studies of excised dysplastic or malignant tissue. Long term clinical follow-up of lesions is mandatory, of course, to develop meaningful predictive analyses of malignant transformation risk; such data are infrequently reported in the literature. If objective and reproducible cell proliferation measurements can be shown to have a definite role in identifying lesions at risk of severe dysplasia, or perhaps more fundamentally malignant transformation, this would provide an objective and independent assessment of adverse lesion behaviour readily applicable to the clinical management of patients. Clearly, the key to such research is the ability to examine archival tissue specimens from known clinical cases to determine objective assessments and then to measure these parameters against well-defined and detailed clinical outcome data.

In order to characterize epithelial biology changes in oral mucosa in more detail during carcinogenesis, 10 archival paraffin-embedded specimens of 4 oral SCCs and 6 dysplastic PMD lesions managed by the author in Newcastle, and with known 3-year post-treatment clinical outcomes, were therefore examined. Immunohistochemical analyses of Ki-67 and cyclin A revealed labelling indices ranging from 15.8 to 39.5% and 4.8 to 17.2% respectively, confirming increased proliferative activity in increasingly dysplastic and neoplastic tissue, together with a significant increase in supra-basal epithelial proliferation. This latter observation illustrates the significance of hierarchical change within oral epithelium during dysplasia dysregulation. The importance of defining clinical outcome categories was discussed for the first time in this research project and the categories of: no

recurrent disease, recurrent or further disease at the same site, new disease at different sites and the development of cervical nodal metastasis were all recognised. Interestingly, poor clinical outcome, in terms of disease recurrence or lymph node metastasis, was associated with not only an increase in quantitative labelling indices but also in particular with identification of excessive supra-basal proliferative activity. The latter observation probably represents a significant overall increase in proliferation within tissue reflecting larger growth fractions and shortened cell cycle times consequent upon cell replication out with the basal layers¹³. Figure 9.3 illustrates cyclin A supra-basal labelling in dysplastic floor of mouth mucosa.

To explore these issues more fully, a further study was undertaken in which cyclin A expression was quantified in 33 excised oral lesions with known 3-year post treatment outcome data. Histopathological diagnoses ranged from mild, moderate and severe dysplasia or carcinoma-in-situ in 26 and invasive SCC in 7 patients. There was a definite trend for increased cyclin A activity to be associated with increasing dysplasia, with labelling indices ranging from 5.5 to 32.1%, although this was not statistically significant. Of additional interest was the recognition that labelling indices were often higher in severe dysplasia and carcinoma-in-situ than SCC, suggesting perhaps a role for cyclin A in the earlier stages of carcinogenesis. Clinical outcome was stratified as: no disease, persistent disease or further disease (including local recurrence, second primary tumours or cervical nodal metastasis). High cyclin A activity was a predictor of persistent or further disease development, with a particularly significant relationship seen between increased supra-basal cyclin A labelling and the worst clinical outcome categories, which confirmed our previous findings and suggested that there may indeed be an important predictive role for cyclin A measurement¹⁴.

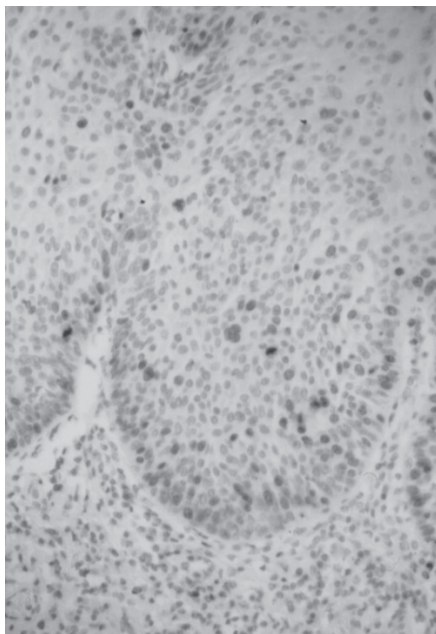
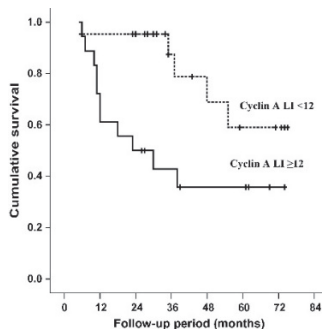
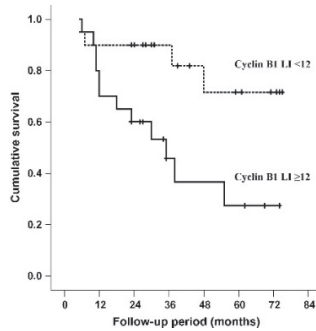


Figure 9.3: Photomicrograph of cyclin A labelled dysplastic floor of mouth leukoplakia demonstrating increased supra-basal labelling (magnification x40).

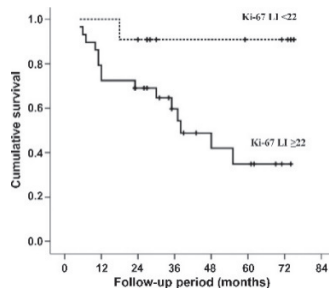
In an additional Newcastle investigation, 40 patients with single-site PMD lesions treated by laser excision and followed for 5-years post-surgery were studied in more detail. Histopathology diagnoses for the mucosal lesions included: 2 mild, 16 moderate and 22 severe dysplasias. Excision specimens were assessed for cyclin A, B1 and Ki-67 activity, with their resultant labelling indices ranging from 3.9 to 31.3%, 0 to 28.3% and 3.5 to 54.5% respectively. No recurrent disease was seen in 24 patients, whilst 16 developed further PMD disease during the follow-up period; in this study, however, no instances of SCC development were recorded. Assessed specifically against either disease free or further disease outcome categories, a significant predictive ability of cell proliferation measurement was demonstrated, whereby lesions with proliferative indices in excess of median values, specifically $> 12\%$ for cyclins and $> 22\%$ for Ki-67, equated with a significantly increased risk of disease progression following treatment. Figure 9.4 illustrates Kaplan-Meier disease free survival plots for these labelling indices, using onset of further disease as step functions¹⁵.



A



B



C

Figure 9.4: Kaplan-Meier analyses showing influence of cyclin A (A) cyclin B1 (B) and Ki-67 labelling indices (C) on disease-free survival following laser surgery treatment of PMD lesions.

Overall, therefore, utilising our current knowledge regarding deregulation of cyclins during oral carcinogenesis and the specific results of our patient treatment studies, it is highly likely that they are pragmatic and useful biomarkers for both diagnosis and prognosis of PMD, and may well have a role as therapeutic targets in future oral cancer management strategies¹⁶.

Field Change Cancerization

The original, highly prescient observations of Slaughter et al¹⁷ that, despite successful treatment of a primary head and neck cancer second primary tumour development may occur led to the fundamental concept of ‘field cancerization’ whereby carcinogen-induced changes were hypothesized to exist throughout all the affected upper aero-digestive tract mucosa. Satellites of dysplastic epithelium identified adjacent to invasive SCC may thus explain the phenomena of both multiple primary tumour development and recurrence following apparently complete tumour resection. The cancerization concept is supported by clinical, histopathological and molecular evidence, in which clinically normal control epithelium adjacent to tumour tissue often shows very similar subcellular or biochemical changes. Field change may result from expansion and then subsequent migration of clonally related pre-neoplastic cells¹⁸.

In a study carried out in Manchester, we utilised in vitro 3HTdR and BrdU double labelling techniques to assess excised samples of normal looking oral mucosa harvested from 10 patients previously treated for oral SCC. Few studies had previously analysed cell kinetics in human oral SCC, although labelling indices of between 10 to 36% were reported. We demonstrated a significant increase in oral epithelial proliferative labelling indices, similar to that seen in invasive carcinoma (floor of mouth 15%, ventral tongue 15.7%), for both clinically normal looking floor of mouth (14%) and ventral tongue mucosa (16.2%). Proliferative indices may thus complement the intrinsically static, observational nature of traditional descriptive histopathology, and offer additional insights into carcinogenesis^{2,10}.

This specific and important cell kinetic observation that discovered that normal looking oral mucosa may already harbour enhanced proliferative activity in patients at risk of oral carcinogenesis, prompted a subsequent clinical study in to field change in Newcastle. In this investigation, 26 consecutive new (untreated) patients presenting with unilateral PMD lesions (8) or SCC (18) underwent ‘mirror image’ biopsies from clinically

normal looking mucosa at corresponding contralateral oral sites. Eighteen floor of mouth and ventro-lateral tongue, 6 soft palate or fauces and 2 buccal mucosa samples were thus harvested. Interestingly, only 11 were deemed 'normal' following microscopic examination, with the remaining 15 patients exhibiting varying degrees of cellular atypia or dysplasia, and in 2 cases actually early invasive carcinoma development. These surprising observations clearly highlighted significant field change effects and, indeed, suggested that such widespread change may be a much greater clinical problem in oral carcinogenesis than previously recognized. Although not statistically significant, the floor of mouth and ventrolateral tongue appeared particularly susceptible to dysplastic change in this study¹⁹.

Thus, we highlighted the reality that 'field change' carcinogenesis existed in approximately 60% of Newcastle PMD patients. Multifocal PMD presentation is seen in around 3 to 7% of cases worldwide, whilst up to 24% of SCC patients are known to be at risk of developing new, primary tumours over a 5-year period. The specific observation that clinically normal looking oral mucosa may harbour significant histopathological features of dysplastic disease, and also abnormally high cell proliferative activity, has helped to progress the debate in the literature over the true significance of oral dysplasia 'field change' and emphasized the limitations inherent in conventional oral examination and histological diagnosis^{10,19}.

'Premalignant fields' probably precede tumour formation, therefore, with SCC development arising in a sub-clone within the field following additional genetic damage. The field then expands through oral epithelium at the expense of normal surrounding mucosa, probably due to the higher proliferation rate of the abnormal epithelium. High proliferation rates increase the likelihood of malignant change in epithelia, because dividing cells become more sensitive to carcinogenic influence. Tumour proliferation rates are also probably determined by the proliferative rate of the premalignant epithelium in which they arise, with speed of proliferation a particularly important prognostic feature^{10,14,15,20}.

Clearly, the recognition of such a 'premalignant field' is important for prevention, interventional therapy and prognosis throughout all stages of PMD management. The use of 'mirror image' biopsies as a pragmatic diagnostic technique is now established in contemporary clinical practice, although the specific management of field change and widespread oral dysplastic disease remains a challenging problem²¹.

Single versus Multiple Lesion Disease

PMD, as we have discussed, almost certainly share the same developmental risk factors as oral SCC so it is perhaps unsurprising that they are also affected by field cancerization, and that there exists a particular subgroup of patients exhibiting a high incidence of multiple lesion and subsequent multifocal tumour development. In Newcastle, we found that up to 24% of our PMD patients were affected by field cancerization and thus presented with multiple lesions or pan-oral PMD. Multiple lesion disease presents one of the most challenging management situations, due to the diffuse nature of the disorder and the increased risk of SCC development. It seemed clear that further research to investigate risk factors and clinico-pathological features specific to patients with multi-focal lesions was warranted.

Adapting our original proliferative mapping technique described earlier, we therefore devised a new diagnostic strategy of 'field mapping' dysplasia in our multi-focal disease patients. Formal oro-pharyngeal examination, usually under general anaesthesia to optimise access, was then followed by multiple field mapping biopsies to identify the sites exhibiting most significant pathological change. In one study, we discovered 70 clinically identifiable lesions in 16 consecutive, newly presenting multiple lesion patients. Whilst most patients presented with 3 to 5 distinct lesions, others exhibited as many as 6, with the majority presenting as homogenous leukoplakia on the buccal mucosa, alveolus and lateral tongue. Histopathological examination of biopsy specimens guided laser excision to 11 severely dysplastic lesions in 6 patients, particularly affecting faucial pillar, floor of mouth and ventral tongue sites. Overall, a number of pertinent new discoveries were made following this study: leukoplakia on hard palate and alveolar mucosa is predominantly homogenous in appearance demonstrating hyperkeratosis on biopsy, the soft palate and/or fauces harbour non-homogenous lesions with significant dysplasia or carcinoma-in-situ, buccal homogenous leukoplakia represents hyperkeratosis whilst non-homogenous or erythroplakic buccal lesions can exhibit severe dysplastic change. In addition, lesions arising at ventral tongue and floor of mouth sites, regardless of appearance, are at high risk of 'high grade' dysplastic change. This work facilitated, probably for the first time ever in clinical practice, objective and accurate targeting by surgical excision of the most significant areas of PMD disease. This pragmatic approach to the dilemma of multifocal oral disease has been adopted as the 'gold standard' investigation in the assessment of pan-oral disease patients^{22,23}.

In further work, initially described earlier in this chapter in relation to proliferative labelling indices, we followed 96 new, previously untreated Newcastle PMD patients for 5 years following laser surgery to excise 132 dysplastic lesions from 78 single and 18 multiple lesion patients. Whilst leukoplakia remained the commonest clinical appearance, we were able to characterize a number of significant clinico-pathological differences between single and multiple PMD disease, thus helping to delineating multiple lesion disease as a distinct clinical entity. Whilst single PMD lesions were most commonly seen on floor of mouth and ventro-lateral tongue sites, multiple lesions were more usually concentrated on the buccal and palatal mucosa. Although multiple lesions exhibited less severe dysplastic features than single lesions, as well as lower cell proliferative activity (as reported above), the overall risk of malignant transformation was higher for multiple lesion patients. During follow-up, three from the 78 single lesion patient group and four out of the 18 multiple lesion patients developed SCC, primarily at sites distant from their presenting lesions. This may be due to the larger areas of inherently unstable mucosa at risk of carcinogenesis in multiple lesion cases. Single lesions, of course, are easier to identify and completely excise, in contrast to the widespread areas of dysplastic mucosa seen in pan-oral disease¹¹.

Regular and careful clinic review is of special importance during the management of field change patients in order to identify dysplastic disease or diagnose SCC, potentially at multiple oral sites, at the earliest possible stage. There remains a need for more objective and reproducible clinical assessment tools to attempt to quantify mucosal instability. Prolonged follow up strategies and multiple treatment interventions in specialist clinics may require health service resource allocation but it is certainly this author's philosophy that this is not only clinically justifiable but is clearly in the best interests of patients.

Conclusions

Successful research leads to discovery and then, hopefully, an incremental growth in both knowledge and understanding. We have seen that cell proliferation studies can inform not only the scientific basis of carcinogenesis, but also explain site-specific disease development, aid prediction of mucosal lesion behaviour and characterize field change cancerization. Whether discoveries truly result in innovation, and thus demonstrable improvements in procedure and/or process, is probably dependent upon the environment in which they occur. Medical

environments, unfortunately, can be notoriously slow to embrace discovery and change. Our ability to better understand carcinogenesis within the oral cavity and thereby improve the identification and effective treatment of 'high risk' lesions and 'at risk' patients during the earliest stages of cancer development remain important objectives for the research work and discoveries presented in this chapter. Indeed, it is within these specific areas that clinical innovation is most required. In the following chapters, we need to explore exactly how we might achieve this important innovation.

References

1. Thomson PJ. An investigation into the effects of growth factors on oral epithelium. MSc Thesis, University of Manchester. 1993.
2. Thomson PJ. An investigation into oral epithelial cell activity and the pathogenesis of squamous cell carcinoma. PhD Thesis, University of Manchester. 1997.
3. Thomson PJ. Oral Carcinogenesis. In: PJ Thomson (ed) Oral Precancer – Diagnosis and Management of Potentially Malignant Disorders. Chichester: Wiley-Blackwell; 2012. p31-47. ISBN 978-1-4433-3574-3.
4. Thomson PJ, McGurk M, Potten CS, Walton GM, Appleton DR. Tritiated thymidine and bromodeoxyuridine double-labelling studies on growth factors and oral epithelial proliferation in the mouse. *Archives of Oral Biology* 1999 44: 721-734.
5. Appleton DR, Thomson PJ, Donaghey CE, Potten CS, McGurk M. Stimulation of cell proliferation in mouse oral epithelium, and the action of EGF: evidence for a high degree of synchronisation of the stem cells. *Cell Proliferation* 2002 35(Suppl.1): 68-77.
6. Thomson PJ, Potten CS, Appleton DR. In-vitro labelling studies and the measurement of epithelial cell proliferative activity in the human oral cavity. *Archives of Oral Biology* 2001; 46: 1157-1164.
7. Thomson PJ, Potten CS, Appleton DR. Mapping dynamic epithelial cell proliferative activity within the oral cavity of man: a new insight into carcinogenesis? *British Journal of Oral & Maxillofacial Surgery* 1999 37: 377-383.
8. Watanabe S, Watanabe R, Oton-Leite AF, Alencar RCG, Oliveira JC, Leles CR, Batista AC, Mendonca EF. Analysis of cell proliferation and pattern of invasion in oral squamous cell carcinoma. *Journal of Oral Science* 2010 52: 417-424.

9. Ramasubramanian A, Ramani P, Sherlin HJ, Premkumar P, Natesan A, Thiruvengadam C. Immunohistochemical evaluation of oral epithelial dysplasia using cyclin-D1, p27 and p63 expression as predictors of malignant transformation. *Journal of Natural Science, Biology & Medicine* 2013 4: 349-358.
10. Thomson PJ, Potten CS, Appleton DR. Characterization of epithelial cell activity in patients with oral cancer. *British Journal of Oral & Maxillofacial Surgery* 1999 37:384-390.
11. Hamadah O, Goodson ML, Thomson PJ. Clinicopathological behaviour of multiple oral dysplastic lesions compared with that of single lesions. *British Journal of Oral & Maxillofacial Surgery* 2010 48:503-506.
12. Pich A, Chiusa L, Navone R. Prognostic relevance of cell proliferation in head and neck tumours. *Annals of Oncology* 2004 15: 1319-1329.
13. Thomson PJ, Soames JV, Potten CS, Booth C. Epithelial cell proliferative activity and oral cancer progression. *Cell Proliferation* 2002 35(Suppl.1):110-120.
14. Thomson PJ, Hamadah O, Goodson ML, Booth C, Cragg N. Cyclin A predicts clinical outcome in oral precancer and cancer. *International Journal of Oral & Maxillofacial Surgery* 2006 35:1041-1046.
15. Thomson PJ, Goodson ML, Booth C, Cragg N, Hamadah O. Predicting recurrence after treatment of oral precancer: Use of cell cycle analysis. *British Journal of Oral and Maxillofacial Surgery* 2008 46:370-375.
16. Mishra R. Cell cycle-regulatory cyclins and their deregulation in oral cancer. *Oral Oncology* 2013 49: 475-48.
17. Slaughter DP, Southwick HW, Smejkal W. Field cancerization in oral stratified squamous epithelium: clinical implications of multicentric origin. *Cancer* 1953 6: 963-968.
18. Califano J, van der Riet P, Westra W, Nawroz H, Clayman G, Piantadosi S, Corio R, Lee D, Greenberg B, Koch W, Sidransky D. Genetic progression model for head and neck cancer: implications for field cancerization. *Cancer Research* 1996 56: 2488-2492.
19. Thomson PJ. Field change and oral cancer: new evidence for widespread carcinogenesis. *International Journal of Oral & Maxillofacial Surgery* 2002 31:262-266.
20. Gonzalez-Moles MA, Ruiz-Avila I, Gil-Montoya JA, Esteban F, Bravo M. Analysis of Ki-67 expression in oral squamous cell carcinoma: Why Ki-67 is not a prognostic indicator. *Oral Oncology* 2010 46: 525-530.

21. Hebbale M, Krishnapra R, Bagewad IA, Keluskar V, Kale A, Halli R. Evaluation of mirror image biopsy for incidence of multiple premalignant and malignant lesions in oral cancer. *Journal of Indian Academy of Oral Medicine & Radiology* 2012 24: 194-199.
22. Thomson PJ, Hamadah O. Cancerisation within the oral cavity: The use of 'field mapping biopsies' in clinical management. *Oral Oncology* 2007 43:20-26.
23. Bagan JV, Scully C. Recent advances in Oral Oncology 2007: Epidemiology, aetiopathogenesis, diagnosis and prognostication. *Oral Oncology* 2008 44: 103-108.

CHAPTER TEN

PERSPECTIVES

'...looking and perceiving through different eyes...'

Introduction

Irrespective of discoveries and knowledge advancement, the diagnosis and management of PMD involves a complex interaction between presenting patients and their information and management needs, clinicians' views on disease recognition and treatment, and histopathological assessment and diagnosis of mucosal biopsy specimens. Unfortunately, and as we have now seen, uncertainty regarding the concept of the 'potentially malignant state' remains a difficult and pernicious influence throughout this entire process. It is thus important to explore these issues which, taken together, are inevitably a significant and fundamental influence on clinical management strategies for patients.

The principal dilemma facing clinicians upon new patient presentation with PMD is to establish a definitive histopathological diagnosis and to confirm the optimal management strategy for that individual patient^{1,2}. As Field et al² have pertinently observed, 'clinicians have a duty of care to patients to offer advice and management'. This can be very difficult, of course, when the evidence base for treatment guidelines is weak and knowledge limited by lack of relevant clinical trial data. Fundamentally, however, it remains important to attempt to identify individual patients and oral mucosal lesions at risk from the most progressive types of PMD and, ultimately of course, those with the greatest likelihood of malignant transformation.

The chapter will thus review a number of clinical studies carried out in Newcastle in order to gain an improved understanding of these particular issues, and which I believe benefit substantially by collating data from a number of different but complimentary perspectives: those of the clinicians, the patients and pathology. Published papers resulting from

these studies are referenced in the text for those readers wishing to undertake a more detailed study of these topics.

The Clinicians' Perspective³

As we have previously discussed, PMD management relies heavily upon the clinical recognition of suspicious mucosal lesions followed by incision biopsy to facilitate histopathological assessment of epithelial dysplasia and grading of disease severity. Whilst excision of 'high risk' lesions and long-term patient surveillance to monitor for further disease has long been the preferred approach in Newcastle, management decisions may vary considerably, from wide surgical excision to clinical observation only, often based upon an individual clinician's personal experience and preference. In the absence, therefore, of evidence-based guidelines and treatment consensus, a UK-based study was carried out with the aim of determining contemporaneous clinicians' views on available management strategies. Clinicians' perspectives on PMD diagnosis and treatment are fundamental, of course, not only to clarify current practice but also to ensure that in the future any proposed clinical trial would be relevant, pragmatic and sustainable by effective recruitment of both clinicians and patients. It is, unfortunately, well recognized that recruitment failure in particular has significantly limited successful completion of prospective, randomized trials of PMD management⁴.

We therefore determined to elicit detailed views from clinicians regarding contemporaneous PMD management. Utilizing significant, administrative help from the Facial Surgery Research Foundation (Saving Faces), and its clinical trials unit the National Facial, Oral and Oculoplastic Research Centre (NFORC), 251 clinicians from oral and maxillofacial surgery, oral medicine, ENT and plastic surgery specialties were invited to complete a web-link questionnaire regarding treatment decisions for 3 different, fictitious clinical scenarios; thus comprising one of the largest ever clinician surveys on PMD. A number of general questions were first asked of participants covering aspects of diagnosis, histopathological assessment and treatment of PMD. The specific scenarios included a 62-year old male smoker with severe dysplasia arising on the tongue, a 44-year old male ex-smoker with mild dysplasia on the floor of the mouth and a 56-year old non-smoking female presenting with moderate dysplasia of the tongue, all of whom were presenting for management as new patients.

Overall, whilst most participating clinicians clearly favoured excision of 'high-risk' PMD, with 99% of respondents reporting that they would always treat severely dysplastic lesions by excision or laser ablation, only 8% regularly excised lesions with mild dysplasia. Perhaps unsurprisingly, the greatest equipoise in decision making was seen for cases of moderate dysplasia, for which 27% of clinicians favoured observation only rather than intervention, probably reflecting the prognostic uncertainty of 'mid-grade' dysplastic change. As a general observation, if intervention was the treatment of choice, the majority of clinicians advised excision rather than ablation.

Although it was encouraging that a degree of consensus regarding management was apparent, the majority of responding clinicians were practicing surgeons and perhaps more likely therefore to recommend intervention. The results also reflect an assumption, which as we have seen may be misplaced, that it is possible to reliably characterize a group of mucosal lesions as having 'low-risk' disease; this issue in particular is explored in Chapter 4.

Clinicians' views have been sought before, of course, initially in two papers by Marley et al^{5,6} who clearly highlighted a significant lack of agreement in PMD treatment decisions from 141 UK oral and maxillofacial surgeons, whose management protocols included elimination of potential sources of mucosal trauma, prescription of anti-fungal agents, surgical excision, laser ablation and even radiotherapy treatment. Epstein et al⁷ similarly elicited a varying range of treatment responses including surgery, laser and cryotherapy, from 65 US oral medicine clinicians. More recently, Kanatas et al⁸ elicited the opinions of 199 UK surgeons regarding assessment, biopsy and follow-up of PMD lesions and found wide-ranging views and practice, with little in the way of consensus.

There are signs, however, that there now may be a move towards greater agreement supporting surgical intervention as the preferred treatment option for PMD, with increasing reports in the literature confirming efficacy of disease resolution and possible reduction in malignant transformation risk^{9,10}. The evidence base supporting these concepts remains limited, unfortunately, so that the important principles governing the interventional management of PMD outlined in Chapter 3 remain as fundamental 'guideposts' in contemporary clinical practice.

The Patients' Perspective¹¹⁻¹⁴

Whilst many studies have appropriately examined quality of life issues related to oral cancer diagnosis and treatment, there is very little in the literature regarding PMD. Assessment of patients' quality of life is now considered an integral component of evaluating disease outcome, especially for chronic disease states and malignant conditions. In attempting a recent systematic literature review, however, Tadakamadla et al¹⁵ found a paucity of data regarding quality of life studies for patients with PMD, despite the significant effects such disorders must inevitably have on oral and facial function, appearance and social interaction.

In order to find out more about patients' perspectives of PMD, a series of qualitative studies were carried out in Newcastle primarily utilising interview techniques to explore patients' views of their disease and treatment experience. Following ethical approval and informed patient consent, a number of PMD patients attending clinics in North-East England were recruited to a series of studies. Criterion-based sampling was employed to ensure a breadth of patient experience was established, whilst in-depth qualitative interviews allowed exploration of patients' views and experiences in detail. Interviews were digitally audio-recorded and transcribed verbatim. Data collection and analysis was an iterative process following the principles of the constant comparative method¹⁴.

In an initial survey of 16 patients, it became clear that there were significant variations in both conception and misconception regarding PMD disease and its cause. On the other hand, the impact of such a diagnosis on their lives and the difficulties of unmet information needs were clearly important and consistent patient concerns. The individual clinician-patient relationship was deemed especially important, with patients particularly emphasizing the need for 'expert' knowledge and consistency from clinicians during their clinical management; these are invaluable insights into patients' experiences, and highly pertinent to inform future clinical studies¹¹.

In a development of this first study, data from a further 28 qualitative interviews were reviewed to document patients' experience of their progression through their local healthcare systems, following in detail their individual journeys from initial primary care contact through to attendance and treatment at secondary care specialist services. Interviews were conducted in an identical manner, with 14 men and 14 women aged between 30 to 80 years, and ranging from 24 to 57 minutes in duration.

Emerging themes from this group were similar, again emphasizing the important role of the clinician-patient relationship, highlighting concern over time between appointments, the importance and personal impact of continuity of care and the significance of the information provided by clinicians about their condition. Timely referral to appropriate specialist care was seen as particularly important to help reduce uncertainty, reduce the feeling of being 'in limbo' and to help allay feelings of 'powerlessness' during the health care journey. The initial hospital visit and specialist consultation was consistently reported as an important landmark, heralding the beginning of a new clinician-patient relationship. It was evident that, especially at this juncture, patients must feel able to access full information relevant to their needs. I believe this is a particularly pertinent issue in PMD management, because by addressing such information needs it may be possible to avoid unnecessary uncertainty, reduce feelings of powerlessness and thereby prevent patients from developing perceptions of limited or minimal personal involvement in their care¹².

It was interesting that 'timely' referral from primary care to specialist services was very important to patients to reduce anxiety, and we will return to examine the role of treatment times in PMD management in a later chapter of this book. It was also insightful to discover that PMD patients reported significant uncertainty at a number of stages throughout their diagnosis, treatment and clinic follow-up. For many, such uncertainty was seen as a major, negative experience which deleteriously impacted on both their working and social lives¹³.

Documenting patients' views and experience are important, if not actually mandatory, issues in modern healthcare provision and research, and these interview studies provide a unique insight into patients' experiences of PMD. In particular, recognizing the extent of uncertainty in contemporary practice is of vital importance in attempting to improve quality of patient care. Opportunities undoubtedly exist throughout the patient journey, commencing at initial diagnosis, during active treatment and at each follow-up appointment to provide clarity and consistency in conveying patient information and to recognize and meet individual patient needs. It is perhaps self-evident that patients must be fully engaged in all aspects of their treatment decisions and embrace the necessary health-related behaviour changes for PMD management to be optimally effective¹⁴.

Whilst patients' understanding of PMD may be highly variable, it can undoubtedly be positively influenced by the quality of communication

with clinicians and by the specific use of terminology. Whilst ‘lay’ terms are often favoured by clinicians in attempting to explain the concept and nature of a ‘potentially malignant’ disease process, patients may well prefer and often subsequently require more precise definitions and terminology in order to access supplemental information, especially via internet sources. It seems clear, therefore, that more attention is required to meet patients’ information needs and to improve their overall understanding of PMD¹⁴. Ford & Farah¹⁶ emphasized the importance of exploring both the individual patient experience and the overall support needs of patients with PMD.

Unfortunately, as previously discussed, the dual challenges of uncertainty and unpredictability can affect clinicians as much as patients during the PMD treatment journey. van der Waal¹⁷ commented that clinicians may experience real difficulties in conveying PMD diagnoses and prognoses to patients, observing that whilst some patients will be able to balance uncertainties regarding treatment efficacy and morbidity, others will experience confusion and concern surrounding clinicians’ inability to either predict or prevent malignant transformation. These are very important issues, many of which the author recognizes from his own personal experience in advising and counselling many patients through the years.

It is encouraging, therefore, that despite these inherent uncertainties and the lack of consensus-based clinical guidelines, patients clearly value and support ‘expert’ knowledge and opinion, especially when combined with a consistent approach to their individual management. These have always been core components of the Newcastle treatment philosophy and are undoubtedly facilitated by the provision of dedicated and coordinated specialist services. Many of these issues will be visited again in later chapters of this book when we review and analyze clinical outcome data following PMD treatment.

The Pathology Perspective^{18,19,21}

Histopathological examination and dysplasia grading of oral mucosal biopsies is fundamental to assess disease status and malignant transformation risk in clinically recognisable PMD lesions, although it is recognised that these processes are inevitably somewhat subjective in nature. However, it is probably true to state that in clinical practice biopsy results effectively determine all subsequent management decisions. As

outlined previously, however, incision biopsies alone may be unreliable investigations due to their non-representative sampling of widespread mucosal abnormality.

In order to explore this concern, we retrospectively reviewed 152 PMD cases that had undergone laser surgery to treat single-site leukoplakia over a 5-year period (2006-2010), and directly compared initial, incision biopsies with their post-laser excisions. Unsurprisingly, perhaps, the majority of lesions (101) originated at floor of mouth and ventro-lateral tongue sites. In 50% of cases, there was a significant diagnostic mismatch with incisional biopsy diagnoses subsequently requiring up-grading to more severe disease status. This actually involved every diagnostic category: 15 cases initially reported as hyperkeratosis (in 4 of which, the incision biopsy had actually missed an invasive SCC), 10 mild dysplasia, 7 moderate dysplasia, and 3 severe dysplasia all requiring up-grading, and 2 carcinoma-in-situ cases re-graded as SCC following excision; the mean time between incision and excision biopsies was 4.43 months effectively excluding long-term disease progression between investigations. These were concerning observations and unquestionably provide significant evidence that incision biopsies can only be considered provisional in nature, and that full PMD lesion excision and histopathological assessment are mandatory for definitive diagnosis. It also clearly highlights the importance of lesion excision in the 'opportunistic treatment' of unexpected or 'occult' pre-existing SCC¹⁸.

In an important extension of this work, a much larger study was undertaken to try to determine the relevance of established histopathological diagnoses for previously identified oral precursor lesions on their subsequent malignant transformation. By retrospectively reviewing pathology data from 1,248 SCCs diagnosed in oral and maxillofacial surgery units in North-East England between 1996 and 2009, only 58 (4.6%) previously biopsied same-site precursor lesions were identified. In these patients, SCC most frequently arose at ventro-lateral tongue and floor of mouth sites, were more common in patients with regular and heavy alcohol consumption, and exhibited a mean transformation time of 29.2 months. Interestingly, only 25 of the cases showed either dysplasia or carcinoma-in-situ on initial biopsy, with the single most common finding in 19 out of the remaining 33 being hyperkeratosis and lichenoid inflammation, with no discernible features of dysplasia. The study again highlights the inherent limitations of incision biopsy diagnosis and dysplasia grading as predictive tools, supports the view that SCC may well arise in the absence of recognizable epithelial

dysplasia and emphasizes concerns regarding an increased cancer risk in oral lichenoid lesions. At the same time, this study clearly re-affirms the importance of clinical vigilance and active surveillance in the management of all clinically suspicious oral lesions irrespective of histological findings; an important clinical lesson^{19,20}.

Although unquestionably the gold standard for PMD diagnosis, tissue biopsy and histopathological grading of dysplasia have been criticized as invasive, expensive, subjective and, as evidenced above, potentially unrepresentative especially for large or multifocal lesions. A range of less invasive adjunctive diagnostic tools have been utilized in recent years, in attempts to improve detection of early cancer change in oral mucosa; these have been discussed in Chapter 5, of course, and include vital tissue staining, optical imaging and brush biopsy cyto-diagnosis. Reports of their effectiveness are often anecdotal, however, and there is criticism that they rarely reveal features not demonstrable by conventional techniques. An investigation was thus established in Newcastle to examine the efficacy of minimally invasive oral brush biopsy as a specific adjunct to traditional biopsy techniques.

A retrospective review of PMD patients treated between 2009 and 2014 identified that 310 had undergone brush biopsy sampling and liquid-based cytological examination in addition to conventional biopsy as part of their established clinical management. The majority of PMD lesions presented as leukoplakia on the floor of mouth and ventro-lateral tongue, with histopathology diagnoses revealing 165 'normal', 131 exhibiting dysplasia and 14 carcinoma-in-situ or SCC. Cytology diagnoses strongly correlated with 164 'normal', 137 showing dyskaryosis (the cytological equivalent of dysplasia) and 9 suggestive of SCC. Although not a substitute for biopsy and histological examination (which remains essential for SCC diagnosis), brush biopsy was highly acceptable to patients and thus appears to offer additional opportunities for less invasive repeat sampling and monitoring particularly of large, widespread or multifocal PMD during long-term follow-up and surveillance²¹.

Overall, the role of the pathologist in PMD management has been described as twofold: firstly, to exclude benign disease processes and secondly, to determine the presence and degree of epithelial dysplasia thus estimating the risk of cancer development²². The importance of full and effective communication between laboratory-based diagnostic pathologists and oral clinicians, especially in the management of PMD, can never be over-estimated. Many pathologists will also utilize second opinions and

consensus dysplasia grading to improve objectivity²³. Nonetheless, it is evident that dysplasia grading alone must be considered limited both as a diagnostic tool and as a predictor of clinical outcome. Perhaps of greatest significance are our study observations above that only 25 out of 58 malignant precursor lesions (43%) were dysplastic in nature, and that 19 non-dysplastic lichenoid lesions (33%) progressed to SCC, often aggressive, advanced-stage malignancies²⁰.

Of course, the potential for malignant change within oral lichenoid lesions has been recognized, and has remained controversial, for many years. There is little doubt that red and white mucosal lesions, clinically resembling lichenoid disease, can exhibit dysplastic features on histopathological examination and progress rapidly to SCC^{24,25}. It is also known that both dysplasia and lichenoid inflammation can co-exist in lesions, which adds to the on-going uncertainty and debate regarding the overall malignant potential of oral lichenoid lesions^{20,26}.

Regardless of clinical appearance, however, the histological finding of dysplasia within lichenoid disorders is probably the most salient diagnostic factor and such lesions should be regarded as 'high-risk' PMD. It may well be that the intense inflammatory cell infiltrate seen within the immediate sub-epithelial tissue represents an enhanced immune response to antigenically disturbed dysplastic epithelium. Long-term follow-up of affected patients in specialist clinics is thus advised^{17,25}. Many of these issues were first introduced in Chapter 3, and will be explored further in the patient cohort studies to be presented in Chapter 12.

Conclusions

Throughout the perspectives presented in this chapter is the central theme of a fundamental lack of understanding of the natural history of PMD, which affects both clinicians and their patients. In order to address the significant gaps in our knowledge, therefore, the work presented in the next 2 chapters of this book will attempt, using observational and longitudinal cohort studies of PMD patient populations from North-East England, to delineate a better understanding of the demographics, clinical presentation, efficacy of interventional treatment, and the significance of long term follow-up for patients with PMD.

References

1. Thomson PJ. The role of interventional surgery in oral potentially malignant disorders. *Faculty Dental Journal* 2014 5: 84-89.
2. Field EA, McCarthy CE, Ho MW, Rajlawat BP, Holt D, Rogers SN, Triantafyllou A, Field JK, Shaw RJ. The management of oral epithelial dysplasia: The Liverpool algorithm. *Oral Oncology* 2015 51: 883-887.
3. Thomson PJ, McCaul JA, Ridout F, Hutchison IL. To treat...or not to treat? Clinicians' views on the management of oral potentially malignant disorders. *British Journal of Oral & Maxillofacial Surgery* 2015 53: 1027-1031.
4. Nankivell P, Dunn J, Langman M. Feasibility of recruitment to an oral dysplasia trial in the United Kingdom. *Head & Neck Oncology* 2012 4: 40.
5. Marley JJ, Cowan CG, LameyP-J, Linden GJ, Johnson NW, Warnakulasuriya KAAS. Management of potentially malignant oral mucosal lesions by consultant UK oral and maxillofacial surgeons. *British Journal of Oral & Maxillofacial Surgery* 1996 34: 28-36.
6. Marley JJ, Linden GJ, Cowan CG, Lamey P-J, Johnson NW, Warnakulasuriya KAAS, Scully C. A comparison of the management of potentially malignant oral mucosal lesions by oral medicine practitioners and oral & maxillofacial surgeons in the UK. *Journal of Oral Pathology & Medicine* 1998 27: 489-495.
7. Epstein JB, Gorsky M, Fischer D, Gupta A, Epstein M, Elad S. A survey of the current approaches to diagnosis and management of oral premalignant lesions. *Journal of the American Dental Association* 2007 138: 1555-1562.
8. Kanatas AN, Fisher SE, Lowe D, Ong TK, Mitchell DA, Rogers SN. The configuration of clinics and the use of biopsy and photography in oral premalignancy: a survey of consultants of the British Association of Oral and Maxillofacial Surgeons. *British Journal of Oral & Maxillofacial Surgery* 2011 49: 99-105.
9. Mehanna HM, Rattay T, Smith J, McConkey CC. Treatment and follow-up of oral dysplasia – a systematic review and meta-analysis. *Head & Neck* 2009 31: 1600-1609.
10. Thomson PJ. The role of interventional surgery in oral potentially malignant disorders. *Faculty Dental Journal* 2014 5: 84-89.
11. Green RA, Exley C, Thomson PJ, Steele JG. Understanding patient views and experience of oral pre-cancer. *Journal of Dental Research* 2010 89B: 2571.

12. Green RA, Thomson PJ, Exley C, Steele JG. Understanding the transition from primary to secondary care: experiences of patients with oral pre-cancer. *British Journal of Oral & Maxillofacial Surgery* 2011 49 Suppl. 1: S60.
13. Green RA, Exley C, Steele JG, Thomson PJ. Patients understanding of the unknown: oral pre-cancer. *Journal of Dental Research* 2014 93B: 1515.
14. Green RA. Patient and professional views and experience of oral precancer. PhD Thesis, Newcastle University. 2013.
15. Tadakamadla J, Kumar S, Johnson NW. Quality of life in patients with oral potentially malignant disorders: a systematic review. *Oral Surg Oral Med Oral Pathol Oral Radiol* 2015 119: 644-655.
16. Ford PJ, Farah CS. Early detection and diagnosis of oral cancer: strategies for improvement. *Journal of Cancer Policy* 2013 1 : e2-e7 <http://dx.doi.org/10.1016/j.jcpo.2013.04.002>.
17. van der Waal I. Oral potentially malignant disorders: is malignant transformation predictable and preventable? *Med Oral Patol Oral Cir Bucal* 2014 19: e386-390.
18. Goodson ML, Kumar A, Thomson PJ. Oral precancer excision is required for definitive diagnosis: incisional vs. excisional biopsies in oral leukoplakia management. *Oral Oncology* 2011 47 S128-129. doi:10.1016/j.oraloncology.2011.06.414.
19. Goodson ML, Sloan P, Robinson CM, Cocks K, Thomson PJ. Oral precursor lesions and malignant transformation – who, where, what and when? *British Journal of Oral & Maxillofacial Surgery* 2015 53: 831-835.
20. van der Meij EH, Mast H, van der Waal I. The possible premalignant character of oral lichen planus and oral lichenoid lesions: a prospective five-year follow-up study of 192 patients. *Oral Oncology* 2007 43: 742-748.
21. Goodson ML, Smith DR, Thomson PJ. Efficacy of oral brush biopsy in potentially malignant disorder management. *Journal of Oral Pathology & Medicine* 2017 46: 896-901.
22. Speight PM, Torres-Rendon A. Oral epithelial dysplasia may progress to squamous cell carcinoma. *Pathology Case Reviews* 2011 16: 141-144.
23. Mullin MH, Brierley DJ, Speight PM. Second opinion reporting in head and neck pathology: the pattern of referrals and impact on final diagnosis. *Oral Surg Oral Med Oral Pathol Oral Radiol* 2015 119: 656-660.

24. Lovas JG, Harsanyi BB, ElGeneidy AK. Oral lichenoid dysplasia: a clinicopathologic analysis. *Oral Surg Oral Med Oral Pathol* 1989 68: 57-63.
25. Thomson PJ, Goodson ML. Clinical Presentation of Oral Precancer. In: PJ Thomson (ed) *Oral Precancer – Diagnosis and Management of Potentially Malignant Disorders*. Wiley-Blackwell; 2012. p48-74. ISBN 978-1-4443-3574-3.
26. Patil S, Rao R, Sanketh S, Warnakulasuriya S. Lichenoid dysplasia revisited – evidence from a review of Indian archives. *Journal of Oral Pathology & Medicine* 2014 44: 507-514.

CHAPTER ELEVEN

DEMOGRAPHICS

‘...the statistical characteristics of a population...’

Introduction

There are very few meaningful studies in the literature that address the specific epidemiology of PMD, so it is thus difficult to report accurate incidence or prevalence data. Napier & Speight¹ suggested a global prevalence of 1 to 5% for all PMD, whilst Petti² estimated between 1.5 and 2.6% for leukoplakia, the commonest PMD. Epidemiological studies such as these are often flawed, however, due to inconsistent diagnostic methodology, non-representative study populations and a lack of confirmatory histopathological data³. This is compounded by the realization that no data exist at all to document either national or regional UK statistics.

As outlined in Chapter 1, we first established the Newcastle PMD clinic in 1996, initially in conjunction with the regional Oral and Maxillofacial Oncology service at Newcastle General Hospital and then from 2010 onwards as a specific, weekly clinic in the out-patient Maxillofacial Unit at the Royal Victoria Infirmary (RVI). By 2015, we recorded approximately 1200 PMD patient attendances each year, comprising both new patient referrals and follow-up appointments for previously treated cases. Assuming a Newcastle upon Tyne population of around 280,000, an annual prevalence estimate of 0.43% may be made. This, of course, is a rather crude calculation with no discrimination between new patient presentations, review cases, or patient treatment episodes.

In this chapter, therefore, we will review three studies carried out in Newcastle upon Tyne in 2015 in an attempt to characterise PMD disease presentation, patient demographics and treatment intervention within the region⁴.

Study 1: Demography of PMD Patients in Newcastle upon Tyne (2015)

Aim of the Study

The aim of this simple, cross-sectional study was to determine a more detailed demographic profile of a defined cohort of patients attending for diagnosis and treatment at the specialist Newcastle upon Tyne Hospitals NHS Foundation Trust PMD clinical service during a four-week period in 2015. In this manner, a more objective record of patient numbers, age, sex, oral lesions and interventional PMD management occurring in North-East England would be characterized.

Method

Caldicott Approval

Applying appropriate principles to creation of new, demographic and clinico-pathological oriented databases, formal Caldicott approval was obtained from the Joint Newcastle University / Newcastle upon Tyne Hospitals NHS Foundation Trust to collect anonymized data from medical records, operating logs and pathology reports from PMD patients treated by the author and attending specialist Oral and Maxillofacial services at the RVI⁵. Individual patient consent was not sought for data collection, because no patient identifiable material was used and no individual treatment, clinical intervention or clinical outcome was influenced by database construction and analysis.

Patient Demography

During four consecutive weeks in 2015, commencing Monday 12 January and finishing Friday 6 February, anonymized demographic and clinico-pathological details were recorded prospectively for consecutive patients attending clinics or undergoing surgery for PMD. Each patient was assigned a study number and the following data documented for each case: age, sex, smoking and alcohol habits, reason for hospital attendance (new presentation, review patient or surgical treatment), clinical appearance (leukoplakia, erythroleukoplakia or erythroplakia) and anatomical site of oral mucosal lesions, whether single-site or multiple-lesion disease presentation, histopathology diagnoses, together with details of the treatment modality patients underwent (clinical observation, medical treatment or CO₂ laser surgery intervention).

Histopathology Diagnosis

All biopsy procedures on PMD patients were carried out, as deemed appropriate by well-defined existing management protocols, in Oral and Maxillofacial Surgery clinics under the direction of the author and formalin-fixed tissue specimens subsequently assessed via standardized histopathology examination by experienced oral pathologists at the RVI working to agreed diagnostic criteria. Using the World Health Organization (WHO) classification, specimens were graded into mild, moderate or severe dysplasia categories, carcinoma-in-situ (CiS) or squamous cell carcinoma (SCC). In addition, the presence of hyperkeratosis, lichenoid inflammation (LI), or the diagnoses of proliferative verrucous leukoplakia (PVL) or chronic hyperplastic candidosis (CHC) were recorded^{6,7}.

Results

A total of 75 patients attended the Newcastle PMD service during the four-week period. If patients presented with multiple lesions or had undergone more than one biopsy procedure, a single 'most significant' histopathological diagnosis was determined by the author from a review of the relevant clinical records for each case.

In terms of ethnicity, 74 patients (98%) were white European and 1 was Asian. The patient population included 46 males (with an age range of 41 to 83 years, and a mean of 60.9 years) and 29 females (age range from 29 to 85 years, with a mean of 58.1 years). The cohort varied between 13 to 26 patients per week and overall comprised 20 new referrals, 51 review patients and 4 surgical cases, as summarized in Figure 11.1 and Table 11.1.

Although data relating to the numbers of cigarettes smoked per day or units of alcohol consumed per week were not fully completed for every patient in this study, the majority reported that they currently smoked cigarettes or were recent ex-smokers (67%), as shown in Table 11.2, and all patients confirmed either regular or occasional alcohol consumption.

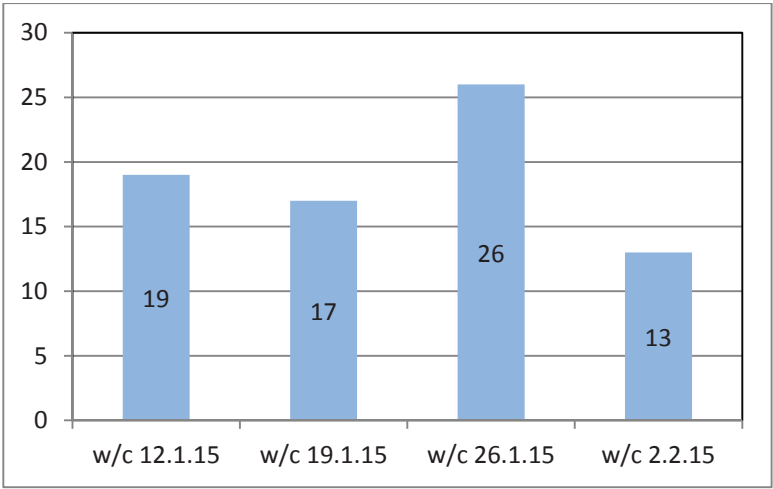


Figure 11.1: PMD patient attendances each week during the period 12 January to 6 February 2015 (w/c week commencing).

Table 11.1: Reasons for Patient Attendance at the PMD Service

Patient Activity	No. of Patients	%
New Patients	20	27
Review Patients	51	68
Patients Undergoing Surgery	4	5
Total	75	100

Table 11.3 shows that 84% of patients presented with oral leukoplakia, whilst erythroleukoplakia and erythroplakia were much less common; 11% and 5% respectively. Fifty patients (67%) presented with single-site disease and 25 (33%) exhibited multiple PMD lesions at distinct or bilateral anatomical sites; in 20 cases (27%) 2 sites were involved, whilst in a further 5 patients (7%) 3 sites were affected.

In total, 100 oral lesions were seen in the 75 patients and Table 11.4 lists the numbers at each anatomical site, together with the distribution of single and multiple lesion presentations. Overall, the floor of mouth and ventro-lateral tongue comprised the most commonly affected region (46%), with buccal mucosa next most common (14%). Multiple lesion disease appeared to present most frequently at gingiva/alveolus, buccal mucosa and floor of mouth sites.

Following lesion biopsy, histopathological diagnoses were available for 74 patients (1 patient failed to return for biopsy investigation), and these are listed in Table 11.5. Although a total of 100 mucosal lesions were identified, not all were biopsied and therefore a single, most significant, histopathology diagnosis was identified by the author and assigned to each patient. Whilst a wide range of diagnoses were recorded, the presence of epithelial dysplasia or carcinoma-in-situ was identified in the majority of cases (53 or 71%). In 17 cases a diagnosis of PVL, most commonly with the additional presence of dysplasia, was made.

Review of clinical management in Table 11.6 shows that the majority of patients, 52 (69%), had been treated by interventional laser surgery, 20 were managed by clinical observation alone and 2 were treated medically (systemic anti-fungal treatment for chronic hyperplastic candidosis); 1 patient failed to return following initial consultation. During the 4-week study period, 4 patients attended theatre for laser treatment, primarily to excise dysplastic leukoplakia arising on the tongue.

Table 11.2: Smoking Habits of PMD Patients

Current Tobacco Use	No. of Patients	%
Smoker	38	51
Ex-Smoker	12	16
Non-Smoker	25	33
Total	75	100

Table 11.3: Clinical Appearance of PMD Lesions

Clinical Appearance	No. of Patients	%
Leukoplakia	63	84
Erythroleukoplakia	8	11
Erythroplakia	4	5
Total	75	100

Table 11.4: Anatomical Site Distribution of PMD Lesions

Anatomical Site	Total Lesions	Single Lesions	Multiple Lesions
Floor of Mouth	21	13	8
Ventral Tongue	11	9	2
Lateral Tongue	14	11	3
Tongue Dorsum	2	2	0
Buccal Mucosa	14	4	10
Labial Commissure	5	3	2
Labial Mucosa	2	1	1
Palate	9	7	2
Fauces	2	1	1
Retromolar Region	2	0	2
Gingiva	8	2	6
Alveolus	10	2	8
Totals	100	55	45

Table 11.5: Histopathology Diagnoses for PMD Patients

Histopathology Diagnosis	No. of Patients	%
Unknown	1	1.3
Hyperkeratosis	4	5.3
Hyperkeratosis + Lichenoid Inflammation (LI)	8	10.7
Chronic Hyperplastic Candidosis	5	6.7
Proliferative Verrucous Leukoplakia (PVL)	2	2.7
Mild Dysplasia	20	26.7
Mild Dysplasia + LI	2	2.7
Mild Dysplasia + PVL	12	16.0
Moderate Dysplasia	10	13.3
Moderate Dysplasia + LI	3	4.0
Moderate Dysplasia + PVL	3	4.0
Severe Dysplasia	2	2.7
Carcinoma-in-Situ	1	1.3
Squamous Cell Carcinoma (SCC)	2	2.7
Total	75	100.0

Table 11.6: PMD Patient Management

Management	No. of Patients	%
Interventional Laser Surgery	52	69
Clinical Observation	20	27
Medical Treatment	2	2.7
Did Not Re-Attend	1	1.3
Total	75	100

Discussion

Patient Numbers and Demographics. Seventy-five Newcastle PMD patients (55 review or treatment cases, and 20 new referrals) were identified during the 4-week study period; extrapolated over 12 months, this amounts to around 900 clinical cases, and is similar to un-published audit data obtained for the Maxillofacial Oncology / Dysplasia service during 4 weeks in January 2008 in which 97 cases, 17 new and 80 follow-up patients were identified. These patient figures appear reasonably large in number when compared with Marley et al⁸ who reported that the majority of UK Oral and Maxillofacial Surgeons saw less than 50 PMD patients per year and also more recently Kanatas et al⁹, in a questionnaire-based study of 199 UK surgeons, who reported even lower patient figures: only 38% of responding clinicians saw more than 30 new PMD patients per year, whilst a further 38% estimated they reviewed less than 30 in their clinics. In addition, the majority of clinicians (59%) did not provide designated, specialist clinics so the potential to concentrate expertise in diagnosis and management of their PMD patient cohorts must inevitably be reduced.

Overall, the patient group in this study appeared fairly representative of the Newcastle upon Tyne population, which has a self-reported ethnicity of 95% white British/Other and a median age of 41 years (Office for

National Statistics 2012). Male patients, with a mean age of 60.9 years, accounted for 61% of the study group. Unfortunately, there are very few comparable data sets in the literature to compare these results, although Napier and Speight¹ previously observed leukoplakia to be most common in males between the fourth and seventh decades of life. In an earlier UK study, Jaber et al¹⁰ reviewed 630 patients with dysplastic PMD lesions attending specialist Oral Medicine clinics in Southern England (Bristol and London) between 1972 and 1996 and found that 56% were male, with a mean age of 55 years. Warnakulasuriya et al¹¹ reported on 1,357 PMD patients seen in Oral Medicine clinics at Guy's Hospital in London over a 10-year period in the 1990's, noting that the majority (61%) were female and that 70% were over 47-years of age; this cohort, however, comprised primarily patients with oral lichen planus and, as only 15% of oral lesions exhibited epithelial dysplasia, these data may not be wholly relevant or indeed comparable to the Newcastle study group.

Worldwide, data is more difficult to interpret owing to significant variation in risk factor behaviour and disease presentation. In Brazil, Pulino et al¹² analyzed biopsy results from 252 patients with suspicious oral lesions attending specialist clinics at the University of Sao Paulo over a 7-year period, but confirmed only 29 intra-oral PMD lesions (11.5%); mean age was 57.8 years, again with male predominance. Villa & Gohel¹³ identified only 27 PMD patients out of a total of 3,142 (0.9%) attending specialist diagnostic clinics at Boston University's School of Dental Medicine during an 8-month review, but similarly noted that males and current smokers were most likely to exhibit PMD.

Clinico-Pathological Features

63 patients in this study (84%) presented with leukoplakia, with floor of mouth and ventro-lateral tongue sites most commonly affected (46%); Jaber et al¹⁰ reported similar findings with around 42% of lesions arising on ventro-lateral tongue and floor of mouth sites, although only 50% presented as leukoplakia. In this study, both the labial commissure/buccal mucosal region and the palate/faucets/retromolar complex accounted for 19% of PMD cases, with gingiva and alveolar mucosa providing a further 18%; these sites accounted for 22%, 12% and 10%, respectively, of oral lesions reported by Jaber et al¹⁰. Napier & Speight¹ usefully observed that PMD site is highly dependent upon both ethnicity and tobacco habit, with labial commissure/buccal mucosa particularly affected in South-East Asian patients using oral tobacco products and floor of mouth/ventral tongue sites more common in European populations smoking cigarettes.

Twenty-five patients (33%) presented with multiple-lesion disease, with the buccal mucosa, floor of mouth, and gingiva/alveolar mucosa most frequently involved (32 out of 45 lesions, or 71%); Table 11.4. We have previously shown multiple lesion disease to particularly affect buccal mucosa and floor of mouth sites (27 out of 54 lesions, or 50%) in a North-East population of 96 PMD patients¹⁴. There were no specific age, sex or tobacco use influences on disease presentation in either this or our earlier study but, as previously noted, comprehensive details relating to the amount of tobacco consumed were not available for all patients in this study¹⁴.

A wide range of histopathological diagnoses were recorded for the 75 study patients. Overall, 53 patients exhibited some degree of dysplasia on biopsy: 34 mild (64%), 16 moderate (30%) and 3 severe dysplasia or carcinoma-in-situ (6%); Jaber et al¹⁰ noted 47%, 29% and 24%, respectively, for these categories. Many of the lesions in this study exhibited, sometimes in combination with dysplasia, the varying presence of lichenoid inflammation (5) or PVL (15). These later histological categories have, of course, become more pertinent in histopathology diagnoses in recent years. In 2 cases (2.7%), SCC was identified unexpectedly following laser excision of dysplastic lesions. We have previously reported a 9% incidence of unexpected SCC in laser excision specimens and such early diagnosis and treatment of invasive cancer provides strong evidence to support interventional treatment protocols^{15,16}.

Patient Management

Having previously documented the interventional laser surgery protocol practiced in Newcastle, it is unsurprising that 52 study patients (69%) were treated by CO₂ laser: 48 attended for post-operative follow-up during the study period, with 4 actively undergoing surgery^{6,17}. Whilst no universal consensus on treatment exists, complete excision of 'high risk' lesions is recommended and most authorities now advise that surgical excision or ablation of identifiable lesions is likely to be more effective than observation, both for treating PMD disease and preventing progression to malignancy. The difficulty remains in defining precisely which oral mucosal lesions are 'high risk', and this is an important issue which will be further addressed in this book^{18,19}.

Limitations of the Study

Cross-sectional studies are, of course, disadvantaged by their ‘snap-shot’ nature and the potential for prevalence-incidence bias, although there does appear reasonable consistency through recent years when the data are compared with that from our 2008 audit. A further limitation of this particular data set is the recognition that ‘other’ Newcastle PMD patients may have presented to alternate clinical services during the study period, including ‘general’ Oral and Maxillofacial Surgery and other Dental or Oral Medicine clinics. It remains our experience, however, that over time the majority of Newcastle patients diagnosed with PMD are referred during their ‘treatment journey’ to the specialist PMD service for advice and treatment²⁰.

Conclusions

The data collected in this study, I believe, helped gain additional insight into the contemporaneous presentation and treatment of PMD disease in Newcastle upon Tyne, yet it remains a small ‘snap-shot’ of that overall activity. It is also disappointing for a specialist clinic service that comprehensive details of the amounts of tobacco and alcohol consumed were not recorded for every PMD patient at each clinic or treatment visit. Nonetheless, this study adds detailed information to our current knowledge base and may well help in the planning of future clinical service provision. It seems clear, however, that analyses of patient presentation, diagnosis and treatment over a longer time period is necessary to provide further and more detailed data regarding PMD disease in North-East England.

Study 2: A Retrospective Review of the Use of Interventional CO₂ Laser Surgery in Newcastle (1996 – 2014)

Aim of the Study

Whilst evidence-based guidelines for PMD management remain limited, most authorities agree that initial incision biopsy to identify dysplasia should be followed by attention to patient risk factor behaviour and subsequent lesion excision for definitive diagnosis and optimal treatment¹⁷. Whilst a variety of surgical procedures have been proposed over the years, including scalpel excision, electro-surgery, cryotherapy,

and photodynamic therapy, use of the CO₂ laser has become increasingly recommended^{21,22}.

Minimally invasive laser surgery can be performed under general or local anaesthesia, facilitating precise excision with improved haemorrhage control and excellent visibility, analgesia by sealing of local nerve endings, minimal damage to adjacent tissue thus reducing the post-surgical inflammatory response, reduced scarring and contraction encouraging excellent soft tissue mobility and minimal oral dysfunction. In addition, full histopathological assessment of tissue specimens is facilitated, repeat surgery may be carried out if required and both patient follow-up and surveillance strategies are better coordinated¹⁷. Whilst laser ablation (superficial lesion destruction) may be indicated for smaller or anteriorly-sited lesions, particularly less dysplastic ones on visible gingiva, most patients are treated by excision. All patients are usually managed in the theatre environment to ensure optimal operating conditions and appropriate laser safety precautions^{6,17}. Figure 11.2 illustrates intra-operative use of the CO₂ laser in the operating theatre.

The specific aim of this retrospective study was to review the use of interventional laser surgery in the management of PMD, by the author using a standardised treatment protocol, over a 19-year period.

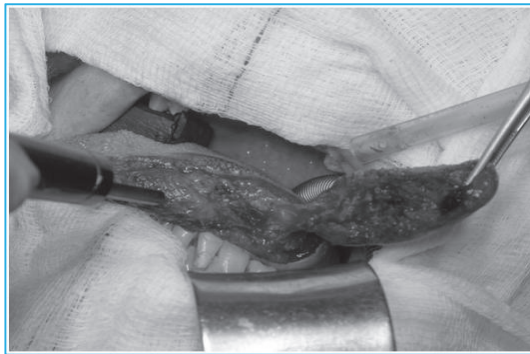
**A****B**

Figure 11.2: Interventional Laser Surgery showing (A) CO₂ laser in use in the operating theatre for PMD treatment under general anaesthesia, and (B) intra-operative view during excision of dysplastic lateral tongue mucosa.

Method

A retrospective audit of Newcastle Oral and Maxillofacial theatre operating lists was undertaken to determine anonymized treatment details for patients attending for laser treatment of PMD disease between August 1996, when the author commenced clinical practice in Newcastle, and December 2014 (inclusive). All lesions underwent incision biopsy assessment prior to laser intervention, and both laser excisions and ablations were carried out, as deemed appropriate, by the same operator

working to standardised protocols with consistent diagnostic and treatment decisions⁷. It was not the intention of this study to document the demographics of treated patients, to record clinico-pathological diagnoses for individual mucosal lesions or to review clinical outcomes.

Results

In total, 773 CO₂ laser operations were carried out on 590 patients during the 19-year period, with a clear trend for increasing numbers of treatments to be performed through the years, as illustrated in Figure 11.3. Whilst the majority of patients, 513 (87%) required only 1 laser surgery intervention, 77 (13%) required multiple treatments most frequently 2 or 3 sequential procedures over time; these latter data are listed in Table 11.7.

Laser excision (removing the entire visible mucosal lesion) was the preferred technique in 650 cases (84%), but as can be seen from Figure 11.4 a trend for increasing numbers of ablation procedures was evident as the years progressed, with 123 (16%) ablations carried out in total. Figure 9.5 also reveals a similar trend for increasing use of local anaesthesia for laser surgery, although most operations were still performed under general anaesthesia (608 cases or 79%); only 2 cases were operated under local anaesthesia and intravenous sedation techniques.

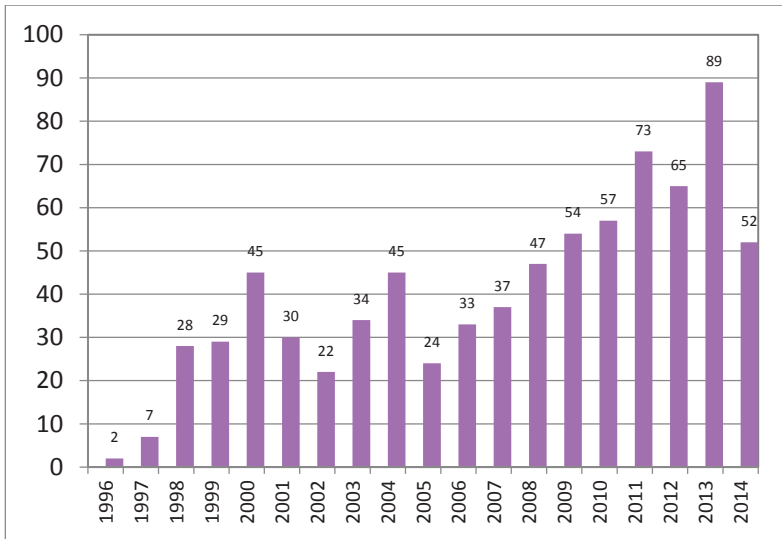


Figure 11.3: Number of Interventional Laser Surgery Operations carried out each year between 1996 and 2014.

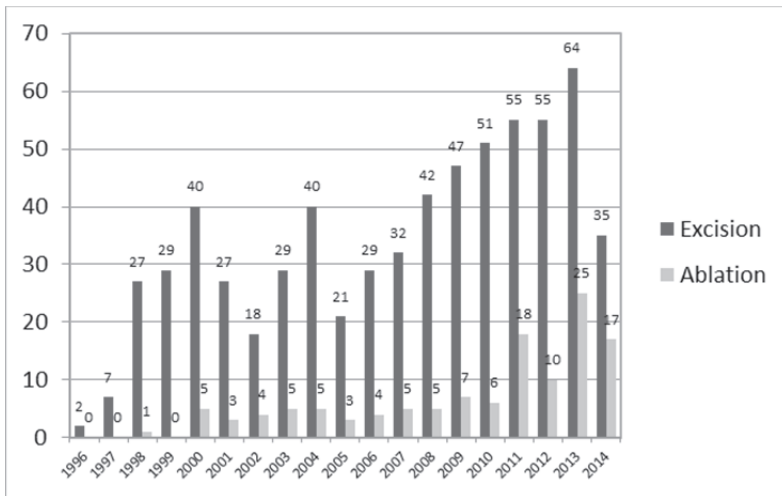


Figure 11.4: Number of Laser Excision and Ablation Procedures carried out each year between 1996 and 2014 (total number of procedures = 773).

Table 11.7: Number of Laser Procedures Required per Patient each Year

Year of Presentation	No. Of Laser Procedures					
	1	2	3	4	5	>5
1996	0	0	1	0	0	1
1997	5	1	1	0	0	0
1998	13	2	1	0	0	0
1999	22	2	1	0	0	0
2000	35	1	0	1	1	1
2001	21	1	2	0	0	0
2002	12	3	0	1	0	0
2003	24	2	2	1	0	0
2004	30	1	1	0	0	0
2005	13	0	0	0	0	0
2006	17	3	0	0	0	0
2007	22	2	2	0	0	0
2008	31	5	1	0	1	0
2009	35	2	2	1	0	0
2010	36	5	1	0	0	0
2011	50	8	4	0	0	0
2012	50	2	1	0	0	0
2013	64	8	0	0	0	0
2014	33	1	0	0	0	0
Totals	513	49	20	4	2	2

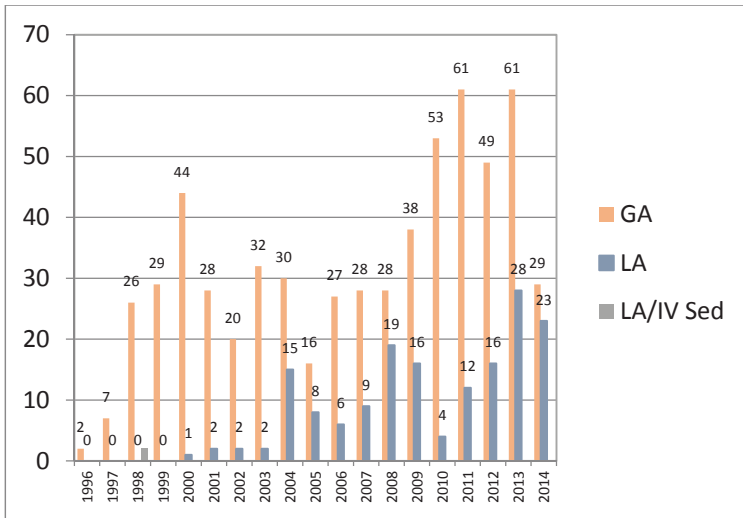


Figure 11.5: Type of Anaesthesia Used for Laser Surgery each year between 1996 and 2014 (total number of procedures = 773); GA General Anaesthesia, LA Local Anaesthesia, LA/IV Sed Local Anaesthesia supplemented by intra-venous sedation.

Discussion

Interventional Laser Surgery

This study provides one of the largest laser surgery data sets in the contemporary literature; Jerjes et al²³, for example in one of very few similar studies, reported on only 123 laser procedures carried out on 77 patients during a 6-year period at the Head and Neck Unit at University College Hospital in London. It is clear that the use of CO₂ laser surgery increased during our study, peaking at 89 operative interventions in 2013. This undoubtedly reflects an increase in patient throughput through the Newcastle PMD service and probably an increasing trend to offer intervention to patients, although it is unclear whether it reflects any rise in PMD disease incidence in North-East England over this period.

The majority of patients (513) required only 1 laser treatment, although 77 underwent multiple treatments, ranging from 2 to more than 5, although most commonly only 2 or 3 were required (in 69 patients). In their study, Jerjes et al²³ observed that 62 out of 77 treated PMD patients required only

one round of laser treatment, whilst a further 15 cases required up to 5 episodes of treatment during follow-up. Whilst the details of individual patient histories were not examined in this study, the most common reasons for repeat laser treatment are usually recurrence of oral lesions (same site) or appearance of further lesions (new site) over time.

Whilst a variety of lasers have been used to treat oral mucosal disease, including higher potency and deeper penetrating neodymium:yttrium-aluminium garnet (Nd:YAG) and potassium-titanyl-phosphate (KTP) lasers, the CO₂ laser has become the preferred modality, primarily due to its ease of intra-operative use and its effective oral soft tissue interaction^{17,19,22-25}. Lim et al²⁵ reported reduction in rates of leukoplakia recurrence when KTP was used instead of CO₂, but this was a small, retrospective ablative study and did not examine the efficacy of laser excision.

We have previously reported upon common complications following intra-oral laser surgery in 82 treated PMD patients, including pain, bleeding, submandibular salivary gland swelling following floor of mouth interventions, and lingual nerve dysaesthesia as a consequence of lateral tongue surgery, but most of these proved minor and transitory in nature resolving within the first few post-operative months²⁶. Laser surgery is probably, therefore, the preferred treatment intervention for PMD because of its reliability and reproducibility.

Laser Excision versus Ablation

The fundamental distinction between laser excision and ablation is the specific advantage that excision biopsy facilitates histopathological analysis of mucosal lesions in their entirety, thus providing a definitive diagnosis and reducing the risk of 'under-diagnosis' inherent in incision biopsy sampling; we have previously reported 'under-diagnosis' of dysplasia in 28%, and masking of invasive cancer in 9%, of treated PMD lesions^{26,27}. Whilst a number of authors have reviewed the use of intra-oral CO₂ laser ablative surgery²⁸⁻³¹ or excision surgery^{24,32} they have actually treated relatively small numbers of leukoplakia patients and have not carried out any comparative analyses of technique efficacy.

Brouns et al³³ more recently described the treatment of 144 leukoplakia patients with surgical excision, laser ablation or clinical observation alone but did not feel able to compare treatment modalities due to the highly variable indications for treatment. In a direct, retrospective comparison of

laser excision and ablation treatment for 77 leukoplakias, Del Corso et al³⁴ found no significant difference in clinical outcome, although recommended excision of lesions exhibiting dysplasia to prevent recurrence; this study was flawed, however, because although CO₂ laser was used for excision, Nd:YAG was employed for every ablation procedure rendering meaningful comparison difficult.

In Newcastle, we usually only performed ablation for lesions arising on tightly-bound mucoperiosteal surfaces such as gingiva, alveolar mucosa and hard palate to avoid bony dehiscence, or in soft palate sites to avoid the risk of post-excision oro-nasal fistula; all lesions still underwent pre-laser incision biopsy^{17,35}. Ishi et al³⁶ also advised laser excision of PMD lesions on non-keratinised tongue and buccal mucosa, but believed ablation suitable for gingival cases. On occasion, however, ablation may also be a pragmatic solution if small lesions (usually less than 1cm² size arising on non-keratinised epithelium) are to be treated, because the resultant thermal artefacts seen in small excision specimens render accurate dysplasia grading unreliable and impractical; this technique, as applied to a floor of mouth lesion is illustrated in Figure 11.6.



A

**B**

Figure 11.6: Laser Ablation showing (A) localised, small patch of non-homogeneous, mildly dysplastic leukoplakia arising in the left floor of mouth and (B) appearance post-CO₂ laser ablation following superficial mucosal vapourisation without excision.

Type of Anaesthesia

Figure 11.5 clearly shows an increasing number of local anaesthetic procedures carried out over time, and interestingly this parallels the similar rise seen in the use of ablative surgery (Figure 11.4). This most likely reflects the increasing personal experience of the operator and more discretionary application of varying laser techniques to different clinical scenarios. Laser ablation is usually a shorter and less technically demanding procedure, which is well tolerated by conscious patients¹⁷. Not all local anaesthetic procedures are undertaken to facilitate ablation, however, as some patients' general medical status and/or cardio-respiratory co-morbidities inevitably contra-indicate the elective use of general anaesthesia for oral surgery; only 2 patients in the study required intravenous sedation to supplement local anaesthesia.

Laser excision of large dysplastic lesions arising on floor of mouth and ventro-lateral tongue sites can, of course, be technically demanding and may be poorly tolerated by conscious patients. The additional requirements of adjacent soft tissue retraction, haemostasis, accuracy in visualisation of the operative field and lack of patient movement usually necessitate the use of general anaesthetic techniques; an example of partial glossectomy under general anaesthesia to treat a dysplastic tongue lesion is shown in Figure 11.2B.

Limitations of the Study

Although a large number of CO₂ laser interventions over a 19-year period have been listed and reviewed in this study, the significance of the results is limited by the one-centre basis of the work and particularly by inevitable clinician bias inherent in treatment selection for these patients. Similarly, the study primarily lists and describes the numbers and types of CO₂ surgical procedures carried out, with little context to explain either the clinical or the histopathological background of treated disease.

Conclusions

Interventional management is now more commonly recommended for PMD management, with laser surgery often preferred as the treatment intervention. Laser, the acronym for 'light amplification by stimulated emission of radiation' delivers monochromatic, coherent waves of light energy to target tissue, so that the effective photo-thermal reaction produces vapourisation, allowing the surgeon to incise, resect or ablate lesions. The carbon dioxide (CO₂) laser is preferred for treatment of oral mucosal disease because CO₂ generated laser light is within the mid-infrared range (10,600nm), close to the spectroscopic absorption peak for water, rendering successful interaction of oral soft tissues with the laser beam^{16,17,37}.

Study 3: A Prospective Study Documenting Interventional CO₂ Laser Surgery Use in Newcastle During 2015

Aim of the Study

Directly following on from the previous study, the aim of this further investigation was to document prospectively in detail the use of CO₂ laser surgery by the author in the management of PMD in Newcastle during the 12 months of the calendar year 2015, and to thereby confirm both the pattern of disease presentation and mode of treatment.

Method

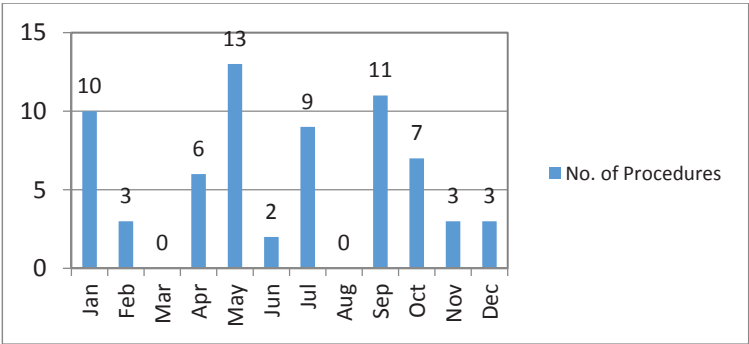
The author thus recorded full but anonymised details of laser operations carried out during this 12 month period. Details of age and sex of treated

patients, presenting clinical lesions, histopathological diagnoses, length of time between treatment decision and subsequent attendance for surgery, mode of intervention (whether excision or ablation), and use of general anaesthesia (GA) or local anaesthesia (LA) were all recorded.

Results

In total, 67 laser operations were performed during the 12-month period, summarized in Figure 11.7; the number of procedures carried out each month ranged from 0 to 13 dependent upon operating theatre timetabling and patient and surgeon availability.

Figure 11.7: Number of Laser Surgery Procedures Performed Each Month During 2015 (total number of procedures = 67).



Clinico-Pathological Features

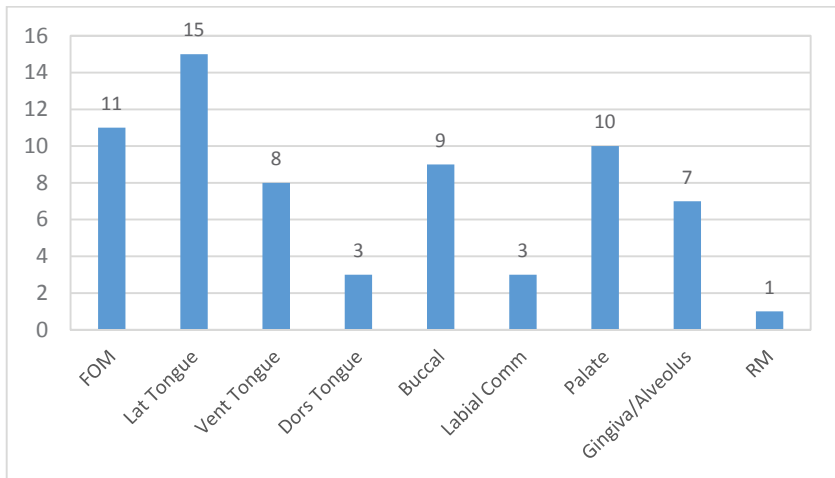
39 male patients (age range 38-84yrs; mean age 59.8yrs) and 28 female patients (age range 37-81yrs; mean age 58.5yrs) were treated during this period. 51 patients were new PMD referrals undergoing laser surgery for the first time, whilst 16 cases attended for repeat laser surgery; none of the 67 patients underwent more than 1 laser surgery procedure during the 12-month study period. The majority of treated PMD lesions appeared clinically as leukoplakia (56 or 83.5%), with erythroleukoplakia and erythroplakia much less common, as shown in Table 11.8. Figure 11.8 confirms that most laser-treated lesions presented on floor of mouth and ventrolateral tongue sites (34 or 50.7%). In terms of histopathological diagnoses, Table 11.9 reveals that 41 lesions (61%) exhibited features of either epithelial dysplasia or carcinoma-in-situ, 13 (19.4%) were

diagnosed as PVL, whilst a further 10 (14.9%) showed features of PVL in combination with dysplasia.

Table 11.8: Clinical Appearance of Treated PMD Lesions

Clinical Appearance	No. of Patients	%
Leukoplakia	56	83.5
Erythroleukoplakia	10	15.0
Erythroplakia	1	1.5
Total	67	100

Figure 11.8: Number of Laser Surgery Procedures Performed versus Anatomical Site (total number of procedures = 67).



FOM: Floor of Mouth, Dors Tongue: Dorsum of Tongue, Labial Comm: Labial Commissure, RM: Retromolar Region.

Table 11.9: Histopathology Diagnoses for Treated PMD Lesions

Histopathology Diagnosis	No. of Patients	%
Hyperkeratosis	1	1.5
Chronic Hyperplastic Candidosis (CHC)	2	3.0
Proliferative Verrucous Leukoplakia (PVL)	13	19.4
Mild Dysplasia	24	35.8
Mild Dysplasia + PVL	9	13.4
Moderate Dysplasia	7	10.4
Moderate Dysplasia + PVL	1	1.5
Severe Dysplasia	8	12.0
Carcinoma-in-Situ	2	3.0
Total	67	100.0

Use of Interventional Laser Surgery

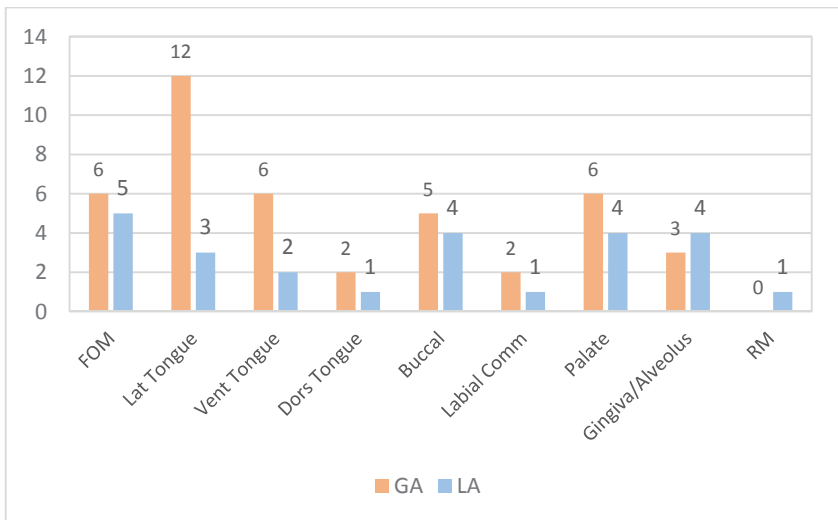
Time to laser treatment, defined as the interval between initial diagnosis and treatment decision to the date when laser surgery was carried out, varied from 2 to 15 weeks, with an overall mean of 8 weeks. In relation to the specific use of CO₂ laser in the 67 cases, most procedures (46) were performed as surgical excision biopsies, with the majority (42) carried out under GA. Table 11.10 confirms that, whilst most laser excision procedures (31) were carried out using GA, ablative surgery was performed in similar numbers under GA and LA; 11 and 10 operations, respectively.

Table 11.10: Use of General Anaesthesia (GA) and Local Anaesthesia (LA) for Laser Excision and Ablation Procedures

	GA	LA	Totals
Laser Excision	31	15	46
Laser Ablation	11	10	21
Totals	42	25	67

Figure 11.9 illustrates the use of GA and LA techniques applied to the varying anatomical sites of treated PMD lesions confirming that, whilst most PMD sites were operated on using either anaesthetic technique, ventrolateral tongue surgery was more often performed under GA (18) compared with LA (5).

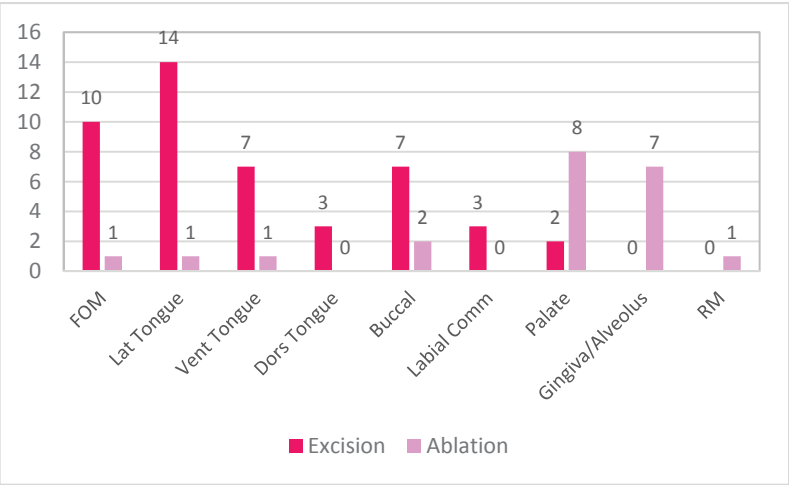
Figure 11.9: Number of GA and LA Laser Surgery Procedures versus Anatomical Site (total number of procedures = 67)



FOM: Floor of Mouth, Dors Tongue: Dorsum of Tongue, Labial Comm: Labial Commissure, RM: Retromolar Region.

Figure 11.10 similarly plots the number of laser excision or ablation techniques performed at each anatomical site, showing a clear predominance for excision surgery to occur at floor of mouth and ventrolateral tongue sites (31), whilst laser ablation was primarily used for palatal, gingival and alveolar lesions (16).

Figure 11.10: Number of Laser Excision and Ablation Procedures versus Anatomical Site (total number of procedures = 67)



FOM: Floor of Mouth, Dors Tongue: Dorsum of Tongue, Labial Comm: Labial Commissure, RM: Retromolar Region.

Discussion

Patient Numbers and Demographics

By carrying out a prospective data collection of CO₂ laser operations, this study has allowed additional characterisation of patients and PMD disease in North-East England over a 12 month period in 2015. Whilst concentrating on patients undergoing intervention, the age and sex profile of these 67 laser patients is very similar to the demographic profile observed in the cross-sectional patient study reported in Chapter 3 with, in addition, the confirmation that the predominant clinical presentation of oral leukoplakia arising at floor of mouth and ventro-lateral tongue sites remains highly consistent between studies.

Clinico-Pathological Features

Unsurprisingly, as a study group undergoing interventional management, the vast majority of PMD lesions were shown to be dysplastic or characterised as exhibiting features of PVL on histopathological examination. It was not, of course, the remit of this study to analyse clinico-pathological data in depth but nonetheless such observation supports the profiling of PMD patients and histopathology data previously reported.

Interventional Laser Surgery

Whilst the previous study reviewed the evolution and overall utilization of CO₂ laser surgery as a treatment modality over a 19-year period, this study was designed to analyse contemporaneous interventional management over a more specific 12-month period. Interestingly, both the numbers of treated patients and the mode of laser treatment remained highly consistent between studies.

It was interesting to note the varying numbers of cases operated upon each month (0 to 13, with a mean of 5.6); these figures were influenced not only by the number of patients presenting for treatment but also the myriad of administrative influences regarding clinic and theatre timetabling and both patient and surgeon availability.

A useful, additional observation in this investigation was the determination of treatment times for patients: 64 patients (95%) were operated on within 12 weeks of diagnosis, whilst 2 patients waiting 14 and 15 weeks for treatment specifically requested a later date for their surgery. Dost et al¹⁶ reported that a 6-month period may be considered as a pragmatic 'cut-off' to account for biopsy sampling error or the co-existence of unexpected malignancy during PMD assessment. Whilst no specific time frame or guidelines have ever been proposed regarding PMD treatment intervention, a 12-week period seems reasonable to rule out significant disease progression between initial incision biopsy diagnosis and intervention; this is the time frame we have tried to adhere to in our treatment protocols^{6,17}.

Diajil et al³⁸ reviewed 100 Newcastle PMD patients and undertook a comprehensive analysis of clinical management times, confirming that 91% of patients were diagnosed and 49% definitively treated within 12 weeks of initial referral. Any delayed management, however, which

primarily affected patients assessed as 'low risk' PMD disease was not found to adversely influence clinical outcome. Issues related to outcome following PMD treatment will be reviewed in more detail in Chapter 10.

Excision versus Ablation

As previously discussed, CO₂ laser surgery usefully offers both excision and ablative modes of treatment, although laser excision biopsy remains the preferred treatment option for oral PMD lesions, confirmed in this study by its use in 46 patients (69%). The role of laser ablation in the superficial destruction of palatal, gingival and alveolar lesions is supported by Figure 9.10 which confirms that 16 out of 18 lesions at these sites were treated by ablation rather than excision. Many of these issues have already been covered in the previous section of this chapter.

Type of Anaesthesia

Although the majority of laser surgery was carried out under GA (42 cases or 63%), Figure 9.9 shows that both GA and LA techniques were utilised at most oral sites during the study except for lateral and ventral tongue lesions which were primarily operated on under GA (18 out of 23 cases). Decisions regarding treatment choice and the use of GA or LA for individual procedures requires careful assimilation of background medical issues, the specific technical requirements of the operative procedure and consideration of overall patient management issues.

Limitations of the Study

This is a review of 12 months laser surgery performed by one clinician treating PMD lesions in Newcastle upon Tyne. Although inevitably limited by its one-site location, vulnerability to treatment bias and its overall descriptive nature, clinico-pathological data for treated patients and their presenting PMD lesions have been usefully expanded upon and further characterised.

Conclusions

Contemporaneous opinion in the PMD literature now emphasizes the role of interventional management so that definitive surgical excision, rather than clinical monitoring or medical therapy, is most often recommended to

treat PMD^{16,37}. It has, of course, been this author's opinion for many years that interventional laser surgery offers a pragmatic and effective therapeutic intervention during oral carcinogenesis, and the unique and substantial data documenting 840 laser surgery operations carried out over a 20-year period, presented and analysed in the latter two studies in this chapter, is a clear testimony to this clinical management strategy. In the next chapter, however, we will attempt to determine the overall efficacy of this treatment intervention by reviewing a number of cross-sectional and longitudinal patient cohort studies.

References

1. Napier SS, Speight PM. Natural history of potentially malignant oral lesions and conditions: an overview of the literature. *Journal of Oral Pathology & Medicine* 2008 37: 1-10.
2. Petti S. Pooled estimate of world leukoplakia prevalence: a systematic review. *Oral Oncology* 2003 39: 770-780.
3. Thomson PJ. Introduction. In: PJ Thomson (ed) *Oral Precancer – Diagnosis and Management of Potentially Malignant Disorders*. Wiley-Blackwell; 2012. p1-12. ISBN 978-1-4443-3574-3.
4. Thomson PJ. An investigation into the efficacy of interventional therapy for oral potentially malignant disorders. MD Thesis, University of Bath. 2016.
5. The Caldicott Committee. Report on the review of patient- identifiable information. 1997. Department of Health, UK.
6. Thomson PJ, Wylie J. Interventional laser surgery: an effective surgical and diagnostic tool in oral precancer management. *International Journal of Oral & Maxillofacial Surgery* 2002 31:145-153.
7. Sloan P. Pathological aspects of oral precancer. In P J Thomson (Ed) *Oral Precancer – Diagnosis and Management of Potentially Malignant Disorders*. Wiley-Blackwell 2012. p93-106. ISBN 978-1-4443-3574-3.
8. Marley JJ, Cowan CG, LameyP-J, Linden GJ, Johnson NW, Warnakulasuriya KAAS. Management of potentially malignant oral mucosal lesions by consultant UK oral and maxillofacial surgeons. *British Journal of Oral & Maxillofacial Surgery* 1996 34: 28-36.
9. Kanatas AN, Fisher SE, Lowe D, Ong TK, Mitchell DA, Rogers SN. The configuration of clinics and the use of biopsy and photography in oral premalignancy: a survey of consultants of the British Association

- of Oral and Maxillofacial Surgeons. *British Journal of Oral & Maxillofacial Surgery* 2011 49: 99-105.
10. Jaber MA, Porter SR, Speight P, Eveson JW, Scully C. Oral epithelial dysplasia: clinical characteristics of western European residents. *Oral Oncology* 2003 39: 589-596.
 11. Warnakulasuriya S, Kovacevic T, Madden P, Coupland VH, Sperandio M, Odell E, Moller H. Factors predicting malignant transformation in oral potentially malignant disorders among patients accrued over a 10-year period in South East England. *Journal of Oral Pathology & Medicine* 2011 40: 677-683.
 12. Pulino BdeFB, dos Santos JFM, Pastore GP, Radaic P, Filho GPdeC, Pereira RA. Oral cancer: potentially malignant lesions and statistics of diagnosed cases in the municipality of Santo Andre-SP. *Journal of Health Sciences Institute* 2011 29: 231-234.
 13. Villa A, Gohel A. Oral potentially malignant disorders in a large dental population. *Journal of Applied Oral Science* 2014 22: 473-476.
 14. Hamadah O, Goodson ML, Thomson PJ. Clinicopathological behaviour of multiple oral dysplastic lesions compared with that of single lesions. *British Journal of Oral & Maxillofacial Surgery* 2010 48: 503-506.
 15. Goodson ML, Thomson PJ. Management of oral carcinoma – benefits of early precancerous intervention. *British Journal of Oral & Maxillofacial Surgery* 2011 49: 88-91.
 16. Dost F, LeCao K, Ford PJ, Ades C, Farah CS. Malignant transformation of oral epithelial dysplasia: a real world evaluation of histopathologic grading. *Oral Surg Oral Med Oral Pathol Oral Radiol* 2014 117: 343-352.
 17. Thomson PJ. Management of Oral Precancer. In: PJ Thomson (ed) *Oral Precancer – Diagnosis and Management of Potentially Malignant Disorders*. Wiley-Blackwell; 2012. p107-137. ISBN 978-1-4443-3574-3.
 18. Arnaoutakis D, Bishop J, Westra W, Califano JA. Recurrence patterns and management of oral cavity premalignant lesions. *Oral Oncology* 2013 49: 814-817.
 19. Kumar A, Cascarini L, McCaul JA, Kerawala CJ, Coombes D, Godden D, Brennan PA. How should we manage oral leukoplakia? *British Journal of Oral & Maxillofacial Surgery* 2013 51: 377-383.
 20. Green RA. Patient and professional views and experience of oral precancer. PhD Thesis, Newcastle University. 2013.
 21. Ishi J, Fujita K, Komori T. Laser surgery as a treatment for oral leukoplakia. *Oral Oncology* 2003 39: 759-769.

22. Mogedas-Vegara A, Hueto-Madrid J-A, Chimenos-Kustner E, Bescos-Atin C. The treatment of oral leukoplakia with the CO₂ laser: a retrospective study of 65 patients. *Journal of Cranio-Maxillo-Facial Surgery* 2015 43: 677-681.
23. Jerjes W, Upile T, Hamdoon Z, Al-Khawalde M, Morcos M, Mosse CA, Hopper C. CO₂ laser of oral dysplasia: clinicopathological features of recurrence and malignant transformation. *Lasers Medicine Science* 2012 27: 169-179.
24. Matsumoto K, Suzuki H, Asai T, Wakabayashi R, Enomoto Y, Kitayama M, Shigeoka M, Kimoto A, Takeuchi J, Yutori H, Komori T. Clinical investigation of carbon dioxide laser treatment for lingual leucoplakia. *Journal of Oral & Maxillofacial Surgery, Medicine & Pathology* 2015 27: 493-497.
25. Lim B, Smith A, Chandu A. Treatment of oral leukoplakia with carbon dioxide and potassium-titanyl-phosphate lasers: a comparison. *Journal of Oral & Maxillofacial Surgery* 2010 68: 597-601.
26. Goodson ML, Sugden K, Kometa S, Thomson PJ. Complications following interventional laser surgery for oral cancer and precancerous lesions. *British Journal of Oral & Maxillofacial Surgery* 2012 50: 597-600.
27. van der Waal I. Potentially malignant disorders of the oral and oropharyngeal mucosa; terminology, classification and present concepts of management. *Oral Oncology* 2009 45: 317-323.
28. Chandu A, Smith ACH. The use of CO₂ laser in the treatment of oral white patches: outcomes and factors affecting recurrence. *International Journal of Oral & Maxillofacial Surgery* 2005 34: 396-400.
29. van der Hem PS, Nauta JMK, van der Wal JE, Roodenburg JL. The results of CO₂ laser surgery in patients with oral leukoplakia: a 25 year follow up. *Oral Oncology* 2005 41: 31-37.
30. Deppe H, Mucke T, Hohlweg-Majert B, Hauck W, Wagenpfeil S, Holzle F. Different CO₂ laser vaporization protocols for the therapy of oral precancerous lesions and precancerous conditions: a 10 year follow-up. *Lasers Medicine Science* 2012 27: 59-63.
31. Brouns ER, Baart JA, Karagozoglu KH, Aartman IH, Bloemena E, van der Waal I. Treatment results of CO₂ laser vaporisation in a cohort of 35 patients with oral leukoplakia. *Oral Diseases* 2013 19: 212-216.
32. Yang SW, Tsai CN, Lee YS, Chen TA. Treatment outcome of dysplastic leucoplakia with carbon dioxide laser – emphasis on the factors affecting recurrence. *Journal of Oral & Maxillofacial Surgery* 2011 69: 78-87.

33. Brouns ER, Baart JA, Karagozoglu KH, Aartman IH, Bloemena E, van der Waal I. Malignant transformation of oral leukoplakia in a well-defined cohort of 144 patients. *Oral Diseases* 2014 20: e19-24.
34. Del Corso G, Bartolomeo Gissi D, Tarsitano A, Costabile E, Marchetti C, Montebugnoli L, Foschini MP. Laser evaporation versus laser excision of oral leukoplakia: a retrospective study with long-term follow-up. *Journal of Cranio-Maxillo-Facial Surgery* 2015 43: 763-768.
35. Thomson PJ, Goodson ML (2015). Transoral Laser Microsurgery of the Oral Cavity. In: M Bernal-Sprekelsen, I Vilaseca (ed) *Transoral Laser Microsurgery of Benign and Malignant Lesions*. Thieme; 2015. p124-130. ISBN 978-3-13-172391-8.
36. Ishi J, Fujita K, Munemoto S, Komori T. Management of oral leukoplakia by laser surgery: relation between recurrence and malignant transformation and clinicopathological features. *Journal of Clinical Laser Medicine Surgery* 2004 22: 27-33.
37. Gomes CC, Gomez RS. Oral leukoplakia: what is achieved by surgical treatment? *Annals of Oral & Maxillofacial Surgery* 2013 1: 9.
38. Diajil AR, Robinson CM, Sloan P, Thomson PJ. Clinical outcome following oral potentially malignant disorder treatment: a 100 patient cohort study. *International Journal of Dentistry* 2013
<http://dx.doi.org/10.1155/2013/809248>.

CHAPTER TWELVE

COHORTS

‘...a group of individuals sharing similar characteristics or experience...’

Introduction

The protocol for interventional laser surgery adopted by the author in Newcastle, whereby PMD lesions are provisionally characterised by incision biopsy and subsequently treated by formal laser excision or ablation of ‘high risk’ dysplastic lesions, has undoubtedly helped rationalize modern management techniques for patients presenting with PMD offering both definitive diagnosis through whole lesion analysis and efficacious, low morbidity treatment^{1,2}. It is encouraging that most contemporaneous authors now support such a management strategy³⁻⁵.

The specific hypothesis that such intervention prevents or reduces the ultimate risk of malignant transformation remains to be proven, however. Edwards⁶ commented that surgical excision of dysplastic oral lesions might reduce the risk of malignancy by 50%, but this is only an estimate and not readily applicable as a statistic during the active treatment of individual patients or lesions.

It is probably true to say that, whilst there is no strictly universally agreed hierarchy of biomedical evidence, randomised controlled trials rank much higher in terms of scientific methodology than observational studies, expert opinion and anecdotal experience. Many authors would add that systematic reviews and meta-analyses should rank even higher than controlled trials as they combine data from a variety of different studies and sources.

Randomised controlled trials are favoured because they eliminate investigator bias and potential confounding factors by randomly assigning patients to one type of intervention or another, or indeed often to a non-intervention or placebo arm. Whilst this may all be scientifically valid,

such trials are not always appropriate or acceptable to patients or clinicians in the medical environment.

The absence of relevant randomised clinical trials, especially comparing the benefits of surgical intervention with clinical observation or lesion surveillance, inevitably weakens the evidence base in PMD studies. It remains difficult, however, to envisage a comprehensive trial design that has both scientific validity and acceptability to clinicians and patients; a ‘non-intervention’ arm to manage lesions exhibiting significant dysplastic change, for example, being especially problematic when there remains such an unpredictable and biologically devastating risk for malignant transformation.

Cohort studies, whilst ranking less highly in the hierarchy of clinical research trials, do offer important opportunities for longitudinal observation of patients sharing common clinical presentations, similar risk factor behaviour and undergoing standardized diagnostic and management protocols. There are actually significant advantages in undertaking patient cohort studies in PMD research and these are summarised in Table 12.1. The longitudinal observation of a group of patients through time and the collection of data at regular intervals can actually produce data superior to that of cross-sectional and retrospective studies and indeed is often the recommended methodology in observational epidemiology.

Table 12.1: Advantages of PMD Patient Cohort Studies

Defined study population sharing common characteristics and risk factor behaviour
Inclusion criteria facilitate recruitment of cases with known dysplasia
Standardised diagnostic process
Coordinated treatment protocol with standardised intervention
Consistent decision making
Longitudinal follow-up of subjects with documented clinical outcome data

In the absence, therefore, of multi-centre, randomised, prospective clinical trials, a number of large PMD patient cohort studies have been undertaken in our clinics in Newcastle upon Tyne. Whilst not necessarily universally applicable, these studies all benefited from a defined and static patient

population known to be at high risk of oral SCC, consistent and coordinated clinical management coordinated by one clinician, and a regular and consistent follow up strategy. In this chapter, we will review the data from these studies to both document clinical outcomes for patients and to try to determine the efficacy of treatment intervention in PMD management.

Initial Cohort Studies^{1,7-10}

In our very first patient cohort study, a retrospective review was carried out of 57 consecutive, PMD patients undergoing CO₂ laser excision of histopathologically proven dysplastic lesions and followed-up for a mean period of 18 months. Laser surgery effectively excised 55 lesions, 11 of which exhibited more severe dysplasia or frankly invasive SCC compared with initial biopsy. Overall, 76% of patients were disease-free, whilst 23% developed new PMD at distinct or multiple sites. Six patients (11%) developed SCC either elsewhere in the oral cavity or upper aero-digestive tract. No clinical or pathological features were predictive of subsequent clinical behaviour, risk of recurrent disease or malignant transformation. This paper was the first in the literature to define and document clinical outcome for a patient cohort undergoing standardised interventional laser surgery to treat PMD as part of a coordinated management protocol. Laser surgery was thus advocated, in contradistinction to conservative management, to facilitate efficacious, low morbidity treatment and to establish definitive histological diagnosis. It essentially formed the basis of a defined interventional management protocol and informed many subsequent clinical research papers on PMD and intra-oral laser surgery¹.

Following on from the first study, we subsequently detailed the clinical outcomes following 248 laser excisions performed on 199 PMD patients during a 7-year period (1997 to 2004). The majority presented with single-lesion leukoplakia arising on floor of mouth and ventro-lateral tongue sites. Twenty-two percent of cases exhibited further PMD, usually at new oral sites and within 24 months of initial presentation, requiring between 1 to 5 additional laser treatments. Malignant transformation occurred in 4%. Neither lesion appearance nor histopathology predicted clinical outcome. This paper reinforces the efficacy of interventional laser surgery in excising dysplastic mucosal lesions and in reducing same site recurrence and overall malignant transformation risk⁷.

Developing this research theme, we followed a further 78 PMD patients and documented clinical outcome data over a mean post-laser follow-up period of 58 months in an attempt to evaluate clinico-pathological factors that may have influenced treatment results. CO₂ laser surgery was again confirmed as an effective treatment modality, with 64% of patients assessed as disease free following excision of their presenting PMD lesions, although 32% developed recurrent or new site PMD and 4% SCC (but at new sites distinct from treatment). No statistical significance was seen between patient age, sex, clinical lesion appearance, anatomical site, histopathological grading, presence of dysplasia in resection margins or alcohol consumption and clinical outcome. Smokers, however, were at higher risk of dysplasia recurrence ($p=0.04$). Regular patient follow-up is necessary due to field cancerisation effects and the risk of recurrent / further disease. This was, in fact, one of the first published studies to define the factors that might influence treatment outcome following laser surgery for PMD⁸.

In a further refinement of this investigative approach, a 100 PMD patient cohort was followed for up to 10-years post laser and a detailed analysis of clinical outcome data was carried out. At the time of most recent follow-up, 62 patients were disease-free following laser treatment, 17 showed same site recurrent PMD, 14 developed new site PMD, 5 underwent same site malignant transformation and 2 developed SCC at new oral sites. The incidence of further disease in these 48 cases increased with the length of follow-up and was also noted to be higher for non-homogeneous leukoplakia, large lesions, more severe dysplasia, floor of mouth and ventral tongue sites and in patients who had never smoked. This significant, new paper provides the most comprehensive patient cohort data published to date detailing clinical outcome following interventional laser surgery for oral potentially malignant disorders⁹.

Directly following on from the above study, a subsequent investigation took place to determine if time delays between initial PMD diagnosis and management influenced eventual clinical outcome. An overall clinical management time was determined for each case, together with measurement of time intervals for provisional and definitive diagnosis, laser intervention and post-operative follow-up; Figure 12.1.

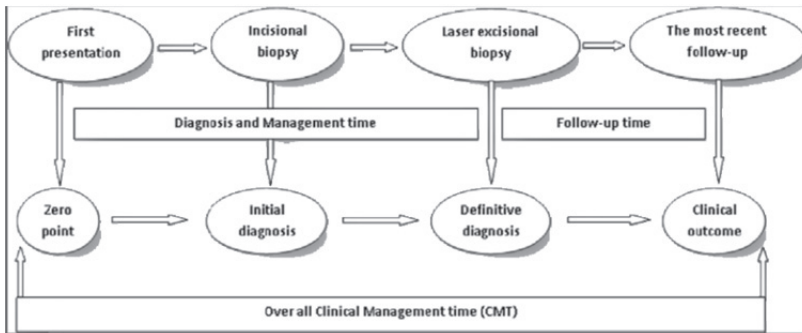


Figure 12.1: Time Points During the Course of PMD Patient Management

Within 3 months of presentation, incision biopsy diagnoses were achieved for 91 patients and 49 excisions of ‘high risk’ lesions were carried out; delayed management of ‘low risk’ patients did not adversely affect outcome. Patients with more severe dysplasia, disease active status or further dysplasia were all treated within the shortest times, emphasizing the appropriateness of clinical judgement in determining risk. As in our previous observations, recurrent or further PMD risk increased with length of follow up. No time to treatment influences were seen for patients developing SCC, however¹⁰.

In view of the lack of meaningful randomised trials in PMD management, we therefore carried out a retrospective review of 2 cohorts of new patients presenting with single, histopathologically confirmed dysplastic PMD lesions. All patients were seen by the author and, according to established protocols¹, patients deemed ‘high risk’ had their lesions excised by laser, whilst ‘low risk’ lesions were observed. Regular follow-up and clinical outcome was documented for 3 years: 78 patients (51 male and 27 female with a mean age of 58 years) underwent laser excision, whilst 39 (20 male, 19 female, with mean age 56 years) were observed. Clinically, the majority of lesions in both groups were leukoplakias arising on the floor of mouth and ventral tongue. Microscopically, 86% of laser excision specimens exhibited moderate or severe dysplasia, whilst 69% of observed lesions showed only mild dysplasia on incision biopsy. Post-laser, 64% of patients were disease free, but only 23% of observed cases showed clinical resolution of their mucosal disease. 32% of the laser group developed further PMD, with another 4% developing SCC (again at sites distant to original PMD presentation). 77% of PMD lesions persisted in the

observation group, but there were no instances of malignant transformation in the 'low risk' group¹¹.

Clearly limited in significance by its non-randomisation and small size, this study nonetheless emphasized again the effectiveness of interventional laser surgery. On the basis of the above cohort studies, it seems increasingly difficult to justify a policy of non-intervention in PMD management. This, however, will be studied in more detail in the next investigation.

The Newcastle 590 Patient Cohort Study¹²

Aim of the Study

The aim of this retrospective, cohort study was to collate and review in detail all available patient demographic, clinico-pathological, diagnostic, treatment and clinical outcome data for patients that attended the Newcastle Oral and Maxillofacial Surgery service for CO₂ laser treatment of new-onset PMD between 1st August 1996, when the author commenced consultant practice and established a dedicated PMD service, and a clinical outcome census date of 31 December 2014. Spanning a 19-year period, and effectively summarizing the majority of the author's clinical practice in this arena, I trust the reader will understand the reasons for presenting and studying this research at some length. In many ways, this is the definitive PMD patient cohort study.

Method

Caldicott Approval

As previously outlined, approval was obtained from Newcastle University / Newcastle upon Tyne Hospitals NHS Foundation Trust to facilitate anonymized, retrospective data collection from medical records, operating logs and pathology reports from PMD patients treated by the author and attending specialist services at Newcastle Dental and Royal Victoria Infirmary hospitals¹³. Inclusion criteria required new, untreated single-site PMD confirmed by incision biopsy. Patients with previous or multi-focal PMD, and those with a history of OSCC or head and neck radiotherapy were excluded.

Patient and Treatment Details

Demographic and clinico-pathological details collected from patients undergoing CO₂ laser surgery between August 1996 and December 2014 comprised: date of treatment, age and sex, clinical appearance and anatomical site of oral lesion, histopathology diagnoses for incision and post-laser excision biopsies, follow-up data and any further laser treatment. Clinical outcome was determined at the study census date (31 December 2014) unless malignancy supervened when this became study exit-point.

Histopathology Diagnoses

Incision biopsies were performed under the direction of the author and excision specimens obtained following interventional laser treatment as detailed previously¹. Laser surgery was carried out by the author, or by colleagues working under direct supervision, within 6 to 12 weeks following incision biopsy to avoid disease progression. Formalin-fixed tissue specimens were assessed via standardized histopathology examination by oral pathologists at the Royal Victoria Infirmary working to agreed diagnostic criteria with peer review and consensus grading¹³. Using the World Health Organization (WHO) classification, specimens were graded as mild, moderate or severe dysplasia, carcinoma-in-situ (CiS) or OSCC. In addition, presence of hyperkeratosis, lichenoid inflammation (LI), or diagnoses of PVL and chronic hyperplastic candidosis (CHC) were recorded.

Clinical Outcome Categories

By reviewing case records, the author assigned patients to one of the following clinical outcome categories: Disease Free (DF), the absence of PMD, Further Disease achieving DF status following additional intervention (Further/DF), Further Disease persisting despite intervention (Further/Persistent) and MT, if SCC was confirmed by histopathological examination.

Statistical Analyses

Descriptive Statistics were used to summarise details of patient demography, clinical features and pathological diagnoses, together with documentation of treatment interventions, clinical outcome and follow-up data. Histopathology diagnoses were treated as categorical variables and

testing of agreement between incision biopsy and post-laser excision biopsy diagnoses carried out using weighted kappa statistics; a coefficient of 1 represented perfect agreement.

Clinical Outcomes were stratified as DF or Persistent Disease (further PMD or MT); success rates and 95% Confidence Intervals (CI) were calculated. Multivariate logistic regression was used to analyse factors potentially prognostic of DF outcome (age at first treatment, sex, lesion appearance, anatomical site and histopathology data). Relationships between factors were explored using chi-square tests for categorical variables or logistic regression to check for collinearity. Factors were first explored univariately and then a multivariate model built using a stepwise procedure until all variables were significant at the 10% level. Candidate variables for the initial model were those significant at the 20% level univariately. If collinearity was suspected only the most significant univariate relationships were included in the model. MT was analysed using univariate Cox regression to investigate clinico-pathological variables that might influence time to transformation. All statistical analyses were performed using SAS/STAT® 9.3 software (SAS Institute Inc, Cary, USA).

Results

Table 12.2 provides an overall summary of the study results.

Patient Demography. 590 PMD patients were treated during the 19-year period. Mean age at presentation was 59.7 years, with 347 males (59%) and 243 females (41%); 513 (87%) were current or ex-smokers and 496 (84%) regularly consumed alcohol.

Clinical Features. 468 lesions were leukoplakias, with erythroleukoplakia (99) and erythroplakia (23) less common. Floor of mouth and ventro-lateral tongue sites were involved in 358 cases.

Table 12.2: Demographic, Clinico-Pathological and Outcome Data (No. of Patients = 590)

Age	
Mean (SD)	59.7 (12.6)
Median (range)	60.0 (23-94)
Sex	No. (%)
Male	347 (58.8%)
Female	243 (41.2%)
Lesion	No. (%)
Leukoplakia	468 (79.3%)
Erythroleukoplakia	99 (16.8%)
Erythroplakia	23 (3.9%)
Site	No. (%)
Floor Of Mouth	172(29.2%)
Lateral Tongue	130 (22.0%)
Buccal Mucosa	59 (10.0%)
Palate	57 (9.7%)
Ventral Tongue	56 (9.5%)
Labial Commissure	29 (4.9%)
Fauces / Retromolar Region	26 (4.4%)
Gingiva	21 (3.6%)
Alveolus	18 (3.1%)
Labial Mucosa	11 (1.9%)
Dorsum of Tongue	11 (1.9%)
Histopathology Diagnosis (Most Significant)	No. (%)
Hyperkeratosis	8 (1.4%)
Hyperkeratosis + Lichenoid Inflammation (LI)	28 (4.8%)
Chronic Hyperplastic Candidosis	17 (2.9)
Proliferative Verrucous Leukoplakia (PVL)	15 (2.5%)
Mild Dysplasia	118 (20.0%)
Mild Dysplasia + LI	28 (4.7%)
Mild Dysplasia + PVL	40 (6.8%)
Moderate Dysplasia	105 (17.8%)
Moderate Dysplasia + LI	24 (4.0%)
Moderate Dysplasia + PVL	15 (2.5%)
Severe Dysplasia	99 (16.8%)
Severe Dysplasia + LI	8 (1.4%)
Severe Dysplasia + PVL	4 (0.7%)
Carcinoma-in-Situ	81 (13.7%)
Duration of Follow up* (Years)	

Mean (SD)	7.3 (5.1)
Median (Range)	6 (0-19)
Treatment Intervention per Patient	
Mean (SD)	1.2 (0.6)
Median (Range)	1 (1-8)
Clinical Outcome	
Disease Free	404 (68.4%)
Further / Disease Free	34 (5.8%)
Further / Persistent Disease	53 (9.0%)
Malignant Transformation	99 (16.8%)

**Time from first treatment to 31st Dec 2014*

Histopathology Features

Histopathological grading, based upon the most significant diagnosis obtained from either incision or laser excision biopsy showed 522 lesions (88.5%) exhibited dysplasia or CiS. Incision and post-laser excision biopsies were available for direct comparison in 609 cases: in 307 (50%) diagnoses agreed, although in 220 (36%) excision specimens were 'upgraded' due to more severe dysplasia (121 or 20%) or OSCC diagnosis (99 or 16%). In 82 cases (14%), excision specimens were less severe than incision samples. Whilst overall kappa agreement was deemed moderate at 0.45 (95% CI 0.40 to 0.51), specific agreement regarding OSCC diagnosis between incision and excision biopsies was only 0.25 (95% CI 0.15 to 0.35).

Patient Management

The initial treatment modality was laser excision in 526 patients (89%) and ablation in 64 (11%). In total, 773 treatments were performed on 590 patients: 513 (87%) underwent 1 laser surgery, whilst 77 (13%) required repeat intervention. The mean number of treatments per patient was 1.2 (Standard Deviation 0.6), with a median of 1 (range 1 to 8).

Clinical Outcome

Mean follow-up was 7.3 years (SD 5.1 years), with a median of 6 years (range 0 to 19 years). 438 patients (74.2%, 95% CI 70.7 to 77.8%) were DF at study census date. 404 patients achieved this immediately following laser surgery, whilst an additional 34 required further laser intervention; 77 repeat treatments were provided with the mean number to achieve DF 2.26 (range of 2 to 4) and a mean time of 32.88 months (range 4 to 130.9

months). Out of 87 patients who required repeat treatment, 53 exhibited persistent PMD at census. MT was seen in 99 cases; in 71 (12%), OSCC diagnosis was made unexpectedly following histopathological examination of laser excision specimens, whilst a further 28 (4.8%) underwent MT during follow-up; median time to malignancy was 87.3 months (95% CI 59.9 to 149.2). Overall, 80 OSCCs were identified at the same site as their PMD precursor whilst 19 arose at new, distinct sites. Erythroleukoplakias were most likely to exhibit malignancy ($p=0.0019$; Fisher's exact test).

Table 12.3: Univariate Analysis of Clinico-Pathological Factors Influencing Disease Free Status

Factor	Logistic p-value
Site	0.001
Age	0.026
Sex	0.112
Lesion	<0.001
Dysplasia (None, Mild, Moderate vs Severe)	<0.001
LI	0.043
PVL	0.289

Statistical Analyses

Univariate logistic regression analyses of clinico-pathological features potentially influencing DF status are summarised in Table 12.3. PVL did not meet the 20% criteria for inclusion in the multivariate model and anatomical site was sparse and highly correlated to a number of other factors therefore was also excluded.

Table 12.4: Final Multivariate Model of Clinico-Pathological Factors Influencing Disease Free Status

Effect		Odds Ratio Estimate	95% Wald Confidence Limits		P-value
Lesion LK	EK vs	0.659	0.269	1.619	0.022
Lesion LK	ELK vs	0.510*	0.314	0.828*	
Dysplasia Severe	Mild vs	2.247*	1.270	3.976*	<0.0001
Dysplasia Severe	Moderate vs	1.693	0.954	3.006	
Dysplasia Severe	None vs	0.628	0.369	1.068	
LI Yes	No vs	0.489*	0.258	0.926	0.028

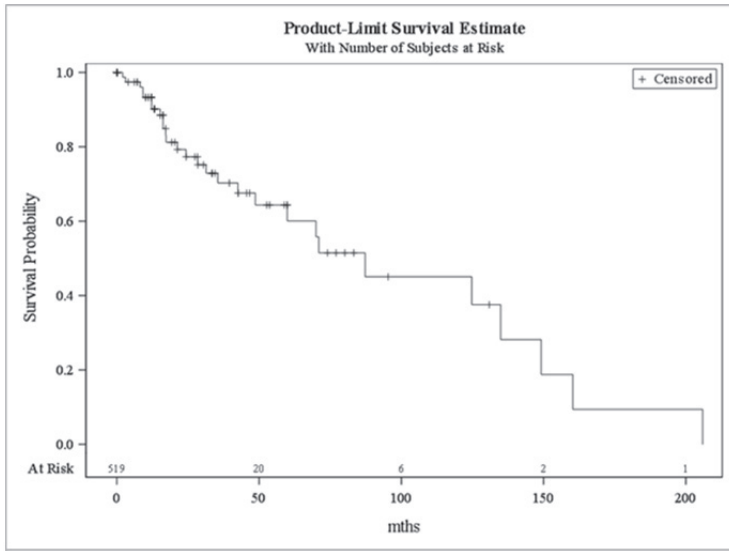
*Significant at the 5% level

Odds Ratio estimates >1 indicate increased likelihood of DF status, <1 decreased likelihood of DF status

(LK=Leukoplakia; ELK=Erythroleukoplakia; EK=Erythroplakia)

The final multivariate model contained lesion appearance ($p=0.022$), dysplasia ($p<0.001$) and the presence of LI ($p=0.028$); Table 12.4. Erythroleukoplakia had significantly lower odds of achieving DF status compared with leukoplakia (OR 0.51, 95% CI 0.31 to 0.83), whilst the odds of DF status were significantly increased for lesions exhibiting mild compared with severe dysplasia (OR 2.25, 95% CI 1.27 to 3.98). The likelihood of DF status was reduced for lesions exhibiting LI features (OR 0.49, 95% CI 0.26 to 0.93). 28 patients underwent MT, with the median time to MT in the cohort 87.3 months (95% CI 59.9 to 149.2); Figure 12.2. Univariate Cox regression analysis showed no significant influence of clinico-pathological variables on MT time, but this may have been due to the small number of events in the analysis.

Figure 12.2: Kaplan-Meier Analysis plotting Time to Malignant Transformation (months) for PMD Precursor Lesions



Discussion

This data set of 590 PMD patients, undergoing standardised and coordinated treatment by a single surgeon offers additional insight into the natural history of PMD in North-East England, albeit in a defined hospital population. The study provides detailed outcome data recorded over a follow-up period of 19 years (mean 7.3 years).

Patient Demographics

Demographics confirmed a median patient age of 60 years and, with 59% of cases male and 41% female, a 1.4:1 male to female ratio. No significant relationships between age/sex and PMD presentation or clinical outcome were characterised which is similar to previous analyses⁷⁻¹⁰. Most patients regularly smoked tobacco and drank alcohol confirming these as relevant aetiological factors in Northern England¹⁵.

Clinico-Pathological Features

The majority of PMD lesions were leukoplakias arising on the floor of mouth and ventro-lateral tongue, consistent with previous observations, probably due to underlying site predisposition to epithelial cell dysregulation and carcinogenic influence^{16,17}. 88.5% of lesions in this study exhibited dysplasia or CiS, emphasizing the ‘high-risk’ nature of PMD disease in this population¹⁸. Re-grading of tissue specimens in a research-orientated approach was not undertaken as this would not have reflected the ‘real-world’ nature of the study⁵. Whilst the prognostic significance of PMD lesions exhibiting LI (sometimes termed lichenoid dysplasias) has proved controversial^{19,20}, this study has confirmed that persistent PMD disease is associated with lesions exhibiting LI. Previous clinical studies have observed isolated erythroleukoplakic lesions with LI arising at ventro-lateral tongue sites to be at ‘high risk’ of MT^{5,21}. Whilst oral lichenoid lesions have not been routinely followed up continuously, this may be advisable to monitor for early cancerous change²⁰.

Laser Treatment

Whilst the use of CO₂ laser as an effective, low-morbidity PMD treatment modality has been documented previously, this study has facilitated analysis of laser treatment in the largest patient cohort reported in the literature¹⁸. Laser excisions were performed in 89% of patients distinguishing this study from previous publications favouring ablative techniques²², the latter disadvantaged by lack of definitive biopsy and repeat application required for disease resolution. It is notable that 87% of patients in this study required only 1 intervention.

Clinical Outcome

This long-term cohort study has facilitated detailed stratification of clinical outcome data, although it is difficult to compare these with other publications due to differing diagnostic and clinical decision making, varying treatment protocols and inconsistent terminology seen in other papers³. 75% of study patients were, however, DF at census date confirming a degree of treatment efficacy for laser intervention, pertinent because nearly 90% of treated lesions exhibited significant dysplasia. In terms of characterisation, DF patients were generally younger with mild or moderate dysplasia and no LI.

Long term clinic follow-up helped distinguish patients DF after further treatment (34 or 5.8%) from persistent disease despite intervention (53 or 9%). Patients in the Further/DF category were younger, developed new lesions at different sites, had less severe dysplasia and disease resolved after multiple treatments. In contradistinction, Further/Persistent patients were older, commonly had PVL lesions on gingiva, alveolus and labial mucosa and underwent ablation rather than excision. Traditionally, PVL diagnoses were made late during disease history following progressive spread, high recurrence and MT^{23,24}. This study helps emphasise the importance of early PVL recognition in specialist PMD clinics, but recognises that ablative treatment intervention may have reduced efficacy.

Malignant Transformation

MT rates for PMDs vary worldwide with quoted values ranging between 0.1 to 40%, and an overall rate estimated at 12%, making it difficult to counsel individual patients³. This study distinguished between 71 cases (12%) in which pre-existing OSCCs were discovered upon PMD laser excision and 28 (4.8%) in which OSCC development occurred post-treatment (4.8%). The significance of early OSCC diagnosis is emphasised because all 71 patients were definitively treated by their initial laser intervention. Overall, 80 OSCC cases were identified at the same-site as precursor lesions whilst 19 developed at new sites during follow-up confirming the need for long-term surveillance post-treatment. Recognisable clinico-pathological features associated with MT included an erythroleukoplakic appearance, severe dysplasia or CiS in initial biopsies and floor of mouth/ventro-lateral tongue sites of origin.

Limitations of the Study

This was not a prospective, randomised controlled trial, nor was it multi-centre, and it is recognised that clinician bias may have influenced both patient recruitment and treatment. Reliance on pre-existing clinical records can be problematic because detail and accuracy vary over time. It was disappointing in this study to find incomplete data regarding tobacco and alcohol use during follow-up as these confounding factors may influence outcome. We have, however, previously observed few changes in tobacco and alcohol use in Newcastle PMD patients following treatment^{8,9}. Patient satisfaction and quality of life issues were not assessed in this study; these areas of research are important in modern healthcare provision and will form an integral part of future, prospective studies²⁵.

Conclusions

This study has succeeded in providing data on the demographics and clinico-pathological profile of PMD disease in North-East England, and has detailed long-term clinical outcome following intervention. Optimal treatment requires consistent diagnoses, effective intervention and coordinated patient follow-up. Whilst these have been demonstrated in this study cohort, we have not demonstrated reduction in overall cancer risk, although the early identification and treatment of OSCC in 12% of cases probably justifies intervention alone. Further analyses of cases with poor clinical outcome, including persistent or treatment resistant PMD and malignant transformation are warranted and these will be examined in the subsequent studies.

Characterizing Treatment Resistance in PMD²⁶

Aims of the Study

The specific purpose of this further study, therefore, was to examine in more detail the clinico-pathological features of the 87 ‘treatment resistant’ PMDs, to review each patient ‘journey’ and try to improve knowledge of the natural history of PMD disease and thereby identify features potentially predictive of poor outcome post-treatment.

Method

Utilizing the same methodology described in Study 1, inclusion criteria for this investigation required new patients who presented with single-site disease resistant to initial treatment intervention. Recorded demographic and clinico-pathological data included: patient age and sex, appearance and site of presenting PMD, histopathology diagnoses, date, number and type of treatment interventions (laser excision or ablation), appearance and site of further or persistent PMD. Clinical outcomes at the study census date (31 December 2014) were defined as: disease free or persistent disease, and distinguished between same-site and/or multi-focal PMD development.

Statistical Analyses

Descriptive Statistics were used to summarise patient demography, clinico-pathological features, clinical outcome and follow-up data. Pearson’s Chi-squared tests (P values computed using Monte Carlo

simulation with 2000 replications) were used to assess the association between PMD clinico-pathological features and post-treatment clinical outcome (disease free / persistent disease). All statistical analyses were carried out using the R Environment for Statistical Computing (version 3.2.5).

Results

Two distinct groups of treatment resistant PMD were identified: 34 patients who achieved disease free status following further intervention, and 53 who exhibited persistent PMD at study census despite treatment. All patients were noted to be tobacco smokers and regularly consumed alcohol.

Disease Free Patients

The 34 disease free patients comprised 18 males and 16 females (age range 43-83yrs; mean 57.7yrs).

Clinical Appearance

Presenting PMD appearance included 25 leukoplakias (74%), 8 erythroleukoplakias (23%) and 1 erythroplakia (3%). In 23 cases (68%), further PMD disease exhibited consistent clinical features, whilst 11 (32%) changed appearance, in 8 (23%) initially presenting erythroleukoplakia transformed into a subsequent leukoplakia.

Site

16 lesions (47%) arose on the ventro-lateral tongue and floor of mouth, 9 (26%) were seen on the buccal mucosa but other oral sites were less frequently involved. 15 further lesions (44%) arose specifically at the same-site as their previous PMD, whilst 19 patients (56%) developed same and new-site (multi-focal) disease.

Histopathology

28 initially presenting lesions (82%) were dysplastic on histopathological examination, with severe dysplasia or CiS seen in 15 (44%); PVL was identified in 5 (15%), lichenoid inflammation in 5 (15%) and CHC in 2 (6%). 43 further PMD lesions were identified in this group over the study period: 13 patients (38%) exhibited the same histological features in both

initial and further lesions, whilst 16 (47%) developed less severe and 5 (15%) more severe pathological change, before ultimately reaching disease free status.

Treatment

In total, 77 interventions were performed in the 34 patients: 61 laser excisions (79%) and 16 (21%) ablative procedures. All patients underwent multiple interventions, with individual patient treatments ranging from 2 to 4 (mean 2.26). Time between first and last treatments varied between 4 and 129 months, with a mean of 33.1 months.

Persistent Disease Patients

53 patients exhibited persistent PMD disease: 31 males and 22 females (age range 24-93yrs; mean 61yrs).

Clinical Appearance

45 initial lesions appeared as leukoplakia (85%), 6 as erythroleukoplakia (11%) and 2 erythroplakia (4%); 45 (85%) retained consistent appearance whilst 8 (15%) changed appearance, with 5 (9%) erythroleukoplakic lesions transforming to leukoplakia.

Site

Initial site involvement included 17 (32%) arising on ventro-lateral tongue and floor of mouth, 14 (26%) on buccal mucosa and 11 (21%) on gingiva / alveolar mucosa, with other sites involved less frequently. 28 subsequent lesions (53%) were identified at the same site as presenting disease, whilst 25 (47%) exhibited same and new-site (multi-focal) lesions.

Histopathology

39 initial lesions (74%) exhibited dysplasia on biopsy, with 29 mild or moderate dysplasia (55%) and only 12 (23%) showing severe dysplasia or CiS. PVL was initially seen in 20 cases (38%) and lichenoid inflammation in 9 (17%); no CHC cases were identified. Comparative histopathology data were only available for 17 cases undergoing further biopsy: 5 (29%) showed similar pathological features with 7 (42%) less severe and 5 (29%) more severe than original biopsies.

Treatment

78 treatment interventions were recorded in this group, with 49 excisions (63%) and 29 (37%) laser ablations. Only 15 patients underwent multiple interventions with the number per patient ranging between 1 and 4 (mean 1.47); the time between first and final intervention for these cases ranged from 6 to 82 months (mean 35.53 months).

Statistical Comparison

Table 12.5 summarises statistical comparisons between disease free and persistent patient groups. No significant differences were seen for patient age and sex, nor for individual PMD lesion clinical appearance, site or histopathology diagnoses, including PVL or LI recognition. Statistical significance was identified, however, for a change in PMD appearance between initial and subsequent lesions ($p=0.004$) and for treatment intervention, both in terms of multiple versus single treatment ($p=0.0005$) and the use of excision rather than ablation techniques ($p=0.027$).

Discussion

The efficacy of interventional laser surgery, as both a diagnostic and treatment tool, has now been well documented. Recognition that 70% of 'high-risk' PMD patients can achieve disease free status by intervention is unquestionably a treatment success. It is, however, the subgroup of PMD patients who respond poorly to treatment that are likely to provide new and salient information regarding the nature of persistent and aggressive PMD disease^{1,2,12}.

Treatment resistance may be defined as PMD which persists or recurs, either at same or new-site origin, following interventional management. In the absence of relevant, prospective randomised trials, comparative studies of outcome in treated patient cohorts provide best contemporaneous evidence to detail PMD natural history and progression⁷⁻⁹. In view of the inability of currently available biomarkers to rationalise clinical management decisions, in-depth study of observed patient outcomes may help validate clinico-pathological predictors of PMD behaviour.

Table 12.5: Statistical Comparison of Clinico-Pathological Features between Disease Free and Persistent Disease Patient Groups (Pearson Chi-Square Testing)

	χ^2	p-value
Age	1.293	p=0.28
Sex	0.259	p=0.67
Initial Lesion Appearance	2.293	p=0.35
Initial Lesion Site	7.659	p=0.36
Initial Histopathology Diagnosis	5.816	p=0.12
PVL in Initial Lesion	3.949	p=0.09
Lichenoid Inflammation in Initial Lesion	0.021	p=1.0
Treatment Intervention (Single vs Multiple)	43.282	p=0.0005*
Treatment Intervention (Excision vs Ablation)	5.058	p=0.027*
Time (months) between Initial and Final Intervention	0.157	p=0.76
Change in Lesion Appearance	8.971	p=0.004*
Change in Lesion Site (Same vs Multi-Focal)	0.077	p=0.83
Change in Histopathology Diagnosis	1.587	p=0.51

*Statistical Significance at $\alpha=0.05$

This study attempted a detailed review of the natural history of 87 patients with treatment resistant PMD. Patients were identified from a previously reported cohort, which benefited from uniform diagnostic techniques, consistent treatment intervention and long-term observation of clinical outcome^{1,2}. Accepting inevitable limitations of a single-centre, retrospective study, it was nonetheless possible to delineate two distinct types of treatment resistance: patients who ultimately achieved disease free status following further treatment and those with persistent PMD despite intervention.

Clinico-Pathological Profiling

Whilst the relatively small patient numbers in the analysis undoubtedly influenced statistical significance, it remains pertinent to characterise the clinico-pathological profiles of the two subgroups because such features may predict outcome and guide patient management decisions in the future.

Disease free patients were slightly younger, often had lesions that changed appearance from erythroleukoplakia to ‘lower risk’ leukoplakia, developed further PMDs at new sites and, whilst often exhibiting quite severe

dysplasia in presenting lesions, generally showed a reduction in severity in subsequent lesions. In contrast, the persistent disease cohort were generally older, more often male, frequently exhibited leukoplakia with PVL features at gingival and alveolar sites, and displayed less severe dysplasia in initial biopsies. Clinical appearance of lesions was more consistent between initial and further presentation, and same-site disease more prevalent.

Diagnoses of PVL, with or without dysplasia, were made more frequently during the later years of the study from 2007 onwards, probably due to enhanced awareness amongst pathologists of the risks for persistent PMD disease and increased malignant transformation in PVL. Although the identification of LI within PMD lesions has been linked to persistent and unfavourable disease outcome, no significant influence was seen on treatment resistance in this investigation^{20,27}.

The Patient ‘Journey’

Active patient surveillance post-intervention is advised, not only to review treatment efficacy but also to effectively monitor patients for further disease, to recognise early signs of malignancy and to improve understanding of PMD natural history^{2,28}. There was a definite cyclical nature of successful intervention for the 34 disease free cases, passing from surgery to surveillance to repeat surgery on recognition of further disease, often taking several years and multiple treatments; CO₂ laser surgery has the advantage of facilitating repeat intervention without compromising oral form or function^{1,2,28}. Despite consistent management decisions and repeated treatment, 53 patient ‘journeys’ exhibited persistent disease outcomes.

Treatment Intervention

Whilst all PMD treatments were coordinated by the author and proceeded along well-established and consistent management guidelines, it is clear that fewer interventions per patient were performed in the persistent disease group. Although many of these treatments comprised laser ablation of gingival and alveolar PVL, as previously advocated for this type of presentation², repeat excision surgeries for more significant dysplastic lesions were also carried out, obviously with reduced efficacy compared to disease free cases.

Whilst it is likely that individual management decisions and choice of treatment modality influence PMD clinical outcome, it remains unclear from this retrospective study whether the inherent nature of the presenting PMD disease or the treatment intervention itself contributes the principal determinant of clinical outcome. Most probably, clinical outcome is the result of a complex interaction between ‘nature’ and ‘nurture’ therefore^{17,18}.

It is, however, notable that repeat excision surgeries were performed much more frequently in patients achieving disease free status than those with persistent disease. Is the answer to PMD treatment resistance, therefore, more treatment? Undoubtedly, future multi-centre, prospective investigations will be required to characterise this issue further.

Clinical Relevance of Treatment Resistant PMD

Despite recognising and defining salient clinico-pathological characteristics of treatment resistant PMD, an important question remains regarding the precise clinical relevance of persistent PMD. The hypothesis is clear: PMD treatment resistance reflects more aggressive disease and an enhanced cancer risk. Current evidence, however, is not wholly supportive of this concept, because none of the 87 treatment resistant patients in this analysis developed SCC. On the contrary, the majority of SCCs identified in the original 590 cohort were pre-existing and diagnosed unexpectedly upon initial PMD lesion excision^{12,30}.

Conclusions

Patient observational studies provide invaluable insight into the natural history of PMD, but it is evident that new approaches to clinico-pathological and biomolecular profiling are urgently needed to characterise disease progression in large population-based investigations. Only in this way will we truly enhance our knowledge and understanding of oral carcinogenesis and improve prognoses for patients.

Profiling Cancer Risk in PMD³⁰

Aims of the Study

It is clear just how important it is in practice for clinicians to be able to predict PMD behaviour and quantify the risk of malignant transformation. Whilst controversy may exist over accurate assignment of that risk, early

diagnosis and intervention during the progression of dysplasia to OSCC should nonetheless have the potential to improve patient prognosis and reduce morbidity and mortality. As this hypothesis remains largely unproven, however, long-term observational studies of PMD patients have been advised to improve knowledge of disease progression, to determine predictors of clinical outcome and establish realistic time-scales for malignant transformation^{31,32}.

As we have seen previously, clinical features associated with malignant transformation include an erythroleukoplakic appearance, the presence of severe dysplasia in initial biopsies and origin on ventro-lateral tongue and floor of mouth sites¹². The specific purpose of this study was thus to re-evaluate the clinico-pathological data for 99 malignant transforming PMD patients and thereby identify features predictive of cancer, enhance our understanding of the carcinogenic pathway and clarify the likely time-course for malignant transformation in PMD patients.

Method

Inclusion criteria for this analysis required PMD patients to have been new presentations of single-site disease with a confirmed diagnosis of SCC. Demographic and clinico-pathological data required patient age and sex, appearance and site of presenting PMD, histopathology diagnoses (pre-operative incision and post-laser excision biopsies), SCC appearance, site and histopathology, and clinical outcome at study census date (31 December 2014).

As described previously, all tissue specimens were assessed using standardized criteria; dysplasia was classified as mild, moderate and severe or carcinoma-in-situ (CiS) with specific categories of micro-invasive and invasive SCC distinguished. Diagnoses of hyperkeratosis, lichenoid inflammation (LI), PVL and chronic hyperplastic candidosis (CHC) were made as appropriate.

Upon recognition of SCC, patients were referred to the multi-disciplinary head and neck clinics at the Freeman Hospital for further assessment and management along established oncology care pathways. Clinical outcomes were stratified as: disease free, further disease or cancer-related death.

Statistical Analyses

Descriptive Statistics were used to summarise patient demography, clinico-pathological features, clinical outcome and follow-up data. Fisher's exact test, Student's t-test and Chi-square testing were used as appropriate to compare clinico-pathological features, assessed as categorical variables, potentially influencing clinical outcome. Due to low study numbers in each category, P values were computed using Monte Carlo simulation and natural logarithmic transformation applied prior to analyses of time influence. Univariate Cox regression analyses of clinico-pathological factors potentially influencing time to malignant transformation, including patient sex, age, precursor lesion site, appearance and histopathology were also performed. Statistical analyses were carried out using SPSS, version 19.0 (Statistical Package for the Social Sciences, Chicago, IL, USA), R Environment for Statistical Computing (version 3.2.5) and SAS/STAT[®] 9.3 software (SAS Institute Inc, Cary, USA).

Results

Two distinct SCC presentations were recognised in the 99 patients: 71 were identified immediately and 'unexpectedly' upon histopathological assessment of laser excision specimens, whilst 28 cases 'progressed' to malignancy at same or new sites during follow-up.

Unexpected SCC

There were 71 'unexpected' cases, involving 50 males (age range 47-83yrs; mean 62.6yrs) and 21 females (age range 33-89yrs; mean 65.3yrs). Initial lesion appearance included 38 leukoplakias (53.5%), 29 erythroleukoplakias (40.9%) and 4 erythroplakias (5.6%). 48 lesions (54.5%) arose on the ventro-lateral tongue and floor of mouth, with other individual sites less frequently involved. 66 presenting lesions (93%) exhibited dysplastic features on histopathological examination, with severe dysplasia or CiS in 52 (73%). All SCCs were completely excised by laser, with 30 (42.3%) classed as micro-invasive. Clinical outcome at study census showed 58 patients disease free (81.7%), 12 developing further PMD disease (16.9%) and 1 SCC-related death (1.4%).

Progression to SCC

The 28 ‘progression’ cases included 16 males (age range 34-84yrs; mean 60.7yrs) and 12 females (age range 45-92yrs; mean 65.3yrs). 19 precursor lesions presented as leukoplakia (68%), with 6 erythroleukoplakias (21%) and 3 erythroplakias (11%). 15 (53.6%) arose on the ventro-lateral tongue and floor of mouth, with other sites again infrequently affected. 27 lesions (96.4%) exhibited dysplasia on initial biopsy, with 17 (60.7%) showing severe dysplasia or CiS. 18 SCCs presented as erythroleukoplakia (64%) with 10 leukoplakias (36%); only 3 SCCs (10.7%) were micro-invasive. In terms of clinical outcome, 12 patients (42.9%) were disease free, 7 (25%) developed further PMD and 9 (32.1%) died from metastatic OSCC.

Change in lesion appearance to erythroleukoplakia was a specific SCC predictor within the ‘progression’ group (Fisher’s exact test: $p=0.0019$), whilst comparison between ‘unexpected’ and ‘progression’ groups highlighted both an increased proportion of invasive SCCs (Chi-squared test: $\chi^2=8.99$; $p=0.004$) and poor clinical outcome including SCC-related deaths (Chi-squared test: $\chi^2=23.75$; $p<0.001$) as a result of ‘progressive’ disease. Patient sex, age, precursor lesion site, appearance and histopathology were not predictive of behaviour; Table 12.6.

Table 12.6: Comparison of Clinico-Pathological Variables Between ‘Unexpected’ (n=71) and Progression SCC (n=28)

Clinico-Pathological Variable	Chi Square	p-Value
Sex	1.59	0.25
Age	0.79	0.50
Precursor Site	12.56	0.24
PMD Lesion Appearance	3.59	0.16
Precursor Histopathology	5.65	0.74
miSCC vs SCC	8.99	0.004
Clinical Outcome	23.75	<0.001

miSCC: micro-invasive squamous cell carcinoma; SCC: squamous cell carcinoma

Table 12.7: Clinico-Pathological Variables Influencing Time to SCC Development (Progression n=28)

Clinico-Pathological Variable	p-Value
Sex	0.58
Age	0.46
Precursor Site*	-
PMD Lesion Appearance	0.55
Precursor Histopathology	0.96

**Insufficient data available in category for analysis*

9 SCCs arose at the same-site as PMD precursor, with 6 (77.7%) arising on ventro-lateral tongue and floor of mouth. For 19 OSCCs developing at new-sites, there were no clear relationships between precursor and subsequent site, although ventro-lateral tongue and floor of mouth precursors were less frequent (8 or 42.2%). Same-site transformation occurred between 3 and 48 months (mean 28 months), whilst new-site OSCC generally took longer, from 9 to 204 months (mean 61.3 months), although the difference was not statistically significant (Student’s t-test: $p=0.21$). Median time to malignancy in the 28 cases was 87.3 months (95% CI 59.9 to 149.2). Analyses of clinico-pathological variables potentially influencing time to malignancy in the 28 cases are summarised in Table 4, but none were significant.

Discussion

Transformation of an identifiable precursor lesion into invasive SCC must rank as the ultimate PMD treatment failure, yet prediction of ‘high-risk’ behaviour and cancer development remains elusive in clinical practice. Published transformation rates vary widely between 0.13 and 50%, with ‘average’ times ranging from 0.5 to 17 years; such data are unhelpful in counselling individual patients in clinical practice, although it is generally believed that risk increases for lesions exhibiting severe dysplasia and over prolonged follow-up³¹⁻⁴⁰. Warnakulasuriya & Ariyawardana⁴¹ reviewed 24 observational studies of leukoplakia and identified advanced age, females, lesion greater than 200mm² in size, non-homogenous clinical appearance and severe dysplasia as high risk. Other authors, however, have not found clinical or pathological observations to correlate reliably with malignant transformation, with currently available biomarkers of little practical use^{20,41-42}.

This study usefully reviewed the clinico-pathological features of 99 PMD patients developing SCC in the Newcastle 590 cohort undergoing laser treatment. Identifying and excising 71 ‘unexpected’ cancers, particularly early stage micro-invasive tumours, is undoubtedly a diagnostic and treatment success, demonstrating efficacy of intervention and supporting the hypothesis that patient morbidity and mortality can be reduced⁴⁴⁻⁴⁶; 81.7% of these patients were disease free with only 1 cancer-related death. In contrast, a further 28 patients developed post-treatment OSCC, 19 at new sites, at a median time of 87.3 months. Whilst long-term follow-up facilitated early OSCC recognition, it is notable that these clinical outcomes were significantly worse with 9 cancer-related deaths and only 42.9% of patients disease free at census ($p<0.001$).

Few studies have reported upon defined PMD cohorts undergoing standardised treatment, so it is difficult to compare data with other publications. Saito et al⁴⁵ reported 6.3% transformation in 142 patients treated by surgery for leukoplakia, although only 91 lesions were dysplastic, whilst Ho et al³⁹ observed a 25% rate in 91 patients monitored over a median 40.3-month period, but provided no treatment details. We have previously identified occult OSCC in 9% of 169 laser excisions⁴⁶, but this current series presents the largest and longest observed cohort.

The clinician’s dilemma remains how to identify and predict PMDs at greatest risk of cancer. Precursor lesions in this Northern England population most frequently presented as leukoplakia (57) on ventro-lateral tongue and floor of mouth sites (63), consistent with previous reports and reflective of inherent disease susceptibility^{1,9,47}. Of clinical relevance is the observation that ventro-lateral tongue and floor of mouth were at particular risk of same-site malignant transformation, both ‘unexpected’ and ‘progressive’, although seemed less likely to be the primary focus in cases of new-site OSCC. Erythroleukoplakia, either as a precursor in ‘unexpected’ cases or as a change in appearance during ‘progression’ was associated with OSCC development, confirming earlier observations and highlighting the importance of its early recognition^{12,41}.

Review of precursor histopathology did not show a reliable predictive role, although 52 of 71 ‘unexpected’ (73.2%) and 17 of 28 ‘progression’ cases exhibited severe dysplasia or CiS on initial biopsy, supporting earlier reports regarding high-grade dysplasia risk^{37,41}. Finding micro-invasive cancers in substantive numbers within the ‘unexpected’ group emphasised not only the difficulty in identifying early cancer change clinically⁴⁴, but also the efficacy of intervention via excision because clinical outcome was

demonstrably better in these patients. In contrast, despite early recognition during follow-up, the increased number of invasive SCCs in the 'progression' group was associated with poor clinical outcome and an increased number of cancer-related deaths.

Time to malignancy varied substantially between 3 to 204 months, although same-site transformation generally occurred earlier than new-site cancer development, probably reflecting variable influence of field change cancerization. Lack of statistical significance in the 'progression' group may relate to the limited sample size of 28 cases.

It is this author's opinion that clarifying terminology will assist future observational studies and therefore I firmly believe that the term 'malignant transformation' should be restricted to PMDs exhibiting same-site SCC, and thus distinguishing 'cancer development' for those who develop new-site disease. Intervention to excise localised lesions may indeed prevent or effectively treat 'malignant transformation' but the risk of subsequent 'cancer development' remains. Active surveillance during patient follow-up is thus an essential component of interventional therapy and allows early signs of further disease to be recognised and treatment initiated².

The precise interplay of epidemiological, diagnostic, histopathological, and bio-molecular factors remains complex, however, with carcinogenesis arising from intrinsic and extrinsic influences acting both synchronously and metachronously throughout ill-defined areas of mucosal field change.

Conclusions

Although this was neither a prospective nor randomized controlled trial and was limited in population size from a single-centre, review of clinico-pathological and patient outcome data has provided additional insight into cancer risk within a defined PMD cohort. Interventional laser surgery facilitates early diagnosis and effective treatment of occult 'unexpected' SCC and reduces morbidity and mortality from same-site transformation, but new-site cancer retains lethality and is a significant long-term risk for all PMD patients.

Oral Lichenoid Lesions and Proliferative Verrucous Leukoplakia (PVL) in PMD⁴⁸

As previously discussed, oral lichenoid lesions and PVL are regarded as specific precursor lesions that show both treatment resistance and high risk for malignant transformation. Utilising the 590 PMD cohort, patients whose lesions exhibited lichenoid or PVL features were identified and their clinico-pathological profile and outcome data post-treatment intervention reviewed.

Overall, one third of the PMD cohort (198) showed lichenoid or PVL features, with 188 lichenoid and 80 PVL, primarily presenting as leukoplakia at ventro-lateral tongue and floor of mouth sites, and equally distributed between males and females. Most lesions exhibited dysplasia on incision biopsy (72% lichenoid; 85% PVL) and were treated by laser excision rather than ablation (88% lichenoid; 86% PVL). Lichenoid lesions appeared more commonly in younger patients (lichenoid 57years; PVL 62years) and were more likely than PVL to have an erythroleukoplakia appearance (Lichenoid 15%; PVL 2.5%). Whilst no significant difference was seen between lichenoid lesions and PVL achieving disease-free status after treatment (lichenoid 69.5%; PVL 65%), this was less than reported for the total 590 cohort (74.2%). Malignant transformation was observed in 2 lichenoid cases (1.7%) and 2 PVL (2.5%) during the follow-up period.

Oral Lichenoid Lesions

Twenty percent of PMD lesions in this 590-study cohort were thus diagnosed as lichenoid in nature; this is similar to previous reports suggesting that up to 29% of PMD exhibit lichenoid features. Although classically described as solitary erythroleukoplakia, and mimicking the appearance of mucosal lichen planus, a strict diagnostic definition has remained elusive and, interestingly, over 80% of lesions in this study presented as leukoplakia. Eighty-five lesions (72%) showed dysplastic features (40 mild, 27 moderate and 16 severe) lending support to the previously mentioned ‘lichenoid dysplasia’ concept. It remains unclear whether lichenoid inflammation drives malignant transformation or is representative of an immune response to atypical oral epithelium^{15,49}. Whilst the prognostic significance of oral lichenoid lesions is likely to be debated for many years to come, there is increasing evidence emerging confirming an enhanced cancer risk for isolated lichenoid abnormalities,

especially those arising on tongue mucosa. Interventional laser surgical excision and continuous patient follow-up are now recommended management techniques, which the observations of this study certainly support.

Proliferative Verrucous Leukoplakia

PVL was diagnosed in 13.6% of the cohort, which is actually much higher than a previously quoted prevalence of 0.1% for a UK population⁵⁰. Perhaps unsurprisingly, lesions most often appeared as leukoplakia (97.5%) with a predilection for labio-buccal and gingiva/alveolar sites (40%) and a more widespread mucosal involvement. Whilst a higher percentage exhibited dysplasia (85%), overall grading showed less significant disease compared to lichenoid lesions (with 45 mild, 18 moderate and 5 severe dysplasia). Traditionally, diagnoses of PVL were only made late during the course of disease once spread to multiple sites, high recurrence following treatment and/or malignant transformation occurred. Increasingly, specialist pathologists have raised awareness of this disorder leading to more frequent diagnoses, especially during recent years.

Interestingly, in 10 patients (5%), both lichenoid and PVL diagnoses were made, primarily for 'same-site' lesions at different time points and with lichenoid inflammatory features subsequently diagnosed as PVL. Whether representing discrepancy between initial incision and subsequent excision biopsies, as discussed in Chapter 9, or evidence of disease evolution remains to be resolved. Certainly, PVL has been shown to exhibit a continuum of morphological development passing through initial hyperkeratosis usually without dysplasia through verrucous hyperplasia leading to verrucous carcinoma and ultimately invasive SCC. Complicating the early phase is the recognition of lymphocytic infiltrates in sub-epithelial tissue similar to lichenoid lesions. It may well be, therefore, that oral lichenoid lesions and PVL are part of the same PMD continuum.

Conclusions

This chapter demonstrates clearly and consistently that patient observational studies can add significant knowledge to our understanding of PMD natural history and oral carcinogenesis. A consistent finding is that early intervention by laser excision is an effective treatment strategy

that significantly improves the chances for PMD patients to be rendered free from disease.

References

1. Thomson PJ, Wylie J. Interventional laser surgery: an effective surgical and diagnostic tool in oral precancer management. *International Journal of Oral & Maxillofacial Surgery* 2002 31 :145-153.
2. Thomson PJ. Management of Oral Precancer. In: PJ Thomson (ed) *Oral Precancer – Diagnosis and Management of Potentially Malignant Disorders*. Chichester: Wiley-Blackwell; 2012. p107-137. ISBN 978-1-4443-3574-3
3. Mehanna HM, Rattay T, Smith J, McConkey CC. Treatment and follow-up of oral dysplasia – a systematic review and meta-analysis. *Head & Neck* 2009 31: 1600-1609.
4. van der Waal I. Potentially malignant disorders of the oral and oropharyngeal mucosa; terminology, classification and present concepts of management. *Oral Oncology* 2009 45: 317-323.
5. Dost F, LeCao K, Ford PJ, Ades C, Farah CS. Malignant transformation of oral epithelial dysplasia: a real world evaluation of histopathologic grading. *Oral Surg Oral Med Oral Pathol Oral Radiol* 2014 117: 343-352.
6. Edwards PC. The natural history of oral epithelial dysplasia: perspective on Dost et al (Editorial). *Oral Surg Oral Med Oral Pathol Oral Radiol* 2014 117 : 263-266.
7. Stocker J, Thomson PJ, Hamadah O. Laser surgery in oral oncology – The Newcastle experience. *The Surgeon: Journal of the Royal College of Surgeons of Edinburgh and Ireland* 2005 Supplement 3(3): S32-33.
8. Hamadah O, Thomson PJ. Factors affecting carbon dioxide laser treatment for oral precancer: A patient cohort study. *Lasers in Surgery and Medicine* 2009 41 :17-25.
9. Diajil AR, Robinson CM, Sloan P, Thomson PJ. Clinical outcome following oral potentially malignant disorder treatment: a 100 patient cohort study. *International Journal of Dentistry* 2013 <http://dx.doi.org/10.1155/2013/809248>.
10. Diajil AR, Goodson ML, Thomson PJ. Time to treat -treatment time does not adversely affect clinical outcome following laser excision of oral potentially malignant disorders. *Journal of Oral and Maxillofacial Surgery* 2014 Photon 117: 169-178.

11. Thomson PJ, Goodson ML, Hamadah O. Cohort studies in oral precancer management: Intervention vs observation. *Oral Oncology* 2009 Suppl 3: 116. Doi:10.1016/j.oos.2009.06.266.
12. Thomson PJ, Goodson ML, Cocks K, Turner JE. Interventional laser surgery for oral potentially malignant disorders – a longitudinal patient cohort study. *International Journal of Oral & Maxillofacial Surgery* 2017 46: 337-342.
13. The Caldicott Committee. Report on the review of patient- identifiable information. 1997. Department of Health, UK.
14. Sloan P. Pathological aspects of oral precancer. In P J Thomson (Ed) *Oral Precancer – Diagnosis and Management of Potentially Malignant Disorders*. Chichester: Wiley-Blackwell; 2012. p93-106. ISBN 978-1-4443-3574-3.
15. Thomson PJ. Oral Carcinogenesis. In: PJ Thomson (ed) *Oral Precancer – Diagnosis and Management of Potentially Malignant Disorders*. Chichester: Wiley-Blackwell; 2012. p31-47. ISBN 978-1-4443-3574-3.
16. Thomson PJ, Potten CS, Appleton DR. Mapping dynamic epithelial cell proliferative activity within the oral cavity of man: a new insight into carcinogenesis? *British Journal of Oral & Maxillofacial Surgery* 1999 37: 377-383.
17. Thomson PJ, Goodson ML, Booth C, Cragg N, Hamadah O. Predicting recurrence after treatment of oral precancer: Use of cell cycle analysis. *British Journal of Oral and Maxillofacial Surgery* 2008 46: 370-375.
18. Thomson PJ. The role of interventional surgery in oral potentially malignant disorders. *Faculty Dental Journal* 2014 5: 84-89.
19. Patil S, Rao R, Sanketh S, Warnakulasuriya S. Lichenoid dysplasia revisited – evidence from a review of Indian archives. *Journal of Oral Pathology & Medicine* 2014 44: 507-514.
20. Goodson ML, Sloan P, Robinson CM, Thomson PJ. Oral precursor lesions and malignant transformation – who, where, what and when? *British Journal of Oral & Maxillofacial Surgery* 2015 53: 831-835.
21. Thomson PJ. Malignant Transformation and Oral Cancer Development. In: PJ Thomson (ed) *Oral Precancer – Diagnosis and Management of Potentially Malignant Disorders*. Chichester: Wiley-Blackwell; 2012. p156-169. ISBN 978-1-4443-3574-3.
22. Brouns ER, Baart JA, Karagozoglu KH, Aartman IH, Bloemena E, van der Waal I. Treatment results of CO2 laser vaporisation in a cohort of 35 patients with oral leukoplakia. *Oral Diseases* 2013 19: 212-216.

23. van der Waal I. Oral lichen planus and oral lichenoid lesions: a critical appraisal with emphasis on the diagnostic aspects. *Med Oral Patol Oral Cir Buccal* 2009 14: e310-314.
24. Cerero-Lapiedra R, Balade-Martinez D, Moreno-Lopez L-A, Esparza-Gomez G, Bagan JV. Proliferative verrucous leukoplakia: a proposal for diagnostic criteria. *Med Oral Patol Oral Cir Bucc* 2010 15: e839-e845.
25. Thomson PJ, McCaul J, Ridout F, Hutchison I. To treat...or not to treat? Clinician views on oral potentially malignant disorder management. *British Journal of Oral & Maxillofacial Surgery* 2015 53: 1027-1031.
26. Thomson PJ, Goodson ML, Smith DR. Treatment Resistance in Potentially Malignant Disorders – ‘Nature’ or ‘Nurture’...? *Journal of Oral Pathology & Medicine* 2017 46: 902-910.
27. Bagan JV, Scully C, Jimenez Y, Martorelli M. Proliferative verrucous leukoplakia: a concise update. *Oral Diseases* 2010 16: 328-332.
28. Thomson PJ. Potentially Malignant Disorders – The Case for Intervention *Journal of Oral Pathology & Medicine* 2017 46: 883-887.
29. Saito T, Sugaira C, Hirai A, Notani K, Totsuka Y, Shindoh M, Fukuda H. Development of squamous cell carcinoma from pre-existent oral leukoplakia: with respect to treatment modality. *International Journal of Oral & Maxillofacial Surgery* 2001 30: 49-53.
30. Thomson PJ, Goodson ML, Smith DR. Profiling Cancer Risk in Oral Potentially Malignant Disorders – A Patient Cohort Study. *Journal of Oral Pathology & Medicine* 2017 46: 888-895.
31. Guneri P, Epstein JB. Why are we still unable to accurately determine the malignant potential or the behaviour of oral mucosal lesions? *Oral Oncology* 2017 71: 177-179.
32. Arduino PG, Bagan J, El-Naggar AK, Carrozzo M. Urban legends series: oral leukoplakia. *Oral Diseases* 2013 19: 642-659.
33. Schepman KP, van der Meij EH, Smeele LE, van der Waal I. Malignant transformation of oral leukoplakia: a follow-up study of a hospital-based population of 166 patients with oral leukoplakia from The Netherlands. *Oral Oncology* 1998 34: 270-275.
34. Cowan GC, Gregg TA, Napier SS, McKenna SM, Kee F. Potentially malignant oral lesions in Northern Ireland: a 20-year population-based perspective of malignant transformation. *Oral Diseases* 2001 7: 18-24.

35. Shiu MN, Chen TH. Intervention efficacy and malignant transformation to oral cancer among patients with leukoplakia. *Oncology Report* 2003 10: 1683-1692.
36. Hsue SS, Wang W-C, Chen C-H, Lin C-C, Chen Y-K, Lin L-M. Malignant transformation in 1458 patients with potentially malignant oral mucosal disorders: a follow-up study based in a Taiwanese hospital. *Journal of Oral Pathology & Medicine* 2007 36: 25-29.
37. Speight PM. Update on oral epithelial dysplasia and progression to cancer. *Head and Neck Pathology* 2007 1: 61-66.
38. Warnakulasuriya S, Kovacevic T, Madden P, Coupland VH, Sperandio M, Odell E, Moller H. Factors predicting malignant transformation in oral potentially malignant disorders among patients accrued over a 10-year period in South East England. *Journal of Oral Pathology & Medicine* 2011 40: 677-683.
39. Ho MW, Field EA, Field JK, Risk JM, Rajlawat BP, Rogers SN, Steele JC, Triantafyllou A, Woolgar JA, Lowe D, Shaw RJ. Outcomes of oral squamous cell carcinoma arising from oral epithelial dysplasia: rationale for monitoring premalignant oral lesions in a multidisciplinary clinic. *British Journal of Oral & Maxillofacial Surgery* 2013 51: 594-599.
40. Field EA, McCarthy CE, Ho MW, Rajlawat BP, Holt D, Rogers SN, Triantafyllou A, Field JK, Shaw RJ. The management of oral epithelial dysplasia: The Liverpool algorithm. *Oral Oncology* 2015 51:883-887.
41. Warnakulasuriya S, Ariyawardana A. Malignant transformation of oral leukoplakia: a systematic review of observational studies. *Journal of Oral Pathology & Medicine* 2015 45: 155-166.
42. Arduino PG, Surace A, Carbone M, Elia A, Massolini G, Gandolfo S, Broccoletti R. Outcome of oral dysplasia: a retrospective hospital-based study of 207 patients with a long follow-up. *Journal of Oral Pathology & Medicine* 2009 38: 540-544.
43. Watabe Y, Nomura T, Onda T, Yakushiji T, Yamamoto N, Ohata H, Takano N, Shibahara T. Malignant transformation of oral leukoplakia with a focus on low-grade dysplasia. *Journal of Oral & Maxillofacial Surgery, Medicine & Pathology* 2016 28: 26-29.
44. Pentenero M, Navone R, Marino R, Gassino L, Broccoletti R, Gandolfo S. Clinical features of microinvasive stage I oral carcinoma. *Oral Diseases* 2011 17: 298-303.
45. Saito T, Sugaira C, Hirai A, Notani K, Totsuka Y, Shindoh M, Fukuda H. Development of squamous cell carcinoma from pre-

- existent oral leukoplakia: with respect to treatment modality. *International Journal of Oral & Maxillofacial Surgery* 2001 30: 49-53.
46. Goodson ML, Thomson PJ. Management of oral carcinoma: benefits of early precancerous intervention. *British Journal of Oral & Maxillofacial Surgery* 2011 49: 88-91.
 47. Thomson PJ, Potten CS, Appleton DR. Mapping dynamic epithelial cell proliferative activity within the oral cavity of man: a new insight into carcinogenesis. *British Journal of Oral & Maxillofacial Surgery* 1999 37:377-383.
 48. Thomson PJ, Goodson ML, Smith DR. potentially malignant disorders revisited – the lichenoid lesion/proliferative verrucous leukoplakia conundrum. *Journal of Oral Pathology & Medicine* 2018 47: 557-565.
 49. Muller S. Oral lichenoid lesions: distinguishing the benign from the deadly. *Modern Pathology* 2017 30: S54-S67.
 50. Gouvea AF, Santos Silva AR, Speight PM. High incidence of DNA ploidy abnormalities and increased Mcm2 expression may predict malignant change in oral proliferative verrucous leucoplakia. *Histopathology* 2013 62: 551-562.

PART FOUR

SOLUTIONS

'the answer to a problem'

CHAPTER THIRTEEN

PREVENTION

‘...stopping something happening or arising...’

Introduction

Preventive healthcare is based upon the principle of applying a wide range of methods and approaches all with the aim of preventing disease development, as opposed to the inevitable consequences and limitations of having to treat an established disease state. Onset of disease may, of course, be influenced by inherent genetic predisposition, exposure to environmental agents and disease vectors, or lifestyle choices and behaviour, with many conditions actually pre-existing in a sub-clinical manner long before an individual may recognize that they are affected. Prevention in clinical practice is therefore delivered by a series of anticipatory interventions that are traditionally described as being primary, secondary, or tertiary in nature.

Primary prevention may comprise generalized health promotion activities to improve well-being, but more specifically can also offer protective measures that are targeted against individual disease entities. Secondary prevention is more focused upon the early detection of latent disease, followed by subsequent intervention to stop asymptomatic conditions progressing to more symptomatic or disabling states. Finally, tertiary preventive strategies are designed to reduce the damage caused by established disease, halt further progression and, at the same time, aim to optimize and/or restore form and function, and encourage longer term patient rehabilitation.

Complicating all this, of course, is the recognition that access to preventive health services can be very unequal for individual patients or indeed whole populations. Probably the most frequent barriers to appropriate utilization of healthcare resources include lack of patient awareness, low socio-economic status, limited education and difficulties

with language; these all combine to enhance the risk of disease progression in disadvantaged social groups.

Whilst there is little evidence to confirm that preventive healthcare measures are cost-effective, they undoubtedly improve quality of life for individual patients and indeed, in the future, it is highly likely that the costs of medical care related to chronic, preventable disease treatment will come under increasing scrutiny by health care economists and managers. Aspects of these issues, in specific relation to interventional management of PMD, will be discussed in more detail in the next chapter.

Oral Cancer Prevention

It is very unfortunate that in the 21st Century oral SCC still justifiably retains its reputation as a lethal and deforming disease, with long term patient prognosis severely compromised by late initial presentation of advanced tumours and ultimately widespread, multi-focal disease extending throughout the upper aerodigestive tract. Much of this, of course, relates to the affected population's poor awareness of oral health and an inability to appropriately access healthcare, which of course limits our ability to launch an effective primary preventive approach to management. We do know that the transformation of normal stratified squamous oral mucosa into premalignant and subsequently malignant tissue is a complex, multistep and multifactorial process in which accumulated genetic alterations disrupt the normal functioning of oncogenes and tumour suppressor genes. We have also seen how disruption of the cell cycle is characterized in its earliest phase by dysregulation, enhanced proliferation and changes in differentiation, DNA repair, apoptosis and cellular immunity^{1,2}.

As reported in Chapter 2, phenotypical epithelial tissue disorganisation and dysmaturation changes preceding SCC are identifiable microscopically, can be defined into varying grades of severity of epithelial dysplasia and are clinically recognisable as PMD, thus offering opportunities to intervene and institute treatment, very much in line with secondary preventive strategies. In order to rationalize perspectives on such preventive healthcare strategies, therefore, and to address long-standing dilemmas relating to the early diagnosis of oral SCC and attempt to determine the role of interventional management in influencing disease progression, this chapter will re-visit and expand upon the following four inter-related topics and questions:

1. Proliferation - What epithelial cell changes precede tumour development? Can we therefore characterize the extent and significance of disruption to cell proliferation during carcinogenesis?
2. Position - Why are certain oral sites so predisposed to cancer? Can we use this information to determine the significance of anatomical site effects and field change cancerization within the oral cavity?
3. Progression – Why do some oral precursor lesions progress to invasive SCC and others do not? By studying this, can we improve our understanding of the natural history of PMD?
4. Prediction - How can we predict individual patient and/or lesion behaviour? With improved predictive ability, can we then rationalize the diagnosis and interventional management of PMD and thereby reduce the risk of malignant transformation and SCC development?

By delineating and stratifying risk for oral carcinogenesis both within a population and for individual patients, it is hoped that we can then facilitate truly effective primary, secondary and tertiary preventive strategies and thereby reduce the overall burden of oral SCC both for individual patients and the wider population at risk³.

Proliferation

Epithelial cell proliferation, differentiation and ultimately apoptosis are all strictly regulated mechanisms that help maintain normal oral mucosa structure and function. Within the progenitor compartment (which we believe is located within basal and immediately supra-basal cells), postulated epithelial proliferative units containing stem cells undergo self-renewal and, by asymmetric division, produce daughter keratinocytes for terminal differentiation⁴. Lack of confirmed biological markers prevents reliable identification of oral epithelial stem cells which is unfortunate, as they are the likely focus of initial carcinogenesis and their isolation and detailed study would prove valuable^{1,5}.

In Chapter 2 we saw that the acquisition of genetic, phenotypic and functional alterations in stem cells appear to combine to result in a loss of normal cell cycle restraint which initiates a transition from benign hyperplasia towards epithelial dysmaturation and dysplastic tissue formation, followed by a loss of replicative senescence and unlimited proliferation all within the potentially reversible stage of ‘pre-

malignancy'; if these processes are unchecked, this will progress on to carcinoma-in-situ and then an invasive oral SCC. Loss of cell cycle control and abnormal cell proliferation are thus the fundamental mechanisms that drive carcinogenesis, with quantitative proliferation indices putative markers of malignant potential, tumour growth and ultimately, perhaps, disease prognosis itself^{4,6-8}.

In Chapter 9 it was discussed that the oral epithelial cells destined for 'pre-malignant' change are most likely to be those that already possess an inherently high proliferative activity. Using in-vitro labelling studies to characterize oral epithelial activity, we have previously demonstrated a significant increase in proliferation indices for both increasingly severe dysplasia and also worsening grades of SCC differentiation⁹⁻¹¹. Overall, the presence of increasing numbers of epithelial cells committed to cell division is probably the defining characteristic of a truly dysplastic PMD lesion^{12,13}. Of particular significance, in terms of approaches to prevention, is our additional, important observation that even 'apparently normal-looking' mucosa from oral SCC patients may exhibit abnormal cell proliferative profiles, often identical to that seen in dysplastic or neoplastic tissue¹⁰.

'Pre-malignant fields', therefore, are most likely to precede tumour formation, with an invasive SCC arising in a field sub-clone probably as a result of specific, additional genetic damage; this field will then expand throughout the oral epithelium at the expense of normal surrounding mucosa due to its inherently high proliferation rate. Resultant tumour proliferation rates may well be determined by the original proliferative rate of the 'pre-malignant' epithelium in which they arise, so that the speed of proliferation may well prove to be a particularly important characteristic. Whilst recognition of a 'pre-malignant field' is undoubtedly important for prevention, therapy and prognosis, especially for patients presenting with clinically recognisable PMD, it is concerning that neither clinical nor histopathological features can reliably identify such change^{1,14}.

Further investigative work is most certainly warranted into the clinical application of cell proliferation measurement and the predictive analysis of oral SCC precursor lesions. Whilst recent research has tended to focus primarily upon molecular biology, quantifiable cell proliferative changes are more likely to reflect the resulting functional changes due to genetic damage within a tissue far better than individual oncogene alterations, and may thus have clinical application as significant markers of prognosis⁶.

Position

In order to reliably characterize and then utilize epithelial proliferative activity data within the oral cavity, it is essential to understand and delineate any pre-existing anatomical site variation. By harvesting normal mucosa from varying sites during oral surgery procedures and measuring their inherent proliferation indices, we have previously demonstrated significantly increased activity and prolongation of S-phase DNA synthesis on the floor of mouth and ventrolateral tongue; these are the sites known to exhibit a particular predilection for oral SCC development. Interestingly, in direct contrast to this, low risk regions for carcinogenesis such as thickly keratinised palatal mucosa and specialised gustatory tongue dorsum mucosa showed correspondingly reduced epithelial activities. Demonstration of inherently high proliferative cell activity is strongly suggestive, therefore, of an underlying predisposition to carcinogenesis within the oral cavity, and it is possible that measurement of both epithelial proliferative activity and chromosomal instability in site-specific lesions may offer predictive roles in identifying early signs of dysplasia and quantifying cancer risk¹⁵⁻¹⁸.

In a study of 26 Newcastle patients presenting with unilateral PMD or oral SCC who underwent 'mirror image' biopsy sampling from apparently normal contralateral mucosa, we found that 15 (58%) exhibited microscopic features of occult dysplasia or even early SCC development. Highly supportive of the concept of field change carcinogenesis within oral mucosa, these observations also re-confirmed that floor of mouth and ventro-lateral tongue sites have an increased susceptibility to field change dysplasia as they most frequently demonstrated histopathological abnormality¹⁹.

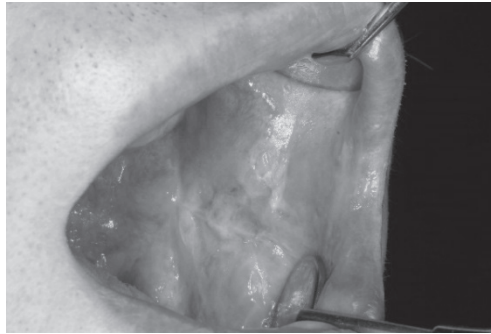
Whilst 'field cancerization' theories propose that carcinogen-induced changes exist throughout the oral cavity and upper aerodigestive tract, a particular subgroup of PMD patients have been shown to exhibit a high incidence of multiple lesion and hence multi-focal tumour development. Detailed follow-up studies have shown that multiple-site disease affects up to 24% of all PMD patients, occurring significantly more frequently in tobacco smokers and in individuals whose diets are low in fresh fruit and vegetable intake. Dysplasia within individual lesions is noted to be less severe, with buccal mucosa sites most frequently affected. In contradistinction, single PMD lesions usually exhibit more severe

dysplasia, have higher epithelial proliferative indices and present more commonly on the floor of mouth and ventrolateral tongue^{20,21}.

A higher incidence of malignant transformation has been reported in multiple lesion disease, probably reflecting more widespread mucosal instability. Figure 13.1 illustrates a patient with widespread, multiple-site PMD. Although a challenging management problem, a pragmatic approach to rationalize diagnosis and targeted intervention utilises a multiple 'field mapping' biopsy technique. The soft palate, faucial pillars, floor of mouth and ventral tongue are recognised as sites most at risk of severe dysplasia, although individual PMD lesions appear to respond well to treatment by CO₂ laser excision. The identification of dysplastic change in clinically normal mucosa co-existing with PMD lesions is most probably indicative of an early 'pre-malignant' event and thus the initiation of field change. Regular and careful clinic review is of special importance during the management of field change patients in order to identify dysplastic disease or to diagnose SCC, potentially at multiple oral sites, at the earliest possible stage. As alluded to earlier, prolonged follow up strategies and multiple treatment interventions in specialist clinics will require significant resource allocation but this appears increasingly justifiable and is probably in the best interests of our patients²¹⁻²⁶.

Progression

We have seen that the 'progression model' for oral carcinogenesis emphasizes that initial, irreversible genotypic damage produces tissue disorganisation and dysmaturation which, if allowed to progress, lead inexorably towards invasive SCC. Recognition of PMD lesions is relatively straightforward upon oral cavity inspection, but our ability to identify and treat 'high risk' lesions and 'at risk' patients at the earliest stage of disease remains problematic, although of course fundamental to a successful interventional management strategy. It is now recognised that PMD appearance, specifically that of proliferative verrucous leukoplakia (PVL), non-homogenous leukoplakia, erythroleukoplakic lesions and erythroplakia, may all be associated with persistent and progressive disease, but these remain generalised observations and do not reliably inform individual patient management decisions^{1,26,27}.



A



B



C

Figure 13.1: Multiple lesion disease affecting (A) left buccal mucosa showing leukoplakia with erosive features erosion, (B) widespread right buccal leukoplakia, and (C) nodular leukoplakia arising on right mandibular buccal sulcus and alveolus

Detailed characterization of phenotypic epithelial changes during carcinogenesis, however, have demonstrated not only increased cell proliferation within increasingly dysplastic and neoplastic tissue but also hierarchical disruption whereby enhanced proliferative activity extends from the basal proliferative units into supra-basal layers. Recognition of increased supra-basal activity, in particular, appears to be associated with a worsening clinical outcome, the persistence and recurrence of PMD lesions, malignant transformation and ultimately cervical lymph node metastases. Whilst the importance of increased proliferation in oral dysplastic lesions is now recognised, many published studies are limited by their observational, cross-sectional nature. We therefore followed Newcastle PMD patients for 5-years post-treatment and did indeed confirm a significantly increased risk of progressive disease when proliferative labelling indices in tissue specimens exceeded median values for their site-specific mucosal lesions^{11,28-32}.

In the absence of readily available predictive biomarkers, long term clinical follow-up of affected patients becomes mandatory for meaningful analysis of PMD disease progression and risk of malignancy. Active patient surveillance, preferably in dedicated specialist clinics, facilitates the recognition of recurrent or further PMD disease, helps identify early signs of SCC development, rationalizes timing and coordination of further treatment intervention, and provides opportunities to modify risk factor behaviour and assess long-term patient risk; all of these act together as integral preventive healthcare strategies²⁷.

Prediction

It is extremely frustrating, for both clinicians and patients, that we remain unable to reliably predict clinical outcome for newly presenting PMD patients or their individual mucosal lesions in contemporary practice. However, as introduced in Chapter 7, the long term follow-up of patients undergoing a coordinated treatment intervention has allowed detailed documentation of clinical outcome, and thus helped define a number of specific outcome categories including: disease free status (patients demonstrating complete clinical resolution), persistent PMD disease (despite intervention), malignant transformation (at the same-site as identified precursor lesions), and oral cancer development (new-site SCC). Indeed, I firmly believe that well-defined outcome categories are not only valuable and pragmatic tools, but also vitally necessary to allow meaningful and reproducible interpretation of patient treatment data.

Retrospective analyses of several patient cohorts have helped to confirm a number of consistent and reasonably predictive clinico-pathological observations. These are summarised in Table 13.1 and, in particular, include the following important points:

- 1. Whilst disease free status is routinely achievable following treatment of PMD cases with mild dysplasia, it appears significantly less likely for lesions presenting clinically as erythroleukoplakia or with features of lichenoid inflammation,
- 2. Persistent PMD disease is seen more frequently following PVL treatment and in the absence of intervention by laser excision surgery,
- 3. Malignant transformation risk is greatest for erythroleukoplakia, for lesions exhibiting high-grade dysplasia and those arising at floor of mouth and ventro-lateral tongue sites.

Table 13.1: Clinico-Pathological Features Associated with Clinical Outcome²³

	Disease Free	Persistent PMD Disease	Malignant Transformation
Patient Age	Younger	Younger	-
Clinical Lesion	Leukoplakia	Leukoplakia	Erythroleukoplakia*
Site	-	-	Floor of Mouth Ventro-Lateral Tongue
Treatment	-	-	-
Histopathology	Mild Dysplasia*	Mild / Moderate Dysplasia Lichenoid Inflammation PVL	Severe Dysplasia* Carcinoma in Situ* Lichenoid Inflammation*

**Statistical Significance No Reliable Association Seen*

As a general observation, the incidence of further PMD disease (both persistent and recurrent) tends to increase with the length of patient follow-up. It is also noted that non-homogeneous leukoplakias, extensive or multi-focal mucosal lesions, more severe dysplasias and floor of mouth and ventral tongue sites are all consistently associated with an enhanced risk of progressive disease. Continued tobacco smoking and alcohol use

following treatment have also been shown to be important risk factors for developing further PMD³³⁻³⁵.

It may be possible, therefore, to delineate ‘high risk’ and ‘low risk’ patient categories on the basis of such available clinico-pathological features, although it is recognised that this is primarily patient cohort based. In the future, it is hoped that individual patient profiling, genomic sequencing and personalised medicine will improve the specificity of predictive diagnoses and allow targeted treatment intervention. We will consider many of these issues in more detail in the following chapters of this book.

Prevention in Practice

In order to improve patient survival and reduce the morbidity following a diagnosis of oral SCC, it is imperative for clinicians to utilize the ‘PMD window’ effectively and to recognise malignant transformation at the earliest possible stage; this allows intervention in an attempt to halt disease progression and ‘stop the oral cancer clock’. Whilst we have shown that surgical excision of PMD lesions may decrease the risk of same-site malignant transformation, it does not, regrettably, eliminate the subsequent risk of new-site cancer development occurring³⁶.

Unfortunately, as discussed previously, there exists considerable public ignorance regarding oral cancer and PMD, and the patient population most ‘at risk’ rarely attends for oral examination or dental care. As general population screening programmes for oral malignancy are thus fundamentally flawed health care interventions, a more pragmatic approach is to identify and specifically target those patient groups deemed to be ‘high risk’ of oral carcinogenesis. The pragmatic difficulty, of course, is how to consistently identify this population prior to disease presentation. Profiling ‘high-risk’ patients in a series of European studies have emphasized the following features: male gender, short stature, low socio-economic status, manual occupation or unemployment, addiction to tobacco and alcohol, diets low in fruit and vegetables, and poor oral hygiene and irregular dental care. It is recognised that the detailed influence of these features will inevitably vary between global regions but these profiling features remain valuable tools in day-to-day clinical practice^{27,37}.

To successfully achieve our ultimate clinical management goal, which is to prevent the development of oral SCC in the first place, all 3 tiers of

preventive healthcare must be utilized and these are intrinsically linked throughout the entire process of diagnosis and treatment of oral mucosal disease:

1. Primary prevention, to avoid disease development, is thus used to remove the principal risks factors of disease and promote protective behaviour within a community or population; in particular, eliminating the use of tobacco products, avoiding excessive alcohol consumption and improving diet and nutrition.
2. Secondary prevention, to detect PMD or early SCC at a stage when intervention leads to cure or significantly reduced morbidity and mortality; this of course is based firmly upon the provision of an effective interventional management strategy to identify and then target the 'high-risk' population.
3. Tertiary preventive strategies attempt to reduce the risk of disease recurrence and minimize disease-related complications in treated patients, and ultimately rely heavily on the provision of appropriate specialist clinical services and the coordination of dedicated patient follow-up protocols.

Utilising and combining these approaches, therefore, Table 13.2 summarizes a number of active preventive strategies that, based upon our current knowledge and anticipated targeted populations, should contribute significantly to improving oral SCC diagnosis and management.

In the future, with the rates of new oral cancer cases rising, it will become increasingly important to strengthen our efforts in improving the primary prevention of PMD. This, however, is not always straightforward. For example, whilst the over use of tobacco products is recognised as one of the commonest risk factors for oral cancer, most smokers will never actually develop the disease. This complicates not only the preventive advice we give to patients but also, of course, underlines the importance of other or unknown risk factors and the probable influence of inherent genetic susceptibilities.

Table 13.2: Preventive Approaches to Oral Cancer Management

Preventive Strategy	Knowledge Base	Target Population	Clinical Intervention
Primary	Patient Profiling Risk Stratification	General	Patient Education Health Promotion Identify & Eliminate Risk Factors
Secondary	Abnormal Cell Proliferation Anatomical Position Disruption of Tissue Hierarchy Field Change Multiple-Site Disease Progressive Disease	‘High-Risk’	Mirror Image Biopsies Field Mapping Biopsies Interventional Surgery
Tertiary	Clinical Outcome Data	Treated Patients	Patient Surveillance Further Intervention

There is increasing evidence that once precursor lesions have arisen, cessation of smoking may aid in the clinical resolution of PMD and may help to prevent further disease from arising following treatment; an important primary strategy with clear secondary preventive application. Thus, greater and improved emphasis on smoking cessation techniques and nicotine replacement therapy is highly pertinent in modern clinical practice and, as we have shown in Chapter 7, probably most effective if provided directly to patients as part of specialist advice in dedicated PMD clinics. Unfortunately, despite increased awareness of smoking as a risk factor and some significant reductions in smoking behaviour, we find ourselves in the midst of a worldwide rise in oral cancer incidence.

It may be that the substantial increases in alcohol consumption reported in many developed countries is partly responsible for the rise in oral cancer. Separating the carcinogenic effects of tobacco from alcohol remains difficult, of course, as many smokers also consume alcohol so the precise effects of alcohol and tobacco acting alone or synergistically are difficult to determine. Population attributable risk for SCC development in PMD recently estimated 25% for smoking alone, 18% for alcohol alone and 40% for combined smoking and alcohol behaviour³⁸. There seems little doubt that, wherever possible, opportunities for clinicians to offer advice to patients on reducing alcohol consumption should be taken and may well prove effective as part of longer term preventive strategies; these may

include cognitive behavioural therapies, effective and assisted alcohol withdrawal protocols, social responsibility and the promotion of abstinence. There is no doubt that public awareness campaigns to prevent drink driving, targeting young drinkers to prevent chronic alcohol abuse and government policies to raise the minimum price for alcoholic beverages have been beneficial and have influenced public behaviour in a positive manner in recent years.

Epidemiological evidence surrounding the role of diet and PMD development remains difficult to assess, although much of the literature suggests a causative or contributory role for low fresh fruit and vegetable intake and oral carcinogenesis. Diets vary tremendously around the world, of course, and the many confounding effects such as high levels of tobacco smoking and the malnutrition consequent upon excessive alcohol consumption complicate accurate dietary assessments in patient care.

Whilst a clear and important relationship has been demonstrated between human papilloma virus (HPV), particularly sub-types 16 and 18, and oropharyngeal SCC, the precise role of HPV in PMD initiation and progression remains unclear. It would seem sensible, however, to support widespread HPV vaccination and improve public education regarding orogenital sexual practices as important and pragmatic preventive initiatives³⁹.

It is very likely that future preventive strategies will all emphasize well balanced diets, general health promotion, weight loss, regular exercise and responsible sexual health for many types of cancer prevention. Health care professionals will be expected to pro-actively engage patients in discussions regarding personal habits and risk factor behaviour, together with strong encouragement to participate in healthy living schemes. Increasingly, public health promotion schemes such as 'Mouth Cancer Awareness Week' and 'Mouth Cancer Action Month' in the UK have raised the profile of oral cancer to the general public, whilst helping to develop greater public understanding of the links between oral and general health. Whether such campaigns will have an effect on clinical disease presentation in the long term is difficult to say because like many public health screening programmes, unfortunately, the people most at risk of disease rarely access such programmes and almost never present for health advice or preventive examinations.

Whilst primary prevention is undoubtedly the initial, and perhaps the most fundamental strategy to reduce oral cancer risk, much of the clinical work presented in this book has concentrated upon secondary and tertiary preventive strategies and the targeting and follow-up of the ‘high risk’ patient population. An important clinical consequence of this, of course, is the realization that patient surveillance, regular clinic monitoring and risk factor profiling remain pertinent for all PMD patients even following successful treatment intervention. Indeed, such long-term patient surveillance has enhanced our understanding of PMD natural history, helped identify and treat the ‘high risk’ patient, ensured recognition and modification of risk factor behaviour, and highlighted the significance of multiple-lesion presentation and field change cancerization^{21,27}.

Conclusions

For many years, early diagnosis of oral SCC and PMD management have been areas of clinical practice in which variability in decision making and lack of high-quality evidence confounded treatment. By combining an understanding of oral epithelial proliferation and anatomical position variance with enhanced knowledge of PMD progression and prediction of clinical behaviour, it is our hope that rationalized preventive strategies may then be targeted appropriately to aid in the early diagnosis and management of individual patients at risk of carcinogenesis. Only in this manner are we truly likely to improve the outcomes for our patients with oral cancer. There remains, however, only limited agreement on contemporary management strategies for treating established PMD. In the next chapter of this book, therefore, we will focus our attention on detailing and defining the precise role that intervention may play in enhancing an active and effective approach to preventive treatment⁴⁰⁻⁴².

References

1. Thomson PJ. Oral Carcinogenesis. In: PJ Thomson (ed) Oral Precancer – Diagnosis and Management of Potentially Malignant Disorders. Chichester: Wiley-Blackwell; 2012. p31-47. ISBN 978-1-4443-3574-3.
2. daSilva SD, Ferlito A, Takes RP, Brakenhoff RH, Valentin MD, Woolgar JA, Bradford CR, Rodrigo JP, Rinaldo A, Hier MP, Kowalski LP. Advances and applications of oral cancer basic research. Oral Oncology 2011 47: 783-791.

3. Thomson PJ. Perspectives on Oral Squamous Cell Carcinoma Prevention – Proliferation, Position, Progression and Prediction. *Journal of Oral Pathology & Medicine* 2018 47: 803-807.
4. Robinson CM, Thomson PJ. Form and Function of the Oral Mucosa. In: PJ Thomson (ed) *Oral Precancer – Diagnosis and Management of Potentially Malignant Disorders*. Chichester: Wiley-Blackwell; 2012. p13-30. ISBN 978-1-4443-3574-3.
5. Mackenzie IC. Growth of malignant oral epithelial stem cells after seeding into organotypical cultures of normal mucosa. *Journal of Oral Pathology & Medicine* 2004 33: 71-78.
6. Pich A, Chiusa L, Navone R. Prognostic relevance of cell proliferation in head and neck tumours. *Annals of Oncology* 2004 15: 1319-1329.
7. Richard V, Pillai MR. The stem cell code in oral epithelial tumorigenesis: 'The cancer stem cell shift hypothesis'. *Biochimica et Biophysica Acta* 2010 1806: 146-162.
8. Mishra R. Cell cycle-regulatory cyclins and their deregulation in oral cancer. *Oral Oncology* 2013 49: 475-481.
9. Thomson PJ, Potten CS, Appleton DR. In-vitro labelling studies and the measurement of epithelial cell proliferative activity in the human oral cavity. *Archives of Oral Biology* 2001 46:1157-1164.
10. Thomson PJ, Potten CS, Appleton DR. Characterization of epithelial cell activity in patients with oral cancer. *British Journal of Oral & Maxillofacial Surgery* 1999 37: 384-390.
11. Thomson PJ, Soames JV, Potten CS, Booth C. Epithelial cell proliferative activity and oral cancer progression. *Cell Proliferation* 2002 35(Suppl.1): 110-120.
12. Torres-Rendon A, Roy S, Craig GT, Speight PM. Expression of Mcm2, geminin and Ki67 in normal oral mucosa, oral epithelial dysplasia and their corresponding squamous-cell carcinomas. *British Journal of Cancer* 2009 100: 1128-1134.
13. Garg KN, Raj V, Chandra S. Evaluation of the efficacy of AgNOR as a proliferative marker in oral leukoplakia: a morphometric analysis. *National Journal of Maxillofacial Surgery* 2013 4: 40-45.
14. Gonzalez-Moles MA, Ruiz-Avila I, Gil-Montoya JA, Esteban F, Bravo M. Analysis of Ki-67 expression in oral squamous cell carcinoma: Why Ki-67 is not a prognostic indicator. *Oral Oncology* 2010 46: 525-530.
15. Thomson PJ, Potten CS, Appleton DR. Mapping dynamic epithelial cell proliferative activity within the oral cavity of man: a new insight into carcinogenesis? *British Journal of Oral & Maxillofacial Surgery* 1999 37:377-383.

16. Zhang L, Cheung KJ, Lam WL, Cheng X, Poh C, Priddy R, Epstein J, Le ND, Rosin MP. Increased genetic damage in oral leukoplakia from high risk sites: potential impact on staging and clinical management. *Cancer* 2001 91: 2148-2155.
17. Watanabe S, Watanabe R, Oton-Leite AF, Alencar RCG, Oliveira JC, Leles CR, Batista AC, Mendonca EF. Analysis of cell proliferation and pattern of invasion in oral squamous cell carcinoma. *Journal of Oral Science* 2010 52: 417-424.
18. Giaretti W, Monteghirfo S, Pentenero M, Gandolfo S, Malacarne D, Castagnola P. Chromosomal instability, DNA index, dysplasia, and subsite in oral premalignancy as intermediate endpoints of risk of cancer. *Cancer Epidemiology Biomarkers & Prevention* 2013 22: 1133-1141.
19. Thomson PJ. Field change and oral cancer: new evidence for widespread carcinogenesis. *International Journal of Oral & Maxillofacial Surgery* 2002 31: 262-266.
20. Mignogna MD, Fedele S, LoRusso L, Mignogna C, de Rosa G, Porter SR. Field cancerization in oral lichen planus. *EJSO* 2007 33: 383-389.
21. Hamadah O, Goodson ML, Thomson PJ. Clinicopathological behaviour of multiple oral dysplastic lesions compared with that of single lesions. *British Journal of Oral & Maxillofacial Surgery* 2010 48: 503-506.
22. Thomson PJ, Hamadah O. Cancerisation within the oral cavity: The use of 'field mapping biopsies' in clinical management. *Oral Oncology* 2007 43: 20-26.
23. Thomson PJ, Goodson ML, Cocks K, Turner JE. Interventional laser surgery for oral potentially malignant disorders: a longitudinal patient cohort study. *International Journal of Oral & Maxillofacial Surgery* 2017 46: 337-342.
24. Giaretti W, Maffei M, Pentenero M, Scaruffi P, Donadini A, DiNallo E, Malacarne D, Marino R, Familiari U, Coco S, Tonini GP, Castagnola P, Gandolfo S. Genomic aberrations in normal appearing mucosa fields distal from oral potentially malignant lesions. *Cellular Oncology* 2012 35: 43-52.
25. Ho MW, Risk JM, Woolgar JA, Field EA, Field JK, Steele JC, Rajlawat BP, Triantafyllou A, Rogers SN, Lowe D, Shaw RJ. The clinical determinants of malignant transformation in oral epithelial dysplasia. *Oral Oncology* 2012 48: 969-976.

26. Thomson PJ. Potentially Malignant Disorders – The Case for Intervention. *Journal of Oral Pathology & Medicine* 2017 46: 883-887.
27. Thomson PJ. Managing oral potentially malignant disorders: A question of risk. *Faculty Dental Journal* 2015 6: 186-191.
28. Cruz I, Napier SS, van der Waal I, Snijders PJF, Walboomers JMM, Lamey PJ, Cowan CG, Gregg TA, Maxwell P, Meijer CJLM. Suprabasal p53 immunexpression is strongly associated with high grade dysplasia and risk for malignant transformation in potentially malignant oral lesions from Northern Ireland. *Journal of Clinical Pathology* 2002 55: 98-104.
29. Abrahao AC, Bonelli BV, Nunes FD, Dias EP, Cabral MG. Immunohistochemical expression of p53, p16 and hTERT in oral squamous cell carcinoma and potentially malignant disorders. *Brazilian Oral Research* 2011 25: 34-41.
30. Dwivedi N, Chandra S, Kashyap B, Raj V, Agarwal A. Suprabasal expression of Ki-67 as a marker for the severity of oral epithelial dysplasia and oral squamous cell carcinoma. *Contemporary Clinical Dentistry* 2013 4: 7-12.
31. Thomson PJ, Hamadah O, Goodson ML, Booth C, Cragg N. Cyclin A predicts clinical outcome in oral precancer and cancer. *International Journal of Oral & Maxillofacial Surgery* 2006 35: 1041-1046.
32. Thomson PJ, Goodson ML, Booth C, Cragg N, Hamadah O. Predicting recurrence after treatment of oral precancer: Use of cell cycle analysis. *British Journal of Oral and Maxillofacial Surgery* 2008 46: 370-375.
33. Diajil AR, Robinson CM, Sloan P, Thomson PJ. Clinical outcome following oral potentially malignant disorder treatment: a 100 patient cohort study. *International Journal of Dentistry* 2013 Article ID 809248, 8 pages <http://dx.doi.org/10.1155/2013/809248>.
34. Goodson ML, Hamadah O, Thomson PJ. The role of alcohol in oral precancer: observations from a North-East England population. *British Journal of Oral & Maxillofacial Surgery* 2010 48: 507-510.
35. Hamadah O, Thomson PJ. Factors affecting carbon dioxide laser treatment for oral precancer: A patient cohort study. *Lasers in Surgery and Medicine* 2009 41: 17-25.
36. Thomson PJ, Goodson ML, Smith DR. Profiling Cancer Risk in Oral Potentially Malignant Disorders – A Patient Cohort Study. *Journal of Oral Pathology & Medicine* 2017 46: 888-895.

37. Williams M, Bethea J. Patient awareness of oral cancer health advice in a dental access centre: a mixed methods study. *British Dental Journal* 2011 210: E9 doi: 10.1038/sj.bdj.2011.201.
38. Awadallah M, Idle M, Patel K, Kademani D. Management update of potentially premalignant oral epithelial lesions. *Oral Surg Oral Med Oral Patol Oral Radiol* 2018 125: 628-636.
39. Speight PM, Khurram SA, Kujan O. Oral potentially malignant disorders: risk of progression to malignancy. *Oral Surg Oral Med Oral Patol Oral Radiol* 2018 125: 612-627.
40. Walsh T, Liu JLY, Brocklehurst P, Glenny A-M, Lingen M, Kerr AR, Ogden G, Warnakulasuriya S, Scully C. Clinical assessment to screen for the detection of oral cavity cancer and potentially malignant disorders in apparently healthy adults. *Cochrane Database of Systematic Reviews* 2013 Issue 11. DOI: 10.1002/14651858.CD010173.pub2.
41. Thomson PJ. The role of interventional surgery in oral potentially malignant disorders. *Faculty Dental Journal* 2014 5: 84-89.
42. Thomson PJ, McCaul JA, Ridout F, Hutchison IL. To treat...or not to treat? Clinicians' views on the management of oral potentially malignant disorders. *British Journal of Oral & Maxillofacial Surgery* 2015 53: 1027-1031.

CHAPTER FOURTEEN

INTERVENTION

'...to become involved in a difficult situation in order to improve it or prevent it getting worse...'

Introduction

So, finally, we move from prevention to consider intervention itself and the particular role that interventional strategies can play in the definitive management of both PMD and early invasive SCC. We have previously established that PMD are recognisable clinically and precede, albeit unpredictably, invasive SCC development. Whilst variable malignant transformation rates have been quoted, systematic review estimates an overall 12% cancer risk over a mean transformation time of around 4 years. The ensuing morbidity and high mortality consequent upon oral SCC diagnosis and treatment are significant problems in contemporary clinical practice. Whilst the objectives of treating PMD have been rather poorly defined in the past, most authorities agree that prevention of malignancy should be considered the number one priority. This objective, however, is complicated because of the widespread, multi-focal nature of disease that may present throughout the entire upper aerodigestive tract^{1,2}.

In Chapter 3, however, we specifically defined a number of salient management goals supporting an interventional strategy for PMD management, and in Chapter 12 detailed the results of a series of long-term patient cohort studies demonstrating the efficacy of intra-oral CO₂ laser surgical excision, both as an accurate diagnostic tool and a reliable treatment modality particularly for managing 'high-risk' PMD. In essence, following initial histopathological characterisation and patient risk assessment, identifiable oral mucosal lesions are then excised by laser with all margins subsequently ablated via de-focused vapourisation techniques which facilitate healing by secondary intention^{1,3-6}.

Criticisms regarding the use of surgical intervention for PMD management are not new, of course, and have been discussed in the literature over many years; these views are collated and summarised in Table 14.1. Of particular concern to this author, however, are the suggestions of ‘over-treatment’, ‘increased cost of care’ and the view that PMD excision ‘does not show benefit with respect to progression to cancer’⁷.

Table 14.1: Criticisms of Interventional Treatment for PMD

Risk of ‘over-treatment’ of benign lesions unlikely to progress to cancer
Cost of treatment
Intervention does not reduce the risk of cancer
Uncertainty over placement and significance of excision margins
Risk of PMD recurrence
No ability to predict clinical behaviour
Poor functional outcome following treatment of widespread lesions

For many years, of course, PMD management has indeed been controversially polarised between on the one hand surgical excision to remove visible mucosal disease and on the other, more conservative medical or observational techniques. We have discussed at some length just how difficult the concept of ‘potential malignancy’ can be for patients and clinicians but that, intuitively, it clearly warrants interventional management rather than just passive observation⁸.

The aim of this chapter is thus to re-examine each of our stated PMD treatment goals and, using the evidence obtained and presented in preceding chapters, to address the perceived criticisms of this approach and to attempt to clarify once and for all the precise role of interventional surgery in contemporary PMD management. We will start, however, by examining the principles behind minimal interventional therapy.

The Concept of Minimal Intervention

The concept of minimal interventional care has gained increasing popularity and acceptance in clinical practice in recent years, both within medicine in general and dentistry in particular. Defined as an overall philosophy embracing prevention, early detection of disease and cure by minimally invasive treatment, it is regarded as holistic in nature being especially cognizant of patients’ needs, desires and expectations^{1,9,10}.

In general, the principles underlying minimal intervention during patient management focus on three inter-related strategies: accurate assessment of

patient risk, earliest possible diagnosis, and efficacious minimally invasive treatment. These are all highly pertinent to the philosophy expounded in this book but, unfortunately, whilst modern oncology management has increasingly emphasized minimally invasive surgery in order to reduce patient morbidity, this remains somewhat elusive for intra-oral cancer management. The potential benefits of the approach to the management of PMD and patients with oral SCC appear obvious, however, and would certainly help to address criticisms suggestive of ‘over-treatment’^{9,11}.

The specific management goals of PMD treatment, discussed in Chapter 3 and originally listed in Table 3.2, align well with the overall principles of minimal interventional care, as re-structured and re-presented in Table 14.2.

Table 14.2: Alignment of PMD Management Goals with Interventional Principles

Interventional Principle	PMD Management Goal
Patient Risk Assessment	Prediction of Clinical Behaviour Prevention of Recurrent or Further Dysplastic Lesions Prevention of Malignant Transformation
Earliest Possible Diagnosis	Accurate and Definitive Diagnosis Early Recognition of Malignancy
Effective Minimal Intervention	Removal of Dysplastic Mucosa Patient Acceptability and Minimal Morbidity Cost-Effectiveness

Patient Risk Assessment

We have previously explored the important concept of patient risk in Chapter 4, clearly defining it as the potential for an individual to lose normal health status. Stratification to quantify risk remains fundamental to our efforts to improve management strategies, specifically to prevent the transformation of mucosal precursor lesions into invasive SCC.

Prediction of Clinical Behaviour

As discussed in the preceding chapter, whilst our ability to predict clinical outcome for individual patients or lesions remains elusive in clinical practice, the long-term follow-up of defined PMD patient cohorts, particularly those undergoing a coordinated interventional treatment

protocol, has facilitated detailed and useful characterisation of specific clinical outcome categories. Well-defined clinical outcome categories are essential prerequisites to inform clinical practice and improve understanding of PMD natural history. By defining these distinct categories, we can now map the trajectory of individual patients and help predict likely outcomes for patients during their follow-up.

We now know, for example, that clinical resolution or disease free status is most likely to occur when patients present with lesions exhibiting mild dysplasia, but is significantly less common with an erythroleukoplakia appearance or with oral lichenoid lesions. We can also predict that PMD is more likely to persist following treatment of PVL and, if lesion excision deemed impractical, ablation surgery used instead. Probably of greatest significance, is that we can predict an increased risk for oral SCC development in erythroleukoplakia, in lesions exhibiting severe dysplasia and in disorders arising on floor of mouth and ventro-lateral tongue sites. These are all pragmatic guidelines informing individual patient management and follow-up⁶.

As a more general observation, we have also seen that the incidence of further or progressive PMD disease increases with length of patient follow-up, with non-homogeneous leukoplakia, widespread or multi-focal disease, higher grade dysplasia and the floor of the mouth and ventral tongue posing the greatest risk⁷. Similarly, we have identified that patients who continue to smoke tobacco and consume alcohol are at greater risk of persisting PMD disease following laser surgery^{12,13}.

Prevention of Recurrent or Further Dysplastic Lesions

An overall review of the literature shows that interventional CO₂ laser treatment for PMD has the potential to render between 50 to 90% of PMD patients free from disease, with only 10 to 34% then exhibiting further or recurrent disease. This would certainly appear to confirm the efficacy of intervention in achieving a successful outcome, and clearly contrasts with an observational approach to treatment in which around 77% of lesions inevitably persist¹⁴⁻²¹.

Of course, it is recognised that following successful primary therapy, local PMD recurrence or development of new-site lesions may occur, but careful patient follow-up facilitates early identification and further laser treatment can be administered as and when required. Whilst most patients

in our cohort studies only ever required one episode of laser treatment, a mean number of 2.26 treatments over a mean period of 32.9 months ultimately rendered over 74% of 590 PMD patients free of disease, despite their initial presentation with significant dysplasia⁶.

Prevention of Malignant Transformation

It is a fundamental hypothesis, and the most significant justification for PMD intervention, that surgical removal of a dysplastic lesion will reduce the risk of malignant transformation. Studies have shown 15% transformation rates for patients whose lesions were not excised, compared with around 5-6% when lesions were removed. Excluding the occult SCCs excised ‘unexpectedly’, which should be considered a considerable interventional treatment success, we have noted between 2 to 5% of PMD patients developing same or new-site cancer formation during post-treatment follow-up. Local surgical excision of dysplastic lesions appears to decrease the risk of same-site malignant transformation, therefore, but does not eliminate the risk of new-site oral cancer development. As we have seen, the clinical outcome for such patients is not always favourable. The clinical consequence is the realization that continued patient surveillance, regular clinic monitoring and risk factor profiling remain pertinent for all PMD cases following treatment^{3-6,22-24}.

Earliest Possible Diagnosis

The earliest possible, most accurate and definitive diagnoses are mandatory for effective recognition of malignant change and to thereby deliver optimal patient treatment. With no predictive biomarkers available for contemporary clinical application, histo-pathological assessment of biopsy specimens effectively remains the diagnostic ‘gold standard’ for confirmation of both dysplastic change and invasive SCC.

Accurate and Definitive Diagnosis

Perhaps the best-defining characteristic of PMD diagnosis overall is indeed the identification on microscopy of epithelial disorganisation and dysmaturation changes and their grading, albeit it subjectively, into increasingly severe categories of dysplasia. Although evidence remains weak, it is generally assumed that more severe or ‘high grade’ dysplasia is at greatest risk of cancer development. Accurate histopathological diagnosis is thus essential in clinical practice and yet, as we have

discovered, incision biopsies are not necessarily representative of the true and evolving nature of PMD, particularly for large and widespread disorders. A significant ‘under-diagnosis ratio’, varying between 14 to 36%, is thus seen when incision specimens are compared with their excision counterparts. Incision biopsy, therefore, can only be regarded as a ‘provisional’ diagnosis, with whole lesion excision now deemed mandatory for ‘definitive’ PMD diagnosis and grading; the latter, of course, is readily facilitated by CO₂ laser excision^{4,6,24-28}.

Whilst thermal cytological artefacts at excision margins have been suggested as a potential limitation of interpreting laser excision biopsies, these features do not appear to adversely affect histopathology assessment and reporting by experienced oral pathologists. In addition, it is also recognised that the absence of dysplasia in incision biopsies cannot exclude the presence of an unidentified pre-existing SCC or indeed the risk for a subsequently developing cancer to arise in any individual PMD lesion; a rather concerning scenario for clinicians. Multiple lesion disease, particularly widespread and pan-oral presentation which we know may affect around 25% of PMD patients, is undoubtedly more challenging to manage but our reported technique of ‘field mapping’ whereby multiple-site incision biopsies are performed to delineate the most significant foci of dysplastic disease facilitates pragmatic, targeted intervention to high-risk regions^{3-6,13,29-33}.

Early Recognition of Malignancy

I believe that sufficient evidence now exists to confirm that PMD excision facilitates early recognition and treatment of oral cancer. Review of surgically treated cases shows that ‘unexpected’ SCCs, often at early invasive stages, are identified histo-pathologically in 7 to 12% of excision specimens; a figure that is remarkably similar to the 12% transformation rate quoted in systematic review and an important diagnostic and treatment success. The efficacy of intervention is confirmed in our study cohorts because few patients required any additional post-laser oncology treatment and long-term follow-up revealed excellent clinical outcomes^{3-6,26-29,34}.

As per our original hypothesis, therefore, SCC detection at an early stage does facilitate curative treatment with a relatively simple and minor surgical intervention. In contrast, the limitations of non-intervention are highlighted by a 25% malignant transformation rate reported in a UK

dysplasia clinic in which there was no apparent interventional treatment protocol and SCC diagnoses were only made during periods of long-term observation³⁵. In addition, our specific study finding that diagnosis and treatment of unexpected SCC has a more favourable prognosis, with over 80% of patients disease free and only one cancer-related death, compared to patients who subsequently developed SCC during follow-up, in which only 40% were free of disease and 9 cancer-related deaths were recorded, clearly emphasizes the efficacy of early intervention and helps refute criticism that surgical intervention does not show benefit with respect to progression to cancer³⁶.

Effective Minimal Intervention

Any therapeutic approach that intervenes effectively to diagnose oral SCC at a 'pre-malignant' or early invasive phase and institutes curative treatment is thus to be embraced and encouraged. It is perhaps self-evident that only a surgical intervention can effectively remove localized areas of abnormal mucosa. PMD, as we have seen, are mucosal conditions only and do not require the aggressive treatment modalities necessary for removal and/or destruction of invasive carcinoma and are the obvious target for a minimally invasive approach to management.

Removal of Dysplastic Mucosa

I think it is now virtually impossible to not recommend an early interventional approach to remove 'pre-invasive' dysplastic mucosa. Whilst surgery can be performed by scalpel, cutting diathermy or photodynamic therapy, I believe the efficacy of dysplasia excision by CO₂ laser is confirmed in our patient cohort studies³⁻⁶. Dysplasia-free margins are reported following histopathological examination of excised specimens in around 75% of treated cases, with no significant association seen between any identifiable foci of dysplasia in resection margins and adverse outcome such as recurrent or further PMD disease, almost certainly due to the ability to extend treatment zones by laser ablating oral cavity margins 2 to 4mm beyond the specimen excision^{3-6,12,13}.

Patient Acceptability and Minimal Morbidity

As CO₂ laser surgery is now recommended as the preferred PMD management choice, it is important that it is both acceptable to patients and that any post-operative morbidity is low. Significant complications

following CO₂ laser treatment are actually quite rare and, whilst some patients report post-operative pain, submandibular salivary gland swelling following floor of mouth procedures and lingual nerve dysaesthesia after tongue surgery, these are usually transient, self-limiting and rarely require additional treatment. A small number of patients report prolonged complications but these are usually after more extensive surgery or, perhaps more significantly, in those who continue to smoke heavily or consume alcohol after treatment. In general, laser surgery is well tolerated and accepted by patients, aids haemostasis, promotes excellent healing and produces minimal scarring with little functional deficit or patient morbidity; this is well illustrated in Figure 14.1. A particular advantage is the ability to repeat excisions or ablations at the same site without compromising oral healing or function. No significant adverse quality of life outcomes for PMD patients have been reported, particularly in contrast to the known physical and psycho-social consequences of advanced oral SCC treatment^{3-6,37-39}.

Whilst no consensus exists to determine the precise nature or the exact duration of PMD follow-up, the policy of active surveillance advocated in this book offers patients a number of additional treatment advantages and also helps to advance our understanding of PMD natural history and disease progression; these are summarized in Table 14.3. Interventional management, I firmly believe, should be considered cyclical in nature, passing from active surgical excision through to surveillance but returning to surgical intervention upon diagnosis of any further or progressive disease. It is, therefore, both a consistent and a determined approach to patient management^{1,3,12}.



Figure 14.1: Excellent healing, with minimal scarring and good function, 6-months following CO₂ laser excision of PMD lesion arising at right floor of mouth and ventral tongue.

Table 14.3: Advantages of Patient Follow-Up & Surveillance Strategies Post-Intervention

Assess efficacy of treatment intervention
Recognise treatment complications
Early identification of recurrent or further PMD disease
Early identification of cancer development
Optimal timing and coordination of further treatment intervention
Opportunities to modify patient risk factor behaviour
Effective assessment of long-term patient risk
Improve understanding of PMD natural history

Cost Effectiveness

It is probably true to say that very few data exist in the literature to support or refute the concept that early and minimal intervention, which as we have seen is delivered primarily as secondary or tertiary preventive strategies to an ‘at risk’ population, is cost-effective; it is not, however, an unreasonable hypothesis. Rather than increasing cost of care, targeted PMD excision is actually likely to prove less expensive than the alternative of multiple, repeat incision biopsies performed over many years during an otherwise observational-type follow-up. There may also

be additional cost savings in centralizing services for PMD patients especially within specialist oral oncology centres^{3,40}.

In considering the wider aspects of health economics, it is necessary of course to attempt to balance PMD treatment efficacy, cost and value for money with the anticipated costs of more comprehensive oncology treatment. In recent years the UK Department of Health Patient-Level Information and Costing Systems (PLICS) were introduced to help estimate the costs incurred by NHS healthcare organizations providing specific treatment interventions. PLICS data was therefore retrieved from the Newcastle upon Tyne Hospitals NHS Foundation Trust over a 6-month period (1st April to 30th September 2015) to contrast diagnostic and surgical services for PMD CO₂ laser surgery (averaged at around £997.90 per treated patient) with multi-disciplinary oral SCC care (£5,471.58 per patient). Initial SCC treatment costs were thus more than 5 times that incurred by surgical intervention for PMD management, without considering the significant additional costs of head and neck cancer care, including adjuvant radiotherapy and/or chemotherapy treatments. I certainly think that this effectively refutes any perceived criticisms regarding the cost of care for PMD treatment.

Conclusions

We have seen that the clinical outcomes for oral cancer are only ever likely to improve by the earlier detection of SCC and application of an effective management strategy for oral precursor lesions with malignant potential. The consequences for an individual patient progressing to SCC are devastating. There seems little to gain from observational or medical treatment strategies, particularly as the substantive evidence presented and reviewed in this chapter, clearly supports the diagnostic and treatment efficacy of intervention as the definitive treatment modality. Table 14.4 contrasts the efficacy of laser surgery with observation and medical therapy for each of our listed management goals; the evidence, I believe, speaks for itself. Interventional laser surgery provides readily available, effective, low morbidity treatment which is successful in excising PMD mucosal lesions, facilitates early diagnosis of occult SCC and indeed may help in reducing the overall risk of SCC development^{41,42}.

Table 14.4: PMD Management Goals and Treatment Efficacy

Management Goals	Observation	Treatment	Modality
		Medical Therapy	Laser Surgery
Accurate and Definitive Diagnosis	No	No	Yes
Prediction of Clinical Behaviour	No	No	Possible
Early Recognition of Malignancy	No	No	Yes
Removal of Dysplastic Mucosa	No	No	Yes
Prevention of Recurrent or Further Dysplastic Lesions	No	No	Possible
Prevent Malignant Transformation	No	No	Possible
Patient Acceptability and Minimal Morbidity	No	No	Yes
Cost-Effective	?	?	Yes

In the future, PMD patients will require better stratification into ‘high’ and ‘low’ risk categories, with individually tailored treatment protocols based upon bio-molecular and genetic profiling of cancer risk. We will discuss these issues in more detail in Chapter 15. Whilst awaiting such refinements, however, and in the absence of meaningful multi-centre, prospective randomised trials, the contemporary case for interventional management has been presented.

References

1. Thomson PJ. Minimal intervention in oral cancer management: idealistic or realistic? *Faculty Dental Journal* 2018 9: 151-154.
2. Thomson PJ. Oral Carcinogenesis. In: PJ Thomson (ed) *Oral Precancer – Diagnosis and Management of Potentially Malignant Disorders*. Chichester: Wiley-Blackwell; 2012. p31-47. ISBN 978-1-4443-3574-3.
3. Thomson PJ. Management of Oral Precancer. In: PJ Thomson (ed) *Oral Precancer – Diagnosis and Management of Potentially Malignant Disorders*. Chichester: Wiley-Blackwell; 2012. p107-137. ISBN 978-1-4443-3574-3.
4. Thomson PJ, Wylie J. Interventional laser surgery: an effective surgical and diagnostic tool in oral precancer management. *International Journal of Oral & Maxillofacial Surgery* 2002 31 :145-153.
5. Diajil AR, Robinson CM, Sloan P, Thomson PJ. Clinical outcome following oral potentially malignant disorder treatment: a 100 patient

- cohort study. *International Journal of Dentistry* 2013 Article ID 809248, 8 pages <http://dx.doi.org/10.1155/2013/809248>.
6. Thomson PJ, Goodson ML, Cocks K, Turner JE. Interventional laser surgery for oral potentially malignant disorders: a longitudinal patient cohort study. *International Journal of Oral & Maxillofacial Surgery* 2017 46: 337-342.
 7. Guneri P, Epstein JB. Why are we still unable to accurately determine the malignant potential or the behaviour of oral mucosal lesions? *Oral Oncology* 2017 71: 177-179.
 8. Thomson PJ. Managing oral potentially malignant disorders: A question of risk. *Faculty Dental Journal* 2015 6: 186-191.
 9. Farah CS, Bhatia N, John K, Lee BW. Minimum intervention dentistry in oral medicine. *Australian Dental Journal* 2013 58(Suppl 1): 85-94.
 10. Goh HKC, Teo DTW. Minimally invasive surgery for head and neck cancer. *Lancet Oncology* 2010 11: 281-286.
 11. Harris AT, Tanyi A, Hart RD, Trites J, Rigby MH, Lancaster J, Nicolaides A, Taylor SM. Transoral laser surgery for laryngeal carcinoma: has Steiner achieved a genuine paradigm shift in oncological surgery? *Annals of the Royal College of Surgeons of England* 2018 100: 2-5.
 12. Thomson PJ. The role of interventional surgery in oral potentially malignant disorders 2014. *Faculty Dental Journal* 5: 84-89.
 13. Hamadah O, Thomson PJ. Factors affecting carbon dioxide laser treatment for oral precancer: A patient cohort study. *Lasers in Surgery and Medicine* 2009 41: 17-25.
 14. van der Hem PS, Nauta JMK, van der Wal JE, Roodenburg JL. The results of CO2 laser surgery in patients with oral leukoplakia: a 25 year follow up. *Oral Oncology* 2005 41: 31-37.
 15. Yang SW, Tsai CN, Lee YS, Chen TA. Treatment outcome of dysplastic leukoplakia with carbon dioxide laser – emphasis on the factors affecting recurrence. *Journal of Oral & Maxillofacial Surgery* 2011 69: 78-87.
 16. Jerjes W, Upile T, Hamdoon Z, Al-Khawalde M, Morcos M, Mosse CA, Hopper C. CO2 laser of oral dysplasia: clinicopathological features of recurrence and malignant transformation. *Lasers in Medical Science* 2012 27: 169-179.
 17. Del Corso G, Bartolomeo Gissi D, Tarsitano A, Costabile E, Marchetti C, Montebugnoli L, Foschini MP. Laser evaporation versus laser excision of oral leukoplakia: a retrospective study with long-term

- follow-up. *Journal of Cranio-Maxillo-Facial Surgery* 2015 43: 763-768.
18. K, Suzuki H, Asai T, Wakabayashi R, Enomoto Y, Kitayama M, Shigeoka M, Kimoto A, Takeuchi J, Yutori H, Komori T. Clinical investigation of carbon dioxide laser treatment for lingual leukoplakia. *Journal of Oral & Maxillofacial Surgery, Medicine & Pathology* 2015 27: 493-497.
 19. Mogedas-Vegara A, Hueto-Madrid J-A, Chimenos-Kustner E, Bescos-Atin C. The treatment of oral leukoplakia with the CO2 laser: a retrospective study of 65 patients. *Journal of Cranio-Maxillo-Facial Surgery* 2015 43: 677-681.
 20. Thomson PJ, Goodson ML, Hamadah O. Cohort studies in oral precancer management: intervention vs observation. *Oral Oncology* 2009 3(Suppl): 116.
 21. Wan Y, Liang F, Nakasone T, Sunakawa H. Development of new leukoplakias and leukoplakia-associated second/multiple primary oral cancers: A case report and literature review. *Journal of Oral & Maxillofacial Surgery, Medicine & Pathology* 2014 26: 166-169.
 22. Arnaoutakis D, Bishop J, Westra W, Califano JA. Recurrence patterns and management of oral cavity premalignant lesions. *Oral Oncology* 2013 49: 814-817.
 23. Lumerman H, Freedman P, Kerpel S. Oral epithelial dysplasia and the development of invasive squamous cell carcinoma. *Oral Surg Oral Med Oral Pathol* 1995 79: 321-329.
 24. Dost F, LeCao K, Ford PJ, Ades C, Farah CS. Malignant transformation of oral epithelial dysplasia: a real world evaluation of histopathologic grading. *Oral Surg Oral Med Oral Pathol Oral Radiol* 2014 117: 343-352.
 25. Pentenero M, Carrozzo M, Pagano M, Galliano D, Broccoletti R, Scully C, Gandolfo S. Oral mucosal dysplastic lesions and early squamous cell carcinomas: underdiagnosis from incisional biopsy. *Oral Diseases* 2003 9: 68-72.
 26. Holmstrup P, Vedtofte P, Reibel J, Stoltze K. Oral premalignant lesions: is a biopsy reliable? *Journal of Oral Pathology & Medicine* 2007 36: 262-266.
 27. Lee J-J, Hung H-C, Cheng S-J, Chiang C-P, Liu B-Y, Yu C-H, Jeng J-H, Chang H-H, Kok S-H. Factors associated with underdiagnosis from incisional biopsy of oral leukoplakic lesions. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2007 104: 217-225.

28. van der Waal I. Potentially malignant disorders of the oral and oropharyngeal mucosa; terminology, classification and present concepts of management. *Oral Oncology* 2009 45: 317-323.
29. Goodson ML, Thomson PJ (2011). Management of oral carcinoma – benefits of early precancerous intervention. *British Journal of Oral & Maxillofacial Surgery* 2011 49: 88-91.
30. Balasundaram I, Payne KFB, Al-Hadad I, Alibhai M, Thomas S, Bhandari R. Is there any benefit in surgery for potentially malignant disorders of the oral cavity? *Journal of Oral Pathology & Medicine* 2013 43: 239-244.
31. Goodson ML, Sloan P, Robinson CM, Cocks K, Thomson PJ. Oral Precursor Lesions and Malignant Transformation – Who, Where, What and When? *British Journal of Oral & Maxillofacial Surgery* 2015 53: 831-835.
32. Hamadah O, Goodson ML, Thomson PJ. Clinicopathological behaviour of multiple oral dysplastic lesions compared with that of single lesions. *British Journal of Oral & Maxillofacial Surgery* 2010 48: 503-506.
33. Thomson PJ, Hamadah O. Cancerisation within the oral cavity. The use of ‘field mapping biopsies’ in clinical management. *Oral Oncology* 2007 43: 20-26.
34. Chiesa F, Sala L, Costa L, Moglia D, Mauri M, Podrecca S, Andreola S, Marchesini R, Bandieramonte G, Bartoli C. Excision of oral leukoplakias by CO₂ laser on an out-patient basis: a useful procedure for prevention and early detection of oral carcinomas. *Tumori* 1986 72: 307-312.
35. Ho MW, Field EA, Field JK, Risk JM, Rajlawat BP, Rogers SN, Steele JC, Triantafyllou A, Woolgar JA, Lowe D, Shaw RJ. Outcomes of oral squamous cell carcinoma arising from oral epithelial dysplasia: rationale for monitoring premalignant oral lesions in a multidisciplinary clinic. *British Journal of Oral & Maxillofacial Surgery* 2013 51: 594-599.
36. Thomson PJ, Goodson ML, Smith DR. Profiling Cancer Risk in Oral Potentially Malignant Disorders – A Patient Cohort Study. *Journal of Oral Pathology & Medicine* 2017 46: 888-895.
37. Mehanna HM, Rattay T, Smith J, McConkey CC. Treatment and follow-up of oral dysplasia – a systematic review and meta-analysis. *Head & Neck* 2009 31: 1600-1609.
38. Goodson ML, Sugden K, Kometa S, Thomson PJ. Complications following interventional laser surgery for oral cancer and precancerous

- lesions. *British Journal of Oral & Maxillofacial Surgery* 2012 50: 597-600.
39. Tadakamadla J, Kumar S, Johnson NW. Quality of life in patients with oral potentially malignant disorders: a systematic review. *Oral Surg Oral Med Oral Pathol Oral Radiol* 2015 119: 644-655.
40. Dost F, LeCao K, Ford PJ, Ades C, Farah CS. Malignant transformation of oral epithelial dysplasia: a real world evaluation of histopathologic grading. *Oral Surg Oral Med Oral Pathol Oral Radiol* 2014 117: 343-352.
41. Thomson PJ. Potentially Malignant Disorders – The Case for Intervention. *Journal of Oral Pathology & Medicine* 2017 46: 883-887.
42. Mishra R. Biomarkers of oral premalignant epithelial lesions for clinical application. *Oral Oncology* 2012 48: 578-584.

CHAPTER FIFTEEN

THE FUTURE

‘...what might happen in the time following the present...’

Introduction

Thus far, we have attempted to review current understanding regarding presentation, diagnosis, management and clinical outcomes for PMD and thereby to improve the early identification and effective targeting of incipient invasive SCC within the oral cavity. It is clear that many questions remain unanswered and gaps, unfortunately, still remain in our knowledge base. Attempts to establish the true carcinogenic risk for PMD will, undoubtedly, be the subject of epidemiological, diagnostic, pathological, molecular and translational research for many years to come. The precise interplay of these factors is complex, of course, and malignant transformation is most probably the result of a combination of intrinsic and extrinsic influences acting both synchronously and metachronously in any individual patient. In this chapter, we will attempt to look towards the future to imagine ways in which both scientific advancement and new approaches to healthcare may aid in the development of robust, future strategies for the prevention, diagnosis, and treatment of oral cancer. Table 15.1 lists a number of priority areas in oral oncology practice that, I believe, will help drive the development of more effective management strategies in the future.

Table 15.1: Priorities for Managing Oral Cancer in the Future

Prevention & Early Diagnosis

Bio-Molecular Profiling & Prediction

High / Low Risk Patient Stratification

Individualised Treatment

Minimally Invasive Surgery

Interestingly, a number of specific research priorities to improve the future management of PMD were usefully summarised by Mehanna et al¹ and included: developing effective prognostic and/or predictive markers in clinical practice, rationalising patient follow-up regimes, determining the efficacy of post-treatment surveillance in the early detection of PMD recurrence and malignant transformation, and refining less invasive but effective treatment interventions. The reader will recognise that much of the work presented and discussed in this book concurs with these aims, and indeed has attempted to contribute significantly to the development of such a programme.

As a one-centre, UK-based, clinical academic unit, however, there were always going to be limitations to both the significance and applicability of our Newcastle PMD research. Having said that, the breadth of the work reported upon and analysed throughout Chapters 9 to 12 and in particular the unique, long-term nature of the major clinical study reported in Chapter 12, with a large sample size of 590 well-defined cases and the methodical and coordinated treatment intervention applied to the patient cohort, still contributes one of the most important and detailed PMD clinico-pathological databases ever reported in the literature. Overall, I hope that this programme of research has both informed and helped influence contemporary clinical practice over recent years^{2,3}. The crucial questions now, of course, are where exactly do we go from here and how do we get there?

Revisiting Oral Carcinogenesis

I think it is true to state that clinical outcomes following oral cancer treatment will only improve by earlier detection of malignant change and more effective management of precursor lesions with malignant potential. Advances in oral cancer biology should offer unprecedented opportunities for future translational research with real clinical impact. Putative markers of carcinogenesis will, of course, require thorough validation before clinical use and others may only be relevant to patients from specific geographical locations because such markers will inevitably vary with race, lifestyle and the type and amount of carcinogen exposure. We will undoubtedly require a far greater understanding of the fundamental mechanisms governing oral carcinogenesis before we can truly optimise prevention, early diagnosis and treatment, and thus improve the prognosis for both PMD and ultimately invasive SCC itself⁴⁻⁶.

Central to future developments in oral oncology is the clear requirement to advance our knowledge of molecular biology. Indeed, as our ability to identify molecular alterations associated with varying disease states increases, the need to analyse these more fully for diagnostic and therapeutic purposes will grow. It is known that the human genome contains in excess of 30,000 genes, at least 40 of which appear to be intimately involved in controlling cell division and proliferation. As discussed in both Chapters 2 and 9, the loss of cell cycle control and the initiation of abnormal proliferative activity are fundamental hallmarks of early carcinogenesis. A more detailed study of these cell cycle progression genes may substantially aid future studies of tumour growth rate, and may also help in achieving more accurate prediction of aggressive clinical behaviour.

Alterations within DNA (the genome), RNA (transcription) and protein (proteomic) levels within the tissue of PMD lesions are all likely to be increasingly and better characterised in the future, with changes that predispose to malignant transformation available for utilisation as predictive biomarkers. For example, DNA ploidy analysis utilises digital imaging of cell nuclei obtained from tissue biopsies to calculate the amount of DNA per cell; aneuploidy, in which the chromosome number is unbalanced, appears to be a potential marker for both dysplastic change and malignant transformation risk, although prospective clinical studies with accurate patient follow up data and defined clinical endpoints are clearly necessary to validate these observations⁷.

Many other investigative approaches are being trialled as innovative diagnostic tests, including microarray technologies to delineate specific RNA or DNA sequences, mass spectrometry to characterise distinct protein networks in tissue or within blood and saliva samples, laser microdissection to facilitate structural based analyses of specific cell populations, along with analyses of mitochondrial DNA and telomere length. Epigenetic events including DNA methylation, histone modification and microRNA regulation may all prove useful as future targets of disease prevention, whilst stem cell analysis and assessment of DNA damage response may offer additional opportunities to unravel the complex process of carcinogenesis⁸⁻¹¹.

The ultimate aim of genotype based predictive tests must be, of course, the ability to better stratify risk, determine prognosis and thus personalise therapeutic intervention at an individual patient level. If truly effective, this should lead to earlier diagnosis for the 'high risk' individual, deliver

more precise treatment interventions with improved response rates and hopefully reduced morbidity with minimal side effects. It is unfortunate, however, that contemporary bio-molecular analyses do not provide practical or reliable diagnostic or predictive tools for the clinical management of oral oncology patients, and it is disappointing that very few scientific advances have, to date, found routine application in the clinical setting^{12,13}.

Effective Prevention and Early Diagnosis

In the future, with rates of new oral cancer cases rising, it will become increasingly important to strengthen efforts to facilitate prevention, especially to help raise a wider public awareness of the disease. At present, approximately 300,000 oral cancer cases arise each year in the world, with 145,000 of them deemed to be fatal primarily because of delayed presentation of advanced stage disease. Whilst traditional exogenous carcinogenic agents such as tobacco and alcohol have been strongly implicated in causation, many younger patients are now presenting with PMD or frankly invasive SCC often in the absence of demonstrable risk factor behaviour, which is extremely concerning; a clinical illustration of this is shown in Figure 15.1^{14,15}.

Reliable identification of individual patients or populations at risk of oral carcinogenesis remains an important but challenging objective for the future. We have clearly demonstrated the benefits of identifying and treating both precursor PMD lesions and early invasive SCC, in terms of improved prognoses and enhanced quality of life, through detailed analyses of several patient cohort studies. Yet, it remains difficult to reliably identify those patients at risk prior to their presentation with demonstrable signs and/or symptoms of disease. Further research is now urgently needed into the delineation of 'high-risk' groups and the appropriate application of preventive techniques to initiate a more structured interventional management protocol¹⁶.

I believe that a significant and pragmatic improvement for future health care provision would be better coordination of services for PMD patients. Indeed, I am absolutely convinced that centralisation of such cases in dedicated clinics with consistent, continually reinforced specialist advice and treatment, together with multidisciplinary support to help identify and effectively modify risk factor behaviours, should help deliver an optimum



Figure 15.1: SCC arising on the left ventral tongue in a patient with no recognisable risk factor behaviour.

management strategy. The resultant concentration of clinical expertise should also facilitate rigorous audit, relevant and meaningful research work and encourage new treatment trials, in contradistinction to many current arrangements whereby patients attend a variety of differing surgical or medical clinics dependent primarily upon individual clinician interest and local or historical clinic arrangements³.

Risk Stratification

The specific relevance of risk as applied to PMD management was explored in Chapter 4. We have consistently attempted in our clinics to delineate patients thought to be at 'high-risk' from those regarded as 'low-risk'. Based upon a combination of their age, sex, medical background and risk factors, together with the anatomical site, size, clinical appearance and histopathology of their presenting oral lesions, these analyses are designed to identify those cases requiring urgent or perhaps systemic interventional treatment to try to prevent cancer development. Whilst both appropriate and pragmatic as an approach to patient management, it nonetheless remains a somewhat crude decision making tool.

In the future we will need to definitively classify individual PMD patients into 'high' and 'low risk' categories and delineate more tailored treatment protocols based upon bio-molecular profiling to target the salient markers of dysplastic change, to facilitate genetic profiling of abnormal mucosa,

and to quantify the risk of malignant transformation and predict outcome. A variety of treatment strategies, ideally marshalling systemic therapies, may well be required for patients in differing risk categories. Better clinical outcomes will require improved response rates to interventional treatment and, perhaps, an enhanced immune response that fundamentally challenges the ‘pre-malignant’ state.

Prognostic Research

Prognosis, as we have seen, relates to the likelihood of an individual patient developing a particular clinical outcome over time, based upon their clinical status and/or treatment. We have previously discussed not only how important this is, but also how frustratingly difficult it can be in clinical practice, to be able to provide such prognostic information to PMD patients. The detailed study of prognostic factors, however, may have the potential to improve clinical practice, healthcare research, and in the further development, evaluation, and targeting of clinical interventions themselves. Prognostic research is best carried out as prospective, cohort studies allowing optimal measurement of individual predictors and outcomes; this I believe is very much the theme of the clinical research programme summarised in Chapter 12. In future clinical research, formal development and validation of prognosis models may help to improve our understanding of the determinants of both the disease course and clinical outcomes for patients with PMD; these would really be important steps forward¹⁷.

Bioinformatics and ‘Big Data’

Bioinformatics, essentially the use of computer technology and mathematical analyses to evaluate large amounts of biomedical data, will undoubtedly become central components of future research into oral oncology. As a strategy, it will require very specific use of advanced predictive and behaviour analytics to extract meaningful information from large data sets; these data may then help identify new correlations and relationships to assist in disease prevention. Whilst attempts to relate ‘big data’ sets to disease status and longitudinal patient outcome may prove particularly useful for population-based studies, on an individual patient basis there would also appear to be real prospects for rationalising the provision of personalized medicine and clinical risk intervention. This may all help in the construction of more reliable and meaningful prediction models for PMD and malignant transformation.

The volume of data generated from healthcare research is only likely to increase in the future. These will include patient generated information, electronic health records, imaging and pathology files, and probably many other forms of unstructured clinical data that will be difficult to process; human inspection alone on this scale will be neither practical nor reliable. Wider use of 'big data' in healthcare, of course, is likely to raise significant ethical challenges as well including risks to individual patient's rights and privacy, together with concerns regarding autonomy, transparency and trust. Nonetheless, the future will unquestionably see all health care services having to pay far greater attention to both data collection and information quality.

Individualised Patient Treatment and Chemoprevention

It is very much hoped that the future will see PMD treatments become much more individualised and in particular patient specific, based upon molecular profiling and targeted therapeutic intervention. Molecular targeted therapy, for example, may be utilised to inhibit tumour growth or metastasis by targeting the neoplastic microenvironment and vasculature, or specifically to disrupt protein and signal transduction pathways within abnormally growing tissue whilst leaving normal cells unaffected. Whilst a variety of molecular targeted chemoprevention techniques have been developed in recent years, including monoclonal antibodies such as CetuximabTM (acting against epidermal growth factor receptor) and BevacizumabTM (an anti-angiogenic agent targeting vascular endothelial growth factor), evidence to support their use is extremely limited, with few ever having been subjected to randomised controlled trials. In addition, little or no work has been carried out in specific relation to PMD treatment, and it is likely to be some time before any specific drugs can be put into routine use as chemopreventive agents for the management of oral carcinogenesis^{18,19}.

In a more generalised approach, a number of epidemiological studies have suggested that regular use of non-steroidal anti-inflammatory drugs (NSAID) may have a protective effect against cancer development. Cyclooxygenase 2 (COX-2), the probable target of NSAIDs, is an enzyme known to be upregulated in tumours and whose actions, probably mediated via prostaglandin production, have been shown to increase cell proliferation, invasion and angiogenesis whilst at the same time decreasing apoptosis and host immune responses¹⁸. Unfortunately, COX-2 specific NSAID use risks unwanted cardiovascular thrombotic side effects and a

number of clinical trials, none of which had actually shown particularly promising results for PMD prevention, have ceased. In a small pilot study, we did investigate the influence of NSAID use in 30 PMD patients, but found no significant difference in disease activity, dysplasia grading, or clinical outcome following laser excision of oral lesions when comparing long-term aspirin users with non-aspirin users²⁰.

Innovative Approaches to Prevention and Intervention

It is to be hoped that the future will see new and innovative approaches to both the prevention of oral cancer and the introduction of early and minimally invasive treatment strategies. To be effective, of course, these will require a greater understanding of the development and natural history of PMD, together with a recognition of the significance of systemic and long-term therapies. Potential strategies include gene therapy (via introduction, modification, stimulation or deletion of genetic material), viral vectors (acting as selective oncolytic agents in neoplastic cells) or immunotherapy (by enhancing the patient's natural immune response to tumour tissue). Unfortunately, all of these have proved somewhat elusive in clinical practice and it remains unclear whether any would have an effective role in targeting dysplastic oral epithelial tissue²¹⁻²².

Maley et al²³ theorised the intriguing concept of a 'benign cell booster' prevention strategy. In this approach, rather than persisting with the somewhat indiscriminate destruction of dysplastic or neoplastic cells within affected tissue, a biological booster would be introduced to increase the 'fitness' of benign cell clones. If effective, this would initiate a competitive dynamic between benign and dysplastic cells within a potentially neoplastic field, adjusting the ecology of the oral cavity and ultimately driving dysplastic cells to extinction, possibly requiring repeat booster application over time.

Whether such a 'benign cell booster' truly exists or whether other therapies such as oral cancer vaccination will ever become available remains to be seen. However, it is likely that it will only be through such innovative treatment proposals that further progress will be made in our on-going fight against oral carcinogenesis.

Future Approaches to Clinical Trials

We have seen on many occasions that uncertainty pervades many aspects of PMD management. In response, many authors in the contemporaneous literature specifically bemoan the lack of randomised controlled trials to document clinical outcomes following PMD treatment and thus to improve our knowledge base. Despite many calls for such research to take place through the years, however, very few, if any, relevant randomised trials have ever been undertaken. It is important to recognise that many previous PMD trials have ultimately proved unsuccessful because of fundamental flaws in their patient recruitment strategies, ill-defined disease stratification, lack of clinician agreement and ineffective treatment intervention often combining to result in the premature closure of individual studies²⁴.

To succeed and provide meaningful results, a relevant and pragmatic clinical trial for the future must be based upon a firm understanding of the scientific basis of oral carcinogenesis, display an enhanced knowledge of the natural history of the potentially malignant state and specifically ensure that effective treatment modalities are utilized with full and appropriate clinician engagement. It is indeed unfortunate, therefore, that our knowledge of these fundamental areas remains limited. Additional practical difficulties inherent in trial design include our limited ability to establish clinicians' equipoise and to effectively challenge long-established practices and beliefs. Core clinical outcomes, such as disease activity, treatment efficacy, quality of life and health resource utilization, would all have to be carefully defined and relevant clinician and patient viewpoints incorporated into study protocols. Feasibility and internal pilot studies will be especially important to ensure trial validity, as well the crucial ability to meaningfully randomize treatment interventions and develop ethically and clinically acceptable patient control groups.^{24,25}

The latter may well be the reason why a prospective, randomised and controlled PMD trial may never be undertaken. There are, quite simply, too many genuine concerns that it would be unethical to deny patients, particularly those presenting with 'high grade' dysplasia, interventional treatment for their PMD lesions. Similarly, should a modified trial design emerge that effectively excludes treated 'high risk' patients, how clinically relevant would it be to then randomise remaining 'low grade' patients into treatment or observation arms? The demonstrable diagnostic and treatment benefits of interventional laser surgery, which we have consistently seen in our patient cohort studies, have been clearly emphasised in this book.

Although it is reasonable to question whether surgical intervention may also have a deleterious influence on the natural history of PMD, we have never identified any evidence of this in treated patients.

To be worthwhile undertaking a large and effective, multi-centre, randomised, controlled longitudinal follow up study, therefore, there would really have to be a clinically relevant and ethical treatment choice for patients that adds to, rather than subtracts from, conventional intervention. At the present time, sadly, it remains extremely unclear exactly what such an additional therapy might be.

Interestingly, it is now recognised that randomised treatment trials may be less reliable for research concerned with patient prognosis due to concerns regarding the relevance of the study population, eligibility criteria and low patient recruitment and consent issues¹⁷. What then could form the basis of a pragmatic PMD trial in the future? It may well be that a more realistic approach would be to prospectively recruit and document in an agreed and coordinated manner all treatment and long-term clinical outcome data from a large number of PMD patients attending multiple, participating treatment centres. Only in this manner, may we be able to improve our knowledge base sufficiently to truly define the role of interventional management in PMD treatment in the 21st Century.

Patient Experiential Studies

In recent years increasing attention has, quite rightly, been paid to encouraging the active participation of patients themselves in biomedical research. Patients undoubtedly acquire very specific knowledge based upon their own personal experiences of their disease conditions as well as with their overall care, treatment and exposure to health care systems. 'Experiential knowledge' is the term used to define the personal insight that arises as an individual patient learns to cope with their particular illness. It is anticipated that, particularly when patients combine their individual experiences and develop a communal body of knowledge, explicit patient needs, ideas and judgements may significantly contribute to the relevance and quality of future biomedical research²⁶.

Patients with oral cancer have previously described their mouths as becoming 'unreal' or 'uncanny', affected firstly by 'invasion by cancer' followed by the inescapable consequences of experiencing a 'wounded mouth' during therapy and finally at treatment end suffering from 'disablement'; a sobering but very insightful resume of the oral cancer

patient's journey who clearly desires a return to normal mouth functioning²⁷. In general, patients report significant changes in their oral health needs following treatment for oral cancer, specifically the chronic and debilitating side effects following surgery and radiotherapy, and it is interesting how often peer support and access to specialist oral and dental oncology services are identified as integral to patient recovery²⁸.

It would seem logical that both the overall uncertainty and the specific but unquantifiable risk of malignancy inherent in a diagnosis of PMD will adversely affect patients' general well-being. As reported in Chapter 10, we undertook a small qualitative study to document the in-depth personal experiences of 16 PMD patients following their diagnosis and treatment. Several new and informative insights into patient views and understanding were obtained, including a number of misconceptions over disease aetiology, the impact of undergoing interventional treatment, the significance of the clinician-patient relationship, the importance of unmet information needs and, indeed, the overall negative impact that a diagnosis of PMD had upon their everyday lives²⁹.

More recent studies have utilised quality of life questionnaires to assess the impact of PMD diagnosis and treatment on patient groups, although most information appears to have been acquired from oral lichen planus or submucous fibrosis cases rather than, for example, oral leukoplakia. Nonetheless, consistent findings included difficulties in understanding diagnostic terminology and functional limitations which increase with disease progression and/or treatment^{30,31}. Whilst it is clear that individual and local population experiences may vary considerably, future patient experiential research is certainly to be encouraged and may substantially add to our overall understanding of the natural history of PMD and ultimately improvements in oral cancer management and patient rehabilitation.

Conclusions

The translational research presented in this book has facilitated the development and implementation of a rational and pragmatic approach to the early diagnosis of oral malignancy, attempted to stratify cancer risk and to thereby provide an overall and effective interventional management approach to PMD. Future research directions will rely upon innovative and transdisciplinary approaches to optimise impact. Moving forwards, a variety of treatment strategies, ideally marshalling biological and systemic

therapies, will be required, tailored individually for patients and based upon accurate assessment of individual risk; innovative approaches to treatment should continually be sought. Whether such techniques will truly be able to address mucosal abnormalities at the molecular level, preventing evolution to SCC, or whether dysfunctional epithelial cells can be positively influenced by adjustment of their immediate microenvironment all remains to be seen. Our ability to improve clinical outcomes will depend upon earlier detection of disease and better response rates to interventional treatments. Ultimately, it will only be by marshalling preventive and appropriately targeted early interventional strategies to effectively treat PMD that we will see a reduction in the incidence of new cases of oral cancer, overall improvements in patient morbidity and mortality and then perhaps finally a halt to the impending threat of a worldwide epidemic of oral cancer^{32,33}.

References

1. Mehanna HM, Rattay T, Smith J, McConkey CC. Treatment and follow-up of oral dysplasia – a systematic review and meta-analysis. *Head & Neck* 2009 31: 1600-1609.
2. Thomson PJ, Goodson ML, Cocks K, Turner JE. Interventional Laser Surgery for Oral Potentially Malignant Disorders – A Longitudinal Patient Cohort Study. *International Journal of Oral & Maxillofacial Surgery* 2017 46: 337-342.
3. Thomson PJ. Management of Oral Precancer. In: PJ Thomson (ed) *Oral Precancer – Diagnosis and Management of Potentially Malignant Disorders*. Chichester: Wiley-Blackwell; 2012. p107-137. ISBN 978-1-4443-3574-3.
4. daSilva SD, Ferlito A, Takes RP, Brakenhoff RH, Valentin MD, Woolgar JA, Bradford CR, Rodrigo JP, Rinaldo A, Hier MP, Kowalski LP. Advances and applications of oral cancer basic research. *Oral Oncology* 2011 47: 783-791.
5. Mishra R. Biomarkers of oral premalignant epithelial lesions for clinical application. *Oral Oncology* 2012 48: 578-584.
6. Thomson PJ. Oral Carcinogenesis. In: PJ Thomson (ed) *Oral Precancer – Diagnosis and Management of Potentially Malignant Disorders*. Chichester: Wiley-Blackwell; 2012. p31-47. ISBN 978-1-4433-3574-3.
7. Sperandio M, Brown AL, Lock C, Morgan PR, Coupland VH, Madden PB, Warnakulasuriya S, Moller H, Odell EW. Predictive value of dysplasia grading and DNA ploidy in malignant transformation of oral

- potentially malignant disorders. *Cancer Prevention and Research* 2013 8: 822-831.
8. Thompson A M. Dissecting the molecular mechanisms of human cancer: Translating laboratory advances into clinical practice. *Surgeon* 2004 2: 1-6.
 9. Shieh D B, Chou W P, Wei Y H, Wong T Y, Jin Y T. Mitochondrial DNA 4,977-bp deletion in paired oral cancer and precancerous lesions revealed by laser microdissection and real-time quantitative PCR. *Annals of the New York Academy of Sciences* 2004 1011: 154-167.
 10. Chuthapisith S, Layfield R, Kerr I D, Eremin O. Principles of proteomics and its application in cancer. *Surgeon* 2007 5: 14-22.
 11. Willeit P, Willeit J, Mayr A, Weger S, Oberhollenzer F, Brandstatter A. Telomere length and risk of incident cancer and cancer mortality. *JAMA* 2010 304: 69-75.
 12. Hingorani A D, Shah T, Kumari M, Sofat R, Smeeth L. Translating genomics into improved healthcare. *BMJ* 2010 341: 1037-1042.
 13. van der Waal I. Potentially malignant disorders of the oral and oropharyngeal mucosa; present concepts of management. *Oral Oncology* 2010 46: 423-425.
 14. Rao RS, Patil S, Ghosh S, Kumari K. Current aspects and future strategies in oral cancer research: a review. *Journal of Medicine, Radiology, Pathology & Surgery* 2015 1: 8-13.
 15. Del Corso G, Villa A, Tarsitano A, Gohel A. Current trends in oral cancer: a review. *Cancer Cell & Microenvironment* 3: e1332. doi: 10.14800/ccm.1332.
 16. Thomson PJ, Su R, Choi S-W. Oral cancer in Hong Kong: identifying and managing the 'high-risk' population. *Faculty Dental Journal* 2018 9: 116-121.
 17. Moons K G M, Royston P, Vergouwe Y, Grobbee D E, Altman D G. Prognosis and prognostic research: what, why, and how? *BMJ* 2009 338: 1317-1320.
 18. Toomey D P, Murphy J F, Conlon K C. COX-2, VEGF and tumour angiogenesis. *Surgeon* 2009 7: 174-180.
 19. Vokes E, Cohen E, Mauer A, Karrison T, Wong S, Skoog-Sluman L et al. A phase I study of erlotinib and bevacizumab for recurrent or metastatic squamous cell carcinoma of the head and neck. *Journal of Clinical Oncology* 2005 23: 5504.
 20. Goodson M L, Thomson P J, Hamadah O. Oral dysplasia: Effect of aspirin on p53 and surgical outcome. *Journal of Dental Research* 2007 86 Special Issue A: 1820.

21. Barbellido S A, Trapero J C, Sanchez J C, Perea Garcia M A, Castano N E, Martinez A B. Gene therapy in the management of oral cancer: Review of the literature. *Med Oral Patol Oral Cir Buccal* 2008 13: E15-E21.
22. Rudin C M, Cohen E E, Papadimitrakopoulou V A, Silverman S, Recant W, El-Naggar A K et al. An attenuated adenovirus, ONYX-015, as mouthwash therapy for premalignant oral dysplasia. *Journal of Clinical Oncology* 2003 21: 4546-4552.
23. Maley CC, Reid BJ, Forrest S. Cancer prevention strategies that address the evolutionary dynamics of neoplastic cells: simulating benign cell boosters and selection for chemosensitivity. *Cancer Epidemiology Biomarkers and Prevention* 2004 13: 1375-1384.
24. Nankivell P, Dunn J, Langman M. Feasibility of recruitment to an oral dysplasia trial in the United Kingdom. *Head & Neck Oncology* 2012 4: 40.
25. Thomson PJ, McCaul JA, Ridout F, Hutchison IL. To treat...or not to treat? Clinicians' views on the management of oral potentially malignant disorders. *British Journal of Oral & Maxillofacial Surgery* 2015 53: 1027-1031.
26. Caron-Flinterman J F, Broerse E W, Bunders J F G. The experiential knowledge of patients: a new resource for biomedical research? *Social Science & Medicine* 2005 60: 2575-2584.
27. Roing M, Hirsch JM, Holmstrom I. The uncanny mouth – a phenomenological approach to oral cancer. *Patient Education & Counselling* 2007 67: 301-306.
28. Pateman KA, Ford PJ, Batstone MD, Farah CS. Coping with an altered mouth and perceived supportive care needs following head and neck cancer treatment. *Supportive Care in Cancer* 2015 23: 2365-2373.
29. Green R A, Exley C, Thomson P J, Steele J G. Understanding patient views and experience of oral precancer. *Journal of Dental Research* 2010 89 Special Issue B: 2571.
30. Tadakamadla J, Kumar S, Johnson NW. Quality of life in patients with oral potentially malignant disorders: a systematic review. *Oral Surg Oral Med Oral Pathol Oral Radiol* 2015 119: 644-655.
31. Tadakamadla J, Kumar S, Laloo R, Gandhi Babu DB, Johnson NW. Impact of oral potentially malignant disorders on quality of life. *Journal of Oral Pathology & Medicine* 2018 47: 60-65.
32. Nikitakis N, Pentenero M, Georgaki M, Poh CF, Peterson DE, Edwards P, Lingen M, Sauk JJ. Molecular markers associated with development and progression of potentially premalignant oral

- epithelial lesions. *Oral Surg Oral Med Oral Pathol Oral Radiol* 2018 125: 650-669.
33. Ai R, Tao Y, Hao Y, Jiang L, Dan H, Ji N, Zeng X, Zhou Y, Chen Q. Microenvironmental regulation of the progression of oral potentially malignant disorders towards malignancy. *Oncotarget* 2017 8: 81617-81635.

CHAPTER SIXTEEN

CONCLUSIONS

‘...a final summation...’

Introduction

We have seen that oral cancer is a lethal and deforming disease, and that there is a significant threat of a global epidemic affecting many more patients in the latter half of the 21st Century. Whilst advances in diagnostic technique, refinements in ablative tumour surgery and improvements in complex reconstruction of the mouth and face, together with modern chemo-radiotherapy regimes, have all improved loco-regional control and quality of life for patients, 5-year mortality rates remain high at around 50%. Patients are dying as a consequence of widespread blood borne metastases or from the deleterious effects of second or even third primary tumours arising out of field cancerisation within the upper aero-digestive tract.

Further improvements in the treatment of oral SCC unquestionably require effective intervention during the earliest stages of carcinogenesis. The oral cavity, unlike other high risk sites, is readily inspected by oral examination and SCCs are known to be preceded by detectable, pre-invasive PMD. Figure 16.1, for example, illustrates a tongue SCC that has arisen from a pre-existing but untreated leukoplakic lesion. As we have discussed, the clinical recognition of a PMD mucosal abnormality may be relatively straightforward, but the precise diagnosis ascribed to an individual patient can be highly demanding. A particularly important aim is to be able to distinguish between ‘high risk’ and ‘low risk’ cases in terms of future cancer development¹.

In this book, I have presented a case for proactive prevention and targeted interventional management, based upon laser surgical excision of individual PMD lesions and careful, detailed post-treatment follow up and regular, active oral surveillance. It is a simple, but yet a determined and

resolute approach. The ultimate aim of diagnosis and management of PMD is, of course, the prevention of oral cancer, or at the very least minimizing the deleterious effects of malignant transformation. Interventional surgery has



Figure 16.1: Exophytic squamous cell carcinoma arising from pre-existent but untreated leukoplakia on the right lateral tongue.

been shown to be effective in removing PMD, and thus preventing same-site malignant transformation in nearly two thirds of patients, facilitating definitive diagnoses and, crucially, identifying and treating pre-existing, clinically undetectable SCC in around 12% of patients. It seems very difficult, therefore, to support alternative strategies based upon observational or medical management which do not offer such comprehensive opportunities for diagnosis and efficacious treatment. In this, the final chapter of this book, we will review, re-examine and confirm the fundamental principles and hypotheses outlined in Chapter 8 that underpin the prevention to intervention treatment philosophy.

Patients

It remains, unfortunately, problematic to definitively characterise the demographic and clinico-pathological profile of PMD disease either within the UK or indeed globally, but the data presented in this book usefully ‘sets the scene’ for North-East England. By attempting to delineate PMD presentation within a defined, specialist clinical service in Newcastle upon

Tyne and then reviewing clinical outcomes following specific and coordinated treatment interventions in longitudinal patient cohort studies, it is the author's hope to have substantially improved the current knowledge base regarding both diagnosis and management of the oral potentially malignant state.

Unlike malignant neoplasms, there are no comprehensive classification systems for PMD and, as an illustration of such difficulties worldwide, the 10th Revision of the International Classification of Diseases and Related Health Problems (ICD-10) is particularly unhelpful as a diagnostic tool, including only 'leukoplakia and other disturbances of oral epithelium, including tongue' (Chapter XI; K13.2) as the only relevant PMD entry (World Health Organisation 2010). This is hardly representative of the complex and challenging disease spectrum we have examined throughout the preceding fifteen chapters of this book.

Perhaps the patient sub-groups which most require further and intensive study and investigation include those one third of cases in which PMD unfortunately persists, recurs or develops into further lesions at new oral sites following successful, initial intervention. It is presumed, not unreasonably, that it is within this particular group that PMD disease is at its most aggressive and unstable, and it is also likely to be these patients who are at the greatest risk of malignant transformation¹.

Whether the biological nature of PMD truly varies between disease free or recurrent and further disease patients, between single lesion and multiple lesion presentation, or indeed is actually more of a disease continuum, reflecting the disorder severity and/or progression at a particular moment in time in any one individual patient, remains to be seen. There do appear, however, to be real clinical and pathological differences in these differing patient groups, certainly as recorded in our Newcastle population studies, and such observations may well have practical application in developing appropriately tailored and specific management strategies in the future².

Diagnosis

As previously documented, the diagnostic process for PMD is recognised as an on-going difficulty in contemporary clinical practice, not only in terms of accurately defining what exactly constitutes a potentially malignant disease state but also in managing individual presenting patients and their oral lesions. PMD demonstrate a considerable heterogeneity in clinical presentation with an unpredictable potential for change over time

and it must, therefore, be recommended that oral clinicians remain alert for signs of potentially malignant lesions together with an acute awareness of the features of early cancer development in all patients when performing routine oral and dental examinations. Whilst this may be especially relevant for patients who over-use tobacco and regularly consume alcohol, it has now been clearly shown that patient risk profiling is actually a highly complex task and that an individual clinician's experience and an appropriate level of suspicion are probably the most applicable and consistently reliable diagnostic tools in practice; an important and fundamental issue for the dental profession as a whole to recognise. Provision of specialist PMD services, employing the latest knowledge and understanding of disease progression, emphasizing consistency in clinical management and patient education, together with the provision of coordinated post-operative follow-up regimes, are more likely to achieve optimal diagnoses and definitive treatment in contemporary health care practice^{1,3}.

Pathology

It was stated earlier in this book, and very much based upon conventional understanding, that the assessment of standard clinico-pathological features is highly limited in its ability to predict disease progression or clinical outcome during PMD management. Whilst this hypothesis is indeed partially supported, results from the patient cohort studies analysed in Chapter 12 have actually shown that certain, salient clinico-pathological features may at least provide pragmatic guidance regarding prognosis during the overall management of PMD patients. For example, increased patient age, oral mucosal lesions presenting as erythroleukoplakia, identification of severe or 'high grade' epithelial dysplasia on histopathological examination, together with the presence of lichenoid inflammation and proliferative verrucous leukoplakia, have all been shown to be associated with either progressive PMD disease or indeed malignant transformation. Although it is quite clear that further research is warranted to delineate the relevance and importance of individual clinico-pathological factors in the prediction of PMD clinical behaviour, these specific observations are actually of considerable practical value during the 'day-to-day' management of individual PMD patients⁴⁻⁸.

It has also been a central theme of the work presented in this book that incision biopsy techniques are insufficient for definitive histopathological diagnosis, which therefore requires whole lesion excision for full

microscopic examination. This hypothesis is strongly supported, in particular by the direct comparison carried out between the 609 incision and excision biopsy diagnoses obtained during the clinical study reported in Chapter 12. Perhaps of most clinical significance were the observations that histopathological agreement was seen in only 50% of cases (307), whilst 36% (220) required 'up-grading' to more significant epithelial dysplasia or in the worst case scenario actually SCC diagnosis following laser excision, together with the very poor sensitivity of incision biopsy as a diagnostic technique to recognise invasive SCC within presenting PMD lesions. The important clinical relevance is that entire mucosal lesion excision must now be considered mandatory for definitive histopathological diagnosis of PMD, together with the pragmatic realization that such diagnoses are readily facilitated by the use of interventional CO₂ laser surgery as the treatment modality⁵.

Prevention

Prevention of oral cancer remains of fundamental importance, of course, in view of the serious morbidity and mortality consequent upon developing fully established oral malignancy, and is absolutely vital to the success of an active, interventional strategy. Indeed, we have clearly seen how all three classic tiers of preventive medicine have proven relevant throughout the effective diagnosis and management of PMD. The particular benefit of primary prevention is clearly in its specific aim to avoid entirely the development of disease, thus emphasizing the importance of eliminating principal risks factors and promoting protective behaviour within a community or population. For oral cancer this includes limiting the use of tobacco, discouraging various chewing habits, avoiding excessive alcohol consumption and improving diet and nutrition in the 'high risk' population. Whilst this seems an eminently sensible approach, especially for patients who present with PMD lesions, we have also seen just how difficult it can be in practice to influence an individual patient's risk factor behaviour, certainly in the longer term. Secondary prevention, detecting a 'pre-malignant' condition or early malignant disease at a stage when intervention leads to either cure or significant reduction in morbidity and mortality, has of course formed the entire basis for this book and remains unquestionably the most pragmatic preventive approach to overall PMD management. Finally, we have also demonstrated the vital role of tertiary prevention in attempting to reduce disease recurrence and/or progression following PMD treatment and its ability to minimise disease-related

complications; this is particularly relevant during longer term patient follow up and active surveillance post-treatment^{1,9}

Intervention

The hypothesis that interventional laser surgery is an effective tool for definitive diagnosis and effective treatment of PMD is, I believe, strongly and unequivocally supported by the patient treatment data presented in Chapter 12 of this book, and subsequently defended in Chapter 14. Indeed, the surgical excision of PMD lesions is probably the most optimal patient management technique yet available, facilitating as we have seen full and definitive histopathological diagnoses, early recognition and treatment of malignancy, effective removal of dysplastic tissue, minimal patient morbidity and the real possibility of reducing the risk of further PMD disease. Observation alone as a treatment modality, on the other hand, offers little to commend it as an appropriate or modern management tool. Continued, active surveillance post-treatment remains essential, but the frequency and duration of follow-up is best 'tailored' to individual patient risk. For example, patients with milder disease who stop smoking and are disease free for 3 years post treatment may be safely followed up by their general dental practitioner; this presupposes that the patient has their own dentist and that they do indeed attend for regular 6 monthly check-ups. In contrast, patients with more severe dysplastic disease, multiple lesion presentation or cases in which PMD exists in the absence of exposure to risk factors are undoubtedly better followed up in a specialist clinic environment¹. The difficulties of risk stratification have been explored in some detail but, whilst remaining limited in accuracy, it is hoped that this will indeed become a reliable and more pragmatic clinical tool in the years ahead, based more in the future perhaps upon individual patient genetic profiling and bio-marker analyses^{5,10-17}.

Clinical Outcome

It is frustrating, both for clinicians and patients alike, that we still lack the ability to predict clinical outcome or disease progression for individual patients or PMD lesions. Nonetheless, observational data obtained from several Newcastle patient cohort studies have contributed additional knowledge and a number of significant predictors of outcome have now been identified and have been highlighted in this manuscript. Defining the parameters by which outcome are measured, as documented in Chapter 7, and the longitudinal study of these patient cohorts over time offers the

most practical opportunities to improve our understanding of the natural history of PMD and early SCC development, and ultimately of course to determine the efficacy of treatment intervention itself^{12,18}.

Malignant Transformation

It is well understood that PMD have a variable and unpredictable risk of SCC development. Malignant disease can arise at the same-site of a precursor lesion as transformation, or as new-site disease at distant oral sites as a result of field cancerisation. An important hypothesis underpinning the treatment approach proposed in this book is that active intervention during the progress of ‘pre-malignancy’ halts the progress of oral carcinogenesis and reduces the risk of cancer development. Overall, it has to be said that this remains unproven, unfortunately. Whilst 12% of PMD patients in our 590 cohort benefited, in a clinically highly significant and fortuitous manner, from the early diagnosis and effective treatment of an unexpected SCC upon CO₂ laser excision, this cannot be considered to equate with ‘halting’ the carcinogenic process. In addition, the majority of the 4.8% of patients who subsequently developed SCC during follow-up did so at new oral sites distant from their presenting lesions, with ultimately poor long-term prognosis. Thus, it is fair to state that interventional laser surgery appears to reduce the risk of same-site malignant transformation, but new-site cancer remains an important and significant risk for patients^{5,19,20}.

Pathways

Central to the diagnosis and management of PMD is, undeniably, the overall care pathways we construct and then provide for our patients. In this book, we have proposed, explained and I believe confirmed the especial benefits of a well-structured and coordinated interventional management strategy. We have also seen very clearly that, due to the unpredictable risk of subsequent PMD or SCC development, all patients, irrespective of their initial presenting disease and treatment outcomes, should be carefully followed up long term. The opportunity to continually reinforce the benefits of reducing harmful risk factor behaviour and the ability to carry out mucosal surveillance for recurrent or further oral lesions thereby facilitates both risk reduction and early diagnosis of disease, continuing the important theme of prevention throughout the interventional strategy¹.

Whilst there are inevitably health care costs associated with long term follow up of patients, this is relatively inconsequential compared to the financial burden associated with the treatment of established head and neck malignancy; cost-effectiveness of interventional management was discussed in Chapter 14. It is this author's opinion that the ideal environment for managing PMD patients is to be found in dedicated, specialist clinics. Within such a service, a multi-disciplinary clinical team approach is desirable, and the essential components of a viable and successful PMD clinical service can easily be summarised, as shown in Table 16.1¹.

In addition, Figure 16.2 summarizes the contemporaneous management pathway for PMD that has evolved following the pragmatic application of the research work presented in this book¹. The importance of a consistent approach and the availability of the same clinical team to attend patients cannot be over emphasised, not only in terms of delivering high quality clinical care but also in relation to patient involvement, engagement and acceptance of that care which is, of course, fundamental not only for interventional treatment but perhaps even more so for effective preventive strategies. Many of these patient-focused issues were reviewed in Chapter 10, although there is clearly more work to be done in enhancing quality of life issues for patients at risk of oral carcinogenesis¹.

Table 16.1: PMD Clinical Service

Clinical Team –	Lead Clinician, Oral & Maxillofacial Surgeon and/or Oral Physician
	Dedicated and Regular Nursing Staff
	Smoking Cessation Service
Clinical Facilities –	Dedicated Clinic for New Referrals and Follow Up Cases
	Immediately Accessible Biopsy Service
	Range of Diagnostic Adjunctive Techniques
	Access to Operating Theatre Facilities & Laser Surgery
Support Services –	Specialist Oral & Maxillofacial Pathology and Cytology Services
	Anaesthetic Services Specialised in Intra-Oral Laser Surgery
	Medical Physics Support for Laser Devices
	Head and Neck Radiology and Imaging
	Medical Photography
Access to –	Multidisciplinary Head and Neck Cancer Team

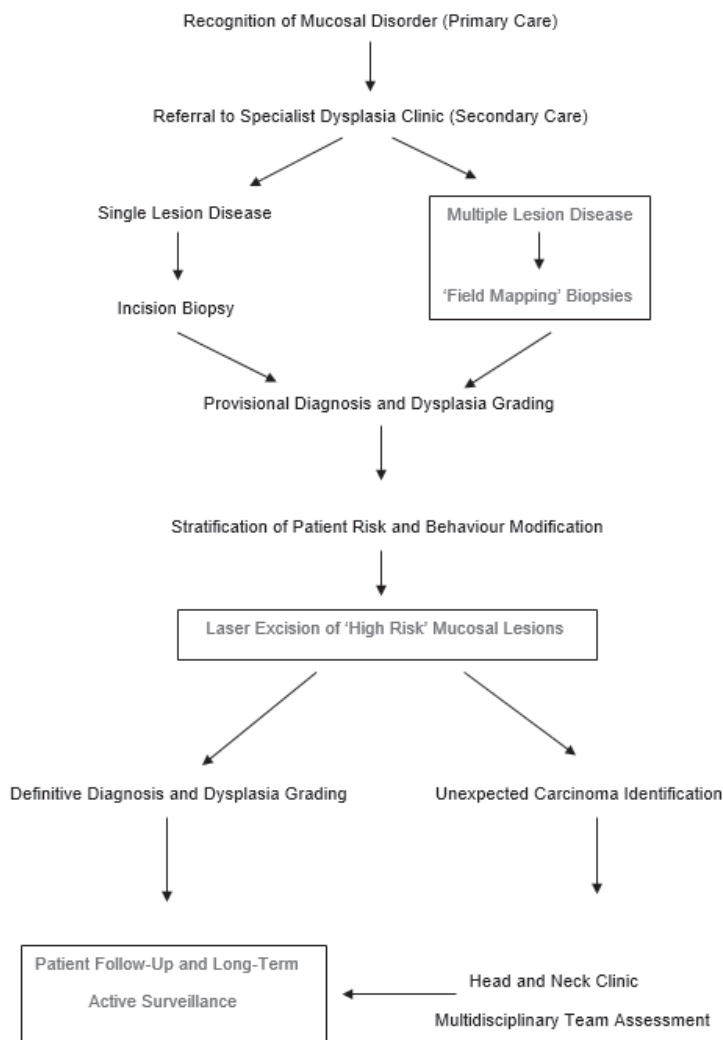


Figure 16.2: PMD Management Pathway

Clinical Impact

The clinical impact of new knowledge, a treatment innovation or an improved management protocol can only be truly judged by the influence

they ultimately have on the long-term outcome of a specified medical disorder. Despite the demonstration of new knowledge or an innovative clinical application, instigating change in established practice is known to take time, unfortunately often measured in decades rather than months or years. Delays in information dissemination, reluctance of clinicians to alter long-established decision making, cultural influences favouring preservation of the status quo and resource implications all appear to be the principal detractors of change.

Overall, however, I believe there are 3 important and fundamental areas of clinical practice which have been significantly and positively influenced by the studies presented in this book:

1. Perhaps of greatest importance is the widespread acknowledgement that observational or medical treatments are ultimately unsatisfactory in PMD management, and that formal surgical excision of the entire oral mucosal lesion is necessary for both a definitive diagnosis of the presenting condition and efficacious, low morbidity treatment^{1,21}.
2. There is now increased realization that field cancerization effects within the oral cavity are more significant than previously recognized, that inherent anatomical site differences affect disease presentation and that multiple lesion disease may represent a distinct PMD entity with an increased risk of malignancy requiring proactive, targeted and often repeated treatment intervention²²⁻²⁵.
3. Recognition that patient profiling, risk factor stratification and active long-term surveillance are all part of the fundamental management strategy for patients, which commences at the point of PMD diagnosis and continues throughout preventive strategies, interventional treatment and during long-term follow-up. Patient surveillance strategies have substantially enhanced our understanding of the natural history of PMD disease and helped identify high risk patients and behaviours. The specific role of dedicated specialist clinics has similarly evolved through recognition of the significant practical benefits that they bring to both patients and clinicians alike^{1,26}.

Public Health

Whilst all of the above patient-centred care provides a pragmatic and reasonably successful strategy for managing those patients who present to clinicians with identifiable PMD, there remains, of course, the much wider problem that the majority of patients with ‘high risk’ factor behaviour rarely, if ever, attend for regular oral examination, advice or treatment. More widespread oral cancer and PMD preventive strategies will become increasingly important in the years ahead, as will attempts to identify and target those ‘high risk’ individuals or specific patient groups at enhanced risk of oral cancer to facilitate early diagnosis and intervention on a population wide basis^{1,14}.

Final Thoughts on Science, Surgery and Surveillance

Lavelle & Scully²⁷ highlighted the formidable, multi-factorial influences and heterogeneous challenges that frustrate early identification of individuals at high risk of oral cancer development. These difficulties, of course, very much inspired the programme of clinical research presented and discussed in this book. It is clearly pertinent and important to consider what progress, if any, has been made.

In a North-East England population, I believe we have characterised PMD patients more fully than ever before. Most commonly, patients present in the 5th and 6th decades of their life, with a distinct male predominance and a predilection to arise in lower socio-economic groups. Although not exclusively so, patients usually demonstrate long-term abuse of tobacco and alcohol products, with an overwhelming tendency for their mucosal disease to present as leukoplakia on the floor of mouth and ventrolateral tongue, usually exhibiting features of significant epithelial dysplasia on biopsy.

As I reflect back over the years and the various studies that comprise the body of work presented in this manuscript, I am struck by how often the powerful triumvirate of science, surgery and surveillance have combined synergistically to address the problems of diagnosis and management and help to address the unknowns and resolve the dilemmas so inherently associated with PMD. Utilising the scientific study of oral epithelial cell biology, defining a pragmatic surgical intervention and developing innovative patient profiling and clinic surveillance strategies, I believe has facilitated development of a coordinated and methodical clinical

management protocol that can effectively intervene to disrupt or at times even halt the carcinogenic process. Whilst efficacious in most patient groups studied, it is perhaps most pertinent for those individuals deemed to be at 'high risk' of malignant transformation.

Overall, the recognisable clinical manifestations of PMD present clinicians with a 'therapeutic window' of opportunity to intervene during the process of oral carcinogenesis, although I accept that in reality this window may be unpredictably opaque. It is the author's fundamental opinion, however, that the interventional surgical management technique described in this book provides a readily available, effective and low morbidity treatment which is successful in excising or ablating PMD mucosal lesions, facilitates early diagnosis of occult malignancy, and may well help reduce the overall risk of SCC development in individual patients particularly at the site of previously identifiable precursor lesions.

The risk of recurrent or further PMD development and ultimately malignant transformation has been shown to increase with the length of patient follow-up post-intervention. Continued, active surveillance of all PMD patients thus remains essential to ensure early recognition of such adverse outcomes which arise almost certainly as a consequence of field cancerization. Precise data governing the length of patient follow-up or the optimal time intervals between appointments are not known at present and require further research. Whilst multi-centre, prospective, ideally randomized and controlled trials are needed to confirm the efficacy of interventional laser surgery, to better delineate the nature of patients with progressive PMD disease, and to disseminate research findings more widely, it is recognised how difficult, if not impossible, such an objective may be.

However, it is very much my hope that for now the clinical research work carried out over 30 years by this author and presented and analysed in this book will help improve the evidence base of our scientific literature, inform and encourage further relevant research into oral cancer and PMD and, perhaps most significantly of all, help develop new and innovative treatment strategies for our patients. In this way, together we may finally achieve a reduction in the incidence of disease and an improvement in morbidity and mortality outcomes for invasive oral SCC, the deadliest enemy to confront both our patients and our profession.

References

1. Thomson PJ. Management of Oral Precancer. In: PJ Thomson (ed) Oral Precancer – Diagnosis and Management of Potentially Malignant Disorders. Chichester: Wiley-Blackwell; 2012. p107-137. ISBN 978-1-4443-3574-3.
2. Hamadah O, Goodson ML, Thomson PJ. Clinicopathological behaviour of multiple oral dysplastic lesions compared with that of single lesions. *British Journal of Oral & Maxillofacial Surgery* 2010 48: 503-506.
3. Thomson PJ, Goodson ML. Diagnostic Methods. In: PJ Thomson (ed) Oral Precancer – Diagnosis and Management of Potentially Malignant Disorders. Chichester: Wiley-Blackwell; 2012. P75-92. ISBN 978-1-4433-3574-3.
4. Goodson ML, Sloan P, Robinson CM, Thomson PJ. Oral precursor lesions and malignant transformation – who, where, what and when? *British Journal of Oral & Maxillofacial Surgery* 2015 53: 831-835.
5. Thomson PJ, Goodson ML, Cocks K, Turner JE. Interventional Laser Surgery for Oral Potentially Malignant Disorders – A Longitudinal Patient Cohort Study. *International Journal of Oral & Maxillofacial Surgery* 2017 46: 337-342.
6. Thomson PJ, Goodson ML, Smith DR. Profiling Cancer Risk in Oral Potentially Malignant Disorders – A Patient Cohort Study. *Journal of Oral Pathology & Medicine* 2017 46: 888-895.
7. Thomson PJ, Goodson ML, Smith DR. Treatment Resistance in Potentially Malignant Disorders – ‘Nature’ or ‘Nurture’...? *Journal of Oral Pathology & Medicine* 2017 46: 902-910.
8. Thomson PJ, Goodson ML, Smith DR. Potentially Malignant Disorders Revisited – The Lichenoid Lesion / Proliferative Verrucous Leukoplakia Conundrum. *Journal of Oral Pathology & Medicine* 2018 47: 557-565.
9. Thomson PJ. Perspectives on Oral Squamous Cell Carcinoma Prevention – Proliferation, Position, Progression and Prediction. *Journal of Oral Pathology & Medicine* 2018 47: 803-807.
10. Thomson PJ, Wylie J. Interventional laser surgery: an effective surgical and diagnostic tool in oral precancer management. *International Journal of Oral & Maxillofacial Surgery* 2002 31:145-153.
11. Hamadah O, Thomson PJ. Factors affecting carbon dioxide laser treatment for oral precancer: A patient cohort study. *Lasers in Surgery and Medicine* 2009 41:17-25.

12. Diajil AR, Robinson CM, Sloan P, Thomson PJ. Clinical outcome following oral potentially malignant disorder treatment: a 100 patient cohort study. *International Journal of Dentistry* 2013 Article ID 809248, 8 pages <http://dx.doi.org/10.1155/2013/809248>.
13. Thomson PJ. The role of interventional surgery in oral potentially malignant disorders. *Faculty Dental Journal* 2014 5: 84-89.
14. Thomson PJ. Managing oral potentially malignant disorders: A question of risk. *Faculty Dental Journal* 2015 6: 186-191.
15. Diajil AR, Thomson PJ. Risk factors of oral cancer and potentially malignant disorders (PMDs) – Developing a high / low risk profiling system. *Journal of Baghdad College of Dentistry* 2016 28: 63-72
16. Thomson PJ. Potentially Malignant Disorders – The Case for Intervention. *Journal of Oral Pathology & Medicine* 2017 46: 883-887.
17. Thomson PJ. Minimal intervention in oral cancer management: idealistic or realistic? *Faculty Dental Journal* 2018 9: 151-154.
18. Thomson PJ. Clinical Outcome. In: PJ Thomson (ed) *Oral Precancer – Diagnosis and Management of Potentially Malignant Disorders*. Wiley-Blackwell; 2012. p139-155. ISBN 978-1-4443-3574-3.
19. Thomson PJ. Malignant transformation and oral cancer development. In: PJ Thomson (ed) *Oral Precancer – Diagnosis and Management of Potentially Malignant Disorders*. Wiley-Blackwell; 2012. p156-169. ISBN 978-1-4443-3574-3.
20. Goodson ML, Thomson PJ. Management of oral carcinoma – benefits of early precancerous intervention. *British Journal of Oral & Maxillofacial Surgery* 2011 49: 88-91.
21. van der Waal I. Potentially malignant disorders of the oral and oropharyngeal mucosa; present concepts of management. *Oral Oncology* 2010 46: 423-425.
22. Thomson PJ. Field change and oral cancer: new evidence for widespread carcinogenesis. *International Journal of Oral & Maxillofacial Surgery* 2002 31: 262-266.
23. Thomson PJ, Hamadah O. Cancerisation within the oral cavity: The use of ‘field mapping biopsies’ in clinical management. *Oral Oncology* 2007 43: 20-26.
24. Bagan JV, Scully C. Recent advances in Oral Oncology 2007: Epidemiology, aetiopathogenesis, diagnosis and prognostication. *Oral Oncology* 2008 44: 103-108.
25. Arduino PG, Bagan J, El-Naggar AK, Carrozzo M. Urban legends series: oral leukoplakia. *Oral Diseases* 2013 19: 642-659.

26. Ho MW, Field EA, Field JK, Risk JM, Rajlawat BP, Rogers SN, Steele JC, Triantafyllou A, Woolgar JA, Lowe D, Shaw RJ. Outcomes of oral squamous cell carcinoma arising from oral epithelial dysplasia: rationale for monitoring premalignant oral lesions in a multidisciplinary clinic. *British Journal of Oral & Maxillofacial Surgery* 2013 51: 594-599.
27. Lavelle C, Scully C. Whither screening for oral cancer? *Oral Oncology* 2007 43: 423.