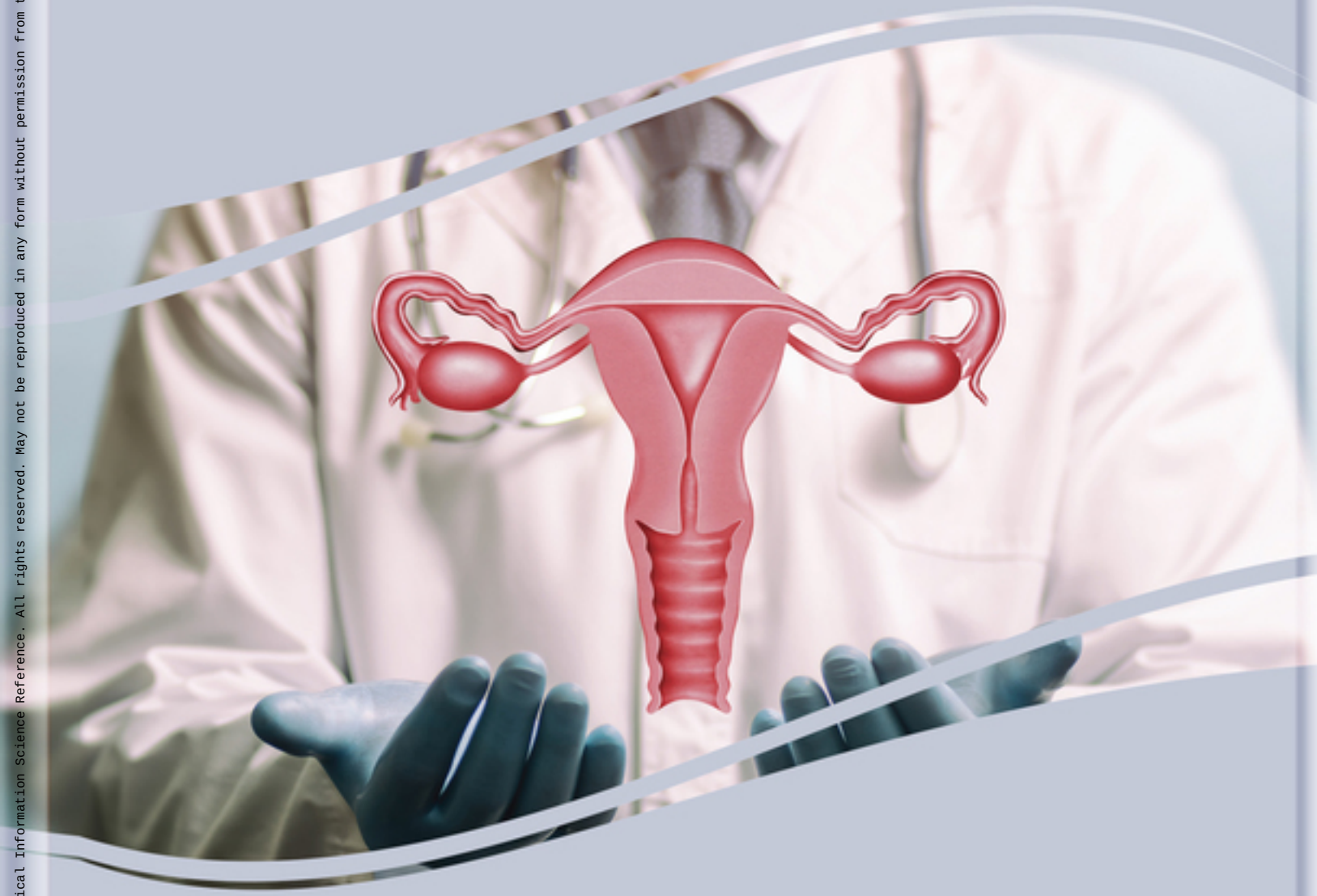
Handbook of Research on

Oncological and Endoscopical Dilemmas in Modern Gynecological Clinical Practice



Konstantinos Dinas, Stamatios Petousis, Matthias Kalder, and George Mavromatidis

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Handbook of Research on Oncological and Endoscopical Dilemmas in Modern Gynecological Clinical Practice

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Screening and Follow-Up

The main screening tests that are used for the prevention and early diagnosis of gynaecological cancer are bimanual pelvic examination, transvaginal and transabdominal ultrasound, cervical cytology testing (Papanicolaou test), clinical breast examination, mammography, breast ultrasound, as well as newer diagnostic methods, such as HPV-DNA test and cancer biomarkers. Even though most of the above methods are widely used in everyday practice in gynaecology, it remains a subject for further discussion which of them should be used as screening tests and whether they increase safety in clinical approach of a patient, considering the danger of overdiagnosis and the role of screening test in personalized management of patients. The purpose of this chapter is to analyze the clinical benefit and safety of diagnostic methods related to prevention of various types of gynaecological cancer and in particular endometrial, ovarian, cervical, and breast cancer.

Patients at high risk for gynaecological cancer consist of a specific category of patients in which clinical, imaging, and laboratory surveillance may actually be differentiated compared with low-risk patients. The chapter aims to summarize current evidence and recommendations regarding optimal clinical management of high-risk patients for all forms of gynaecological cancer, namely cervical cancer, endometrial cancer, ovarian cancer, and breast cancer. Furthermore, it aims to approach critically the need for estimating cost-benefit of all preventative modalities along with discrepancies in existing guidelines.

More than 100,000 cases of gynecologic cancer are diagnosed every year in the USA. Women who survived primary treatment for gynecologic cancer are estimated at more than 8 million and are likely to increase at about 10 million in the coming decade. It is obvious that there is a growing population group that needs a proper care by a team of health professionals. Post-treatment monitoring of gynecologic cancer survivors ideally has to achieve three major objectives: 1) to diagnose, as early as possible, the recurrence of the disease, either local or distant; 2) to improve the quality of life of cancer survivors; and 3) to achieve all the above goals with a reasonable cost for the Health Providing Systems. In this report, the authors refer to post-treatment monitoring of women with all kinds of gynecologic cancers (endometrial, ovarian, vulvar, vaginal, and cervical) and the follow up of women after primary treatment for breast cancer.

Whether fertility treatments and in particular IVF are related to carcinogenesis in women is a rather interesting issue, which is of interest in more than one specialty. The female malignancies we refer to are mainly those of the breast, endometrium, and ovary, with breast cancer being the most common malignancy in the female population affecting 1 in 8 women worldwide; ovarian cancer is the 6th in frequency, and endometrial cancer, which is the most common gynecological cancer after breast cancer, has an incidence of 8% of all. The chapter aims to present current evidence regarding correlation between IVF treatment and risk of various gynaecological cancers.

Endometrial polyps are endometrial masses that consist of glands, stroma, and vessels. They can be single or multiple, sessile or pedunculated, and range in size from some millimeters up to several centimeters. Despite the fact they rarely cause symptoms, they are usually found on a routine examination. Therefore, they are a common problem on daily clinical practice. The question of potential malignancy risk as well as the necessity of further treatment are often posed. The present chapter summarizes current evidence regarding risk of malignant transformation as well as indications and methods of appropriate treatment.

Section 4
Cervical and Vulvar Pathology

The dramatic decline in cervical cancer in women is attributable first to screening with the Papanicolaou (Pap) test, followed later by the addition of the Human Papilloma Virus (HPV) test, which enhanced screening sensitivity. In association with this excellent performance record, resulting from the combination of Pap Test and HPV Test, known also as Co-Testing, the current standard of care for cervical cancer screening for most women (those over 30) is Co-Testing with Pap + HPV tests, as currently recommended by U.S. guidelines. The challenge is to improve screening cost-effectiveness without compromising efficacy. The notion that screening with one test may be more cost-effective than two tests seems reasonable upon first consideration, but closer examination may dispute this assumption. The chapter aims to analyze costs and benefits regarding optimal screening method for daily clinical practice.

Personalised medicine and precision medicine are being applied in more medical fields in the last years. The need for personalisation is especially pronounced in cervical pathology, since in the majority of cases an abnormal screening test does not necessarily imply high-grade lesion, regardless of whether the screening test is cytology or HPV testing. The chapter aims to summarize the exact added value that mRNA presents for management in clinical practice as well as highlight comparative advantages and disadvantages with other triage strategies.

Large Loop Excision of the Transformation Zone (LLETZ) is thought to be the treatment of choice for the high-grade precancerous lesions. The cone is also the "gold standard" specimen for the diagnosis of the underlying cervical disease once it includes the entire area of carcinogenesis for the squamous epithelium (transformation zone). In most research studies, therapeutic success after conization is a term generally assigned for disease clearance, that is, absence of residual high grade/CIN2+ histology by the end of a reasonable follow-up period, aiming at risk reduction for future recurrence and development of invasion. Conversely, positive cone margins as a reflection of an incomplete excision may, to some extent, represent a negative prognostic factor. Therefore, margin status may also be regarded as an indicator for the quality of a clinical service. The chapter summarizes all current evidence regarding optimal treatment of positive margins after LEEP.

Recent advances in screening and early diagnosis have decreased cervical cancer incidence and mortality rate in high-resource settings. The postponement of childbearing and the young age of women at diagnosis produced new challenges in the management of this disease. In recent years, attention has been directed to assessing more conservative procedures that can reduce treatment-related morbidity, without

compromising oncologic safety and reproductive potential. Fertility sparing surgery (FSS) procedures, including cervical conization, simple or radical trachelectomy with pelvic nodes dissection or sentinel lymph node assessment, and neoadjuvant chemotherapy followed by conization, have shown encouraging results. In this chapter, the authors discuss the role of conservative surgery in the management of early-stage cervical cancer focusing on obstetrical and oncological outcomes.

Cervical and vulvar cancer represent two clinical entities whose diagnosis and management are often challenging. They are frequently diagnosed in the early stages, therefore leaving chances for optimal treatment and prognosis. The aim of this chapter is to answer two oncological issues concerning early stage cervical and vulvar cancer. First, is still room for surgical treatment for early stage cervical cancer or should we suggest chemoradiotherapy instead? Second, when is a limited surgical intervention sufficient for early stage vulvar cancer?

Section 5
Ovarian Pathology

During 1960s and 1970s, the first laparoscopic procedures concerned the treatment of benign diseases. Today the indications have significantly increased even in ovarian borderline tumours and in ovarian cancer. Furthermore, the role of diagnostic laparoscopy remains apparent in the overall therapeutic setting of advanced ovarian cancer as well. The chapter aims to summarize current evidence regarding potential role of laparoscopy in ovarian cancer treatment as well as indicate potential difficulties its usage may pose.

successfully be applied laparoscopically. Manipulations during surgery should be limited, and biopsies for rapid biopsy should be done within an endoscopic bag.

Chapter 17

The prevalence of cystic masses in pregnancy varies from 0.1 to 2.4% and approximately 1 to 6% of these masses are malignant. The clinical presentation of cystic masses in pregnancy varies widely. The majority of cystic masses identified in pregnancy are benign simple cysts less than 5mm in diameter. Malignant neoplasms may be developed, and it is of paramount importance for the attending physician to be able to identify them. Ultrasonography is an excellent tool for the detection of cystic masses and for the discrimination between benign and malignant masses. IOTA group has proposed simple ultrasound rules in order to distinguish between benign and malignant cystic masses. In some cases where there is uncertainty about the type of mass, the MRI has high diagnostic value. Tumor markers that used in epithelial and nonepithelial cancers in nonpregnant women are difficult to interpret in pregnancy, because they are involved in biological functions associated with fetal development, differentiation, and maturation.

Chapter 18

Laparoscopy can be used for almost all gynecological procedures and is considered as the indicated method for specific procedures. This is especially true for adnexal surgery. Of course, while it is considered a method of choice for the treatment of benign ovarian tumors, the same does not apply to malignant ones, although treatment of ovarian cancer either at an early or even at a more advanced stage is feasible with laparoscopy. Finding malignancy, when not suspected, during laparoscopic treatment of an ovarian cyst is a situation raising several issues, depending on whether the identification of malignancy is intra- or post-operative, which involve inadequate surgical staging, peritoneal spread of cancer cells, intraoperative rupture of a malignant ovarian cystic tumor, and port site metastasis. This chapter analyzes the possible adverse events related to the use of laparoscopy in the treatment of adnexal masses considered as benign but turn out to be malignant, and how they can be mitigated with careful preoperative patient selection and with adequate surgical experience.

Endometriosis is a chronic condition that affects 5-10% of women of reproductive age. It is characterized by the presence of endometrial tissue outside the uterus, which induces a chronic inflammatory reaction and formation of scar tissue and adhesions, resulting in the deformation of the female pelvis anatomy. Twenty-five to fifty percent of women with infertility suffer from endometriosis, while 30-50% of infertile women are diagnosed with the disease. Endometrioma is a benign cyst of the ovary that contains ectopic endometrial tissue and is a common cause of endometriosis. There are some gray areas regarding clinical decisions and endometriotic cysts. The chapter aims to present current evidence regarding optimal management of endometriotic cysts.

Uterine leiomyomas are benign neoplasms derived from the smooth muscle cells of the myometrium. In contrast, uterine sarcomas are rare tumors, with a prevalence of 3-7 per 100,000 women, originating from myometrial cells or endometrial connective tissue. Uterine sarcomas and especially leiomyosarcomas are more aggressive than uterine epithelial neoplasms. The differential diagnosis between leiomyoma and uterine sarcoma preoperatively remains challenging for the clinical practitioner in order to determine optimal treatment. The chapter aims to summarize current evidence regarding differential diagnosis and optimal management of these two challenging clinical entities.

Hysterectomy is the most common gynecological operation after cesarean section. The majority of hysterectomies are performed for the treatment of benign diseases, which, although not life-threatening,

may have a negative impact on the quality of patient's life. Abnormal uterine bleeding is the most common indication for hysterectomy in premenopausal women and is usually a result of myomas and adenomyosis. Another indication is chronic pelvic pain that is usually caused by endometriosis and/or adenomyosis. A simple hysterectomy can be the treatment of choice in early stages of endometrial, cervical cancer, sarcomas, or gestational trophoblastic disease. Laparoscopic hysterectomy is superior to laparotomy when a vaginal hysterectomy is contraindicated.

vNOTES or vaginal Natural Orifice Transluminal Endoscopic surgery is a new paradigm shift in gynaecological surgery. A first paradigm shift from conventional surgery into laparoscopic surgery was firstly observed in the 1980s and 1990s. vNOTES may represent a shift from 90° to parallel surgery. Almost all benign gynaecological operations can be performed via vNOTES. The chapter presents the technique of vNOTES along with results of various benign and mainly malignant cases. In parallel, the clinical approach of endometrial cancer is widely discussed.

Chemoprevention in breast cancer represents one of the most important therapeutic regimens in an effort to optimize survival and prevent breast cancer recurrence. The chapter aims to analyze below all potential medical regimens used in breast cancer chemoprevention, along with explaining the reasons why those are the ones selected: their characteristics, their mechanism of action, and their side effects. Among these, we may report tamoxifen, raloxifen, aromatase inhibitors, and new therapeutic regimens such as polyphenoles.

Section 8
Miscellaneous

Gynaecological oncology treatment yields no fewer complications and side effects than those met in any other oncology field. Patients and clinicians are highly alerted by the ominous diagnosis and sometimes seek for high risk, experimental, or even unproven therapies and are consequently prepared to accept high complication rates that would otherwise be unacceptable. Still, risk reduction remains a high priority. This is achieved by appropriate risk assessment, risk-to-benefit ratio balancing, treatment individualisation, close follow up through all treatment stages, and prompt patient informing and participation in decision making. The chapter aims to summarize the main complications of surgery, chemotherapy, and radiotherapy as well as the main ways to overcome them.

After 2000, specific legislation on civil liability and ethics of nurses and doctors was introduced, as well as specific acts. For nurses and the nursing profession, since 2001, the Code of Nursing Ethics (NCSD, Presidential Decree 216/2001) has been in force. In 2005, the current Code of Medical Ethics (KID, Law 3418/2005) was passed. Special Law 3305/2005 on the application of assisted reproduction methods was introduced to specify how the methods introduced in the Civil Code were applied as methods of generating kinship among persons under Law 2089/2002 (MAP). The chapter summarizes the main points regarding civil liability of medical and nursing activity with a special focus on oncological patients.

Preface

Current gynecological practice is characterized by the continuously increasing rate of gynaecological cancer cases. Despite the fact that therapeutic modalities are widely expanding and prognosis has been improved, there is still much effort to be done in order to optimize therapeutic management. This effort could actually be summarized in four main domains:

- Early and accurate diagnosis even in precancerous stage
- Optimal surgical approach
- Optimization of enrolled therapeutic modalities such as chemotherapy, radiotherapy and newly developed molecules
- Appropriate follow-up adhering to cost-effectiveness strategy but also with the maximum diagnostic accuracy

Apart from these challenges, modern clinical practice is also characterized by the need to establish minimally invasive surgical treatment when applicable. Laparoscopic management of cancer may not further be considered as luxury service, but should rather be the common practice. Besides, the ongoing increase of infertility diagnosis along with efforts to treat infertility poses further challenges regarding oncological cases with desire for fertility preservation, along with the debate around the safety of IVF protocols.

Despite the great advancement of research in the majority of domains of gynaecologic oncology, daily routine practice of a gynaecologic oncologist indicates that there are still questions without commonly accepted answers in many issues referring to aforementioned domains. In simple words, there are still daily-practice issues not being clearly and scientifically answered, which may pose therapeutic dilemmas not only in the general Obstetrician-Gynaecologists but also in the specialized practitioner.

Taking into consideration the need to summarize the state-of-the-art about gynaecologic oncology as well as the need to help every practitioner with issues upraised in daily clinical practice, we were motivated to write the present book with a very specific target: to give simple answers to everyday clinical dilemmas or rather indicate the non-availability of widely accepted management in order to motivate the individualized management of patients. This goal refers both to gynaecologic oncology issues as well as issues raised from endoscopic practice with direct or indirect connection to Gynaecologic Oncology.

THE CHALLENGES

Main challenges of modern gynaecologic oncology management are:

- To achieve early diagnosis in precancerous stage of all gynaecological malignancies
- To treat the majority of cases with minimally invasive surgery without compromising oncological outcome
- To establish state-of-the-art diagnostic and therapeutic algorithms for the the treatment of cases
- To enroll effectively and safely current therapeutic modalities in the overall multidisciplinary treatment of gynaecological cancer

In this field, there is absolute need to summarize state-of-the-art evidence when applicable, while also demonstrating controversies and lack of evidence in clinical issues daily preoccupying the management of oncological patients.

SEARCHING FOR A SOLUTION

The solution to optimize management of oncological patients lies absolutely to the implication of optimal therapeutic modalities in all aspects of treatment of oncological patient.

This necessitates thorough and comprehensive knowledge of evidence and guidelines as well as the individualization of the management according to patient, disease and also personal clinical experience of the practitioner.

ORGANIZATION OF THE BOOK

The book is organized into 25 chapters, divided in six thematic areas in order to serve its goals.

The first two chapters represent a small introduction to the epidemiology and genetics of gynaecologican cancer. Chapter 1 presents the recent epidemiological data regarding both gynaecological and breast cancer along with modern knowledge of incidence, survival and also mental health issues. Chapter 2 reports all what is known about hereditary syndromes correlated with gynaecological cancer.

Chapters 3-5 deal with state-of-the-art knowledge about screening and follow-up of gynaecological malignancies. Chapter 3 talks about the necessity of screening tests for gynaecological cancer early diagnosis, chapter 4 about the optimal clinical approach of high-risk patients for gynaecological cancer and chapter 5 about the short-term and long-term follow-up of gynaecological oncologic patients.

Chapters 6-7 refer to very hot issues of daily clinical practice of Reproductive Medicine affecting gynaecologic oncology. Chapter 6 answers the question whether IVF really increases risk for gynaecological cancer, while chapter 7 deals with the necessity or not to treat endometrial polyps in reproductive age.

Chapters 8-12 refer to cervical and vulvar pathology issues. Specifically, they discuss the role of co-testing in cervical cancer screening, the potential added value of mRNA, while the issue of non-free surgical margins after LEEP is discussed in Chapter 10. Chapters 11-12 refer to the optimal treatment of early-stage cervical cancer as well as the optimal approach of vulvar cancer.

Chapters 13-19 represent one of the most interesting domains of the book, dealing with issues of ovarian pathology. They are discussing the role of laparoscopy in ovarian cancer (Chapter 13), surgical prevention and optimal strategy (Chapter 14), optimal treatment of postmenopausal ovarian cyst (Chapter 15), optimal management of the challenging diagnosis of borderline ovarian tumors (Chapter 16) and cystic masses during pregnancies (Chapter 17). Furthermore, the issue of ovarian cancer as random finding during laparoscopy, taking into consideration also medicolegal issues, is discussed in Chapter 18, while optimal management of endometriotic cysts, which is also an often clinical issue, is thoroughly presented in Chapter 19.

Chapters 20-22 refer to endometrial pathology. The dilemma between uterine leiomyoma and sarcoma is posed in Chapter 20, the issue of minimal approach of simple hysterectomy for endometrial cancer is discussed in chapter 21, while an innovative surgical approach of vNOTES is discussed in chapter 22.

Chapter 23 presents the modern chemoprevention strategies in breast cancer.

Finally, the last two chapters 24-25 report on complications of surgical management, radiotherapy and chemotherapy, which is a frequent clinical issue of the daily management of oncological patients as well as potential medicolegal issues arising from daily clinical practice, not only in gynaecologic oncology but in all aspects of medical practice.

Dear colleagues, we hope you find this book useful in your daily effort to fight for the best of our patients and against gynaecological cancer. It would be our honor even if we manage to optimize treatment of a single patient by simply reading this book. Internationally recognized authors and members of editorial board have given their best to provide a useful supplement of our daily clinical effort. The fight against gynaecological cancer is our common concern and the effort to optimize treatment should always be our daily goal. We wish you to enjoy and profit every single moment of the readership of our book.

Section 1
Epidemiology and Genetics

Chapter 1
Epidemiology of Gynaecological and Breast Cancers:
Incidence, Survival, and Mental Health

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ABSTRACT

This chapter describes the incidences of breast cancer, genital organ cancer, in particular cervical cancer and ovarian cancer, including the five-year survival rates among women with these cancer diagnoses. Additionally, these incidences will be presented from different countries of the world. The absolute five-year survival rate indicates how many cancer patients are still alive at a certain point after diagnosis. Moreover, the age structure of women with cancer in Germany is shown. Additionally, anxiety and depression are common comorbidities of cancer and will serve in this chapter to give an example of applied epidemiology. These two conditions result from the uncertain course of the cancer disease, reduced life expectancy, and profound life changes. The impact of breast cancer or genital organ cancer on mental health is described, and it is shown which psychiatric diagnoses and symptoms potentially will occur during the course of the cancer disease.

INTRODUCTION

Epidemiology is concerned with the distribution of diseases, physiological variables, and social sequelae in human populations and the factors that influence this distribution. The most important measures in descriptive epidemiology include prevalence and incidence.

Prevalence describes the frequency with which people in the population studied suffer from a particular disease. For example, if the number of women diagnosed with breast cancer in a country is divided by the number of women living in that country, the result is the prevalence of breast cancer.

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Incidence describes the frequency with which people in the population under investigation are newly diagnosed with a particular disease. Unlike prevalence, the incidence is not presented as a percentage, but as the number of new cases in the observation period divided by the number of person-years at risk. "Number of person-years at risk" means the sum of observation years for the population at risk. "Population at risk" refers to people in the population examined who are not yet affected by the disease at the beginning of the observation period but may develop it over time. The incidence rate is the most common epidemiological measure used for cancer. The World Cancer Research Fund (WCRF) investigates current incidence rates for various cancers and publishes them on its website (www.wcrf.org).

Another very important measure in cancer epidemiology is the five-year survival rate. For many types of cancer, patients who have survived the first five years after diagnosis have a good chance of a permanent cure, as relapses are usually less likely after this period. A distinction is made between the absolute and relative five-year survival rates. The absolute five-year survival rate indicates how many cancer patients are still alive at a certain point after diagnosis. To calculate the relative survival rate, the absolute survival rate of cancer patients is divided by the expected survival rate in the general population.

Incidence Rates

The following information about incidence rates was published by the WCRF and can be found on its homepage.

Breast cancer is the most common cancer in women worldwide, with 2.1 million new cases diagnosed in 2018, representing about 25% of all cancers in women. Incidence rates vary across the world. In Middle Africa and Eastern Asia, for example, there were much less cases in 2018 compared to Northern America. Belgium had the highest rate of breast cancer in women per 100,000 (203.7), followed by the Netherlands (188.9), Italy (187.8), Luxembourg (175.4), Germany (172.2), Finland (169.8), France (169.4), Malta (165.1), United Kingdom (164.5), and Switzerland (163.1)

Cervical cancer is the 4th most commonly occurring cancer in women, with over 500,000 new cases diagnosed in 2018. The top 10 countries with the highest rates of cervical cancer were in 2018: Eswatini (52,9), South Africa (44,4), Malawi(43,1), Lesotho (41.0), Zimbabwe (36,7), Bolivia (34,8), Comoros (34,2), Zambia (33,7), Jamaica (33,4), and Madagascar (33,1).

Endometrial cancer is the 6th most common cancer in women worldwide. In 2018, around 350,000 new cases were recorded. The highest incidence rates of endometrial cancer are in North America and Central and Eastern Europe and the lowest in Middle and Western Africa.

Ovarian cancer is the 7th most common cancer in women worldwide, with approximately 295,000 cases recorded in 2018 (4% of all new cancer cases in women). Age-standardized incidence rates range from more than 11 per 100,000 in Central and Eastern Europe to less than 5 in some African countries. In 2018, Latvia had the highest rate of ovarian cancer (27.5), followed by Serbia (26,8), Poland (25,8), Hungary (25,7), Belarus (24,9), Lithuania (23,7), Croatia (22,8), Estonia (21,5), Slovakia (20,9), and Ukraine (19,9).

Number of new cases and incidence rates per 100,000 for breast, cervical, and ovarian cancer are shown in tables 1-3.

Cancer Survival

In 2018, Allemani et al. published a global surveillance of trends in cancer survival based on the records of 37,513,025 patients diagnosed with cancer between 2000 and 2014 from 322 population-based registries in 71 countries. The five-year age-standardized net survival (%) rates for women diagnosed with breast cancer in the time period between 2010 and 2014) are shown in Figure 6, those for cervical cancer in Figure 7, and those for ovarian cancer in Figure 8.

Mental Health in Women With Gynecological and Breast Cancers

Anxiety and depression are common comorbidities of cancer. These conditions result from the uncertain course of the disease, reduced life expectancy, and profound life changes. The fears that can occur in the course of cancer can relate to very different areas. Individuals may not only experience fear of dying from the disease or fear of pain and suffering, but also fear of professional and personal decline, even where the prognosis is good. The fear of what might happen is so great that, in most cases, the patient is unable to focus on anything else. Treatment takes time, and the woman's overall energy is affected by the disease itself, as well as by the therapy.

As a general rule, breast surgery is experienced as a fracture in the female identity. It is associated with a loss of female attractiveness, along with fears of having to renounce physical closeness and partnership altogether in the future.

Despondence, lack of drive, or fear of the future in cancer patients are often attributed to the crisis they are currently facing. Only if these symptoms persist for a long time can depression be diagnosed.

The impact of cancer as a whole and breast or genital organ cancer in particular on mental illness has been the subject of much research worldwide. However, the incidences found were dependent on several factors.

There are four different clinical pictures that may include symptoms such as despondence, grief, anxiety, and their physical manifestations. These include a depressive episode (ICD-10: F32) or major depressive disorder (ICD-10: F33), generalized anxiety disorder (ICD-10: F41), reaction to severe stress and adjustment disorders (ICD-10: F43), and somatoform disorders (ICD-10: F45). Prevalence rates varied widely depending on whether all four or only one of these diagnoses were considered.

Furthermore, there are many ways to measure depression. For example, depression can be measured using the depression module of the Personal Health Questionnaire (PHQ-9), which consists of 9 items addressing the symptoms of depression and their frequency [Kroenke et al. 2001]. The other main method often used in breast cancer studies to evaluate symptoms of anxiety and depression was the Hospital Anxiety and Depression Scale (HADS). This scale excludes the somatic symptoms of depression and anxiety, such as fatigue, loss of appetite, pain or insomnia [Trinca et al. 2019]. Beck's Depression Inventory (BDI) has occasionally been used to assess the degree of depression (Salibasic & Delibegovic 2018). Several other questionnaires have also been developed to measure depression and anxiety.

Table 1. Estimated number of new breast cancer cases and incidence rates per 100,000 in 2018

Population	Number of Cases	Uncertainty Interval	Crude Incidence Rate**
World	2 088 849	[2003730.0-2177580.0]	55.2
China	367 900	[346754.0-390335.0]	53.3
United States of America	234 087	[232580.0-235604.0]	141.9
India	162 468	[158245.0-166804.0]	24.9
Brazil	85 620	[83292.9-88012.1]	79.8
Germany	71 888	[67275.4-76816.8]	172.2
Russian Federation	71 426	[70275.4-72595.5]	92.7
Japan	66 101	[64823.5-67403.6]	101.6
Indonesia	58 256	[54948.2-61762.9]	44.0
Italy	57 039	[54764.6-59407.9]	187.8
France	56 162	[53709.9-58726.0]	169.4
United Kingdom	55 439	[54425.7-56471.2]	164.5
Pakistan	34 066	[32167.8-36076.2]	34.9
Spain	32 825	[30722.2-35071.7]	138.8
Canada	28 172	[27454.7-28908.1]	151.3
Mexico	27 283	[25975.8-28656.0]	41.6
Nigeria	26 310	[23610.0-29318.7]	27.2
Philippines	24 798	[24026.4-25594.4]	46.8
Korea, Republic of	23 476	[22994.6-23967.5]	91.8
Egypt	23 081	[21734.0-24511.5]	47.0
Turkey	22 345	[20336.7-24551.7]	53.8
Argentina	21 558	[21248.2-21872.3]	94.5
Poland	20 203	[19082.6-21389.1]	102.5
Thailand	19 510	[17958.7-21195.3]	55.0
Ukraine	18 958	[18396.3-19536.9]	80.1
Australia	18 558	[18009.2-19123.5]	149.3
The Netherlands	16 209	[15561.1-16883.9]	188.9
Ethiopia	15 244	[13248.2-17540.4]	28.3
Viet Nam	15 229	[14432.8-16069.1]	31.2
South Africa	14 097	[13309.5-14931.1]	48.2
Iran, Islamic Republic of	13 776	[13441.1-14119.2]	33.8
Colombia	13 380	[12430.1-14402.5]	53.2
Bangladesh	12 764	[4774.5-34123.1]	15.5
Belgium	11 851	[11430.5-12287.0]	203.7
Algeria	11 847	[11311.2-12408.2]	57.0
Morocco	10 136	[9449.1-10872.8]	55.5
Romania	9 629	[9405.7-9857.6]	95.4
Venezuela, Bolivarian Republic of	9 215	[8480.0-10013.7]	56.6
Hungary	8 215	[7518.2-8976.4]	161.8
Sweden	8 017	[7756.9-8285.8]	160.9
Greece	7 734	[7185.2-8324.7]	136.7
Malaysia	7 593	[7287.3-7911.6]	48.9
Czechia	7 436	[7094.9-7793.5]	137.7
Switzerland	7 029	[6652.1-7427.2]	163.1
Peru	6 985	[6557.0-7441.0]	42.9
Portugal	6 974	[6748.7-7206.8]	128.7
Myanmar	6 277	[4378.8-8998.1]	22.8
Congo, Democratic Republic of	6 149	[4896.1-7722.5]	14.6
Kenya	5 985	[5348.8-6696.9]	23.4
Austria	5 915	[5616.8-6229.0]	132.7
Serbia	5 809	[5513.3-6120.6]	129.6
Korea, Democratic Republic of	5 779	[4619.7-7229.2]	44.2
Sudan	5 677	[4685.5-6878.3]	27.3
Chile	5 393	[4811.8-6044.3]	58.7
Iraq	5 141	[4944.7-5345.0]	26.5
Syrian Arab Republic	4 935	[1786.4-13633.5]	54.5
Finland	4 770	[4624.0-4920.6]	169.8
Ghana	4 645	[4208.3-5127.1]	31.4
Denmark	4 628	[4135.6-5179.0]	160.0
Cuba	4 496	[4147.5-4873.8]	78.3
Belarus	4 496	[4274.9-4728.6]	89.0
Israel	4 250	[3946.3-4577.1]	100.0

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Table 1. Continued

Population	Number of Cases	Uncertainty Interval	Crude Incidence Rate**
Kazakhstan	4 211	[4060.1-4367.5]	44.4
Bulgaria	4 016	[3758.6-4291.0]	111.0
Norway	3 803	[3600.4-4017.0]	143.5
Saudi Arabia	3 629	[3091.8-4259.5]	25.3
Uzbekistan	3 508	[3325.0-3701.0]	21.6
New Zealand	3 504	[3280.8-3742.4]	145.1
Ireland	3 334	[3059.4-3633.2]	137.7
Cameroon	3 273	[2672.9-4007.9]	26.6
Lebanon	3 219	[3052.3-3394.9]	106.0
Dominican Republic	3 158	[2462.9-4049.3]	57.8
Singapore	3 136	[2605.5-3774.5]	107.0
Sri Lanka	3 091	[2951.4-3237.2]	28.4
Afghanistan	3 062	[1145.4-8185.9]	17.4
Tanzania, United Republic of	3 037	[2201.8-4189.1]	10.2
Slovakia	2 999	[2875.5-3127.8]	107.1
Croatia	2 856	[2500.3-3262.3]	132.4
Ecuador	2 787	[2576.2-3015.1]	33.0
Côte d'Ivoire	2 659	[2356.0-3001.0]	21.6
Yemen	2 445	[2180.8-2741.2]	17.1
Puerto Rico	2 367	[2181.5-2568.2]	124.6
Uganda	2 318	[1924.0-2792.6]	10.4
Tunisia	2 305	[2137.9-2485.1]	39.1
Angola	2 158	[1718.3-2710.2]	13.8
Jordan	2 143	[1852.2-2479.5]	43.8
Nepal	2 068	[1357.3-3150.9]	13.6
Azerbaijan	1 994	[1879.4-2115.5]	40.0
Zimbabwe	1 886	[1626.5-2186.8]	21.8
Uruguay	1 860	[1757.4-1968.6]	103.8
Somalia	1 823	[1274.0-2608.7]	23.9
Guatemala	1 791	[1471.5-2179.9]	20.5
Senegal	1 758	[669.6-4615.5]	21.2
Mali	1 755	[1503.5-2048.6]	18.4
Lithuania	1 742	[1549.0-1959.0]	112.3
Chad	1 648	[1312.2-2069.7]	21.5
Republic of Moldova	1 646	[1397.7-1938.4]	78.2
Paraguay	1 616	[1334.5-1956.9]	47.5
Cambodia	1 592	[1110.6-2282.1]	19.1
Niger	1 585	[1195.7-2101.0]	14.3
Benin	1 526	[1316.0-1769.5]	26.5
Costa Rica	1 501	[1331.7-1691.9]	60.6
Papua New Guinea	1 493	[1218.3-1829.6]	36.1
El Salvador	1 487	[1092.6-2023.8]	43.7
Bolivia, Plurinational State of	1 458	[1215.6-1748.7]	26.0
Burkina Faso	1 436	[547.0-3770.1]	14.5
South Sudan	1 407	[983.2-2013.4]	21.8
Bosnia and Herzegovina	1 386	[1242.5-1546.1]	77.7
Slovenia	1 377	[1234.7-1535.7]	131.5
Mozambique	1 364	[1089.5-1707.7]	8.7
Madagascar	1 335	[932.9-1910.4]	10.1
Latvia	1 266	[1102.4-1453.8]	121.3
Malawi	1 216	[875.5-1689.0]	12.6
Honduras	1 195	[978.2-1459.9]	25.3
Georgia	1 141	[454.8-2862.8]	55.9
Rwanda	1 131	[822.2-1555.9]	17.8
Haiti	1 105	[595.8-2049.4]	19.7
United Arab Emirates	1 054	[981.8-1131.5]	39.5
Armenia	1 054	[468.6-2371.0]	67.8
Sierra Leone	1 035	[951.6-1125.8]	26.6
Panama	1 022	[788.2-1325.1]	49.2
Nicaragua	1 013	[795.7-1289.6]	31.8
The former Yugoslav Republic of Macedonia	1 000	[745.5-1341.3]	95.9
Jamaica	974	[792.1-1197.6]	66.9
Albania	973	[806.7-1173.5]	66.9

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Table 1. Continued

Population	Number of Cases	Uncertainty Interval	Crude Incidence Rate**
Lao People's Democratic Republic	892	[622.3-1278.7]	25.6
Zambia	888	[680.1-1159.5]	10.0
Gaza Strip and West Bank	879	[318.2-2428.3]	35.3
Kuwait	814	[658.3-1006.5]	45.5
Estonia	801	[671.2-955.9]	115.4
Libya	753	[601.7-942.3]	23.5
Turkmenistan	747	[294.8-1893.1]	25.1
Togo	746	[678.1-820.7]	18.6
Eritrea	740	[517.1-1058.9]	28.6
Cyprus	725	[629.2-835.4]	122.0
Kyrgyzstan	697	[551.6-880.7]	22.5
Mauritius	659	[552.5-786.0]	102.7
Trinidad and Tobago	657	[469.5-919.4]	94.3
Burundi	634	[443.1-907.2]	11.1
Guinea	605	[414.7-882.7]	9.3
Central African Republic	537	[427.6-674.4]	22.4
Tajikistan	530	[414.1-678.4]	11.7
Luxembourg	515	[364.5-727.7]	175.4
Oman	454	[314.7-655.0]	27.8
Montenegro	420	[272.1-648.3]	131.8
Liberia	414	[157.7-1086.9]	17.2
Mauritania	412	[156.9-1081.7]	18.3
Congo, Republic of	394	[325.4-477.1]	14.6
France, La Réunion	376	[332.8-424.8]	82.5
Malta	355	[256.0-492.2]	165.1
Namibia	318	[263.8-383.4]	23.9
Fiji	305	[290.6-320.2]	67.9
France, Martinique	287	[205.1-401.6]	136.7
France, Guadeloupe	276	[236.8-321.7]	114.4
Bahrain	227	[190.9-270.0]	39.6
Iceland	225	[170.1-297.7]	133.8
Qatar	190	[169.0-213.6]	28.1
Gabon	179	[139.6-229.5]	17.8
Mongolia	178	[146.2-216.8]	11.3
France, New Caledonia	178	[148.5-213.4]	128.1
Botswana	177	[144.8-216.3]	15.0
Djibouti	176	[123.0-251.9]	36.4
Guyana	170	[131.3-220.1]	43.9
Suriname	169	[116.1-246.0]	59.7
Bahamas	166	[120.8-228.1]	81.5
Barbados	164	[102.2-263.1]	109.8
Guinea-Bissau	163	[62.1-427.9]	16.8
Lesotho	153	[86.1-272.0]	13.1
Brunei	132	[98.4-177.1]	62.6
Equatorial Guinea	131	[104.3-164.5]	22.4
French Polynesia	112	[88.3-142.1]	79.8
Solomon Islands	105	[99.3-111.0]	34.3
Timor-Leste	99	[69.1-141.9]	15.2
French Guiana	77	[51.1-115.9]	53.1
Eswatini	75	[46.7-120.5]	10.4
Maldives	73	[27.3-195.2]	38.2
Samoa	67	[51.3-87.5]	70.0
Saint Lucia	61	[35.1-105.9]	66.5
Belize	57	[31.1-104.4]	29.7
The Republic of the Gambia	48	[32.6-70.7]	4.4
Cabo Verde	48	[25.3-91.1]	17.3
Guam	45	[38.9-52.1]	55.0
Comoros	42	[29.4-60.1]	10.2
Vanuatu	35	[22.4-54.6]	25.1
Bhutan	16	[14.4-17.7]	4.2
Sao Tome and Principe	12	[4.6-31.5]	11.4

(Source: International Agency for Research on Cancer)

Table 2. Estimated number of new cervical cancer cases and incidence rates per 100,000 in 2018

Population	Number	Uncertainty Interval	Crude Rate**
World	569 847	[545771.0-594985.0]	15.1
China	106 430	[103074.0-109895.0]	15.4
India	96 922	[93365.0-100615.0]	14.9
Indonesia	32 469	[30005.4-35134.9]	24.5
Russian Federation	18 164	[17728.2-18610.5]	23.6
Brazil	16 298	[15318.7-17339.9]	15.2
Nigeria	14 943	[12945.7-17248.5]	15.5
United States of America	14 065	[13724.4-14414.0]	8.5
Japan	13 277	[12653.2-13931.6]	20.4
South Africa	12 983	[12220.7-13792.8]	44.4
Tanzania, United Republic of	9 772	[8064.5-11841.0]	32.7
Thailand	8 622	[8246.4-9014.7]	24.3
Bangladesh	8 068	[5772.3-11276.7]	9.8
Mexico	7 869	[7469.1-8290.3]	12.0
Philippines	7 190	[6784.4-7619.9]	13.6
Myanmar	6 472	[3619.6-11572.2]	23.5
Uganda	6 413	[5607.4-7334.4]	28.8
Ethiopia	6 294	[5056.8-7833.9]	11.7
Congo, Democratic Republic of	5 762	[4346.9-7637.8]	13.7
Ukraine	5 733	[5450.4-6030.3]	24.2
Pakistan	5 601	[4537.8-6913.3]	5.7
Kenya	5 250	[4615.3-5972.0]	20.5
Germany	4 608	[4332.1-4901.4]	11.0
Argentina	4 484	[4068.0-4942.5]	19.7
Madagascar	4 353	[2843.7-6663.3]	33.1
Mozambique	4 291	[3767.8-4886.9]	27.5
Viet Nam	4 177	[3833.5-4551.2]	8.6
Venezuela, Bolivarian Republic of	4 174	[3838.2-4539.2]	25.6
Malawi	4 163	[3499.9-4951.8]	43.1
Peru	4 103	[3775.5-4458.9]	25.2
Colombia	3 853	[3420.7-4339.9]	15.3
United Kingdom	3 430	[3237.3-3634.2]	10.2
Morocco	3 388	[3004.2-3820.8]	18.6
Korea, Republic of	3 348	[3165.4-3541.2]	13.1
Romania	3 308	[3155.8-3467.6]	32.8
Poland	3 220	[2994.2-3462.8]	16.3
Zimbabwe	3 186	[2892.7-3509.0]	36.7
Ghana	3 151	[2803.1-3542.1]	21.3
Italy	3 105	[2903.0-3321.0]	10.2
France	3 067	[2835.6-3317.2]	9.3
Zambia	2 994	[2589.4-3461.9]	33.7
Angola	2 949	[2224.8-3909.0]	18.8
Nepal	2 942	[1892.4-4573.8]	19.3
Burkina Faso	2 517	[958.7-6608.1]	25.4
Turkey	2 356	[2125.1-2612.0]	5.7
Cameroon	2 356	[1878.3-2955.1]	19.1
Mali	2 206	[1923.8-2529.5]	23.1
Bolivia, Plurinational State of	1 949	[1732.0-2193.2]	34.8
Spain	1 942	[1750.9-2154.0]	8.2
Korea, Democratic Republic of	1 922	[1647.7-2242.0]	14.7
Senegal	1 876	[714.6-4925.3]	22.6
Burundi	1 859	[1214.4-2845.6]	32.6
Guinea	1 810	[1449.0-2261.0]	27.8
Côte d'Ivoire	1 789	[1528.3-2094.1]	14.5
Kazakhstan	1 729	[1633.3-1830.3]	18.2
Malaysia	1 682	[1550.7-1824.5]	10.8
Ecuador	1 612	[1461.6-1777.9]	19.1
Uzbekistan	1 608	[1491.8-1733.2]	9.9
Algeria	1 594	[1402.1-1812.2]	7.7
Chile	1 549	[1300.6-1844.9]	16.9
Guatemala	1 503	[1300.4-1737.2]	17.2
Canada	1 434	[1255.2-1638.2]	7.7
Serbia	1 327	[1205.3-1461.0]	29.6
Hungary	1 312	[1124.5-1530.8]	25.8
Rwanda	1 304	[968.6-1755.5]	20.5
Cuba	1 231	[1065.2-1422.6]	21.4
Sri Lanka	1 136	[1050.9-1228.0]	10.4
South Sudan	1 101	[719.3-1685.3]	17.1
Sudan	1 084	[750.9-1564.9]	5.2

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Table 2. Continued

Population	Number	Uncertainty Interval	Crude Rate**
Bulgaria	1 080	[954.3-1222.2]	29.9
Paraguay	1 033	[841.9-1267.4]	30.4
Papua New Guinea	1 024	[890.3-1177.8]	24.8
Cambodia	993	[555.4-1775.5]	11.9
Somalia	989	[646.1-1513.9]	13.0
Dominican Republic	981	[806.5-1193.3]	17.9
Belarus	979	[860.0-1114.5]	19.4
Egypt	969	[713.3-1316.4]	2.0
Australia	924	[832.0-1026.2]	7.4
Iran, Islamic Republic of	917	[833.0-1009.4]	2.2
Haiti	835	[264.7-2633.6]	14.9
Czechia	813	[710.7-930.1]	15.1
Honduras	804	[666.2-970.3]	17.0
Benin	783	[650.6-942.4]	13.6
Portugal	750	[684.0-822.4]	13.8
Chad	742	[559.8-983.6]	9.7
El Salvador	724	[604.0-867.8]	21.3
Greece	696	[523.8-924.7]	12.3
Afghanistan	694	[496.5-970.0]	3.9
Slovakia	692	[634.7-754.5]	24.7
Nicaragua	677	[533.4-859.3]	21.2
The Netherlands	670	[583.5-769.3]	7.8
Belgium	640	[570.4-718.0]	11.0
Republic of Moldova	639	[509.4-801.6]	30.4
Kyrgyzstan	601	[452.5-798.3]	19.4
Togo	568	[516.4-624.8]	14.2
Sweden	558	[496.1-627.7]	11.2
Bosnia and Herzegovina	556	[473.8-652.5]	31.2
Liberia	548	[208.7-1438.7]	22.8
Niger	543	[335.6-878.5]	4.9
Jamaica	486	[323.8-729.3]	33.4
Mauritania	481	[183.2-1262.8]	21.4
Lesotho	477	[366.3-621.2]	41.0
Panama	432	[334.0-558.8]	20.8
Lithuania	431	[370.4-501.6]	27.8
Singapore	429	[282.2-652.2]	14.6
Denmark	415	[355.6-484.3]	14.3
Azerbaijan	397	[351.2-448.8]	8.0
Turkmenistan	397	[298.4-528.1]	13.4
Austria	390	[313.8-484.7]	8.7
Eswatini	380	[305.7-472.4]	52.9
Mongolia	370	[326.6-419.1]	23.4
Norway	361	[304.6-427.8]	13.6
Costa Rica	351	[263.0-468.4]	14.2
Ireland	340	[264.4-437.2]	14.0
Latvia	339	[260.2-441.6]	32.5
Botswana	333	[287.4-385.9]	28.2
Lao People's Democratic Republic	320	[179.0-572.2]	9.2
Libya	319	[223.6-455.1]	9.9
Saudi Arabia	316	[185.8-537.4]	2.2
Sierra Leone	299	[275.4-324.6]	7.7
Georgia	297	[201.0-438.9]	14.5
Uruguay	288	[230.8-359.3]	16.1
Tunisia	285	[228.5-355.4]	4.8
Congo, Republic of	278	[219.4-352.2]	10.3
Central African Republic	276	[208.2-365.8]	11.5
Croatia	266	[207.5-340.9]	12.3
Puerto Rico	262	[229.1-299.6]	13.8
Syrian Arab Republic	259	[123.2-544.6]	2.9
Switzerland	258	[224.8-296.1]	6.0
Iraq	244	[204.5-291.2]	1.3
Israel	241	[195.7-296.7]	5.7
Namibia	236	[190.8-291.9]	17.8
Estonia	230	[184.3-287.0]	33.1
Tajikistan	220	[157.4-307.5]	4.9
Eritrea	218	[142.4-333.7]	8.4
Armenia	196	[123.7-310.5]	12.6

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Table 2. Continued

Population	Number	Uncertainty Interval	Crude Rate**
Lebanon	192	[154.3-238.9]	6.3
Guinea-Bissau	191	[72.8-501.5]	19.7
New Zealand	190	[144.6-249.7]	7.9
The Republic of the Gambia	184	[106.5-317.8]	16.8
Finland	182	[144.1-229.9]	6.5
Yemen	170	[115.3-250.6]	1.2
Gabon	156	[125.2-194.4]	15.5
The former Yugoslav Republic of Macedonia	151	[106.7-213.7]	14.5
Comoros	141	[92.1-215.8]	34.2
Trinidad and Tobago	140	[85.8-228.5]	20.1
Albania	134	[88.9-202.0]	9.2
Guyana	124	[98.6-156.0]	32.0
Fiji	124	[102.3-150.3]	27.6
Mauritius	120	[85.3-168.8]	18.7
Slovenia	110	[73.7-164.1]	10.5
United Arab Emirates	108	[88.7-131.5]	4.1
Jordan	104	[76.1-142.2]	2.1
Equatorial Guinea	100	[75.4-132.6]	17.1
Suriname	85	[57.3-126.1]	30.0
Oman	77	[52.2-113.5]	4.7
France, La Réunion	70	[52.8-92.8]	15.4
Kuwait	59	[41.8-83.3]	3.3
Solomon Islands	55	[44.2-68.4]	17.9
Montenegro	54	[29.0-100.6]	16.9
Djibouti	52	[34.0-79.6]	10.7
Brunei	52	[33.2-81.4]	24.7
Timor-Leste	50	[28.0-89.4]	7.7
Cabo Verde	50	[29.1-86.0]	18.0
Bhutan	48	[42.9-53.7]	12.5
Belize	46	[26.8-79.1]	23.9
Cyprus	45	[30.3-66.7]	7.6
Maldives	41	[29.3-57.3]	21.4
France, Guadeloupe	39	[26.1-58.2]	16.2
Gaza Strip and West Bank	38	[18.1-79.9]	1.5
Barbados	38	[22.3-64.7]	25.4
France, Martinique	32	[21.6-47.5]	15.2
France, New Caledonia	30	[18.8-47.9]	21.6
French Guiana	29	[16.0-52.4]	20.0
Bahamas	29	[16.4-51.3]	14.2
Luxembourg	25	[11.3-55.5]	8.5
Vanuatu	21	[12.2-36.2]	15.1
Bahrain	19	[10.7-33.7]	3.3
Qatar	19	[13.4-27.0]	2.8
Guam	18	[14.4-22.6]	22.0
French Polynesia	17	[9.3-30.9]	12.1
Sao Tome and Principe	16	[6.1-42.0]	15.3
Saint Lucia	15	[7.3-31.0]	16.4
Iceland	15	[8.8-25.7]	8.9
Malta	11	[5.7-21.4]	5.1
Samoa	10	[5.1-19.6]	10.5

(Source: International Agency for Research on Cancer)

However, physicians do not just use standardized questionnaires. Sometimes the symptoms reported by patients and their duration are sufficient to diagnose depression or another psychiatric disorder, although in such cases the diagnoses made are not necessarily reliable. Individual physicians differ in their assessments and diagnoses, and general practitioners and hospital doctors sometimes make different diagnoses. Finally, general practitioners are much more involved in diagnosing and caring for patients with mental disorders than gynecologists, who, in turn, are much more frequently responsible for caring for women with breast or genital cancers.

Table 3. Estimated number of new ovarian cancer cases and incidence rates per 100,000 in 2018

Population	Number	Uncertainty Interval	Crude Rate**
World	295 414	[280962.0-310609.0]	7.8
China	52 971	[50685.5-55359.6]	7.7
India	36 170	[34265.7-38180.1]	5.5
United States of America	24 469	[24010.4-24936.4]	14.8
Russian Federation	13 936	[13544.8-14338.5]	18.1
Indonesia	13 310	[11768.9-15052.9]	10.0
Japan	10 672	[10139.6-11232.3]	16.4
Germany	6 781	[6303.4-7294.8]	16.2
Brazil	6 686	[6128.5-7294.2]	6.2
United Kingdom	6 407	[6082.2-6749.2]	19.0
Poland	5 077	[4757.3-5418.1]	25.8
Philippines	5 069	[4733.4-5428.4]	9.6
France	4 985	[4689.7-5298.9]	15.0
Italy	4 981	[4748.0-5225.5]	16.4
Mexico	4 759	[4375.8-5175.8]	7.2
Ukraine	4 718	[4500.4-4946.1]	19.9
Pakistan	4 504	[3813.4-5319.6]	4.6
Turkey	3 729	[3436.9-4045.9]	9.0
Spain	3 427	[3145.7-3733.4]	14.5
Thailand	3 254	[3032.8-3491.3]	9.2
Bangladesh	3 063	[1950.7-4809.5]	3.7
Ethiopia	2 872	[2091.1-3944.6]	5.3
Nigeria	2 792	[2025.7-3848.1]	2.9
Canada	2 716	[2528.4-2917.5]	14.6
Egypt	2 674	[2241.9-3189.3]	5.4
Korea, Republic of	2 656	[2471.4-2854.4]	10.4
Colombia	2 414	[2023.6-2879.7]	9.6
Argentina	2 330	[2040.0-2661.2]	10.2
Romania	1 840	[1750.8-1933.7]	18.2
Iran, Islamic Republic of	1 773	[1657.1-1897.1]	4.3
Myanmar	1 648	[872.1-3114.3]	6.0
Viet Nam	1 500	[1326.1-1696.8]	3.1
Australia	1 496	[1346.4-1662.3]	12.0
South Africa	1 371	[1162.0-1617.6]	4.7
Peru	1 331	[1151.2-1538.9]	8.2
Hungary	1 305	[1153.0-1477.0]	25.7
Malaysia	1 271	[1156.0-1397.5]	8.2
Belarus	1 256	[1089.0-1448.6]	24.9
The Netherlands	1 216	[1141.4-1295.5]	14.2
Serbia	1 200	[1057.7-1361.4]	26.8
Venezuela, Bolivarian Republic of	1 144	[982.7-1331.8]	7.0
Morocco	1 092	[888.7-1341.7]	6.0
Kazakhstan	1 053	[979.6-1131.9]	11.1
Czechia	1 012	[920.9-1112.1]	18.7
Algeria	992	[848.9-1159.2]	4.8
Korea, Democratic Republic of	981	[707.9-1359.4]	7.5
Kenya	971	[724.4-1301.5]	3.8
Sudan	959	[629.9-1460.1]	4.6
Greece	903	[810.7-1005.8]	16.0
Ghana	861	[695.9-1065.2]	5.8
Sri Lanka	856	[784.8-933.7]	7.9
Chile	841	[638.4-1107.9]	9.2
Nepal	838	[443.4-1583.9]	5.5
Congo, Democratic Republic of	787	[443.9-1395.1]	1.9
Austria	761	[702.4-824.5]	17.1
Bulgaria	718	[641.2-804.1]	19.9
Belgium	692	[598.0-800.8]	11.9
Uganda	596	[411.3-863.7]	2.7
Slovakia	584	[531.4-641.8]	20.9
Sweden	583	[510.8-665.3]	11.7
Portugal	574	[509.4-646.8]	10.6
Ecuador	573	[480.7-683.1]	6.8
Switzerland	560	[511.9-612.6]	13.0

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Table 3. Continued

Population	Number	Uncertainty Interval	Crude Rate**
Singapore	550	[377.6-801.2]	18.8
Uzbekistan	546	[486.9-612.3]	3.4
Iraq	534	[475.6-599.6]	2.7
Cuba	515	[425.7-623.0]	9.0
Croatia	492	[427.7-565.9]	22.8
Niger	464	[276.7-778.0]	4.2
Ireland	456	[361.4-575.3]	18.8
Afghanistan	450	[286.6-706.6]	2.6
Syrian Arab Republic	449	[184.4-1093.1]	5.0
Finland	440	[371.1-521.8]	15.7
Denmark	433	[366.7-511.2]	15.0
Saudi Arabia	409	[318.6-525.0]	2.9
Cameroon	385	[223.6-662.9]	3.1
Tanzania, United Republic of	379	[181.5-791.2]	1.3
Cambodia	376	[199.0-710.5]	4.5
Lithuania	367	[293.8-458.5]	23.7
Republic of Moldova	343	[251.0-468.8]	16.3
Norway	329	[271.8-398.2]	12.4
Azerbaijan	322	[281.2-368.7]	6.5
Bosnia and Herzegovina	321	[254.3-405.2]	18.0
Somalia	321	[145.0-710.4]	4.2
Israel	318	[268.6-376.4]	7.5
Côte d'Ivoire	296	[204.5-428.4]	2.4
El Salvador	293	[205.3-418.2]	8.6
Lebanon	291	[244.7-346.0]	9.6
Latvia	287	[236.6-348.1]	27.5
New Zealand	280	[230.6-340.0]	11.6
Tunisia	267	[212.3-335.9]	4.5
Angola	265	[149.5-469.8]	1.7
Guatemala	264	[187.3-372.2]	3.0
Senegal	260	[42.7-1582.0]	3.1
Yemen	255	[199.1-326.6]	1.8
South Sudan	252	[113.9-557.7]	3.9
Chad	251	[141.6-445.0]	3.3
Papua New Guinea	247	[181.2-336.8]	6.0
Mali	243	[162.8-362.7]	2.5
Kyrgyzstan	232	[165.2-325.8]	7.5
Zimbabwe	226	[163.3-312.8]	2.6
Uruguay	222	[161.7-304.7]	12.4
Puerto Rico	213	[166.9-271.9]	11.2
Burkina Faso	211	[34.7-1283.9]	2.1
Malawi	211	[105.5-421.9]	2.2
Georgia	208	[90.5-477.8]	10.2
Haiti	198	[122.2-320.8]	3.5
Jordan	197	[140.8-275.6]	4.0
Paraguay	192	[125.1-294.8]	5.6
Bolivia, Plurinational State of	177	[122.8-255.2]	3.2
Honduras	166	[110.7-248.9]	3.5
Lao People's Democratic Republic	165	[87.3-311.8]	4.7
Slovenia	162	[116.5-225.2]	15.5
Madagascar	150	[67.8-332.0]	1.1
Estonia	149	[116.0-191.4]	21.5
Nicaragua	149	[112.9-196.7]	4.7
Costa Rica	146	[105.1-202.9]	5.9
Libya	145	[88.5-237.7]	4.5
Jamaica	145	[71.3-294.7]	10.0
Dominican Republic	144	[106.6-194.5]	2.6
Mozambique	142	[76.1-265.1]	0.91
The former Yugoslav Republic of Macedonia	141	[72.6-274.0]	13.5
Armenia	136	[59.7-309.7]	8.8
Turkmenistan	136	[74.7-247.5]	4.6
Burundi	125	[56.5-276.6]	2.2
Eritrea	125	[56.5-276.6]	4.8

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Table 3. Continued

Population	Number	Uncertainty Interval	Crude Rate**
Zambia	115	[57.2-231.0]	1.3
Panama	114	[82.7-157.1]	5.5
Benin	111	[73.4-167.8]	1.9
Togo	110	[86.4-140.1]	2.7
Guinea	108	[46.8-249.2]	1.7
Rwanda	107	[53.6-213.8]	1.7
Tajikistan	97	[61.8-152.3]	2.1
United Arab Emirates	95	[77.7-116.2]	3.6
Sierra Leone	89	[70.9-111.7]	2.3
Albania	84	[53.0-133.1]	5.8
Trinidad and Tobago	80	[42.7-150.0]	11.5
Gaza Strip and West Bank	76	[31.2-185.0]	3.1
Central African Republic	75	[42.3-133.0]	3.1
Mongolia	73	[56.1-95.1]	4.6
Cyprus	67	[49.1-91.5]	11.3
Mauritius	65	[48.9-86.4]	10.1
Congo, Republic of	64	[39.6-103.5]	2.4
Kuwait	62	[44.1-87.2]	3.5
Mauritania	59	[9.7-359.0]	2.6
Fiji	58	[49.8-67.5]	12.9
Liberia	55	[9.0-334.7]	2.3
Luxembourg	50	[32.2-77.7]	17.0
France, La Réunion	46	[32.3-65.5]	10.1
Oman	40	[24.5-65.2]	2.4
Brunei	38	[22.6-63.9]	18.0
Malta	35	[24.4-50.2]	16.3
Bahrain	35	[22.5-54.4]	6.1
Gabon	35	[22.4-54.7]	3.5
Montenegro	32	[16.7-61.4]	10.0
France, Guadeloupe	30	[18.7-48.0]	12.4
Namibia	30	[16.6-54.3]	2.3
Guyana	30	[16.4-55.0]	7.8
Djibouti	28	[12.7-62.0]	5.8
Lesotho	27	[13.3-55.0]	2.3
Botswana	25	[14.9-41.9]	2.1
Timor-Leste	24	[12.7-45.4]	3.7
Qatar	23	[16.3-32.4]	3.4
Guinea-Bissau	23	[3.8-139.9]	2.4
France, Martinique	22	[13.4-36.2]	10.5
Iceland	21	[12.8-34.5]	12.5
Barbados	21	[10.6-41.8]	14.1
Solomon Islands	20	[16.8-23.8]	6.5
Suriname	19	[9.0-40.1]	6.7
Bhutan	19	[16.2-22.3]	4.9
France, New Caledonia	19	[10.9-33.1]	13.7
Equatorial Guinea	19	[10.7-33.7]	3.2
Maldives	16	[10.2-25.1]	8.4
Eswatini	15	[8.4-26.8]	2.1
Bahamas	13	[5.8-29.0]	6.4
French Guiana	11	[4.4-27.8]	7.6
French Polynesia	9	[3.8-21.4]	6.4
Guam	8	[5.5-11.7]	9.8
Sao Tome and Principe	6	[1.0-36.5]	5.7
Samoa	5	[1.9-13.2]	5.2
Saint Lucia	4	[2.2-7.1]	4.4
Vanuatu	4	[1.1-14.4]	2.9
Comoros	3	[1.4-6.6]	0.73
The Republic of the Gambia	3	[1.2-7.3]	0.27
Cabo Verde	3	[1.2-7.5]	1.1
Belize	2	[1.1-3.6]	1.0

(Source: International Agency for Research on Cancer)

Table 4. Five-year age-standardised net survival (NS, %) for women initially diagnosed with breast cancer in 2010-2014

Country	NS (%)	95% CI
Africa		
Algeria	77.0	68.5 – 85.6
Morocco	99.7	95.8 – 100.0
Nigeria	97.5	89.9 – 100.0
South Africa	40.1	30.7 – 49.6
America (Central and South)		
Argentina	84.4	82.6 – 86.2
Brazil	75.2	73.9 – 76.5
Chile	75.5	69.4 – 81.5
Colombia	72.1	69.0 – 75.2
Costa Rica	86.7	84.6 – 88.9
Cuba	75.1	73.7 – 76.5
Ecuador	75.5	72.4 – 78.7
Guadeloupe	50.2	39.6 – 60.8
Martinique	89.8	84.5 – 95.1
Peru	84.0	81.4 – 86.7
Puerto Rico	84.1	82.0 – 86.3
America (North)		
Canada	88.2	87.8 – 88.6
United States	90.2	90.1 – 90.4
Asia		
China	83.2	82.1 – 84.3
Hong Kong	83.3	82.1 – 84.6
India	66.1	51.5 – 80.8
Israel	88.0	87.0 – 89.0
Japan	89.4	88.9 – 89.9
Jordan	84.4	80.9 – 88.0
Korea	86.6	85.8 – 87.5
Kuwait	75.2	66.4 – 83.9
Malaysia	65.0	52.1 – 78.0
Mongolia	76.1	63.8 – 88.4
Qatar	71.9	58.4 – 85.5
Singapore	80.3	78.4 – 82.2
Taiwan	84.2	83.3 – 85.1
Thailand	68.7	66.6 – 70.8
Turkey	82.1	80.7 – 83.5
Europe		
Austria	84.8	84.1 – 85.5
Belgium	86.4	85.9 – 86.9
Bulgaria	78.3	77.2 – 79.4
Croatia	78.6	77.4 – 79.7
Czech Republic	81.4	80.7 – 82.1
Cyprus	92.8	89.7 – 95.9
Denmark	86.1	85.4 – 86.9
Estonia	76.6	73.8 – 79.3
Finland	88.5	87.7 – 89.3
France	86.7	85.5 – 88.0
Germany	86.0	85.7 – 86.4
Iceland	89.1	85.1 – 93.1
Ireland	82.0	80.7 – 83.3
Italy	86.0	85.5 – 86.4
Latvia	82.2	80.3 – 84.2

continued on following page

Table 4. Continued

Country	NS (%)	95% CI
Lithuania	73.5	71.3 – 75.7
Malta	86.9	83.1 – 90.6
Netherlands	86.6	86.1 – 87.1
Norway	87.7	86.6 – 88.8
Poland	76.5	76.1 – 77.0
Portugal	87.6	85.9 – 89.3
Romania	74.8	68.5 – 81.1
Russian Federation	70.8	69.5 – 72.1
Slovakia	75.5	72.4 – 78.5
Slovenia	83.5	81.8 – 85.2
Spain	85.2	84.0 – 86.5
Sweden	88.8	88.2 – 89.4
Switzerland	86.2	85.1 – 87.3
United Kingdom	85.6	85.4 – 85.9
Oceania		
Australia	89.5	89.1 – 90.0
New Zealand	87.6	86.4 – 88.7

(Source: Allemani et al. 2018)

Over the last decade (2008-2018), more than 100 articles have been published on the incidence of depression in breast cancer patients. Most of these studies were based on small numbers of patients and the reported prevalence rates varied widely.

The larger studies of depression and anxiety prevalence performed during this period, which included at least 1,000 women with breast cancer, are listed in the table below.

Pilevarzadeh et al. have conducted a systematic review and meta-analysis of the prevalence of depression among women diagnosed with breast cancer using 72 studies from 30 countries. The global prevalence of depression was 32%. The prevalence rates determined by individual studies varied between 5% and 96%. The prevalence rates found in meta-analyses were highest in Arab countries (52%) and lowest in the Americas (25%) (Pilevarzadeh et al 2019).

In a study conducted at the University of Munich, Voight and colleagues scientifically monitored approximately 160 breast cancer patients over a period of one year and examined all participants for symptoms of posttraumatic stress at three points in time. In total, 83% of all patients exhibited posttraumatic stress symptoms prior to the start of treatment. One year later, approximately 57% were still suffering from posttraumatic symptoms (Voight et al. 2017).

In a large retrospective study based on data from general and gynecological practices in Germany 37% of women in general and 35% in gynecological practices had been diagnosed with depression or anxiety within 5 years of follow-up (Jacob et al. 2016). In another study by the same authors, the incidence of depression and anxiety was 8.8 per 100 person-years in women with breast cancer, and was especially high in young women and women with a metastatic disease (Jacob et al. 2017).

Factors associated with psychiatric disorders in women with breast cancer may include:

1. Age

Longer-term depression and anxiety were associated with younger age (Burgess et al. 2005, Mehnert 2008, Christensen 2009, Boing et al. 2019).

Table 5. Five-year age-standardized net survival rates (NS, %) for women initially diagnosed with cervical cancer in 2010–2014

	NS (%)	95% CI
Africa		
Algeria	72.4	66.0 – 78.7
Nigeria	49.8	36.5 – 63.1
South Africa	37.1	31.4 – 42.9
America (Central and South)		
Argentina	52.7	48.7 – 56.7
Brazil	60.3	56.3 – 64.3
Chile	56.7	50.0 – 63.4
Colombia	49.4	46.5 – 52.3
Costa Rica	78.0	74.8 – 81.2
Cuba	72.9	70.5 – 75.2
Ecuador	52.0	49.3 – 54.7
Guadeloupe	19.4	9.0 – 29.9
Martinique	57.5	46.2 – 68.8
Peru	57.2	54.8 – 59.6
Puerto Rico	63.5	57.9 – 69.1
Uruguay	56.5	51.8 – 61.1
America (North)		
Canada	66.6	65.1 – 68.1
United States	62.6	62.0 – 63.1
Asia		
China	67.6	65.8 – 69.5
Hong Kong	65.8	63.6 – 68.1
India	59.0	47.5 – 70.5
Israel	66.6	63.2 – 70.1
Japan	71.4	70.4 – 72.3
Jordan	56.4	48.2 – 64.6
Korea	77.3	76.6 – 78.0
Kuwait	56.6	44.2 – 69.0
Malaysia	57.1	48.3 – 65.9
Qatar	63.5	44.2 – 82.8
Singapore	63.4	60.2 – 66.6
Taiwan	70.0	68.9 – 71.1
Thailand	53.9	52.1 – 55.8
Turkey	60.7	58.1 – 63.3
Europe		
Austria	63.9	61.6 – 66.2
Belgium	65.4	63.5 – 67.2
Bulgaria	54.8	53.3 – 56.3
Croatia	63.2	60.8 – 65.6
Czech Republic	61.0	59.5 – 62.4
Cyprus	73.3	65.1 – 81.6
Denmark	69.5	67.0 – 72.0
Estonia	66.5	62.2 – 70.7
Finland	67.4	63.8 – 71.1
France	65.0	60.3 – 69.7
Germany	65.2	64.0 – 66.4
Iceland	80.1	71.2 – 89.1
Ireland	63.6	60.1 – 67.2
Italy	66.8	65.1 – 68.5
Latvia	56.0	52.6 – 59.5
Lithuania	59.2	56.4 – 62.0
Malta	57.4	46.8 – 68.1
Netherlands	67.5	65.6 – 69.3
Norway	73.3	70.3 – 76.3
Poland	55.1	54.2 – 55.9
Portugal	66.2	62.6 – 69.8
Romania	65.3	59.7 – 70.9
Russian Federation	57.7	55.7 – 59.7
Slovakia	60.5	56.2 – 64.9

continued on following page

Table 5. Continued

	NS (%)	95% CI
Slovenia	65.5	61.3 – 69.8
Spain	64.5	60.8 – 68.1
Sweden	68.3	66.1 – 70.4
Switzerland	71.4	66.6 – 76.2
United Kingdom	63.8	62.8 – 64.7
Oceania		
Australia	66.4	64.5 – 68.2
New Zealand	67.4	63.4 – 71.5

(Source: Allemani et al. 2018)

2. Education

Less educated women presented more depressive symptoms than women with a higher educational level (Boing et al. 2019).

3. Symptoms

Patients with more severe symptom burdens were more likely to develop a depressive disorder than those displaying normal activity without any symptoms or with some symptoms (Tsaras et al. 2018).

4. Type of surgery

Women who had undergone radical mastectomy had a higher prevalence of depression symptoms than women with breast-conserving surgery (Boing et al. 2019).

5. Stage of cancer

Patients who were diagnosed with stage IV breast cancer were at a high risk of depression and anxiety compared to stage I patients (Tsaras et al 2018, Fradelos et al., 2017).

6. Residency

Participants living in rural areas were more likely to develop depressive disorders than those living in urban areas (Tsaras et al. 2018).

7. Comorbidity

Patients with higher comorbidity scores were more likely to develop depression or anxiety than women with low comorbidity scores (Mehnert et al. 2008, Boing et al. 2019).

8. Pessimism

Pessimism was a predictor of change in both anxiety and depression 5 years after breast cancer diagnosis (Faye-Schjøll & Schou-Bredal 2019).

Table 6. Five-year age-standardized net survival rates NS, (%) for women initially diagnosed with ovarian cancer in 2010–2014

	NS (%)	95% CI
Africa		
Algeria	66.5	53.5 – 79.5
Nigeria	49.1	33.8 – 64.4
South Africa	67.8	47.4 – 88.2
America (Central and South)		
Argentina	38.6	34.3 – 42.9
Brazil	34.9	29.5 – 40.3
Chile	28.0	21.3 – 34.7
Colombia	33.3	28.2 – 38.4
Costa Rica	56.9	49.1 – 64.7
Cuba	49.3	45.0 – 53.5
Ecuador	37.9	32.1 – 43.7
Guadeloupe	29.5	13.8 – 45.2
Martinique	35.7	23.4 – 48.0
Peru		–
Puerto Rico	37.3	32.0 – 42.6
Uruguay	37.4	31.4 – 43.4
America (North)		
Canada	40.9	39.9 – 41.8
United States	43.4	43.1 – 43.8
Asia		
China	41.8	39.8 – 43.7
India	15.6	10.2 – 21.1
Israel	45.0	42.3 – 47.7
Japan	46.3	44.9 – 47.7
Korea	47.5	46.2 – 48.9
Kuwait	35.1	25.6 – 44.7
Malaysia	46.8	34.5 – 59.0
Qatar	39.2	26.3 – 52.1
Singapore	43.9	40.7 – 47.0
Taiwan	48.8	46.9 – 50.8
Thailand	37.2	34.0 – 40.5
Turkey	39.7	37.3 – 42.0
Europe		
Austria	41.0	39.4 – 42.7
Belgium	43.1	41.6 – 44.6
Bulgaria	37.3	35.4 – 39.1
Croatia	36.0	33.9 – 38.2
Czech Republic	36.5	35.2 – 37.8
Cyprus	46.4	40.0 – 52.7
Denmark	39.7	37.8 – 41.6
Estonia	42.3	37.4 – 47.1
Finland	41.1	39.2 – 43.0
France	43.5	40.0 – 46.9
Germany	41.2	40.2 – 42.2
Iceland	40.3	31.2 – 49.4
Ireland	32.8	30.3 – 35.3
Italy	39.4	38.3 – 40.5
Latvia	45.5	41.9 – 49.0
Lithuania	35.0	32.0 – 37.9
Malta	28.0	21.4 – 34.6
Netherlands	37.5	36.2 – 38.7
Norway	45.5	43.3 – 47.7
Poland	37.5	36.7 – 38.3
Portugal	43.6	38.7 – 48.4
Romania	37.2	29.7 – 44.6
Russian Federation	34.8	32.8 – 36.8
Slovakia	33.4	28.6 – 38.2
Slovenia	37.0	33.4 – 40.5
Spain	39.8	36.9 – 42.7
Sweden	46.5	44.8 – 48.2
Switzerland	44.1	41.3 – 46.8
United Kingdom	36.2	35.7 – 36.8
Oceania		
Australia	42.0	40.8 – 43.2
New Zealand	36.7	34.1 – 39.3

(Source: Allemani et al. 2018)

Table 7.

Authors	Year	Region	Study Design	Number of Patients Included	Prevalence of Depression
Chen, X.	2009	China	Cross-sectional	1,400	39.0
Christensen, S.	2009	Denmark	Cohort	3,321	13.7
Hopwood, P.	2010	UK	Cross-sectional	2,208	3.0
Linden, W.	2012	Germany	Cross-sectional	2,250	7.4
Walker, J.	2014	UK	Cross-sectional	8,461	9.3
Vin-Raviv, N.	2015	USA	Cross-sectional	4,164	8.5
Chang, H. Y.	2015	South Korea	Cross-sectional	2,244	10.4
Jones, S. M.	2015	USA	Cross-sectional	6,949	13.3
Jacob L et al.	2016	Germany	Cohort	44,55	36.0
Park, B.	2017	South Korea	Cross-sectional	3,120	7.6
Puigpinos-Riera, R.	2018	Spain	Cohort	2,235	15.0

Although there are several large studies focusing on psychiatric disorders in women with gynecological cancers, most of these were performed in Asia.

A survey of 220 respondents indicated that the prevalence of symptoms of depression and anxiety was 47% and 52% respectively in Chinese ovarian cancer patients (Liu et al. 2017). Another study included patients with newly-diagnosed cervical cancer from the National Health Insurance Research Database in Taiwan (Shyu et al. 2019) and reported a low prevalence of depressive disorders of 4.2% in the cervical cancer cohort. A large retrospective study performed in Denmark, in which women over 19 years of age with gynecological cancers were observed, found a greatly increased likelihood of treatment with antidepressants among women treated for ovarian (HR 4.1), endometrial (HR 2.19), and cervical cancer (HR 3.1) one year after diagnosis. This increased risk persisted years after diagnosis in all three groups, lasting longest in women with ovarian cancer (Horsboel et al. 2019). In an Australian prospective study, more than 40% of women with ovarian cancer experienced clinical anxiety or depression during treatment or in the first 3 years of follow-up, which persisted for 25% (Webb et al. 2018).

Watts et al. identified a population of 3,623 women with ovarian cancer in several largely cross-sectional surveys investigating anxiety and depression. In their meta-analysis, the prevalence of depression before the initiation of treatment was 25%, dropping to 13% after the cessation of treatment. The prevalence of anxiety was 19% prior to treatment and 27% after the cessation of treatment.

Factors associated with psychiatric disorders in women with gynecological cancer are partly the same as in women with breast cancer and include the following:

1. Age

The risk of depression is higher among women younger than 50 years (Jacob et al. 2017, Horsboel et al. 2019).

2. Education

Less educated women were at a higher risk of developing depression (Horsboel et al. 2019).

3. Gynecological cancer subtype

Women with ovarian and cervical cancer had the highest risk of depression in the first year after diagnosis (Horsboel et al. 2019).

4. Stage of cancer

Patients with metastases had a higher risk of being depressed and anxious than those without (Price et al. 2010, Jacob et al. 2017, Horsboel et al. 2019).

5. Symptom burden

Patients having high levels of symptom burden were more likely to develop a risk for depression (Price et al. 2010).

6. Psychosocial factors
7. Lower social support was associated with a higher risk of anxiety, and lower levels of optimism were associated with both anxiety and depression (Price et al. 2010).

A specialist or general practitioner can reliably diagnose depression or anxiety disorder and determine the severity of the depression. It is very important that the physician, including gynecologists, checks women with cancer regularly for symptoms of depression. If primary care physicians and gynecologists identify patients as being at a high risk for psychiatric disorders, they should refer these patients to psychiatrists, psychologists, and other specialists in order to help the patient manage her depression and significantly improve her quality of life.

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Chapter 2
Hereditary Syndromes and Gynaecological Cancer

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ABSTRACT

Hereditary cancer has been a long-standing research field, but recent advances in technology have allowed for extensive gene expression analysis, offering results for large populations. The growing volume of data presents an advantage in the validity of conclusions, but on the other hand is accompanied by new dilemmas and questions on data interpretation. However, despite increasing availability of gene testing globally, hereditary cancer still remains a rare event. The majority of cancer cases are sporadic, without any correlation with known pathogenic gene mutations. Gradually, the ratio of hereditary to sporadic cancers is expected to increase, as more patients are tested and more mutations are registered as pathogenic. The chapter summarizes the main hereditary syndromes related with gynaecological cancer along with current implications and innovations in clinical practice.

INTRODUCTION

Hereditary cancer has been a long-standing research field, but recent advances in technology have allowed for extensive gene expression analysis, offering results for large populations. The growing volume of data presents an advantage in the validity of conclusions, but on the other hand is accompanied by new dilemmas and questions on data interpretation.

However, despite increasing availability of gene testing globally, hereditary cancer still remains a rare event. The majority of cancer cases are sporadic, without any correlation with known pathogenic gene mutations. Gradually, the ratio of hereditary to sporadic cancers is expected to increase, as more patients are tested and more mutations are registered as pathogenic.

Regarding patient and family genetic counseling, it is important to clarify that the identification of a mutation in a healthy carrier, does not confer a cancer diagnosis, but only expresses a possibility. This possibility may lead to cancer at some point during lifetime, but quite often it is extremely difficult to

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give an accurate estimation. Several mutations may appear in one gene, each with different oncogenic potentials. This explains the wide variations in risk assessment found in literature, as it is impossible to design clinical trials where all patients will carry exactly the same mutation. Data analysis is performed on gene mutation levels and penetrance is not assessed individually. It is also significant to remember that lifestyle may also affect cancer risk in different carriers of the same mutation.

Tumor Suppressor Genes

Most cancer-related mutations refer to tumor-suppressor genes, whose function regulates maintenance of the double DNA strand integrity. These genes are either involved in the repair of the numerous breaks that daily occur in the DNA strand (BRCA1/2), or act as checkpoint regulators that hold the cell cycle until all errors in the chain replication are fixed (p53, Rb). In case of irreparable damage, they will lead the cell to apoptotic death. When one of the alleles is mutated, the gene may become inactive immediately or at a later time if the other allele also becomes mutated, as this event leads to the encoding of a non-functioning protein.

Each gene comprises of two alleles, one inherited from each parent, therefore there is 50% chance for each decendant to inherit a mutation from one parent within the autosomal dominant pattern. All correlations between mutations and gynecologic cancers regard this pattern of inheritance. It is also important during documentation of family history, to clarify to the patients that breast and gynecologic cancers have equal possibilities to be inherited from each parent, in contrast to the wide -spread impression that women can only inherit them from their mothers' side.

Inherited and Non-Inherited Mutations

Genetic counseling information should include the difference between germline mutations that can be inherited because they are located in the germ cells that form the embryo and are the progenitors of all cells and the somatic mutations that only exist in the tumor cells and are significant to know in regards of treatment decisions and management of the disease of the particular patient. As new targeted treatments emerge, more options may become available for treating tumors with specific mutations. This can never have any interest for the healthy family members, who can only be tested for germline mutations.

Genetic Counseling

Patients undergoing genetic testing are expected to manage large-volume complicated information and the treating physicians are also expected to extend their consultation to the relatives who need guidance for the test results, regardless of the findings and their clinical significance. These consultations should only be performed by specialized health professionals, who can be Genetics doctors, specially trained Genetic Counselors with a background in molecular biology or nursing or Medical Oncologists who have also trained in Cancer Genetics. However, lack of specialized health professionals often results in having the genetic counseling performed by the treating oncologist or surgeon. This situation may have various consequences and is definitely not recommended neither for the patient nor for the healthy carriers within their family.

The increasing population undergoing genetic testing has led to the fast increase in the identification of mutations of unknown malignant potential, that have not been characterized as pathogenic in the

international databases. These are called Variants of uncertain Significance (VUS) and once registered, they are then followed prospectively in order to get them classified either as deleterious or not the soonest possible. When classification is confirmed, known carriers are informed accordingly.

Another rising issue that follows the spread of gene panels in genetic testing is the diagnosis of mutations that are not correlated with the family history and clinical manifestations, i.e. BRCA mutations in colorectal cancer. Therefore, the professional who discusses genetic information is expected to include such events in the consultation.

All this bulk of information that extends beyond the interaction between the treating physician and the patient and involves all the healthy relatives, has created a new need within the health services that requires highly specialized medical staff to provide it. Guidelines are yet to cover all cases and are expected to undergo many revisions as new data keep flowing in.

HEREDITARY SYNDROMES AND GYNECOLOGIC CANCERS

BRCA1/2-Related Hereditary Breast and Ovarian Cancer (HBOC)

HBOC is characterized by increased risk for female and male breast cancer, cancer of the ovary, salpinx and peritoneum and less frequently prostate, pancreas and melanoma, especially among the BRACA2 carriers. Initial diagnosis occurs in a patient with heterozygous germline mutation in one of the genes, found in genetic testing. Indications for testing are based on particular characteristics in the clinical manifestations and family history:

- Breast cancer before age of 50
- High-grade ovarian cancer
- >1cancers in the same breast or bilateral breast cancer
- Male breast cancer
- Same patient with breast and ovarian or combinations of pancreatic and prostate cancer
- Triple-negative breast cancer
- 2 or more relatives with breast cancer, with one younger than 50 on diagnosis
- 3 or more relatives with breast cancer, independent of age
- Breast cancer and Ashkenazi origin
- Breast cancer in a family with known BRCA mutation

When there are more patients in the family, it is preferable to start testing from the one diagnosed younger. If this is not feasible, testing starts from the available one. The only case to start from healthy relatives is when there are no patients alive and there is strong family history. However, it should be made clear that failing to find a mutation in one healthy relative does not exclude the possibility of mutations in the family. Frequency of BRCA mutations is estimated between 1:400- 1:500, rising up to 1:40 in the Ashkenazi Jews. (Anglian Breast Cancer Study Group, 2000).

Breast cancer is the most common neoplasm in the HBOC syndrome, with a risk up to 87% to the age of 70 among the BRCA1 carriers. (Ford, 1994). The same group presents an increased frequency for the triple-negative (ER-/PR-/HER2-) subtype with myeloid features and poor differentiation, while HER2 positive cancers appear less frequently compared to the general population (Lee, 2011). In the

BRCA2 carriers, triple -negative cases range between 3-17% (Couch, 2015). A retrospective analysis of 10180 patients from 16 trials demonstrated that presence of mutations in the BRCA genes does not have any correlation with overall survival (Templeton, 2016). The risk for cancer in the contralateral breast is increased and a British study estimated this risk to be 83% for the BRCA1 carriers and 62% for the BRCA2 up to the age of 70 (Mavaddat, 2013).

The risk for ovarian cancer is estimated around 63% and 27% for the two genes respectively, up to the age of 70 (Easton, 1995; Ford,1998). The most common histology is the high -grade serous adenocarcinoma and the majority of these tumors are considered to originate from the epithelial cells of the tube rather than the ovary (McLaughlin, 2013; Fujiwara, 2012). Survival data for ovarian cancer have correlated the presence of BRCA mutations with better prognosis, possibly due to the increased platinum sensitivity, but this remains controversial, as other researchers have only found the correlation in the short-term follow-up, and not in the overall survival (Bolton, 2012; Mc Laughlin, 2013).

RECOMMENDATIONS FOR PRIMARY PROPHYLAXIS OF THE BRCA MUTATION CARRIERS

Breast Cancer

- Prophylactic bilateral mastectomy
- Tamoxifen administration (for the BRCA2 carriers), although there are no prospective data
- Lactation for a minimum of 12 months in total
- Salpingoophorectomy before menopause has in some studies shown a decrease in the risk for breast cancer, but data require confirmation

Ovarian Cancer

- Bilateral salpingoophorectomy after completion of family (Rebbeck, 2002)
- Salpingectomy is being assessed as a prophylactic measure, following the conclusion regarding the origin of the high-grade serous tumors from the tube, in order to avoid premature menopause toxicity. Currently, the safety of this method is yet to be prospectively confirmed.
- Contraceptive agents. Long-term use of contraceptives has been correlated with a drop in the risk for ovarian cancer from 38 to 14% (Whittemore, 2004).

Lynch Syndrome

Diagnosis requires the presence of one heterozygous pathogenic mutation in one of the MLH1, MSH2, MSH6 or PMS2 genes or a deletion in the EPCAM gene. Frequency is estimated around 1:440 for the general population (Chen, 2006). It is correlated with increased risk for colorectal, gastric, endometrial, ovarian and other cancers of lower incidence. The risk for endometrial cancer is 25-60%, with median age of onset between 48-62 and for ovarian cancer 4-12%, median age 42,5 years and 30% of cases occurring before age of 40. Part of the endometrial cancer patients will on the following develop colorectal cancer, while there is a 26% chance of developing endometrial cancer, within 10 years from diagnosis of colorectal cancer (Lu, 2005; Obermair, 2010).

Recommendations for Primary Prophylaxis

- Total abdominal hysterectomy and bilateral salpingoophorectomy following completion of family
- Yearly total colonoscopy from age 20-25
- Smoking cessation

Li Fraumeni Syndrome

LF is a rare syndrome with germline mutations in the p53 gene as the underlying disorder, that is correlated with high incidence of malignancies including soft tissue sarcoma, osteosarcoma, breast cancer, leukemia and cancers of the brain and adrenals. Frequency in the general population is estimated between 1:5000-1:20000. Breast cancer development involves premenopausal ages, with all cases diagnosed before age of 50 and one third of them being younger than 30 (Birch, 1994). Recent literature reports increased incidence of the triple-positive subtype (Masciari, 2012; Ruijs, 2010; Thull, 2004; Syngal, 2015). Relative risk for breast cancer is estimated to 6.4 (range 4.3-9.3) compared to the general population.

Primary Prophylaxis

- Regular medical follow-up and testing, tailored to the specific clinical manifestations within the family
- Prophylactic bilateral mastectomy
- Total colonoscopy
- Avoid exposure to ionizing radiation, smoking and all known carcinogens

Peutz -Jeghers Syndrome

The underlying disorder is a pathogenic mutation in the STK11 gene and is inherited by the autosomal dominant pattern. Clinical manifestations include numerous polyps in the gastrointestinal and other systems, mucocutaneous hyperpigmentation and increased risk for several malignancies.

The risk for breast cancer is estimated between 32-54%, with average age at diagnosis 37-59 years. The risk for ovarian cancer is 21% versus 1.6% for the general population and average age of onset is 28years. The rare entity of adenoma malignum of the uterine cervix, with a frequency of <1% in the general population has a risk of 10% and age of onset between 34-40 in the STK11 mutation carriers. The risk for uterine cancer is increased from 2.7% to 9% and average age at diagnosis is 43 years (Tan, 2012).

Primary Prophylaxis

- GI endoscopy from age 8
- Gynecologic examination, breast examination and MRI from age 18
- For men, testicular examination and ultrasound if indicated (Sertoli tumors)
- Genetic Counseling

Cowden Syndrome

Cowden syndrome is included in the group of syndroms that develop hamartomatous tumors related to PTEN mutations. Criteria for diagnosis include the cerebellar dysplastic gangliocytoma and mucocutaneous lesions. Breast and endometrial cancer are included in the major criteria for diagnosis, together with macrocephaly and thyroid cancer. PTEN mutation carriers have up to 85% risk for developing breast cancer, mostly at age <50. Endometrial cancer has a risk of 28% at age of 40 or younger (Nelen, 1999).

The estimated frequency of the syndrome is 1:200000, but it is believed to be less rare, as it may have atypical manifestations and therefore remain undiagnosed in several cases (24).

For women under 30 recommendations include annual mammography and breast MRI and transvaginal ultrasound with endometrial biopsy if indicated.

Other pathogenic mutations conferring increased risk for breast cancer include CHEK2, PALB2, ATM and many other genes of lower penetrance, for which regular surveillance is recommended, but specific guidelines are still under development.

CONCLUSION

Diagnosis and management of breast and gynecologic cancers related to inherited mutations are expected to attract increasing attention in the near future. Growing accessibility to genetic testing allows for easier diagnosis and forms a specific group of patients and healthy carriers, who require genetic counseling and medical guidance towards decisions of primary prophylaxis. The need for State -of the Art centers that can offer high quality health services for this population represents a new challenge for Public Health systems worldwide.

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Section 2
Screening and Follow-Up

Chapter 3
Screening Tests for Gynaecological Cancer: Do They Increase Safety?

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ABSTRACT

The main screening tests that are used for the prevention and early diagnosis of gynaecological cancer are bimanual pelvic examination, transvaginal and transabdominal ultrasound, cervical cytology testing (Papanicolaou test), clinical breast examination, mammography, breast ultrasound, as well as newer diagnostic methods, such as HPV-DNA test and cancer biomarkers. Even though most of the above methods are widely used in everyday practice in gynaecology, it remains a subject for further discussion which of them should be used as screening tests and whether they increase safety in clinical approach of a patient, considering the danger of overdiagnosis and the role of screening test in personalized management of patients. The purpose of this chapter is to analyze the clinical benefit and safety of diagnostic methods related to prevention of various types of gynaecological cancer and in particular endometrial, ovarian, cervical, and breast cancer.

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INTRODUCTION

The term primary prevention refers to the use of means and methods that aim at preventing a disease through controlling risk factors, while secondary prevention is defined as presymptomatic mass population testing (screening), aiming at preventing as well as early diagnosing diseases. Preventive strategies may be applied in general population or in targeted high risk groups. In order to be approved as appropriate for screening, a method should have high sensitivity and specificity, easy and simple application, low cost, safety, credibility and acceptance from a great proportion of population (Maxim D.L. et al., 2014; Pinsky P.F. et al, 2015)

The main screening tests that are used in everyday practice of gynaecology and especially gynaecological oncology for the prevention and early diagnosis of gynaecological cancer are the following: bimanual pelvic examination, transvaginal and transabdominal ultrasound, cervical cytology testing (Papanicolaou test), clinical breast examination, mammography and breast ultrasound. Over the last few years, there is a lot of discussion around the application of newer diagnostic methods, such as HPV-DNA test and cancer biomarkers.

Even though most of the methods mentioned above are widely used in common gynaecological practice for the early diagnosis of gynaecological cancer, it remains a subject for further discussion which of them should be used as screening tests and whether they actually increase safety in clinical approach of a patient. The use of each diagnostic means should be carefully weighed, considering the delicate balance between achieving clinical benefit for the patient and avoiding overdiagnosis, which may lead to unnecessary further diagnostic tests or even invasive procedures. It is a major subject of dispute whether the establishment of diagnostic methods as screening tests is compatible with personalized clinical approach of patients or leads to indiscriminate, one-fits-all management of the population undergoing testing, in favor of cost-effectiveness.

The purpose of this chapter is to analyze the clinical benefit and safety of diagnostic methods related to prevention of various types of gynaecological cancer and in particular endometrial, ovarian, cervical and breast cancer.

ENDOMETRIAL CANCER

Uterine cancer is the most common gynecological cancer in high-income countries and the second most common gynecological cancer worldwide (after cervical cancer) when both high- and low-income countries are considered (Bray F. et al., 2018). Uterine cancer incidence is highest in North America and Northern Europe, intermediate in Southern Europe and temperate South America, and lowest in Southern and Eastern Asia and most of Africa. This likely reflects prevalence differences in main risk factors associated with uterine cancer, such as obesity and reproductive patterns (Felix A. et al., 2018). In 2017, ~61,000 new uterine cancer diagnoses were globally reported and nearly 11,000 women were estimated to have died from the disease, primarily affecting postmenopausal women, considering the fact that mean age of diagnosis was 62 years of age (Ginger C. et al., 2019).

Over 90 percent of uterine cancers are endometrial, originating in the epithelium; most of the remainder are mesenchymal, originating in the myometrial muscle or, less commonly, the endometrial stroma (Bray F. et al., 2018). Endometrial cancer is the most common gynaecological cancer and the second most common female malignancy, after breast cancer, in the developed world. In 2012, the number of

new cases and deaths due to endometrial cancer worldwide was 319,605 and 76,160 respectively (Raglan O. et al., 2019). Taking into consideration that endometrial carcinomas represent the vast majority of uterine cancers and a leading cause of mortality among women, it is justified that screening policies are currently focusing on detecting risk factors and on early diagnosing this type of uterine cancer.

Risk factors associated with endometrial cancer occurrence include early menarche & late menopause, obesity, family history of endometrial cancer (especially among close relatives), radiation exposure, and infertility particularly in the presence of Polycystic Ovarian Syndrome. There is also evidence that risk of endometrial cancer is positively correlated with older age, as well as long-term use of unopposed estrogens for hormone replacement therapy and tamoxifen administration for breast cancer treatment, diabetes mellitus and obesity (defined as body mass index [BMI] of $\geq 30\,kg/m^2$) (Ginger C. et al., 2019; Aus T.A. et al., 2013).The most important epidemiologic risk factors for the development of endometrial cancer, with their respective relative risks are presented in table 1 (Renaud M.C. et al, 2018).

Table 1. Epidemiologic risk factors for the development of endometrial cancer

Risk Factor	Relative Risk
Unopposed estrogen replacement	2 to 10
Late menopause > 55 years	2.4
Nulliparity	2
Chronic anovulation	3
Hypertension	1.5
Obesity	10
Diabetes	2.8
HNPCC syndrome	22% to 50% lifetime risk
Tamoxifen use	6 to 8

The main examination performed in the context of endometrial cancer prevention is the transvaginal ultrasound and more specifically the measurement of endometrial thickness in asymptomatic postmenopausal women. The official guidelines on endometrial cancer by European Society of Gynaecological Oncology (ESGO) suggest that there is no efficient evidence on the use of screening methods for endometrial cancer prevention in general population (level II of evidence) (Colombo N. et al., 2016). This statement is supported by the American College of Obstetricians and Gynecologists (ACOG), which underlines in its guidelines upon endometrial cancer management that at present, there is no available recommended routine screening test to identify endometrial cancer (Committee on Practice Bulletins - Gynecology and the Society of Gynecologic Oncology, 2015). In addition, preventive testing is not recommended by ESGO guidelines in asymptomatic women with obesity, polycystic ovary syndrome, diabetes mellitus, infertility, nulliparity or late-onset menopause (level III of evidence). Moreover, preventive testing is not suggested in asymptomatic women who use tamoxifen (level III of evidence). The only group of patients indicated to benefit from annual preventive gynaecological examination and gynaecological ultrasound are Lynch syndrome mutation carriers over 35 years old and until undergoing hysterectomy (level IV of evidence). The Royal College of Obstetricians and Gynaecologists (RCOG) recognizes in its guidelines issued upon management of endometrial hyperplasia, that transvaginal

ultrasound may have a role in diagnosing endometrial hyperplasia in pre- and postmenopausal women, but this suggestion only represents a recommended best practice based on the clinical experience of the guideline development group and it is not proposed as an official screening routine for general population (Royal College of Obstetricians and Gynaecologists, 2016). Similar conclusions are reported in the Spanish Society of Medical Oncology (SEOM) recently published guidelines for endometrial cancer, where it is stated that there are no high-quality data to support the efficacy of screening for reducing endometrial cancer-associated mortality and that routine screening of asymptomatic women at average or increased risk of endometrial cancer is not recommended (level II of evidence). However, for women with Lynch syndrome, according to these guidelines, screening should be offered in asymptomatic women who have not completed childbearing or women that refused prophylactic surgery beginning at the age of 30–35 or 5–10 years prior the earliest age of first diagnosis of Lynch-associated cancer in the family. It is further supported that annual endometrial sampling (level II of evidence), transvaginal ultrasound with endometrial aspiration and serum CA 125 are usually recommended to be performed every year in women with Lynch syndrome (level IV of evidence) (Santaballa A. et al., 2018). These recommendations on endometrial cancer screening are also confirmed and supported by respective guidelines issued by International Federation of Gynecology and Obstetrics (FIGO) and Society of Obstetricians and Gynaecologists of Canada (SOGC) (Renaud M.C. et al., 2018; Amant F. et al., 2018).

Despite the fact that ESGO and other official guidelines question the use of transvaginal ultrasound as a screening method in general population, numerous published articles point out the high prognostic value of measurement of endometrial thickness in early diagnosis of endometrial cancer, especially in postmenopausal women. Indicatively, Seckin et al. (Seckin B. et al., 2016) in a recent prospective study of 602 postmenopausal women concluded that endometrial thickness $\geq$ 8mm has 75% sensitivity and 74% specificity in detecting endometrial cancer. Respectively, Alcazar et al. (Alcazar J.L. et al., 2018) in a recent systematic review and meta-analysis proposed that the risk of endometrial cancer or endometrial hyperplasia with atypia in postmenopausal women with endometrial thickness $\geq$ 11mm is 2,6 times higher. A similar conclusion is reached in a study by Hefler et al. (Hefler L. et al., 2018), which also proposes 11mm as a limit for distinction between "normal" and "abnormal" endometrial thickness.

The diagnostic value of measurement of endometrial thickness in asymptomatic women is questioned by several other studies, which report the inability of setting a reliable cut-off point in endometrial thickness for predicting the occurrence of endometrial cancer. In a recent study of 276 cases, Yasa et al. (Yasa C. et al., 2016) underline the low accuracy of transvaginal ultrasound in the detection of endometrial cancer. Respectively, another study by Israeli Gynecology Oncology Study Group (Gemer O. et al., 2018) concludes that that the early diagnosis of endometrial cancer with the use of transvaginal ultrasound is not necessarily associated with a higher survival rate. Besides, it is well known that the mean endometrial thickness in patients with endometrial serous-papillary carcinoma is under 5 mm, indicating that the measurement of endometrial thickness does not necessarily contributes to the early diagnosis of all types of cancer.

In conclusion, despite strong indications that transvaginal ultrasound contributes to the early diagnosis of endometrial cancer, further research is required in order to validate the use of transvaginal ultrasound as a screening test for endometrial cancer. It is, though, well established that increased thickness of endometrium, especially above 10mm, raises strong suspicion for endometrial abnormalities, even in asymptomatic postmenopausal women.

OVARIAN CANCER

Ovarian cancer is the 5th leading cause of cancer-related deaths in United States, while similar rates are reported in European countries as well. In 2008, approximately 225,500 women were diagnosed with ovarian cancer worldwide. In 2012 it was estimated that 238,700 new cases were detected and 151,900 women died of ovarian cancer. In general, ovarian cancer is more common in developed than in developing countries with the highest incidence in Northern Europe (13.3 per 100,000 per year) and the lowest incidence in North Africa (2.6 per 100,000 per year) (Nyoman G.B. et al., 2019). The epidemiological diversity of ovarian cancer in different regions can be attributed to different prevalence of risk factors that account for the occurrence of ovarian cancer, as well as to differences in access to diagnostic and therapeutic services. For the same reasons, the mortality of ovarian cancer has a different pattern among continents and countries, with the highest mortality being reported in African populations (Momenimovahed Z. et al., 2019).

As for the factors involved in ovarian cancer development, risk factors as well as protective factors are acknowledged and reported, including demographic, reproductive, gynaecologic, hormonal, genetic and lifestyle-associated factors. It has been shown that women with early menarche (age <12 years) and late menopause (age >50 years) are at higher risk for ovarian cancer due to a higher number of ovulatory cycles, while epidemiological studies have discovered a link between the incidence of endometriosis and ovarian cancer through an uncertain mechanism. Genetic predisposition is found in 10-15% of cases of ovarian cancer. BRCA1 and BRCA2 gene mutations, first discovered in 1994 and 1995 respectively, are associated with ovarian and breast cancer and to date are the genes that have the strongest influence in ovarian cancer incidence. On the other hand, breastfeeding, pregnancy, and the use of oral contraceptive pills, which suppress ovulation, are protective factors for ovarian cancer (Nyoman G.B. et al., 2019). Risk and protective factors related to ovarian cancer are presented in Table 2 (Momenimovahed Z. et al., 2019).

Table 2. Factors related to ovarian cancer

Factors		Protective	Predisposing
DEMOGRAPHIC	Age		✓
REPRODUCTIVE	Menstrual-related factors		✓
	Age of menarche and menopause		✓
	Parity	✓	
	Higher age of childbirth	✓	
GYNAECOLOGIC	Endometriosis		✓
HORMONAL	Contraceptive methods	✓	
GENETIC	Family history		✓
	BRCA mutations		✓
	Lynch syndrome		✓
OTHER	Lactation	✓	
	Lower socioeconomic status		✓

Ovarian cancer accounts for 2.5% of all malignancies among females and 5% of female cancer deaths because of low survival rates, largely driven by late stage diagnoses (Torre A.L. et al., 2018). About 68% of ovarian cancer cases are diagnosed at a late stage and as a consequence, survival rates of those patients are significantly lower compared to those receiving diagnosis at an earlier stage. Ovarian cancer has a far lower survival rate than other cancers, due to the fact that patients are unaware that a vast majority of its risk factors and symptoms are easily disguised as normal menstrual problems or other abdominal ailments and diseases. As a result, ovarian cancer is mostly detected at a late stage, in which it is usually considered untreatable, resulting in unfavorable prognosis for a great proportion of patients (Umakanthan S. et al., 2019).

Taking all the above into consideration, it is rather expected that one of the research priorities in gynaecology is the development and application of more efficient screening methods for ovarian cancer, given the fact that the lack of clinical symptoms in its early stages leads to low rates of early detection. However, according to current scientific knowledge, it is doubtful that benefits of screening tests application outweigh the dangers that accompany potential overdiagnosis of ovarian cancer.

Hederson et al. (Henderson J.T. et al., 2018), recently published, on behalf of U.S. Preventive Services Task Force, a systematic review and meta-analysis of all prospective randomized studies which conducted to determine the benefits of screening tests application. The final outcome was that all possible combinations of transvaginal ultrasound and CA-125 level measurements on a 6-month or annual basis are not associated with statistically significant difference in the survival rate of patients diagnosed with endometrial cancer. More specifically, possible early diagnosis in the group of patients undergoing regular screening testing was not associated with decreased mortality rate, compared to the group of patients who were referred for evaluation and testing after the occurrence of symptoms. On the contrary, an important increase in false positive test cases was reported, leading to an increase in unnecessary surgical procedures and severe post-operative complications. In particular, overdiagnosis rate was calculated between 9,8% and 44%, depending on the diagnostic method applied, unnecessary surgical procedures rate was 1-3.2%, while severe post-operative complications rate was 3-15%. In addition to the above, a 28% increase in negative psychological effects was reported in the group of patients undergoing frequent reevaluations due to screening protocol.

A recent study by Van Nagel et al. (Van Nagel J.R. et al., 2018) questions the results and conclusions presented above. Van Nagel et al. conducted a prospective cohort study, in which 46.101 women from Kentucky state were recruited over the period 1987-2017. Women over 50 years old or over 25 years old with family history of ovarian cancer were under annual screening with transvaginal ultrasound and in case of suspicious findings, they were referred for reevaluation in 4-6 weeks with transvaginal ultrasound and CA-125 level measurement. Comparing results from this group of patients to results from control group, which consisted of women with ovarian cancer who underwent surgery, having received diagnosis without previous screening testing and after the onset of symptoms, it was found that cancer was diagnosed earlier in the first group of patients, who also had significantly increased 5-year, 10-year and 20-year survival rates. This was the first large population study underlining the fact that application of screening tests is strongly associated with an increase in survival rates. However, it should be mentioned that high risk patients with positive family history were also included in the study population, possibly affecting the reported results. Moreover, the study reports that transvaginal ultrasound and CA-125 level measurement were applied as screening testing methods, with no referral to the use of bimanual pelvic examination as part of screening protocols.

The application of transvaginal ultrasound and CA-125 level measurement as screening methods in general low-risk population is not yet officially recommended by international guidelines. The British Gynaecological Cancer Society (BGCS) states, in its recent guidelines, that there is currently no role for organized screening programs in women considered at low risk of development of ovarian cancer, as well as that the role of ovarian cancer screening in women at high risk of ovarian cancer has yet to be established. However, it acknowledges the important contribution of CA125 measurement and pelvic and/or transvaginal ultrasound scan as the initial investigation tools for post-menopausal women presenting with signs or symptoms of ovarian cancer, underlining at the same time the need for further strong evidence to support their use in screening policies (Fotopoulou C. et al., 2017).

The use of bimanual pelvic examination as a screening method for ovarian cancer detection is questioned in guidelines issued by many international scientific societies. In particular, it is not recommended by European Society of Gynaecological Oncology (ESGO) (Querleu D. et al., 2017), while American Medical Association recommends against its use for screening purposes. According to a recent meta-analysis, positive predictive value of bimanual pelvic examination is extremely low (0-3.6%), resulting in a remarkably high rate of false positive diagnoses (Guirguis-Blake J.M. et al., 2017). However, it should be noted that American College of Obstetricians and Gynecologists (ACOG) stands in favour of the use of bimanual pelvic examination as a screening method for early detection of suspicious pelvic masses (level IV of evidence) (ACOG Committee Opinion No. 754, 2018).

To conclude, the use of bimanual pelvic examination, as well as transvaginal ultrasound and CA-125 level measurement as screening methods for ovarian cancer is not supported by strong scientific evidence. However, recent studies suggest that patients with ovarian cancer, early diagnosed after participating in presymptomatic screening protocols have increased survival rates. These results should trigger the conduct of large-scale prospective cohort studies on screening strategies for ovarian cancer, in order to provide definitive answers and reliable evidence-based recommendations.

CERVICAL CANCER

Cervical cancer screening is a success story of screening strategies, considering that the prevalence of the disease was significantly lower after the establishment of presymptomatic population testing and especially Papanicolaou test. Ten years ago, cervical cancer was ranked as the third most common cancer among women worldwide, while in the majority of low-resource countries, it was the most common cancer in women. The knowledge that persistent infection with carcinogenic human papillomavirus (HPV) types is the main cause triggering the development of cervical cancer has opened new pathways for primary and secondary prevention. The treatment of precancerous lesions detected by microscopic inspection of cells scraped from the cervix has been the paradigm of secondary prevention of cervical cancer for half a century (Arbyn M. et al., 2019). The dissemination of cervical smear cytology as a screening method over the last 50 years in western countries led to a remarkable decrease in incidence and mortality rates of cervical cancer, marking it as the most successful screening test applied in general population (Fotiou S., 2009). Papanicolaou test is currently the main screening test for cervical cancer, approved by the majority of scientific associations and it is recommended that it should be repeated every 3 years for low-risk women over 21 years of age (World Health Organization - WHO guidelines, 2013).

Despite the wide application of Papanicolaou test and a subsequent impressive decline in cervical cancer incidence rate, complete eradication of the disease was not achieved. Cervical cancer remains

the fourth most common female malignancy worldwide, ranking after breast cancer (2,1 million cases), colorectal cancer (0,8 million) and lung cancer (0,7 million) and represents a major global health challenge. Indicatively, more than 33.000 new cases of cervical cancer were reported in 2002 in Europe, accompanied by approximately 15000 cervical cancer-related deaths (Fotiou S., 2009). Each year, more than half a million women are diagnosed with cervical cancer and the disease results in over 300.000 deaths worldwide. Only in 2018, 570.000 cases of cervical cancer and 311.000 deaths from the disease were reported. Approximately 90% of cervical cancers occur in low-income and middle-income countries that lack organized screening and HPV vaccination programs. In high-income countries, cervical cancer incidence and mortality have more than halved over the past 30 years since the introduction of formal screening programs, but their rates still remain relatively high (Cohen A.P. et al., 2019). A possible explanation might lie in the low rates of participation in screening programs, estimated even below 75%. Uptake of screening programs may be enhanced by raising awareness about cervical cancer risk factors, including human papillomavirus infections, young age at first sexual intercourse, multiple male sexual partners, high parity, young age at first full-term pregnancy, prolonged use of oral contraceptives and HIV infections (Kashyap N. et al., 2019). In addition to the above, in recent meta-analyses, the sensitivity of cervical cytology is reported to be low even in HGSIL cases (53%), while its reproducibility is also under dispute.

Despite advances in prevention, screening, diagnosis, and treatment during the past decade, substantial regional and global disparities in cervical cancer outcomes have led international gynaecological cancer societies to publish evidence-based management guidelines that aim to improve the quality of care for patients.

In this context, apart from Papanicolaou test, HPV-DNA test is gradually gaining popularity among screening methods as a main screening test for cervical cancer prevention. A recent systematic review and meta-analysis by U.S. Preventive Services Task Force suggests that the diagnostic accuracy of HPV-DNA test is 2-3 times higher, regarding the detection of high-grade intraepithelial cervical lesions (Melnikow J. et al., 2018). The popularity of HPV-DNA test application in screening strategies is increasing in such a rate, that in a recent study, it is estimated that in the next 25 years, human papillomavirus (HPV) screening will be officially established as the primary test for cervical cancer in England, UK (Castanon A. et al., 2017). However, it is accompanied by an important drawback, which is its low specificity, especially in younger age groups, where HPV infections are commonly self-restricted. Based on the above, the American College of Obstetricians and Gynaecologists recommends HPV-DNA test application every 5 years for women aged 30-65 years, who haven't been diagnosed with cervical intraepithelial neoplasia according to previous Papanicolaou test results (ACOG Practice Bulletin No.157, 2016).

Combined application of HPV-DNA test and cervical cytology (usually called co-testing) is also a suggested screening method for cervical cancer prevention and detection of pre-invasive lesions. Despite that it is considered to be an acceptable screening policy, there is no scientific evidence demonstrating that co-testing is diagnostically superior compared to the sole use of HPV-DNA test (Tracht J. et al., 2017). Respectively, while newer diagnostic tests such as detection of E6 oncoprotein could significantly contribute to the evaluation of evolutionary potential of a lesion, there is no sufficient evidence to support their application as general population screening tests.

An important question to be answered, considering the patients undergoing repeated HPV-DNA tests every 5 years as a screening method for early detection of cervical cancer, is whether this strategy is followed by a decrease in routine gynaecological examinations, as well as clinical implications. Although annual routine gynaecological examination is recommended for all women by ACOG (level IV of evi-

dence), it is not yet scientifically proven that women who neglect annual examination but fully comply with screening policies recommended by guidelines for the prevention of cervical cancer, are more likely to develop gynaecological cancer (Guirguis-Blake J.M. et al., 2017). Nonetheless, more cohort studies are required to evaluate the use of routine gynaecological examination as a screening method.

Despite the fact that HPV-DNA test is well-established as a screening test for cervical cancer, its low specificity in detecting high-grade (especially CIN3+) lesions remains one of its main disadvantages. Regarding this limitation, E6/E7 oncoprotein mRNA detection has been studied as a possible presymptomatic population screening method. HPV E6/E7 mRNA testing has both high sensitivity and specificity in detecting CIN2+ lesions, which rise above 90%, and compared to HPV-DNA test, this feature represents an important advantage. In addition, it is considered to have higher positive and negative predictive value, regarding the evaluation of patients with ASCUS or LSIL cytology results (Camus C. et al., 2018; Sørbye S.W. et al., 2016). However, it is not officially recommended by scientific societies as a screening method, mainly due to its cost, but it remains a useful complementary screening tool for patients tested positive for HPV infection.

Taking all the above into consideration, many guidelines issued by national and international scientific associations gradually support the official incorporation of HPV-DNA test in general population screening strategies, alongside Papanicolaou test. The US Preventive Services Task Force, in a recommendation statement published in 2018, supported the application of screening for cervical cancer every 3 years with cervical cytology alone in women aged 21 to 29 years, while for women aged 30 to 65 years, it recommended screening every 3 years with cervical cytology alone, every 5 years with high-risk human papillomavirus (hrHPV) testing alone, or every 5 years with hrHPV testing in combination with cytology (co-testing). Moreover, this statement also included recommendations against cervical cancer screening for women younger than 21 years, as well as for women older than 65 years who have had adequate prior screening and are not otherwise at high risk for cervical cancer (US Preventive Services Task Force, 2018). On 2014, the Medical Services Advisory Committee (MSAC) of Australian Government announced its recommendations for a renewed National Cervical Screening Program. These recommendations included 5-yearly cervical screening of HPV-vaccinated and unvaccinated women aged 25-69 years, using a primary HPV test with partial HPV genotyping and reflex liquid-based cytology (LBC) triage, followed by exit testing of women aged 70-74 years. These recommendations were accepted, and the renewed screening program commenced on 1 December 2017 (Australian Institute of Health and Welfare 2019).

In conclusion, it is established that both Papanicolaou test and HPV-DNA test are reliable screening tests which increase safety in patient management. Despite their respective advantages and disadvantages, as well as the screening policy applied, they are proven to be effective and are rightfully being used as presymptomatic population screening tests. What remains to be scientifically proven is whether regular repeats of these screening tests every 3 years (or less frequently) should be detached from annual preventive gynaecological examinations.

BREAST CANCER

Breast cancer is the most common type of cancer and the leading cause of death among women worldwide. Approximately 13% of women (1 in 8) will be diagnosed with invasive breast cancer in their lifetime. In 2018, breast cancer represented 11.6% of all cancers in terms of incidence which was statistically

equal to the lung cancer incidence and ranked a co-number 1. Deaths-wise, breast cancer's share at the same year was at 6.6% of all cancer-related deaths worldwide and ranked number 1 for women. Over the most recent 5-year period (2012-2016), the breast cancer incidence rate increased slightly by 0.3% per year, largely because of rising rates of local stage and hormone receptor-positive disease. In 2019, approximately 268,600 new cases of invasive breast cancer will be diagnosed among US women, and 41,760 women will die from this disease. Eighty-two percent of breast cancers are diagnosed among women aged ≥50 years, and 90% of breast cancer deaths occur in this age group. As of January 1, 2019, there were more than 3.8 million women with a history of breast cancer living in the United States. This estimate includes more than 150,000 women living with metastatic disease, three-quarters of whom were originally diagnosed with stage I, II, or III breast cancer (DeSantis E.C. et al., 2019). As expected, the best prognosis for breast cancer is reported comes along with a diagnosis at an early stage and when the cancer has not yet metastasized. In 2018, it was estimated that a majority of cases (62%) are diagnosed when they have not yet metastasized, and such patients have a 5-year survival rate of 99%. The patients with invasive breast cancer have 5-year survival rate of 90% and a 10-year survival rate of 83%. The improvements in survival rates have been documented for women representing all major racial groups but they remain about 10% lower in African American women, compared to the white Caucasian women. The reasons behind these racial disparities are not well-understood and a number of molecular as well as epigenetic factors are currently under investigation (Coughlin S.S. et al., 2019).

Breast cancer is a multifactorial disease and various factors contribute to its occurrence. Although the disease occurs all over the world, its incidence, mortality, and survival rates vary considerably among different parts of the world. A lot of factors are being investigated to explain these differences in rates and trends in various countries and populations. These risk factors include nonmodifiable factors such as race, ethnicity, and genetics, as well as modifiable exposures related to diet, physical inactivity, exogenous hormones, and certain female reproductive factors. Mutation in BRCA1 and BRCA2 have been investigated for long time and are risk factors for breast cancer. Other risk factors include changes in menstruation (early menarche age and delayed menopause), reproduction (late age at first birth), hormonal and alcohol intake and obesity. Breastfeeding and physical activity, on the contrary, are protective factors against breast cancer. Risk and protective factors related to breast cancer are presented in Table 3 (Momenimovahed Z. et al., 2019).

Breast cancer screening programs are considered among the most successful cancer screening strategies. The main diagnostic method, which serves as the cornerstone of breast cancer screening strategies is mammography, while breast ultrasound and MRI are used as screening tests among high risk groups of patients.

According to the official guidelines published in 2015 by American Cancer Society (Oeffinger K.C. et al., 2015), it is highly recommended that women at moderate risk for developing breast cancer should undergo screening mammography on a regular, periodic basis after the age of 45 years (strong recommendation), while they should be offered the opportunity to start annual screening between the ages of 40 to 44 years. Screening mammography should be repeated annually between the ages 45 to 54 years and for women over 55 years of age with normal previous mammogram results, it is acceptable to be repeated every two years. It should be emphasized that inclusion in this screening strategy is acceptable until the age that life expectancy is considered to exceed 10 years. On the contrary, clinical breast examination is not recommended as a screening method for women at moderate risk of any age.

Table 3. Factors related to breast cancer

Factors		Protective	Predisposing
DEMOGRAPHIC	Age		✓
	Female gender		✓
REPRODUCTIVE	Late-age of menopause		✓
	Full-term pregnancy	✓	
	Ovulatory menstrual cycle	✓	
HORMONAL	Hormonal contraceptive methods		✓
	Postmenopausal hormone therapy		✓
GENETIC	Positive family history		✓
	BRCA mutations/other genetic factors		✓
BREAST RELATED	Lesser lactation duration	✓	
	Benign breast disorders		✓
LIFESTYLE	Obesity and overweight		✓
	Alcohol consumption		✓
	Smoking		✓
	Unhealthy diet		✓
	Vitamin D sufficiency	✓	
	Physical activity	✓	
OTHER	Low socioeconomic status		✓
	Diabetes mellitus		✓
	History of radiation exposure		✓

More specifically, two meta-analyses of prospective randomized studies demonstrated that after 13 years of screening, breast cancer mortality rate decreased by 18-20% (Independent UK Panel on Breast Cancer Screening, 2012; Tonelli M. et al., 2011). Respectively, studies comparing breast cancer mortality rate before and after screening policies application resulted that it is decreased by 28-36% (Broeders M. et al., 2012). According to UK Independent Review, for every 180 women attending regular screening, one breast cancer case per decade is prevented. Regarding the rate of false positive diagnosis, Hubbart et al. concluded that it varies between 61.3% (for annual screening) and 41.6% (for biennial screening) (Hubbart R.A. et al., 2011), but there are not properly weighed studies offering overdiagnosis rates of breast cancer, in order to support modifications of current screening strategies (Oeffinger K.C. et al., 2015).

Breast ultrasound is the diagnostic method of choice for women under 35 years of age, as it is considered comparatively superior in visualizing breasts with a higher proportion of glandular tissue. The combination of breast ultrasound and mammography significantly increases the sensitivity and specificity of mammography, from 57-90% and 60-90% respectively to approximately 95% [30]. However, combined breast ultrasound and mammography is not commonly applied in screening programs, mainly due to its high cost.

Official guidelines by scientific associations converge that clinical breast examination is not proven to contribute significantly in the prevention of breast cancer. On the contrary, there are indications that it increases false-positive rate when it is combined with mammography. Respectively, it is not scientifically proven that regular breast self-examination leads to earlier detection of breast cancer when it is combined with screening imaging methods and it is not officially recommended as a screening test.

Magnetic resonance imaging (MRI) is officially recommended by American Cancer Society (ACS) (Saslow D. et al., 2007) as an annual screening test for BRCA mutation carriers, first-degree relatives of BRCA mutation carries, women with lifetime breast cancer risk above 20% according to current prediction models. The aforementioned recommendations rely on evidence-based medical research. Moreover, MRI is recommended by expert consensus for women with history of radiation to chest between age 10 and 30 years, Li-Fraumeni, Cowden and Bannayan-Riley-Ruvalcaba syndrome carriers and first-degree relatives. Although the exact age of screening commencement is under discussion, it is a common practice to start screening five years before the age of the earliest diagnosis of breast cancer in the family.

In conclusion, mammography is proven to be an effective general population screening test for breast cancer and its combination with breast ultrasound is followed by increased diagnostic accuracy, but it is not yet officially recommended as a screening test. Magnetic resonance imaging is recommended for women in high risk for developing breast cancer. Further research is necessary in order to examine the possible contribution of clinical breast examination in breast cancer prevention.

GENERAL CONCLUSIONS

Despite the large number of available diagnostic methods and the combinations between them, there is no sufficient scientific evidence for the majority of them in order to validate their establishment as screening tests. Cervical cytology and HPV-DNA test are scientifically proven to be reliable screening tests and their inclusion in cervical cancer screening strategies is strongly recommended. Respectively, mammography as a general population screening test and magnetic resonance imaging as a screening test for high-risk women are strongly recommended for the prevention of breast cancer. Although there is a great number of studies supporting the diagnostic value of transvaginal ultrasound in early diagnosis of both endometrial and ovarian cancer, it is not officially recommended by scientific societies as a screening method for secondary prevention of these types of cancer. Last but not least, more prospective studies are required to assess the value of bimanual pelvic examination and clinical breast examination in prevention and early detection of gynaecological cancer.

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Chapter 4
High-Risk Patients for Gynaecological Cancer:
What Is the Optimal Clinical Approach?

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ABSTRACT

Patients at high risk for gynaecological cancer consist of a specific category of patients in which clinical, imaging, and laboratory surveillance may actually be differentiated compared with low-risk patients. The chapter aims to summarize current evidence and recommendations regarding optimal clinical management of high-risk patients for all forms of gynaecological cancer, namely cervical cancer, endometrial cancer, ovarian cancer, and breast cancer. Furthermore, it aims to approach critically the need for estimating cost-benefit of all preventative modalities along with discrepancies in existing guidelines.

CERVICAL CANCER

Cervical cancer is one of the most studied gynecological malignancies. It is particularly common in developing countries in Africa and Latin America, and its frequency has declined significantly (up to 60%) over the last few decades in Western countries. Early onset of sexual activity and a high number of sexual partners are factors that increase the risk of cervical cancer. Today it is known that about 99.7%

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of cases of cervical cancer are due to infection with one of the high risk human papilloma virus (HPV). High risk subtypes 16 and 18 are the most common and are responsible for about 70% of cases. However, the virus alone does not cause cancer, but other risk factors are also required such as smoking, immune deficiency, infection and other viruses and poor nutrition.

Population screening for cervical cancer includes Pap smear cytology test and HPV test. According to the guidelines of the American Society of Colposcopy and Cervical Pathology, women with a medium risk of developing cervical cancer are recommended to have a Pap smear cytology test every 3 years between 21-29 years of age, with an HPV test for women above 25 years of age. In women aged 30-65 years, it is recommended to perform a simultaneous Pap smear and HPV test every 5 years. If this is not possible, a Pap smear test is recommended at least every 3 years. Screening for cervical cancer may be discontinued at 65 years old, if three consecutive Pap smear tests have been negative or if two Pap smear and HPV tests are negative (Saslow et al., 2012).

Women at high risk for cervical cancer should follow closer screening programs. Women at high risk for cervical cancer are those who have undergone a solid organ or bone marrow transplantation, HIV-infected women, women exposed in uterus to diethylstilbestrol (DES), women with personal history of dysplasia or cervical cancer, and women with immune suppression of any etiology (Vegunta, Files, & Wasson, 2017).

Transplantation of a Solid Organ or Bone Marrow

Women who have undergone a solid organ transplantation, especially bone marrow, have a reduced ability to cope with HPV infection. This may be due either to immunosuppressive drugs administered either to prior chemotherapy and/or radiation. Women who have undergone a kidney transplantation have an increased risk of dysplasia in the cervix and anus. They have a 50-fold greater risk of developing vulvar cancer and a 15-fold increased risk of developing cervical cancer. These women are suggested ideally prior to transplantation to perform both Pap smear and HPV testing. They should also be vaccinated against HPV. Post-transplantation should be more regularly screened for vulvar, vaginal and anal cancer by annual gynecological examination. Ideally, a Pap smear and HPV test is recommended every 3 years, and if duplicate testing is not feasible, the annual Pap smear cytology test is acceptable. The purpose of more regular screening is the early detection of low-grade dysplasia and the avoidance of progression to high-grade dysplasia and invasive carcinoma.

HIV Infection

Women infected with human immunodeficiency virus (HIV) are at a higher risk for HPV infection and a reduced ability to cope with immunosuppression. The result is an increased risk for dysplasia of the cervix and cervical cancer. In women with acquired immune deficiency syndrome (AIDS) it is estimated that the average development time of a CIN3 lesion in invasive cervical cancer is 3.2 years, as opposed to 5-7 years for middle-aged women. In HIV-infected women, the first Pap smear cytology test should be performed in the first year after the first sexual intercourse and not later than 21 years, followed by a Pap smear cytology test every 3 years to 29 years of age. In women aged 21-29 years, with a newly diagnosed HIV infection, an annual Pap smear cytology test should be performed. If 3 consecutive examinations are negative, it is recommended to perform a Pap smear cytology test every 3 years. In women aged over 30 years with newly diagnosed HIV infection it is recommended to perform a simultaneous Pap

smear cytology test and HPV test at diagnosis. If the results are negative, it is recommended to repeat the double screening every 3 years, and if the HPV test is not feasible, the annual Pap smear cytology test is acceptable. If 3 consecutive tests are negative, the screening can be made every 3 years. Women in this group should perform a Pap smear cytology test after the age of 65 years.

In Uterus Exposure to Diethylstilbestrol (DES)

Women exposed in uterus to diethylstilbestrol are at high risk for developing vaginal clear cells carcinoma and cervical adenocarcinoma. These women have a wider transition band and an increased incidence of dysplasia in the cervix. The risk is greater in adolescence with a peak of 25 years and lasts up to 39 years. This group is proposed to perform a first Pap smear cytology test one year after the first sexual intercourse and not later than 21 years until the age of 29 years. After 30 years of age, it is ideally recommended a simultaneous screening with a Pap smear cytology test and HPV test every 3 years. If this is not feasible, the annual Pap smear cytology test is acceptable. If a woman is hysterectomised for a benign cause, it is ideally recommended to perform a double check of the vaginal cuff every 3 years. If this is not feasible, the annual Pap smear cytology test of vaginal truncation is acceptable.

Personal History of Dysplasia or Cervical Cancer

The incidence of invasive cervical carcinoma increases 2.8 times in women already treated for cervical dysplasia (CIN2, CIN3) or in situ adenocarcinoma of the cervix. This risk is independent of treatment (hysterectomy, ablative or catastrophic cervical interventions) and remains significant for the first 10 years, then decreases to 20 years. These women also have an increased risk for intraepithelial neoplasia of the vagina and vaginal carcinoma and should be routinely screened for at least 20 years after their treatment. Particularly at the age of 21-29, it is recommended to perform a Pap smear cytology test every 3 years. In case of hysterectomy vaginal cuff should be checked, by Pap smear cytology test and HPV test every 5 years. If this is not feasible, Pap smear cytology test every 3 years is acceptable. In women aged over 30 years with or without hysterectomy, a double check by Pap smear cytology and HPV testing is recommended every 5 years, while Pap smear cytology test every 3 years is acceptable.

Immunosuppression of Any Etiology

Women with autoimmune diseases, such as systematic lupus erythematosus and inflammatory bowel diseases, may have immune deficiency and receive immunosuppressive drugs. These women, as well as women with primary immunodeficiency, are at greater risk for developing cervical cancer associated with HPV infection. This group is proposed to perform a first Pap smear cytology test one year after the first sexual intercourse and not later than 21 years until the age of 29 years. After 30 years of age, it is ideally recommended to perform a double check with a Pap smear cytology test and HPV test every 3 years. If this is not feasible, annual Pap smear cytology test is acceptable. If a woman has undergone a hysterectomy for a benign cause, it is not recommended to screen vaginal cuff. However, if a woman with immunodeficiency has undergone hysterectomy for severe dysplasia or cervical cancer, it is ideally recommended to perform Pap smear cytology test and HPV test of the vaginal cuff every 3 years. Annual Pap smear cytology test of the vaginal cuff is also acceptable for 20 years post hysterectomy.

Endometrial Cancer

Endometrial cancer is the fourth most common cancer among women in developed countries. Each year approximately 7400 new cases are reported in the UK and 88068 new cases in the European Union. More than 90% occurs in women over the age of 50, with an average age of 63 years. Histopathologically, there are two types of endometrial cancer. Type I (80%) includes endometrial adenocarcinoma, endometriotic type and grade 1 and 2. This type is characterized by good prognosis and is estrogen-dependent. Type II (10-20%) includes endometrial adenocarcinoma endometriotic type grade 3 and non-endometriotic types (serous, papillary, clear cells, mesonephric, undifferentiated). This type is characterized by a poor prognosis and is not related to estrogen.

Risk factors for endometrial cancer are summarized in Table 1. A main risk factor for endometrial cancer is prolonged exposure to endogenous or exogenous estrogens. Thus, exogenous administration of estrogens systematically without the progestogen's protective action, infertility, early menstruation, late menopause, anovulatory cycles are important risk factors due to the greater effect of estrogens on the endometrium. Endometrial hyperplasia is accompanied by an 8% transformation risk when it is not associated with atypia and 29% when there is atypical endometrial hyperplasia. From woman's personal history, risk factors are advanced age, obesity, hypertension and diabetes mellitus, estrogen-producing tumors as well as the anticipated irradiation of the pelvis (American College of Obstetricians and Gynecologists (ACOG), 2015; Colombo et al., 2016; Kitson, Evans, & Crosbie, 2016; Suri & Arora, 2015).

Table 1. Risk factors for endometrial cancer

Risk Factor	Relative Risk
Age	50-70 years old 1.4% lifetime risk
Estrogens administration	2 - 10
Late menopause	2
Infertility	2
Polycystic Ovary Syndrome	3
Obesity	2 - 4
Diabetes mellitus	2
Endometrial hyperplasia without atypia	8% transformation risk
Atypical endometrial hyperplasia	29% transformation risk
Lynch syndrome	22-50% lifetime risk
Tamoxifen administration	2
Early menstruation	N/A
Estrogen-producing tumors	N/A
Familiar history	N/A

Tamoxifen administration in women aged over 50 years, for breast cancer treatment, is also associated with an increased risk of developing endometrial hyperplasia and endometrial cancer. However, the American College of Obstetricians and Gynecologists and the European Society of Gynecological

Cancer do not recommend any particular screening in women taking tamoxifen (ACOG, 2015; Colombo et al., 2016). Patients receiving tamoxifen need to be informed about both the potential risks and the symptoms that may indicate endometrial hyperplasia or endometrial cancer. Tamoxifen administration is also a risk factor for the development of uterine sarcoma. Several studies report a familial predisposition for endometrial cancer in women with first-degree relatives, who have a history of endometrial cancer. However, genes responsible for this phenomenon have not yet been detected. Significantly some hereditary syndromes and genes are associated with increased risk for endometrial cancer. These include Lynch syndrome (hereditary non-polyps colorectal cancer syndrome), Cowden's syndrome and BRCA genes.

Lynch's syndrome is inherited by the autosomal dominant character and is associated with mutations in the MSH2, MSH6, MLH1, PMS2 genes. These genes are integrated into microsatellite instability mutations in mismatch repair genes. Lynch syndrome is responsible for about 2-5% of cases of endometrial cancer and even younger. Women with Lynch syndrome have a 20-60% chance of developing endometrial cancer, while they are at high risk for ovarian cancer (12%), colon cancer (80%) and more rarely other organs malignancies (Colombo et al., 2016; Faubion, Maclaughlin, Long, Pruthi, & Casey, 2015; Hamilton, 2012; National Comprehensive Cancer Network (NCCN), 2018b). In 50% of cases the first manifestation of the syndrome is the diagnosis of endometrial cancer. Histologically, it is mostly endometriotic type of good prognosis and is usually diagnosed at an early stage. Asymptomatic women with Lynch syndrome are recommended to have annual screening with gynecological examination, transvaginal ultrasound and endometrial biopsy, ideally with hysteroscopy from the age of 30-35 years, or 5-10 years before the onset of Lynch-related cancers in a relative. Both transvaginal ultrasound and Ca-125 measurement and endometrial biopsy are characterized by low prognostic value. Transvaginal ultrasound and Ca-125 are of greater importance for the detection of ovarian cancer in Lynch syndrome (ACOG, 2015; Colombo et al., 2016). In women who have completed childbearing, it is possible to prophylactically recommend hysterectomy with bilateral salpingo-oophorectomy to prevent endometrial and ovarian cancer.

Women who are BRCA mutation carriers have an increased risk of developing breast and ovarian cancer. However, there are data linking mutations of the BRCA1 gene to endometrial cancer (Thompson & Easton, 2002). Prospective study data suggest that there is an increased risk of endometrial cancer only in BRCA mutation carriers, who are treated with tamoxifen (Beiner et al., 2007; Biron-Shental, Drucker, Altaras, Bernheim, & Fishman, 2006).

Cowden syndrome is an inherited autosomal syndrome characterized by a mutation in the tumor suppressor gene PTEN. Cowden syndrome is characterized by an increased risk of hamartomas and cancer in tissues such as skin, mucous membranes, endometrium (19%), breast, thyroid gland and central nervous system. With regard to the risk of endometrial cancer, women with Cowden syndrome should undergo annual transvaginal ultrasound and endometrial biopsy from age 35. Women who have completed childbearing should be proposed to perform a prophylactic hysterectomy with bilateral salpingo-oophorectomy (NCCN, 2018b; Pilarski et al., 2013).

Ovarian Cancer

Ovarian cancer is the leading cause of death from gynecological cancer. In the US in 2017, 22,440 new cases of ovarian cancer were recorded and 14,080 deaths (Siegel, Miller, & Jemal, 2017). The lifetime for ovarian cancer is 1.5%. Epithelial type accounts for 90% of cases of ovarian cancer. Other more rare types are germ cell tumors, stromal tumors, mesenchymal tumors and metastatic tumors. The incidence

of ovarian cancer increases with age and is more common during the sixth and seventh decades of life. The average age of onset of ovarian cancer is 63 years and over 70% is found at an advanced stage (Howlader N. et al, 2016).

Factors that are associated with an increased risk of ovarian cancer are advanced age, infertility, age of first pregnancy over 35 years of age, pelvic inflammatory disease, endometriosis, polycystic ovarian syndrome, use of endometrial contraceptives, hormonal replacement treatment during menopause, early menstruation as well as delayed menopause. In vitro fertilization is associated with an increased risk of developing borderline tumors in the ovary. Smoking is associated with an increased risk of epithelial ovarian cancer and a reduced risk of clear cell ovarian carcinoma. A personal or family history of breast cancer is a risk factor for the development of ovarian cancer. However, in most of these cases, there appears to be a gene mutation (Gates, Rosner, Hecht, & Tworoger, 2010; Salehi, Dunfield, Phillips, Krewski, & Vanderhyden, 2008). Heredity appears to play an important role in ovarian cancer. In 5-10% of cases, ovarian cancer is inherited. Most cases are attributable to mutations of the BRCA1 and BRCA2 tumor suppressor genes. These are located in chromosomes 17 and 13 respectively and are inherited by the dominant character. Women with a mutation in the BRCA1 gene have a life-time risk of 40-60% for ovarian cancer and women with a mutation in the BRCA2 gene have a life-time risk of 16-27%. Lynch's hereditary syndrome (non-polyps colorectal cancer) is associated with genes responsible for repairing DNA damage as mentioned above. The carriers of the syndrome have a lifetime risk of 12% for ovarian cancer. Risk factors for ovarian cancer are depicted in Table 2.

Table 2. Risk factors for ovarian cancer

Advanced age	Polycystic Ovaries Syndrome
Pelvic inflammatory disease	Smoking
Infertility	Personal or family history of breast cancer
Endometriosis	BRCA1,BRCA2 mutation carriers
Menopause hormonal treatment	Lynch Syndrome
Early menarche	Peutz-Jegher Syndrome
Late menopause	IVF (Borderline tumors)

According to the international literature, screening by transvaginal ultrasound and Ca-125 measurement for ovarian cancer is not recommended in general population, as this increases the risk of unwarrantable surgical procedures. However, patients with an increased risk of ovarian cancer, such as a strong family history of breast and ovarian cancer, BRCA1 and BRCA2 gene mutation carriers as well as women with Lynch syndrome should undergo regular gynecological examination, transvaginal ultrasound and Ca -125 measurement, as well as other indicators. The interval to be addressed is not clearly defined. However, the American College of Obstetricians and Gynecologists and the National Comprehensive Cancer Network (ACOG, NCCN) suggest that screening should be performed for BRCA mutation carriers from the age of 30-35 years or 5-10 years before the onset of cancer in the closest relative by performing transvaginal ultrasound and Ca-125 measurement every 6-12 months. Even in this case, the usefulness of screening for the early diagnosis of ovarian cancer is controversial by various studies. The role of human epididymis protein (HE4) in the early diagnosis of ovarian cancer has been examined by

several studies. A prophylactic bilateral oophorectomy with or without hysterectomy should be suggested in high risk women for ovarian after completing their childbearing, as it reduces the risk of developing ovarian cancer by 80% and breast cancer by 30-75%. However, even in this case the risk of peritoneal carcinomatosis is not eliminated (Eleje GU & Okonkwo, 2018; Tobacman et al., 1982).

Breast Cancer

Breast cancer is a major public health problem. The chance that a woman develops breast cancer in the US is estimated at 12.6%, 1 in 8 lifetime risk (up to 110 years). However, over 80% of cases occur in women over 50 years of age. Incidence varies geographically among the populations, with the highest rates in western countries (> 100 cases/100,000 women) and lower rates in Asia (10-15 cases/100,000 women) (Κρεατσάς, 2009).

Risk factors for breast cancer are female gender, advanced age, family history, hereditary breast cancer, as 5-10% of new cases of breast cancer carry mutations in the BRCA1 and BRCA2 genes (Bernstein & Ross, 1993; Lilienfeld, 1956; Wu et al., 2002). From the reproductive history, early menstruation, late menopause, infertility and advanced age of first childbirth are risk factors for breast cancer. Also, breastfeeding appears to be protective with a 4% reduction in risk for every 12 months of breastfeeding (Collaborative Group on Hormonal Factors in Breast Cancer, 2002). The risk of developing breast cancer increases with high estrogen levels (Collaborative Group on Hormonal Factors in Breast Cancer, 1996; Eliassen, Missmer, Tworoger, & Hankinson, 2006; Key, Appleby, Barnes, & Reeves, 2002). Use of contraceptive tablets appears to cause a small increase in risk after long-term administration. This risk appears to be subdued within ten years of discontinuation of tablets. Hormone replacement therapy with a combination of estrogen and progestogen appears to significantly increase the risk of developing breast cancer by 30-45% over five years according to one meta-analysis (Collaborative Group on Hormonal Factors in Breast Cancer, 1997). From another study involving 1,900 breast cancers, it appeared that, except that the risk was greater after over five years of use, the risk was greater with the use of a combination of estrogen and progestogen compared with using only estrogen (Graham A Colditz, 2005). It appears that, contrary to the protective role of progesterone in the endometrium, its role in the breast is exactly the opposite (G A Colditz et al., 1995). Increased alcohol consumption, in uterus exposure to diethylstilbestrol (DES) and obesity also appear to increase the risk for breast cancer (Hamajima et al., 2002). Several benign breast conditions such as intraductal papilloma, sclerosing adenosis, and moderate hyperplasia of the usual type are also risk factors as well as irradiation of the breast (Boyd et al., 2007). Increased breast density in mammography is the second most important risk factor for breast cancer after a strong family history. Women with dense breasts show a four times higher risk than others. It is also known that the density increases in 25-30% of women starting hormone replacement therapy, and that the opposite occurs when they are treated with tamoxifen or raloxifene. Also, despite the relationship between the hormonal environment and the density of the breasts, it is argued that increased breast density is an independent risk factor (Δίνας Δ.Κωνσταντίνος, 2014). Conditions that increase the risk of breast cancer include the presence of hyperplasia of the pore or lobes of the breast with coexisting atypia. In this case, the risk increases by 4-5 times compared with the general population. Moreover, the existence of an in situ lobular breast cancer increases (LCIS) the risk of breast cancer in both breasts. Risk factors for breast cancer are presented in Table 3.

Table 3. Risk factors for breast cancer

Female gender	High breast density
Advanced age	Elevated estrogens levels
Infertility	Obesity, Alcohol consumption
Family history of breast, ovarian and peritoneal cancer	Personal history of breast, ovarian and peritoneal cancer
Benign breast disorders (intraductal papilloma, sclerosing adenosis, and moderate hyperplasia)	BRCA1(60-80%), BRCA2(40-80%) mutation carriers
Menopause hormonal treatment	Li-Fraumeni Syndrome
Hormonal contraception	Cowden Syndrome
Early menarche	Peutz-Jegher Syndrome
Late menopause	LCIS
Radiotherapy to the chest between age 10 and age 30	In utero DES exposure

Regarding the risk of breast cancer in women with a positive family history or known BRCA1 and BRCA2 gene mutations compared with the general population, data are summarized in Table 4.

Table 4. Risk for breast cancer

	Percent of Population	**Percent of All Breast Cancer Cases**	**Average Risk of Breast Cancer to Age 70**
Positive family history breast cancer (first degree relative)	~ 10%	15-20%	10-13%
Positive BRCA1 or BRCA2 mutation	~ 0.1%	5-6%	50-85%
General population without positive family history or BRCA mutation	~ 90%	80-85%	7%

(G A Colditz et al., 1993)

Positive family history in a first-degree relative increases the risk of breast cancer by 2.6 times. However, when two or more first degree relatives have a history of breast cancer, then the risk increases up to 50 times. In these cases mutations are usually present in tumor suppressor genes BRCA1 and BRCA2. Mutations in these genes are more common in women of the Ashkenazi Jewish race. BRCA mutation carriers often have breast cancer of young age as well as bilateral breast cancer. A mutation in the BRCA1 gene is associated with a 60-80% risk of breast cancer, whereas a mutation in BRCA2 is associated with a 40-80% risk of breast cancer. Mutations in the BRCA1/2 genes are responsible for 90% of the familiar breast-ovarian cancer. Mutations in the BRCA2 gene are considered responsible for 35% of multiple cases of breast cancer in families. BRCA2 gene mutation is also associated with breast cancer in men, prostate cancer, pancreas cancer and malignant melanoma (Jemal, Siegel, Xu, & Ward, 2010; NCCN, 2018a). BRCA1/2 gene mutation carriers should be encouraged to breastfeed, maintain normal body weight and avoid alcohol consumption and use of hormone replacement therapy. In addition, they should

be screened at an early age and should be informed from an early age for early breast cancer symptoms. Specifically, women with BRCA1/2 mutation should undergo breast clinical examination every 6-12 months from the age of 25, breast MRI every year from the age of 25, and digital mammography every year from the age of 30. Breast ultrasound can be used in addition to digital mammography at any age, as well as in cases, where breast mammography is not possible. Prophylactic administration of selective estrogen receptor modifiers (tamoxifen, raloxifene) and aromatase inhibitors is under investigation as the data is still limited. Risk-reducing prophylactic mastectomy is the most effective measure to prevent breast cancer in BRCA1/2 mutation carriers, as it reduces the risk of developing breast cancer up to 90% (Paluch-Shimon et al., 2016).

Multiple hamartoma syndrome (Cowden syndrome) is characterized by a mutation in the PTEN gene, inherited with autosomal dominant character and associated with an increased risk of breast (25-50%) and endometrial cancer (10%). With regard to screening, breast clinical examination is recommended every 6-12 months from the age of 20-25 years and breast MRI and/or digital mammography from 30 to 75 years of age. Prophylactic bilateral mastectomy should be discussed with female carriers of this mutation (NCCN, 2018a; Paluch-Shimon et al., 2016).

Li-Fraumeni syndrome, characterized by a mutation in the TP53 gene, is inherited by the autosomal dominant character and is associated with an increased risk of breast cancer under the age of 45 years. In women who are carriers of the syndrome, breast clinical examination is recommended from the age of 20 years and an annual MRI is recommended from the age of 20 to 75 years. If magnetic resonance imaging is not feasible, digital mammography is acceptable. Prophylactic bilateral mastectomy should be discussed with female carriers of this mutation (NCCN, 2018a; Paluch-Shimon et al., 2016).

Peutz-Jeghers syndrome is characterized by a mutation in the STK11 gene and is associated with an increased risk of breast cancer. With regard to screening, breast clinical examination is recommended every 6-12 months from the age of 20-25 years and an annual magnetic resonance imaging (MRI) from the age of 20-29 years. MRI and/or digital mammography is recommended from the age of 30 to 75 years. Prophylactic bilateral mastectomy should be discussed with female carriers of this mutation (NCCN, 2018a; Paluch-Shimon et al., 2016).

Hereditary Diffuse Gastric Cancer Syndrome (HDGC) is characterized by a mutation in the CDH1 gene and is associated with an increased risk of developing lobular breast cancer (40-50%). Clinical examination of the breast is recommended every 6-12 months from the age of 20-25 years and annual MRI from the age of 20-29 years. MRI and/or digital mammography is recommended from 30 to 75 years of age. Prophylactic bilateral mastectomy should be discussed with female carriers of this mutation (Paluch-Shimon et al., 2016).

Hereditary pancreatic cancer syndrome, which is characterized by a mutation in the PALB2 gene, is associated with an increased risk of developing breast cancer by 2-4 times the general population. Regarding to the screening, breast clinical examination is recommended every 6-12 months from the age of 20-25 years and annual MRI from the age of 20-29 years. MRI and/or digital mammography is recommended from 30 to 75 years of age. Prophylactic bilateral mastectomy should be discussed with female carriers of this mutation (Paluch-Shimon et al., 2016).

Updated criteria for hereditary cancer risk evaluation according to National Comprehensive Cancer Network (NCCN) are summarized below (NCCN, 2016):

An individual with breast cancer (including invasive and ductal carcinoma) with any of the following:

- A known mutation in the family of a gene that increases cancer susceptibility

- Breast cancer diagnosed ≤50 years
- Triple-negative breast cancer diagnosed ≤60 years
- Two breast cancers (in a single patient)
- Breast cancer diagnosed at any age, in addition to one of the following:
  - ≥1 close blood relative with breast cancer diagnosed ≤50 years, or
  - ≥1 close blood relative with ovarian, fallopian tube, or primary peritoneal cancer diagnosed at any age, or
  - ≥2 close blood relatives with breast, pancreatic, and/or prostate cancer (Gleason score ≥7) diagnosed at any age, or
  - From a population at increased risk
- Male gender

A patient of Ashkenazi Jewish descent with breast, ovarian, or pancreatic cancer diagnosed at any age
Personal and/or family history of three or more of the following:

- Breast, pancreatic, prostate (Gleason score ≥7), diffuse gastric, colon, endometrial, thyroid, or kidney cancer, melanoma, sarcoma, adrenocortical carcinoma, brain tumors, or leukemia, particularly early onset (and can include multiple primary cancers in the same individual) and/or
- Dermatologic manifestations consistent with Cowden syndrome and/or
- Macrocephaly, hamartomatous polyps of gastrointestinal (GI) tract

Personal history of ovarian cancer
An individual with no personal history of cancer but with:

- A close relative with any of the following:
  - A known mutation within the family of a gene that increases susceptibility to cancer
  - ≥2 breast cancers in a single individual
  - ≥2 individuals with breast cancers on the same side of family with at least one diagnosed ≤50 years
  - Ovarian cancer
  - Male breast cancer
- First- or second-degree relative with breast cancer diagnosed ≤45 years

It is noteworthy, that there are tools for assessing the risk of breast cancer, on the basis of which decisions can be made about the starting age and the type of screening. The most widespread tool is Gail's model from the inventor's name from the National Institute of Cancer, which takes into account various parameters of the woman's personal and family history (age, menstruation age, age of first birth, first-degree relatives with breast cancer, prior breast biopsy and ethnicity/race). It estimates the risk of developing breast cancer for the next 5 years risk and lifetime risk (M H Gail et al., 1989; Mitchell H Gail, 2015). It is noteworthy, that Gail model is intended for women who have never had a diagnosis of breast cancer, ductal carcinoma in situ (DCIS), or lobular carcinoma in situ (LCIS) and who do not have a strong family history suggesting inherited breast cancer (Rockhill, Spiegelman, Byrne, Hunter, & Colditz, 2001; Tice et al., 2008).

However, Gail model has some important limitations. It is not useful for women with strong family history of breast and/or ovarian cancer, such as for older women with competing risks of noncancerous death. Furthermore, it is not applicable to women with more than two first-degree relatives with breast cancer, it does not consider more distant relatives, the age at which relatives developed breast cancer, or a family history of ovarian cancer, and it is not useful for women with a strong family history of breast cancer on the paternal side. In women who have strong family histories, other models may be more useful. Finally, Gail model does not estimate the risk of carrying a *BRCA1* or *BRCA2* gene mutation.

For women with strong history of familiar breast, ovarian, tubal or peritoneal cancer other predictive models have been developed. US Preventive Services Task Force (USPSTF) recommends other screening tools for these women who are in high risk for breast cancer. These five recommended models are:

- Ontario Family History Risk Assessment Tool (Gilpin, Carson & Hunter, 2000)
- Manchester scoring system (Evans et al., 2004)
- Referral Screening Tool (Bellcross, Lemke, Pape, Tess, & Meisner, 2009)
- Pedigree Assessment Tool (Hoskins, Zwaagstra, & Ranz, 2006)
- Family History Screen (FHS-7)

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Chapter 5
Short and Long-Term Follow-Up of Women After Treatment for Primary Gynecological and Breast Cancer

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ABSTRACT

More than 100,000 cases of gynecologic cancer are diagnosed every year in the USA. Women who survived primary treatment for gynecologic cancer are estimated at more than 8 million and are likely to increase at about 10 million in the coming decade. It is obvious that there is a growing population group that needs a proper care by a team of health professionals. Post-treatment monitoring of gynecologic cancer survivors ideally has to achieve three major objectives: 1) to diagnose, as early as possible, the recurrence of the disease, either local or distant; 2) to improve the quality of life of cancer survivors; and 3) to achieve all the above goals with a reasonable cost for the Health Providing Systems. In this report, the authors refer to post-treatment monitoring of women with all kinds of gynecologic cancers (endometrial, ovarian, vulvar, vaginal, and cervical) and the follow up of women after primary treatment for breast cancer.

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INTRODUCTION/EPIDEMIOLOGY

More than 100,000 cases of gynecologic cancer are diagnosed every year in USA (Faubion et al., 2015). Women that survived primary treatment for gynecologic cancer are estimated to more than 8 million (Miller et al., 2016) and are likely to increase at about 10 million in the coming decade (Table 1). Breast cancer, together with lung cancer, are the most common types of cancer in women population in the US (American Cancer Society 2017-2018).

It is obvious that there is a constantly growing population group that needs a proper care by a team of health professionals.

Post treatment monitoring of gynecologic cancer survivors ideally has to achieve three major objectives: 1) to diagnose, as early as possible, the recurrence of the disease, either local or distant, 2) to improve the quality of life of cancer survivors, and 3) to achieve all the above goals with a reasonable cost for the Health Providing Systems.

In this report, we will refer to post-treatment monitoring of all kinds of gynecologic cancers including endometrial, ovarian, vulvar, vaginal and cervical. The type of tests, imaging modalities (ultrasound scans, CT scans, MRI scans) and time intervals are mostly based on the guidelines published by the Society of Gynecologic Oncology in 2017 (Salani et al., 2017). The guidelines emphasize, though, the importance of clinical examination in the early diagnosis of disease recurrence (Salani et al., 2017).

There is also a chapter regarding the monitoring of women after treatment for breast cancer, although it may be found as a separate chapter in other textbooks.

Cancer of the Cervix of the Uterus

Almost 70-80% of recurrence cases will be apparent in the first 2 -3 years after primary treatment (Elit et al., 2010). Symptoms that indicate the possibility of disease recurrence include vaginal discharge, vaginal bleeding, pelvic pain, cough and weight loss (Salani et al., 2017).Patients should be informed to seek medical assistance if they experience such symptoms regardless the monitoring protocol.

The cornerstone of surveillance is physical examination of the pelvis and the vaginal vault, together with the rest of the abdomen and thorax. Most cases of recurrence will be diagnosed by clinical examination, even though women are asymptomatic. The use of Pap test should be considered annually. The tactical use of cytology with or without colposcopy should be preserved for women treated with radiation or in cases of radical trachelectomy (Salani et al., 2017). The use of HPV DNA test has not been studied yet. Routine use of imagining modalities (CT or MRI scan) is not indicated unless there is clinical suspicion or symptoms of disease recurrence (Table 2) .

Cancer of the Vulva

Vulvar cancer represents 4% of gynecological cancers attributed to HPV infection from 30 to 69% of cases. More than 50% of recurrence will appear locally within the first year of treatment although there are reports of recurrence after five years from the initial treatment (Salani et al., 2017). Thorough clinical examination of the vulva and groin is the cornerstone of surveillance (Table 2).

Cancer of the Vagina

Primary cancer of the vagina is extremely rare and in most cases HPV infection is the cause. SGO suggests the same algorithm of surveillance with the cases of vulvar and cervical cancer (Salani et al., 2017), (Table 2).

CANCER INVOLVING THE UTERUS

Endometrial Cancer

Endometrial cancer is the most common type of gynecological cancer. More than 60000 women are diagnosed with the disease every year in the US (Miller et al., 2016). Symptoms involve vaginal bleeding in post-menopausal women or disturbances of the menstrual period including menorraghia and menometrorraghia, in women of reproductive age. Diagnosis is made by endometrial biopsy (Salani et al., 2017).

Recurrence is more likely to happen in those cases where the diagnose was made in advanced disease or most aggressive types of the disease such as serous or clear cell carcinoma .In many of these cases recurrence involves local invasion of the vaginal vault.

The monitoring of these patients is based on the clinical examination of the vaginal vault by speculum together with bimanual examination of the pelvis by the vagina, the rectum and the abdomen, every 3-6 months for the first two years and then annually (Salani et al., 2017).

Routine Pap test of the vaginal vault is not indicated (Rimel et al., 2015) together with the measurement of CA 125 levels, except in cases of serous carcinoma and those cases where levels of CA 125 were elevated before treatment (Salani et al., 2017).

Imaging modalities (CT, MRI scans) of the abdomen, thorax, brain should not been done on routine basis, but only when there is clinical suspicion of disease recurrence (Table 3).

Sarcomas of the Uterus

Uterine sarcomas include several types of meseghymal tumors most common of which is leiomyosarcoma (Salani et al., 2017). They have different clinical behavior and tend to give distant recurrences. Monitoring of patients treated for uterine leiomyosarcoma involves CT or MRI scans of the pelvis, abdomen, thorax or anywhere else clinically suspected every 6-12 months (Salani et al., 2017).

CANCER OF THE OVARY

Epithelial Cancer of the Ovary

Epithelial cancer of the ovary is the most lethal type of gynecological malignancy (Faubion et al., 2015). This fact could be attributed to the lack of any population screening test for ovarian cancer and also to the late appearance of clinical symptoms, usually when the disease has advanced.

After primary treatment, in a quarter to half of the cases recurrence will occur in the pelvis (Gadducci et al., 2007). A careful clinical examination of the pelvis will help the clinician recognize or suspect the relapse of the disease.

The measurement of CA125 levels has been used for a long time to detect recurrence before the appearance of symptoms. The EORTC Study has shown the use of CA 125 levels vs. clinical examination for the detection of recurrence does not improve survival rates of women treated for ovarian cancer (Rustin, & van der Burg, 2009). The SGO advises on the optional use of CA125 levels measurement (Salani et al., 2017).The SGO also advises against the routine use of imaging modalities (Salani et al., 2017). The use and the type of these tests (CT, MRI, PET/CT scan) should be individualized and used when there is clinical suspicion of disease recurrence (Table 4).

Borderline Ovarian Tumors (BOT)

Borderline ovarian tumors account 15-20% of all ovarian tumors (Ureyen et al., 2016). Those tumors tend to appear to women at younger age (young adults) and are less aggressive than epithelial tumors, having better prognosis, and recurrence rate of 5-8%. The ideal treatment in women who want to preserve fertility is not quite clear. In women that had fertility sparing operation (oophorectomy, cystectomy) the follow up includes physical examination, CA125 levels measurement every 3-6 months together with a pelvic ultrasound scan(Salani et al., 2010).If there is any suspicion of local or distant recurrence, it might be followed by a CT scan (Salani et al., 2011).Women that had radical type of surgery usually follow the algorithm for women treated for ovarian epithelial cancer (Salani et al., 2017).

Germ Cell and Stromal Tumors of the Ovary

Germ cell tumors appear at a young age (15-19 years old) with an incidence of 0,34/100000 (Koulouris & Penson, 2009). These tumors tend to produce substances that can be used as biomarkers for the diagnosis and monitoring of the disease. Elevated levels of AFP are usually found in cases of yolk sac tumors, polyembryomas, embryonic carcinomas and immature teratomas. High levels of hCG could be found in cases of choriocarcinomas and embryonic carcinomas.

Recurrence is usually diagnosed within the first two years post initial treatment. Follow up scheme should include the measurement of these biomarkers every two to four months for two years, together with clinical examination (Salani et al., 2011). The use of imaging modalities should be individualized.

The sex cord tumors account for 7% of ovarian tumors (Koulouris & Penson, 2009). Most common type is granulose cell tumor that usually produces high levels of estradiol and anti-Mullerian hormone (AMH). Monitoring of such patients includes clinical examination and measurement of biomarkers (Karkanaki & Vosnakis, et al., 2011).

Breast Cancer

More than 250000 women are diagnosed with invasive breast cancer and in to 2016 there were more than 3,5 million women in surveillance post primary treatment for breast cancer (American Cancer Society 2017-2018). Surveillance of women after primary treatment for breast cancer has to meet these objectives:

- Early diagnose of disease recurrence in the same or the healthy breast

- Early diagnose of distant metastases
- The assessment of the ovaries and uterus
- The overall assessment of well being (evaluation and treatment of side effects of primary treatment such as infertility, osteoporosis, depression)

The cornerstone of post treatment surveillance is self-examination of the breast every month, the physical examination every 3-6 months for the first 3 years (Sisler et al., 2016). The National Comprehensive Cancer Network (NCCN), the American Society of Clinical Oncology (ASCO) and the European Society for Medical Oncology (ESMO) recommend annual use of mammography14 (Piltin & Hieken 2020). All the other imaging modalities such chest X-ray, CT scan and MRI scan, are not necessary unless there is clinical indication (Sisler et al., 2016). There are some data indicating that the preoperative high tumor markers levels are associated with lower survival rates in breast cancer patients (Shao et al., 2015), and many researchers are investigating the use of several markers, such as carcinoembryonic antigen (CEA), CA 15-3 and tissue polypeptide antigen (TPA) (Piltin & Hieken, 2020). However, the advice of ESMO, ASCO and NCCN is that the measurement of tumor markers in breast cancer survivors could be considered only when there is clinical evidence of recurrent disease (Piltin & Hieken 2020).

Gynecological examination together with an ultrasound scan of uterus and ovaries is indicated, once a year, in women taking tamoxiphene. (Sisler et al., 2016)

Women taking GnRH analogues or aromatase inhibitors should measure bone density every two years.

General Considerations of Long Term Health Consequences in Patients Treated for Gynecological or Breast Cancer

Long term monitoring of patients survived gynecological or breast should also be focused in other important issues of general health of these patients and ideally in:

- Prevention of new cancers (besides recurrence of primary cancer) and health comorbidities related to cancer or to cancer treatment,
- Deployment of life-style interventions that would benefit patients general health such as weight loss, smoking cessation and physical exercise and increase their quality of life,
- Recognize and treat psychological problems of patients,
- Evaluate patient's social and economic status.

Prevention of new cancers and health comorbidities in patients survived primary treatment for gynecological cancer or breast cancer.

Prevention of New Cancers

Patients treated for cancer with chemotherapy and/or radiotherapy are at increased risk in developing secondary tumors, especially when the primary tumor was diagnosed in childhood or as a young adult (Nekhlyudov 2020). It has been reported that late effects of radiation treatment for breast cancer was associated with the development of second primary cancer (soft tissue sarcomas of the shoulder, thorax and pelvis) [American Cancer Society (ACS) / American Society of Clinical Oncology (ASCO) guidelines for breast cancer survivors, 2016]. Patients treated with alkylating agents, anthracyclines and other

agents with immunosuppressive potential are at increased risk developing leukemia and myelodysplastic syndrome (ACS / ASCO guidelines for breast cancer survivors, 2016). Women treated with selective estrogen receptor modulators (SERMs) are at increased risk of developing endometrial cancer. All women should be offered a thorough general examination by her general practitioner and have special tests (imaging modalities, blood tests) only when it is clinically indidcated. All women treated with SERMs (i.e. tamoxiphene) should be examined by a gynecologist once a year, unless the patient reports abnormal vaginal bleeding or spotting (ACS / ASCO guidelines for breast cancer survivors, 2016).

PREVENTION OF COMORBIDITIES RELATED TO CANCER TREATMENT

Cardiac Diseases

Hormonal therapy, radiation and chemotherapy have been linked with increased risk for cardiovascular disease in women treated for breast cancer; this risk is even greater in post-menopausal women (Darby et al, 2013). Women receiving epirubicin and doxirobucin have low risk in developing cardiomyopathy, and the use of trastuzumab has been linked with cardiac dysfunction (Curigliano et al, ESMO Clinical Practice Guidelines 2012). The American Cancer Society and the American Society of Clinical Oncology advices primary care physicians to take proper history and apply a thorough clinical examination but not to do routine cardiac tests, unless clinically indicated (ACS / ASCO guidelines for breast cancer survivors, 2016).

Cognitive Function

After primary treatment for breast cancer almost one in three patients report cognitive dysfunction, usually involving difficulties in concentration and memory disturbances (Von et al., 2014). The exact mechanism that breast cancer treatment impairs cognitive function is not clear, but part of it can be attributed to depression and anxiety caused by the disease itself. General practitioners should always ask their patients about cognitive dysfunction symptoms and if there is any suspicion, they should refer their patients to neurologists for further assessment (ACS / ASCO guidelines for breast cancer survivors, 2016).

Fatigue Related to Cancer

Cancer treatment related fatigue is frequently diagnosed among cancer survivors, especially those treated with radiation and/or chemotherapy (Bower et al., 2014). According to the guidelines of the American Society of Clinical Oncology gynecological cancer and breast cancer survivors should be checked by the general practitioner for fatigue annually and if there is suspicion of at least moderate fatigue they should be offered a more comprehensive assessment (including medical history, physical examination, evaluation of disease status and several tests for contributing factors for fatigue such as anaemia, cardiac dysfunction, thyroid diseases) (Bower et al, 2014).The treatment and care map of the guidelines include treatment of contributing factors, such as those that have been already mentioned, encourage physical activity and implement cognitive –behavioral treatments (Bower et al, 2014).

MYOSCELETAL DISEASES

Bone Density

The majority of women treated for breast cancer experience bone loss. Those cancer survivors might have some more contributing factors for developing osteoporosis, that are related to cancer treatment (i.e. the use of GnRH analogs for ovarian suppression, treatment with antiestrogen agents, treatment with glucocorticoids) (Gralow et al., 2013).These women may also other risk factors for developing osteoporosis such as smoking, alcohol consumption and vitamin D deficiency (Gralow et al., 2013). All postmenopausal breast cancer survivors should have a baseline dual-energy x-ray absorptiometry (DEXA) scan. General practioners should refer patients for

repeat DEXA scans every 2 years, women who are taking an aromatase inhibitor, premenopausal women who aretaking tamoxifen and/or a gonadotropin-releasing hormone (GnRH) agonist, and women who have chemotherapy induced premature menopause (ACS / ASCO guidelines for breast cancer survivors, 2016). If there is clinical suspicion or any other concern DEXA Scan should be repeated annually. General preventive strategies to maintain normal bone density include physical exercise, normal body weight, avoid smoking and alcohol consumption and in some cases the use of calcium and vitamin D supplements (Gralow et al., 2013). Pharmacological interventions should be an option in patients with established osteoporosis or in patient with high risk of bone fracture.

Arthralgias/Myalgias

Almost half of women with breast cancer, treated with aromatase inhibitors will suffer joint pain (arthralgias) or and muscle pain (myalgias) and one in five patients will have to stop or change their treatment because it is not responding to painkillers such as paracetamol or non steroid antinflamatory drugs (Henry et al., 2012).Physical excersice and acupuncture are the most effective treatments for arthralgias or and myalgias caused by aromatase inhibitors (ACS / ASCO guidelines for breast cancer survivors, 2016).

Infertility

Infertility could be a result of primary treatment in young patients (less than 45 years old).Young women diagnosed with ovarian tumors or cervical cancer are likely to have hysterectomy or/and oophorectomy as part of their initial treatment. These women should be referred to an infertility specialist prior their treatment and discuss possible management options, for example for women with early stage of cervical cancer the option of radical trachelectomy (Kasuga et al, 2016) or oocyte preservation prior to initial therapy for women with border line ovarian tumors (Fillippi et al, 2020).

Infertility could also be a consequence of chemotherapy especially for breast cancer survivors. Almost 7% of women diagnosed with breast cancer are less than 40 years old in USA (Breast cancer facts and figures 2017-2018, American Cancer Society), and it is very likely that fertility could be an important issue for them. Treatment with chemotheraputic agents, in women with breast cancer, could have as a result reduced fertility or even premature ovarian failure (Kort et al, 2014).The American Cancer Society and the American Society of Clinical Oncology advices that, women desiring pregnancy should discuss with their oncologist for the ideal time to achieve pregnancy after treatment, and also to be referred to an

infertility specialist if they have not achieved pregnancy for six months or more (ACS / ASCO guidelines for breast cancer survivors, 2016).

Sexual Dysfunction

In patients with gynecological cancers, sexual dysfunction affects almost 90% of them (Boa & Grenman, 2018). Sexual dysfunction is a term used to describe several difficulties of intercourse, involving libido, arousal, orgasm and pain. In patients with gynecogical cancer, sexual dysfunction is a result of surgical treatment together with radiotherapy leading to vaginal stenosis and severe vaginal atrophy. However other factors such as anxiety and depression can contribute to that. Sexual dysfunction is,also, a usual complaint of breast cancer survivors. In most cases it appears to be a side effect of chemotherapy or hormonal treatment with aromatase inhibitors or GnRH analogues leading to vaginal atrophy and dryness (ACS / ASCO guidelines for breast cancer survivors, 2016).The American Cancer Society and the American Society of Clinical Oncology advices general practioners to check breast cancer survivors for symptoms and signs of sexual dysfunction and to asses for reversible contributing factors. They could also offer women non hormonal vaginal lubricants for vaginal dryness. Some women might need special treatment involving group therapy, sexual counseling or intensive psychotherapy (ACS / ASCO guidelines for breast cancer survivors, 2016).

Life-style interventions that would benefit gynecological and breast cancer survivors general health

Obesity

Obesity is defined as body mass index (BMI > 30 kg/m2) is greater than 30 kg/m2.Obesity has become the epidemic of our era .In the 2009-2010 NHANES survey among women aged more than 20, 27,9% were overweight (BMI 24-29,9 kg/m^2) 35,5% were obese and 8,1% (BMI>35 kg/m^2) were extremely obese (CDC,NHANES survey 2009-2010). Obesity has been associated as a contributing risk factor for cancer development. Although the exact mechanisms, that link obesity to cancer genesis, are not clear. Several theories have been proposed such as that fat cells produce hormones which can increase cancer risk, also some obese individuals have increased levels of insulin and insulin-like growth factor which may promote carcinogenesis and obese individuals often have chronic, subacute inflammation which has been associated with greater cancer risk (National Cancer Institute .Obesity and cancer risk, 2015).

The association between obesity and cancer development has been proven for low grade endometrial cancer and ovarian cancer. At the moment there is insufficient data to link obesity, as a risk factor, with other gynecological cancers (Webb, 2020). Obesity is also a risk factor for the development of breast cancer (Rutledge and Demark-Wahnefried, 2016). The 2014 statement of the American Society of Clinical Oncology (ASCO) emphasizes that obesity is becoming the leading preventable cause of cancer overtaking tobacco (Ligibel et al., 2014).

Obesity has been also associated with increased risk of recurrence in gynecological and breast cancer patients. Although there is indicating evidence, the data are currently considered insufficient to support the link between obesity and risk of recurrence in endometrial cancer. Obesity is related to reduced survival following ovarian cancer diagnosis. The available data, at the moment are not sufficient to support any correlation between obesity and the other gynecological cancers (Webb, 2013).There is enough evidence, though, to support the relation between obesity and increased risk of recurrence in patient with breast cancer(ACS / ASCO guidelines for breast cancer survivors, 2016). Obesity has been associated

with the development of other comorbidities, such as diabetes mellitus, increased risk for cardiac or vascular incidences,in cancer survivors, which increase the overall mortality and morbidity (Rutledge & Denmark - Wahnefried, 2016).The recommendation of the American Cancer Society and the American Society of Clinical Oncology for breast cancer survivors is to achieve and maintain a normal body weight.

Maintenance of Normal Body Weight

Diet and physical activity are the major tools in order to achieve and maintain normal body weight. A lot of research has been done in the past years in order to estimate the possible benefits of diet and physical activity in cancer patients, regarding improvement of overall mortality and morbidity and also improvement of the quality of life of these patients .Most of these researches has been focused on breast cancer survivors.

Diet/Nutrition

The recommendation of the American Cancer Society and the American Society of Clinical Oncology for breast cancer survivors is to have diet high in fruits, vegetables, whole grains and legumes and low in foods containing saturated fats (ACS / ASCO guidelines for breast cancer survivors, 2016).Although there are no specific guidelines for the nutrition of gynecological cancer survivors, the general ACS guideline (Table 5.) for cancer survivors could be used (Rock et al., 2012).

Physical Activity

Physical activity, in breast cancer survivors improves quality of life (QoL), physical functioning (ACS / ASCO guidelines for breast cancer survivors, 2016).There are also data suggesting that physical activity could be beneficial in either cancer related and overall mortality in breast cancer patients (Schmid et al,. 2014).There are also data showing that exercise improves physical activity and quality of life among women with gynecological cancer (Lin et al., 2019).

The recommendation of the American Cancer Society and the American Society of Clinical Oncology for breast cancer survivors is to return to their usual activities as soon as possible, to exercise at least for 150 minutes per week or 75 minutes of intense aerobic exercise, together with two sessions of strength training per week (Table 6.). Gynecological cancer survivors could follow the American Cancer Society general guidelines for cancer survivors (Rock et al., 2012).The effects of physical exercise on diabetes and cardiovascular diseases specifically in cancer survivors have not been studied, but it is likely to have the same beneficial effects that is seen in general population (Rock et al., 2012).However there are cancer survivors that will not have the ability to exercise or this would be contraindicated (ie. patients with severe anemia, severe cardiovascular disease, compromised immunity or patients experiencing extreme fatigue).

Smoking Cessation /Alcohol Consumption

Smoking has been associated as a risk factor for development of several types of cancer among them breast cancer and gynecological cancers. Smoking has also been linked with worse overall survival in patients with breast cancer compared with patients who didn't smoke or were former smokers (Berube

et al., 2014).There is also evidence suggesting that smoking decreases survival rates among patients with ovarian cancer (Praestegaard et al, 2017) and advanced cervical cancer (Mayadev et al,, 2018). Smoking has been strongly with severe cardiovascular disease that may contribute to overall survival of cancer patients. Smoking cessation could be a preventable risk in cancer development but it could be beneficial in increasing survival rates among women with gynecological cancers or breast cancer. The recommendation of the American Cancer Society and the American Society of Clinical Oncology is that general practitioners should counsel their patients to avoid smoking or seek special help, in order to do so (ACS / ASCO guidelines for breast cancer survivors, 2016).

Increased alcohol consumption has been identified as a risk factor for cancer development. The American Cancer Society and the American Society of Clinical Oncology advices patients limit alcohol intake to one drink per day.

Psychological Disturbances

Cancer survivors often face psychological disturbances including anxiety depression and distress. The prevalence of anxiety and depression among women with gynecological cancer and breast cancer vary and this is attributed to different diagnostic approaches. Walker et al, report that depression prevalence is 10,9% in gynecological cancer patients and 9,3% among breast cancer patients (Walker et al., 2014). The American Cancer Society and the American Society of Clinical Oncology guidelines recommend general clinicians to assess breast cancer survivors for symptoms of depression, anxiety or distress and to offer primary treatment or to refer patients to a specialist.

Fiscal Difficulties

Many cancer survivors will have to carry a major fiscal burden because of primary treatment expenses, but also throughout the surveillance period. The Medical Expenditure Panel Survey, held in USA, showed that cancer survivors aged 18-64 years had nearly double medical expenses than controls and missed more working days, which led to decreased annual income (Guy Jr., et al., 2013).

CONCLUSION

The major objective of surveillance post primary treatment for gynecological and breast cancer patients is early detection of recurrence of the disease. The most helpful tool that would help us diagnose as early as possible the disease recurrence is the detailed physical examination of the patient. Patients have to be educated for those suspicious symptoms that will make them seek medical assistance, regardless of the time of their next appointment (Table 7).Clinicians should be aware of other comorbidities related to cancer itself, and to short and long term side effects of cancer treatment. The deployment of life-style interventions, including weight loss, smoking cessation and physical exercise, would possibly benefit patient's survival and increase definitely their quality of life (Table 8).

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APPENDIX

Table 1. Epidemiologic data regarding gynecological cancer in USA

Categories	Cervix	Endometrium	Ovary	Vulva
New cases per 100000 women	7,8	24,6	12,3	2,4
Deaths per 100000 women	2,3	4,3	7,9	0,5
Women living with the disease	249.632	610.804	188.867	-
Life time risk occurrence	0,7%	2,7%	1,3%	2,4%
Overall survival	67,9%	81,5%	44,6%	70,5%

Adapted from: Faubion et.al, 2015

Table 2. Algorithm of surveillance of patients after primary treatment for vulvar, vaginal and cervical cancer

Time From Treatment	Year 0-1	Year 1-2	Years 2-5	Years >5
Low risk	6 months	6-12 months	yearly	yearly
High risk	3 months	3 months	6 months	yearly
Pap test	yearly	yearly	yearly	yearly
imaging	insufficient	data to	support	routine use
recurrence	CT scans	Or	PET/CT scans	

High risk: advanced stage or high risk histology
Imaging: includes X-rays, CT scan, MRI scan, PET/CT scan, U/S scan
Adapted from: Salani et al., 2017

Table 3. Algorithm of surveillance of patients after primary treatment for endometrial cancer

Time From Therapy	Year 1	Year 1-2	Year 2-5	Year >5
Examination low risk	6 months	6-12 months	yearly	yearly
Examination high risk	3 months	6-12 months	6 months	yearly

High risk: advanced stage or high risk histology
Imaging: may include Xray, PET/CT scan, MRI scan, U/S scan
Adapted from: Salani et.al.,2017

Table 4. Algorithm of surveillance of patients after primary treatment for invasive ovarian cancer

Time From Therapy	Year 0-2	Year 2-3	Year 3-5	Year >5
examination	3-4 months	4-6 months	6 months	yearly
Pap smear	Not indicated			
CA-123	Optional			
Imaging	Insufficient data to support routine use			
Recurrence suspected	CT scans or PET/CT scans CA 125			

Adapted from: Salani et.al.,2017

Table 5. American Cancer Society Guidelines on Nutrition and Physical Activity for Cancer Survivors

Achieve and maintain a healthy weight. 1. If overweight or obese, limit consumption of high-calorie foods and beverages and increase physical activity to promote weight loss.
Engage in regular physical activity. 1. Avoid inactivity and return to normal daily activities as soon as possible following diagnosis. 2. Aim to exercise at least 150 minutes per week. 3. Include strength training exercises at least 2 days per week.
1. **Achieve a dietary pattern that is high in vegetables, fruits, and whole grains**. 2. Follow the American Cancer Society Guidelines on Nutrition and Physical Activity for Cancer Prevention.

Adapted from Rock et al. 2012

Table 6. Examples of moderate and vigorous activities

Moderate Activities	Vigorous Activities
Ballroom and line dancing	Aerobic dance
Biking on level ground or with few hills	Biking faster than 10 miles per hour
Canoeing	Fast dancing
General gardening (raking, trimming shrubs)	Heavy gardening (digging, hoeing)
Sports where you catch and throw (baseball, softball, volleyball)	Hiking uphilll Jumping rope
Tennis (doubles)	Martial arts (such as karate)
Using your manual wheelchair	Race walking, jogging, or running
Using hand cyclers (also called ergometers)	Sports with a lot of running (basketball, hockey, soccer)
Walking briskly	Swimming fast or swimming laps
Water aerobics	Tennis (singles

Adapted from Rock et al. 2012

Table 7. Symptoms that may be related to recurrence of gynecological and breast cancer

	Endometrium	Ovary	Cervix/vagina	Vulva	Breast
Local	Vaginal bleeding	Pelvic mass	Vaginal bleeding	New lesion	Palpable mass
	Vaginal mass	Abdominal mass		pruritus	
Distant	Pelvic/abdominal pain	Pelvic/abdominal pain	Urinary symptoms	Urinary symptoms	headache
	Abdominal distention	Abdominal distention	Pelvic/abdominal pain	Leg/groin pain	Back/hip pain
	cough	Change in bowel habits	cough	cough	cough
	lethargy	Weight loss	Weight loss	Weight loss	Weight loss

Adapted from Salani et al.2017(regarding gynecological cancers)
American Cancer Society.Breast cancer facts and figures 2017-2018(regarding breast cancer)

Table 8. Health promotion guideline for breast cancer survivors

Recommendation	Level of Evidence
It is recommended that primary care clinicians:	
Recommendation: Information	
(a) Should assess the information needs of the patient related to breast cancer and its treatment, side effects, other health concerns, and available support services	0 (Assessment)
(b) Should provide or refer survivors to appropriate resources to meet these needs	0 (Referral)
Recommendation: Obesity	
(a) Should counsel survivors to achieve and maintain a healthy weight	0 (Maintenance)
(b) Should counsel survivors if overweight or obese to limit consumption of high-calorie foods and beverages and increase physical activity to promote and maintain weight loss	IA, III (Weight loss)
Recommendation: Physical activity	
Should counsel survivors to engage in regular physical activity consistent with the ACS guideline, and specifically	
(a) Should avoid inactivity and return to normal daily activities as soon as possible following diagnosis	III (Avoid inactivity)
(b) Should aim for at least 150 min of moderate or 75 min of vigorous aerobic exercise per wk	I, IA (Aerobic exercise)
(c) Should include strength training exercises at least 2 d per wk; emphasize strength training for women treated with adjuvant chemotherapy or hormone therapy	IA (Strength training)
Recommendation: Nutrition	
Should counsel survivors to achieve a dietary pattern that is high in vegetables, fruits, whole grains, and legumes; low in saturated fats; and limited in alcohol consumption	IA, III (Nutrition); 0 (Alcohol)
Recommendation: Smoking cessation	
Should counsel survivors to avoid smoking and refer survivors who smoke to cessation counseling and resources	I

ACS indicates American Cancer Society. Level of evidence: I indicates meta-analyses of randomized controlled trials (RCTs); IA, RCT of breast cancer survivors; IB, RCT based on cancer survivors across multiple sites; IC, RCT not based on cancer survivors but on general population experiencing a specific longterm or late effect (eg, managing fatigue, lymphedema, etc); IIA, nonrandomized controlled trial (non-RCT) based on breast cancer survivors; IIB, non-RCT based on cancer survivors across multiple sites; IIC, non-RCT not based on cancer survivors but on general population experiencing a specific long-term or late effect (eg, managing urinary incontinence, erectile dysfunction, etc); III, case-control or prospective cohort study; 0, expert opinion, observation, clinical practice, literature review, or pilot study

Adapted from Runowicz et al. 2016, American Cancer Society/American Society of Clinical Oncology guidelines for breast cancer survivors

Section 3
Endoscopy and Reproduction

Chapter 6
Does IVF Increase Risk for Gynaecological Cancer?
What Is the Limit?

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ABSTRACT

Whether fertility treatments and in particular IVF are related to carcinogenesis in women is a rather interesting issue, which is of interest in more than one specialty. The female malignancies we refer to are mainly those of the breast, endometrium, and ovary, with breast cancer being the most common malignancy in the female population affecting 1 in 8 women worldwide; ovarian cancer is the 6th in frequency, and endometrial cancer, which is the most common gynecological cancer after breast cancer, has an incidence of 8% of all. The chapter aims to present current evidence regarding correlation between IVF treatment and risk of various gynaecological cancers.

INTRODUCTION

Whether fertility treatments and in particular IVF are related to carcinogenesis in women, is a rather interesting issue, which involves apparently more than one medical specialties. Gynecologists, surgeons, oncologists, mastologists, being some of them but certainly concerns all those involved in malignancies in the females and assisted reproduction.

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The malignancies we refer to, are mainly those of the breast, endometrium and ovary, with breast cancer being the most common in the female population, affecting 1 in 8 women worldwide, ovarian cancer which is the 6th in frequency representing 4% of malignancies and endometrial cancer which is the most common gynecological cancer excluding breast cancer presenting an incidence of 8% of all malignant diseases. Furthermore, it will be of great interest the possible relation of IVF treatments and non-gynecological malignancies like thyroid and colon cancer, melanoma and non-Hodgkin lymphomas.

Estrogens, and progestogens, have long been associated with the development of breast cancer. In fact, this relationship was first described and published in 1896 in Lancet. Of course, this theory was confirmed after many years of research and after the discovery of estrogen and progesterone receptors in the human body. It is well known, that about two-thirds of breast cancers have positive estrogen receptors and 70% have positive progesterone receptors, but then again more than half of them will become resistant to hormone therapy. The truth is that, estrogens are not exactly what causes mutations or breast cancer. However, it is very well known that they have a potent mitogenic activity. Thus, they can develop endometrial cancer after prolonged action upon the endometrium, whereas progesterone, on the contrary, may act protectively on it. In addition, endometrial cancer may be due to various hormonal changes in the secretory phase, to high concentrations of substances due to the action of gonadotropins, to polycystic ovaries, to obesity and after prolonged SERMs administration.

On the other hand, recurrent ovarian epithelial superficial damage, the prolonged action of gonadotropins with corresponding growth factors upon the ovary and finally the dispersal of malignancy by descending epithelial cells from the salpingeal epithelium, have long been proposed as the possible pathogenesis of epithelial ovarian cancer.

Studies have shown that the longer the female body is exposed to the action of female hormones (such as early menstruation and delayed onset of menopause, long-term use of contraceptive or hormone replacement therapy, elevated estrogen levels, or progestogen levels) is associated with an increased risk of developing breast or endometrial cancer. On the other hand, the reduced duration of exposure to these hormones such as the removal of the ovaries while they are active, or the use of anti-estrogens, reduces it.

In IVF, it is well known that we have 2 basic points. First, a brief, transient but significant increase in circulating estrogen levels during ovarian stimulation, as well as a large increase in progesterone levels during luteal phase support. Thus, estrogen levels in an IVF cycle can easily reach 3,000 - 4,000 pg/mL in women with a good ovarian response, which is significantly higher than 300 pg/ml in a normal physical cycle, without any pharmaceutical intervention. Correspondingly, Progesterone levels in a mildly supported luteal phase in IVF are similarly higher than levels in unsupported.

So the logical question to be elucidated is, if this short-term increase in estrogen and progesterone levels, along with the possible additional changes in other reproductive hormones, might increase the risk of breast, endometrial, ovarian cancer or other non-gynecologic female malignancies in patients undergoing IVF.

The answer to this question is very important, as there is a large number of women, counting about one million per year, who want to achieve pregnancy with assisted reproduction techniques and should be properly informed with up-to-date knowledge of their risk (if there is any) regarding the drugs to be used. On the other hand, health professionals need to know what applies to the treatments they submit to their patients, so that they may benefit and not harm them.

GYNECOLOGIC MALIGNANCIES

Breast Cancer Data

It has been 41 years since the implementation of the first IVF. No doubt that this time was more than enough to reveal any possible complications that could be attributed to the drugs used for these assisted reproduction techniques.

Generally speaking and considering the extend of the question, there are not proportionally too many studies that have specifically dealt with this issue. The studies are all retrospective or of cohort-type and a small number of them has been published as case-control research. Clearly, their statistical power is based on the large population samples they have, but on the other hand they suffer from serious heterogeneity problems. Finally, the results and conclusions are not always clear and often contradictory.

The first valid publication on this subject has its origins in Australia and was published in Lancet back in 1995 (Venn et al., 1995). It was a cohort study involving 10.358 women who were observed for 15 years. From the 5.564 who underwent IVF, 16 women developed breast cancer with standardized incidence ratio of 0.89. The standardized incidence ratio (SIR) expresses the impact that we found on the one we expected, which here means that even the expected number of cases did not even occur. In the remaining approximately 4.800 women who did not take any medication, SIR was 0.98, which was slightly worse. The conclusion was, therefore, that the incidence of breast cancer in women taking ovarian stimulation medications for assisted reproduction did not increase.

Four years later, in 1999, the same team published again in Lancet, their new data, which now referred to 29.700 women with infertility (i.e. three times as many), the 20.959 of which underwent typical gonadotrophin stimulated IVF, 9.044 had a natural cycle IVF without any medication and were followed-up for up to 20 years (Venn, Watson, Bruinsma, Giles, & Healy, 1999). The SIR here was 0.91 for the drug-treated group and 0.95 for the women who were just monitored. That means, no difference compared to the general population. However, there was a temporary but significant increase in breast cancer cases just at the first year following IVF.

Another cohort study from Israel that was published in Fertility & Sterility in 2002 by Dor et al, concluded that there was no increased risk of breast cancer in women undergoing ovarian stimulation medication for IVF, having found that from 5.026 women who underwent ovarian stimulation medication for IVF, only 11 cases of breast cancer were developed through their twenty years of follow-up, having an SIR of 0.69 (Dor et al., 2002).

Burkman et al., published in 2003 in Fertility & Sterility, a multicenter case-control study involving 4.575 women with breast cancer. In this study, it was generally concluded that the use of infertility drugs was not associated with an increased risk of breast cancer development. However, the new and interesting issue in this study was the report that the category of women who had been receiving human menopausal gonadotropins for at least 6 months, had a 2.7 to 3.6 fold increase in this probability (Burkman et al., 2003).

The initial French experience published in 2004 in Human Reproduction, by Gauthier et al, showed that the relative risk of developing breast cancer in the 6.602 women who underwent assisted reproductive therapy, was 0.95, since 183 developed the malignancy against 2.388 out of 85.953 in the rest of the study population. There was also, a non-significant increase in those women who had a family history of breast cancer, but family history has always been a prognostic factor in general population. Therefore,

data in France concluded no effect on the breast from any infertility treatment (Gauthier, Paoletti, & Clavel-Chapelon, 2004).

On the other side of the Atlantic, in the same year, L Brinton and colleagues, published in Human Reproduction again, the data from 5 United State centers, in a cohort study, and that analyzed data from 12193 patients who had received IVF drugs. Their conclusions were worthy of comment. The relative risk of developing cancer after taking medication, was insignificant for the first 19 years after treatment. However, it increased by 39-50% twenty years after the treatment and after 6 IVF attempts per person, by 54%. The moral lesson was therefore, that for every 1.000 women undergoing IVF treatment, we would have 4 new cases of breast cancer 20 years post therapy (Brinton et al., 2004).

Back in Europe, in Denmark, the first relevant study was published in 2007, and included the large number of 54.362 women who underwent IVF in their registries, from whom 331 new cases of breast cancer were introduced. Thus, the relative risks of developing breast cancer, were not significantly higher after gonadotropin, clomiphene or GnRH agonist treatment for IVF, but were remarkably and significantly higher, (RR=3.36) after progesterone administration, as well as in the group of nulliparous women who received gonadotropins, compared to the patients who underwent the same IVF treatment but had already a child, presenting a relative risk of 1.6 (Jensen, Sharif, Svare, Frederiksen, & Kjaer, 2007).

In Israel again, Pappo and his colleagues, in 2008, published in the Annals of Surgical Oncology, the relevant data from their national registry, from 1986 to 2003. This cohort study involved 3.375 women who underwent classic IVF, and apparently 35 of them developed breast cancer. Overall, SIR was 1.4, which was not significant, so in all women with IVF, the incidence of cancer remained the same. However, for those over the age of 40, and for those who had undergone more than 4 IVF attempts, it was doubled, while for those with PCOS it there was a threefold increase (Pappo et al., 2008).

The Swedish experience was published by Kallen et al in Human Reproduction in 2011. They mined their data from all Swedish IVF registries and combined or compared them with the corresponding records of breast cancer cases for the years 1982 to 2006. Of the 24.058 women, who underwent IVF, just 95 developed breast cancer later. This incidence was lower than expected and therefore the Odds Ratio in this study was 0.76. The conclusion was that in Sweden, there was a significantly lower chance of developing breast cancer in women who underwent IVF treatment (Kallen et al., 2011).

The next report was in Australia next year, in 2012, when Stewart et al published in Fertility and Sterility, data from their cohort study of 7.381 infertile Australians who underwent medication for ovarian stimulation and 13.644 women who, although infertile they received no treatment at all. All of them were monitored for up to 30 years. 2% (148 women) in the first group and 1.7% (236 women) in the second developed breast cancer. Overall, in vitro fertilization treatments was not found to increase significantly the risk of developing breast cancer (Hazard risk=1.22). But the risk was significantly increased in those who underwent ovarian stimulation before the age of 24 years presenting a relative risk=1.56 (Stewart et al., 2012).

In Israel, in 2013, the data from their most recent records (at that time), which accounted for 25% of the population, was published in a cohort study including 67608 women who underwent some medical treatment for subfertility during the time period 1994 to 2011 and were monitored for 10-20 years. 389 of these women developed breast cancer. They concluded that use of any medication for any subfertility treatment led to a hazard risk of 0.87, that was not significantly reduced. The gonadotrophin group for IVF had a hazard risk of 0.9 while it was 0.89 in the clomiphene group. The number of attempts did not seem to play a role. Therefore, according to their data, no significant correlation was found between exposure to IVF treatments and the incidence of breast cancer (Brinton et al., 2004).

In 2015 and 2017, Reigstad et al, in the International journal of Cancer, and Cancer Epidemiol Biomarkers studied the Norwegians women who gave birth between 1984 and 2010. After IVF treatment delivered 16.626 women, while 792.208 Norwegian women gave birth after natural conception. They found a slight increase in the incidence of breast cancer noting a hazard risk of 1.2, and particularly in the subgroup of those undergoing IVF (HR=1.3) and those who had been followed up for more than 10 years (HR=1.35). However, this study does not does not apply to interest-bearing "IVF or not". It therefore effectively controls the likelihood of breast cancer development, in women who give birth after IVF, and therefore does not include the entire population receiving ART medications (Reigstad et al., 2015, 2017).

In 2016, the Dutch experience was published in Jama, which after 20 years of follow-up in a group of 25.108 women, also showed no harmful effects at the breast, in women receiving medication for ovarian stimulation (van den Belt-Dusebout et al., 2016). It was at least remarkable and strange, the statement of the economic conflicts, between all of the researchers and the companies producing medication for assisted reproduction.

The last publication was in July 2017, when the data from the second edition of the Swedish experience by Frida E. Lundberg et al in fertility sterility came to light. They received all the data from all Swedish registries for 1.340.211 women who gave birth from 1982-2012 (30 years), of whom 38.047 were gave birth after IVF treatment. So they looked at how many of them had breast cancer. In a second group of 1.877.140 women, they studied breast cancer and associated it with the administration or not of ovarian stimulation drugs, which were eventually received by 39.469 women. The follow-up was 35 years and showed no increased incidence of breast cancer in women who received ovarian stimulation medication as part of assisted reproduction techniques or those who gave birth after infertility treatment compared to women who gave birth after spontaneous conception having an adjusted hazard ratio of 0.84 (Lundberg et al., 2017).

However, in addition to the studies mentioned, 6 reviews have been published, 3 of which published by Greek authors. Two of them are most important most integrated and most recent. The first of them, is the comprehensive and valid work, which concerns a systematic review and meta-analysis published in 2014 in Human Reproduction Update, and it appears that (in the absence of data from the Cochrane database of systematic reviews), it will be the reference point until there is a proper re-evaluation of the data so far. This meta-analysis included 11 studies in total (8 cohort and 3 case-control). A total number of 1.554.332 women with 14.961 cases of breast cancer, of which 576 after IVF, were studied and analyzed in this review. The final conclusion, after a very complex statistical analysis, was that there was no significant correlation between ovarian stimulation for IVF and breast cancer incidence (relative risk=0.91-1.02). Therefore, the above treatment does not increase the risk of breast cancer in women who receive it. The fact that in some subgroups of the sample of some studies there is an increased rate of breast cancer, does not seem to affect the overall result (Sergentanis et al., 2014).

The second meta-analysis was from Italy, and published the following year, in 2015, at Breast Cancer Research and Treatment. The authors included 20 studies with 207.914 women, of which 2.347 women developed breast cancer. They concluded that hormonal treatment for infertility (particularly for IVF) did not increase the incidence of breast cancer, keeping only reservations about the use of clomiphene (Gennari et al., 2015).

For statistical-historical-geographical reasons and only to mention that based on the origin of the existing studies, it seems that in the Central and northern European countries apart from Denmark and Norway (ie in the Netherlands, France, Sweden) the studies were reassuring, as well as in most studies

from Israel. The few mildly worrying messages came from studies on women from other continents such as the America or Australia and the minority of studies from Israel. It is also noteworthy that there are no large series from countries with traditionally strong registries in the field of health, such as England or Germany.

Ovarian - Endometrial - Cervical Cancer Data

The most comprehensive and scientifically documented work has been published in the Human Reproduction Update.

Thus in 2013, Siristatidis and colleagues, published the largest work on the subject, which after screening and analyzing 7.785 relevant studies, included only 63 completed papers, and finally using the appropriate evaluation criteria, built their meta-analysis with only 9 eligible studies involving about 110.000 patients, from Australia (2 studies) from Israel (2 studies), from the Netherlands (2 studies), from Sweden (2 studies) and from Finland (1 study). None of them was randomized. In total, 76 cases of ovarian cancer, 18 cases of endometrial cancer and 207 cases of cervical cancer were reported.

Compared to the general population, the relative risks for the corresponding malignancies were 1.5 for ovarian cancer, 2.04 for endometrial cancer, and 0.86 for cervical cancer. Therefore, compared to the general population, there is an increase in the incidence of ovarian and intrauterine cancer, but not cervical cancer, in women who have received IVF medication. However, comparison was performed with infertile women of similar ages, no significant increase in the incidence of these cancers was concluded. This analysis presented data relatively reassuring (Siristatidis et al., 2013).

In 2013, Brinton et al published data from five US states through the National Cancer Institute. Their experience involved 12,193 women who were followed up for 25 years. They concluded that women who received clomiphene or injectable gonadotrophins had a slightly increased – but not statistically significant - risk of developing endometrial cancer, presenting a hazard ratio of 1.39 and 1.34, respectively. There was a significantly increased risk of clomiphene use only before the age of 30 (HR=1.93). Finally, when the combination of clomiphene followed by gonadotrophins, led to a non-significantly increased risk producing a hazard ratio of 1.77.

So despite their reassuring results they suggested to continue monitoring the women in the study until they reached the age at which endometrial cancer reaches its peak incidence (Brinton et al., 2013).

Recently, in summer of 2017, at Current Opinion of Obstetrics & Gynecology, Kroener Lindsay et al. published a review on the development of cancer after infertility treatment. That was the last available review. They concluded that the available data on the risk of developing cancer after the use of infertility drugs are reassuring. They suggest that there may be a slight increase in the risk of developing borderline ovarian tumors, although they acknowledge that there are several important methodological issues in the studies that they had to include, a fact that limits the ability to draw clear and definitive conclusions. Interesting, however, is the authors' question and remark, as they wonder how can infertility alone be an independent risk factor for developing breast, endometrial and ovarian cancer, while the use of drugs to treat infertility, did not manage to prove a significant increase in the risk of developing these malignancies (Kroener, Dumesic, & Al-Safi, 2017).

CONCLUSION

The currently available data assessing the association between fertility drugs and gynecological cancer are limited and principally derived from low power, observational, retrospective studies, mainly cohorts. Methodological issues apply, including small sample sizes, and great heterogeneity in treatment protocols, duration, dose of treatment and follow-up periods.

Most studies are at least reassuring, as they fail to show a significant correlation between medication and breast cancer. Recent meta-analyses agree that there is adequate evidence to support that there is no association of ART medication administration and increase in breast cancer incidence, although that there is some evidence suggesting that women with infertility per se, have an increased risk of breast, ovarian, and endometrial cancer (Pfeifer et al., 2016; Sergentanis et al., 2014; Siristatidis et al., 2013). In the individual questions, like the most dangerous treatment, the critical number of cycles, the critical dose and the critical duration, the answers are few, and they exist in a very small percentage of research. In the majority of the studies so far, there are few, scattered and not powerful data, suggesting that the application of the treatment for more than 4 or 6 cycles may be more dangerous, its application before 24 or after 40 years, in the first year or 10 or 20 years after treatment, nulliparity, women with polycystic ovaries and those taking large doses of progesterone. Finally, most studies agree that the drugs used have more or less the same effect on the breast (Pfeifer et al., 2016; Sergentanis et al., 2014; Siristatidis et al., 2013).

The currently available data provide adequate evidence to support that there is no association of ART medication administration and increase in endometrial and cervical cancer incidence (Pfeifer et al., 2016; Sergentanis et al., 2014; Siristatidis et al., 2013).

Based on available data, we can be reasonably reassured that there is no increased risk of invasive ovarian cancer following the use of fertility drugs in infertile women. The risk of invasive ovarian cancer is not different with the use of different fertility medication. There is a small number of studies suggesting a minimal increase in the absolute risk of borderline ovarian tumors after fertility treatments, but there is no evidence which particular fertility drug increases this risk (Pfeifer et al., 2016; Sergentanis et al., 2014; Siristatidis et al., 2013).

The common denominator of all researchers is that more data through large and well-designed randomized clinical trials are needed to further investigate the safety of IVF medications.

NON-GYNECOLOGIC MALIGNANCIES

These where the data, consisting the evidence that connect the use of assisted reproduction techniques and medication with gynecological cancers (breast cancer included). However, there are limited data regarding the development of non-gynecological malignancies following infertility treatment. With no doubt, the basic question is how would the endogenous hormonal alterations in a female body during IVF treatment, influence a possible malignant development elsewhere, like the endocrine system, the digestive system, the skin, the blood, the lung etc. As a matter of act, the incidence of these cancers is not as high as breast or gynecological malignancies, and their occurrence concerns later stages of woman's life, compared to the age of the reproduction. This exact fact, is an additional real difficulty, if someone wants to acknowledge a causal link. However, the importance of any relation between fertility drugs and cancer risk is mandatory since 1 million in vitro fertilization cycles are being performed yearly.

Thyroid Cancer Data

Thyroid cancer is anyway commoner in females, particularly in younger ages. Hormone replacement therapy, long term use of combined oral contraceptives and high parity have been correlated with increased incidence of thyroid cancer. What we know although, is that the a-subunit of TSH is common to the gonadotrophin's a-subunit, and in fertility treatments increased levels of FSH are the aim and the rule.

Most retrospective studies did not manage to show an increase in the incidence of thyroid cancers after ART treatment (Del Pup, Peccatori, Levi-Setti, Codacci-Pisanelli, & Patrizio, 2018; Pfeifer et al., 2016).

In Denmark a cohort study of 54,362 infertile women showed a significant association between clomiphene use and thyroid cancer, revealing a relative risk of 2.29 after five years of use, with 1–5 cycles, but no increased risk with gonadotropins, based on 29 cases of thyroid cancer (C G Hannibal, Jensen, Sharif, & Kjaer, 2008).

Recently, in their cohort study, L Brinton et al in 2015, concluded that gonadotrophin use, did not increase the risk for thyroid cancer after a follow up of 12 years, having a hazard ratio of 1,17. However the use of clomiphene citrate for more than 12 cycles and in high doses (>2,25gr) revealed a hazard ratio of 1.96 and 1.77 respectively. The combined use of gonadotrophins and clomiphene increased the hazard ratio to 1.83 (Brinton et al., 2015).

In conclusion, there is conflicting data, leading to insufficient and not powerful evidence to support a significant association between fertility medication administration and thyroid cancer. However, there is minimal data deriving from only cohort studies, showing that thyroid cancer could be related to clomiphene use.

Overall, according to the recommendations of the Practice Committee of the American Society for Reproductive Medicine, "there is fair evidence that fertility drugs are not associated with an increased risk of invasive thyroid cancer" (Pfeifer et al., 2016).

Non-Hodgkin Lymphoma

There is scarse data concerning the association of fertility drugs administration and hematological malignancies. Hormonal factors like age at menarche and parity have been associated with non-Hodgkin lymphoma, surprisingly in a similar way to that of breast cancer. However, neither the oral contraceptive use nor the hormone replacement therapy seem to be clearly related to non-Hodgkin lymphoma. Actually oral contraceptives seem to benefit. Nevertheless, one study evaluated the risk for non-Hodgkin lymphoma, following the use of fertility drugs (but not with use of clomiphene alone) and showed an increased risk with ovulation induction therapy among primiparous women and in the first 5 years following birth, presenting a hazard ratio of 2.46 (Calderon-Margalit et al., 2009; Pfeifer et al., 2016).

Therefore, if indeed estrogens are related to the incidence of non-Hodgkin lymphoma, an association between ovulation induction drugs and non-Hodgkin lymphoma is still to be elucidated through further studies.

According to the recommendations of the Practice Committee of the American Society for Reproductive Medicine, "there is insufficient evidence that fertility drugs are associated with an increased risk of lymphoma" (Pfeifer et al., 2016).

Malignant Melanoma

Unfortunately, during the recent decades, more and more studies have revealed an increase in melanoma cases. Particularly in women, its incidence has been associated, among others, with the use of oral contraceptives, low parity and delayed childbearing (Charlotte Gerd Hannibal, Jensen, Sharif, & Kjaer, 2008). This has been explained with the hypothesis that estrogen receptors were identified in melanoma cells, and melanocytic nevi and therefore prolonged estrogen administration and action could result in hyperpigmentation (Dika et al., 2019). Thus, some studies remarked increased risks of melanoma after such drug usage (Modan et al., 1998; Ness et al., 2002) but some others did not conclude the same (Franceschi et al., 1994; Parazzini et al., 2001)

Furthermore, the relation of fertility drugs and melanoma incidence has been evaluated with several studies. The majority of them did not show an overall significantly increased risk after their use (Althuis et al., 2005; Brinton et al., 2015; Charlotte Gerd Hannibal et al., 2008; Luke et al., 2015; Ron et al., 1987; Tomao et al., 2014; Young, Purdie, Jackman, Molloy, & Green, 2001).However, in one study, there was a subgroup of women who after infertility treatment became pregnant and had a significantly increased hazard risk of 3.61, to develop melanoma, compared to those women who did not succeed in their ivf treatments at all (Stewart, Holman, Finn, Preen, & Hart, 2013). Furthermore, the Danish experience (Charlotte Gerd Hannibal et al., 2008) as published in 2008, showed a similar significant increase of melanomas in women who succeeded in their IVF treatments and managed to deliver.

Finally, the use of clomiphene citrate as infertility treatment, had controversial results in terms of consequent melanoma development, showing positive correlation in some studies (Brinton et al., 2015; Calderon-Margalit et al., 2009) and no significant association in others (Althuis et al., 2005; Charlotte Gerd Hannibal et al., 2008; Tomao et al., 2014; Young et al., 2001).

Overall, according to the recommendations of the Practice Committee of the American Society for Reproductive Medicine, there is insufficient evidence either for or against, that fertility drugs are associated with an increased risk of melanoma (Pfeifer et al., 2016).

Colon Cancer

Sex hormones have been proposed to have a role in the etiology of colorectal cancer. Thus, a logical question would be focusing in whether fertility drugs that primary or secondary increase estrogens or/ and progestogens, have any impact on the incidence of colorectal cancer. There are only 3 available studies on this issue, all cohorts.

In one retrospective cohort study of 8.422 women evaluated for infertility, gonadotropins did not increase cancer risk for colon cancer, while clomiphene use, showed a relative risk of 0.83 colon cancer unrelated to dose or cycles used (Althuis et al., 2005).

In Netherland, in 2016, Spaan and his colleagues, published the Dutch experience on the risk of colorectal cancer after ovarian stimulation for in vitro fertilization using their data from the OMEGA-project group. It was a cohort study including 19.158 women who received ovarian stimulation for IVF and 5.950 women who underwent subfertility treatments but not IVF. Colorectal cancer risk in the IVF group was compared, after a median follow-up of 21 years, with those in the general population and in the non-IVF group. They concluded that the risk of developing colorectal cancer was not increased in the IVF group compared to the general population, having a standardized incidence ratio of 1.00, while

the non IVF group had a significantly lower risk of 0.58, and all were irrelevant to the number of the IVF cycles or ampules of gonadotropins used (Spaan, van den Belt-Dusebout, Burger, & van Leeuwen, 2016).

The third study was again a retrospective cohort from the USA and included 9,892 women followed up for more than 30 years (Brinton et al., 2015). They found that clomiphene citrate use was unrelated to colorectal cancer risk presenting a hazard ratio of 0.83. When gonadotrophins were used alone, they reduced the risk to 0.55 and when both drugs were used, the hazard ratio was just 0.35.

Nevertheless, there is insufficient evidence to suggest an association between fertility medication use and colon cancer. Thus according to the recommendations of the Practice Committee of the American Society for Reproductive Medicine, "there is fair evidence that fertility drugs are not associated with an increased risk of invasive colon cancer" (Pfeifer et al., 2016).

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Chapter 7
Endometrial Polyps in Reproductive Age:
Is There Malignancy Potential? Should We Always Treat?

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ABSTRACT

Endometrial polyps are endometrial masses that consist of glands, stroma, and vessels. They can be single or multiple, sessile or pedunculated, and range in size from some millimeters up to several centimeters. Despite the fact they rarely cause symptoms, they are usually found on a routine examination. Therefore, they are a common problem on daily clinical practice. The question of potential malignancy risk as well as the necessity of further treatment are often posed. The present chapter summarizes current evidence regarding risk of malignant transformation as well as indications and methods of appropriate treatment.

INTRODUCTION

Endometrial polyps are endometrial masses that consist of glands, stroma, and vessels (Kim et al, 2004). They can be single or multiple, sessile or pedunculated and range in size from some millimeters up to several centimeters. Since they rarely cause symptoms, they are usually found on a routine examination. While transvaginal ulttasonography is considered as a reliable means for their diagnosis, the combination with liquid infusion in the endometrium (with or without 3D imaging) improves the diagnostic accuracy. However, dilation & curettage (D&C) or endometrial biopsy should not be used as a diagnostic tool.

In premenopausal women, the most common symptom seems to be the abnormal uterine bleeding (AUB). This may have the characteristics of metrorrhagia, spotting, but also menorrhagia. Moreover,

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endometrial polyps are related to infertility, as they have been found to be more common in infertile than in fertile women. In addition, there is evidence of improvement in fertility following the removal of polyps (Hinckley & Milki, 2004; Perez-Medina et al, 2005). In postmenopausal women, the most common symptom is postmenopausal uterine bleeding.

Frequency of Polyps at Women of Reproductive Age

One study investigated the frequency of endometrial polyps in the general Danish population aged 20-74 years (Dreisler et al, 2009). From this population, 429 were premenopausal women with an incidence of endometrial polyps of 5.8%, while in postmenopausal women the incidence was 11.8%. Other studies have also shown that the incidence of polyps increases with age before menopause, and in the 20-29 age group only 0.9% were diagnosed with polyps (Dreisler et al, 2009). In addition, in premenopausal women without AUB, the prevalence of endometrial polyps was 7.6%, while in those with AUB was 3.7% (Dreisler et al, 2009). Another study in the general population of women over 30 years old, without AUB, showed that the frequency of polyps was 10% (Clevenger-Hoeft et al, 1999). In other studies investigating premenopausal women with AUB, the frequency of polyps has been found to range between 10-40% (Nagele et al, 1996; Clevenger-Hoeft et al, 1999; Anastasiadis et al, 2000). The symptoms do not seem to be related to the size, the number, and the position of endometrial polyps (Hassa et al, 2006).

Risk of Malignancy in Endometrial Polyps

There are scanty data about the natural history of endometrial polyps, and their median annual growth rate is estimated to be about 1% (Wong et al, 2017). It has been found that untreated polyps may have a 27% probability of spontaneous regression, during one-year of follow-up (Lieng et al, 2009). Small polyps (<10 mm) are more likely to disappear than larger ones (De Waay et al, 2002; Lieng et al, 2009).

On the other hand, there is evidence that malignancy has been associated with endometrial polyps. However, the possibility of malignant transformation of endometrial polyps is questionable in international literature. There are several studies that describe the incidence of pre-cancerous and cancerous lesions in endometrial polyps of women of all ages. Specifically, the incidence of precancerous and cancer lesions ranges between 0-23.8% and 0-12.9%, respectively. It is undisputed, as shown by numerous studies, that this incidence is higher in postmenopausal women than in premenopausal women, with the latter being generally estimated to have extremely low risk of malignancy in the polyps. One study of 1467 women (269 were pre-menopausal), showed that 10 premenopausal women had malignancy (incidence 0.4%, 10/269). On the other hand, in the postmenopausal women, the incidence of malignancy was significantly higher (13.6%) (Perri et al, 2010). In another study, in 206 menopausal women with endometrial polyps, there was no case of malignancy (Ben-Arie et al, 2004).

Parameters that are significantly associated with cancer in the polyps, are postmenopause, old age (> 60 years) and postmenopausal uterine bleeding (Ricciardi et al, 2014; Costa-Paiva et al, 2011; Wang et al, 2011). In general, AUB has been found to be associated with malignancy of endometrial polyps (Perri et al, 2010). Risk factors for malignancy in endometrial polyps include the polyp size>10 mm (Wang et al, 2010) or>15 mm (Ben-Arie et al, 2004), as well as tamoxifen use (Kedar et al, 1994; Bernstein et al, 1999). Although there is no consensus in the international literature, it has been reported that known risk factors for endometrial cancer (obesity, arterial hypertension and diabetes mellitus) increase the risk of malignancy in endometrial polyps (Anastasiadis et al, 2012; Savelli et al, 2003; AAGL, 2012).

One study showed that among 417 premenopausal women with endometrial polyps, the polycystic ovary syndrome was associated with abnormal histology of polyps (PCOS vs not PCOS, OR, 9.6; 2.5-37) (Kilicdag et al, 2011).

A meta-analysis of 37 studies, totaling 21057 patients with endometrial polyps, showed that the incidence of precancerous and cancer lesions was 3.4% (95% CI, 2.8-4.1). AUB (PR = 1.47, 95% CI 1.27-1.69), postmenopause (PR = 1.67, 1.48-1.89), age>60 years (PR = 2.41, 1.84-3.16), diabetes mellitus (PR = 1.76, 1.43-2.16), hypertension (PR = 1.50, 1.20-1.88), obesity (PR = 1.41, 1.13-1.76), and tamoxifen use (PR = 1.53, 1.06-2.21) were associated with malignancy in the polyps. In contrast, breast cancer, hormone therapy, and polyp size were not statistically significantly related to the likelihood of malignancy (Sasaki et al, 2018).

However, genetic studies have not shown that endometrial polyps are precancerous lesions. In postmenopausal women, expression of 4 genetic markers related to endometrial carcinogenicity (PTEN, BCL2, MLH1, and CTNNB1) did not differ between symptomatic and asymptomatic endometrial polyps, suggesting that they may not be precancerous lesions (Troncon et al, 2017).

In another study, which investigated endometrial polyps, endometrial cancers and normal endometrium, the expression of estrogen and progesterone receptors, Ki-67, endoglin-CD105, adhesion molecules (claudins 3 and 4), and proteins MMP-2 and MMP-9, could not determine the malignant potential of endometrial polyps (Peres et al, 2018).

Microsatellite instability (MSI) is an important pathogenic factor in endometrial carcinogenesis and one study found that only one of the 5 markers of MSI was found in 6.4% of endometrial polyps, without its presence being associated with age, BMI or menopause (Rios et al, 2010). These data, although require further investigation, indicate that MSI is unlikely to predict the malignant transformation of endometrial polyps.

Cytogenetically, in the endometrial polyps, three main categories have been identified with pathological findings (57%), namely with rearrangements in the regions: (1) 6p21-p22, (2) 12q13-15 and (3) 7q22 while in the remaining cases the karyotype was normal (Dal Cin et al, 1995). Similar chromosomal alterations have been found in other benign lesions that do not constitute precancerous lesions. In addition, the development of endometrial polyps due to monoclonal proliferation of their mutant stromal cells is completely different from endometrial intraepithelial neoplasia (EIN) where there is a monoclonal glandular growth with substantial precancerous characteristics (Mutter et al, 2007; Perri et al, 2010).

An epidemiological study investigated the prevalence of endometrial cancer in patients with endometrial polyps, and in patients with leiomyomas compared to the general population. The results showed that endometrial cancer was more common in women with leiomyomas than in women with endometrial polyps, suggesting that the association of cancer with polyps was due to patients' diagnosic bias rather than the probability that polyps are true precancerous lesions (Perri et al, 2010). In addition, a meta-analysis calculated the risk of coexisting endometrial cancer in the non-polypoid endometrium when atypical endometrial polyps were diagnosed (de Rijk et al, 2016). The risk estimate was of 5.6% (95% CI 0.2-17.6%), which is significantly different from the risk of endometrial cancer in non-polypoid atypical endometrial hyperplasia which has been established in the literature to be approximately 42%.

Treatment

As mentioned above, the risk of malignancy in endometrial polyps in premenopausal women is extremely low. In addition, especially small polyps (<10 mm) have a 27% rate of complete regression without treatment. For these reasons, AAGL (American Association of Gynecologic Laparoscopists) proposes, based on evidence (Level A), that conservative management is a reasonable approach especially in small and asymptomatic endometrial polyps (AAGL, 2012). Regarding the larger polyps (> 15 mm) in premenopausal women, there is no consensus of their treatment in international literature, and other authors suggest their removal them while others suggest only monitoring (Ben-Arie et al, 2004; AAGL, 2012; Tanos et al, 2017).

In premenopausal women with AUB, hysteroscopic removal of endometrial polyps is indicated since it significantly improves bleeding. As yet, several studies have investigated the effect of polypectomy on AUB. Both after objective and subjective assessment of the amount of bleeding, it was found that following surgery the symptoms improved in 75-100% of cases.

Regarding infertility, although this was not the subject of the present chapter, there are several studies showing improvement in pregnancy rate after polypectomy.

The method of choice for the removal of endometrial polyps is hysteroscopy (AAGL, 2012), whereas D&C is not recommended since there is a high likelyhood of remaining remnants of polyps. A recent network-meta-analysis included 8 RCTs and compared 5 different hysteroscopic techniques (traditional resectoscopy, monopolar electrode, bipolar electrode, diode Laser, hysteroscopic morcellation) showing that hysteroscopic morcellation of polyps had significantly less operating time, higher success rates and fewer complications (Guo et al, 2019).

The hysteroscopic image of polyps, and especially their increased vascularization may be related to malignancy or hyperplasia (Shor et al, 2019). With hysteroscopic removal, since the resection does not extend to the myometrium, there is virtually no risk of endometrial adhesions.

The risk of polyps recurrence after polypectomy is related to the number of endometrial polyps, endometriosis, and the history of previous polypectomy (Gu et al, 2018). The removal of more than 6 polyps is associated with a four-fold risk of recurrence after polypectomy compared to the removal of single polyps (Gu et al, 2018; Yang et al, 2015). Also, with increasing follow-up time, the risk of polyp recurrence increases significantly (quadruples) after 3 years (Yang et al, 2015).

If atypical hyperplasia or malignancy in the endometrial polyps is diagnosed histopathologically, the patient is treated similarly to the treatment for atypical hyperplasia and endometrial cancer, respectively.

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Section 4
Cervical and Vulvar Pathology

Chapter 8
Co-Testing:
Pap-Test and mRNA HPV-Test for Cervical Cancer Screening

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ABSTRACT

The dramatic decline in cervical cancer in women is attributable first to screening with the Papanicolaou (Pap) test, followed later by the addition of the Human Papilloma Virus (HPV) test, which enhanced screening sensitivity. In association with this excellent performance record, resulting from the combination of Pap Test and HPV Test, known also as Co-Testing, the current standard of care for cervical cancer screening for most women (those over 30) is Co-Testing with Pap + HPV tests, as currently recommended by U.S. guidelines. The challenge is to improve screening cost-effectiveness without compromising efficacy. The notion that screening with one test may be more cost-effective than two tests seems reasonable upon first consideration, but closer examination may dispute this assumption. The chapter aims to analyze costs and benefits regarding optimal screening method for daily clinical practice.

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INTRODUCTION

The dramatic decline in cervical cancer in women is attributable first to screening with the Papanicolaou (Pap) test, followed later by the addition of the human papilloma virus (HPV) test, which enhanced screening sensitivity (International Agency for Research on Cancer [IARC], 2012; Schiffman & Solomon, 2007, 2013).

In keeping with this excellent performance record resulting from the combination of Pap Test and HPV Test, known also as Co-Testing, the current standard of care for cervical cancer screening for most women (those over 30), as currently recommended by U.S. guidelines, is Co-Testing with Pap Test + HPV test (Massad et al., 2013; Saslow et al., 2012).

In 2014, the Food and Drug Administration (FDA) approved an HPV assay to be used alone as a primary screening test, initiating a debate about what is the best way to detect cancer (U.S. Food & Drug Administration [FDA], 2014).

It is advocated by the scientific community that to more fully investigate the potential benefits of HPV-only screening, HPV-only test results must be compared with cotest results in the detection and prevention of invasive cervical cancer in real-world clinical practice with clinical populations that are not preselected.

Moreover, HPV-only primary screening for cervical cancer presents many challenges for clinicians. Questions arise regarding its effectiveness, its long-term risk, and when it is the best option for a particular patient (Austin & Zhao, 2014).

Comparison of Diagnostic Approaches

Since this FDA decision, a retrospective, cross-sectional analysis performed in 256,648 women demonstrated that HPV-alone testing missed 18.6 percent of 526 cervical cancer cases detected by Co-Testing (HPV Test + Pap Test) (Blatt et al., 2015).

The objective of this study, colloquially known as Quest Diagnostics Health Trends study, was to provide a real-world, retrospective comparison between three (3) screening approaches for cervical cancer (Pap-only testing, HPV-only testing, and Pap/ HPV Co-Testing). Blatt et al. (2015) retrospectively analyzed clinical records for 256,648 average-risk women, ages 30 to 65, all of whom underwent Co-Testing as a screen for cervical cancer and subsequently had a cervical biopsy within a year of Co-Testing. The primary objective was to determine the sensitivity of the three screening methods for detection of biopsy-proven ≥CIN3, including squamous cell carcinoma, adenocarcinoma, and cervical intraepithelial neoplasia (CIN) grade 3 or greater (>CIN3).

The results showed that 74.7% (191,776 of 256,648 samples) of women were positive for HPV, 73.8% (189,304 of 256,648 samples) of women had an abnormal Pap test (atypical squamous cells of undetermined significance or worse), 89.2% (229,020 of 256,648 samples) of women had a positive cotest, and 1.6% (4090 of 256,648 samples) of women exhibited >CIN3.

Biopsy results showed that Co-Testing had the highest sensitivity for ≥CIN3 (98.8% versus 94% for HPV test only and 91.3% for Pap testing alone, $P<0.0001$). Co-Testing detected 4040 of 4090 specimens of all >CIN3 cervical biopsy results. The Pap test had greater specificity versus HPV testing alone or Co-Testing (26.3% versus 25.6% versus 10.9%, $P<0.0001$).

Investigators identified 526 patients who developed biopsy-proven invasive cervical cancer. Of those patients, 98 tested negatives by HPV assay only, 64 by Pap test only, and 29 by co-testing. The data

suggest that approximately 19% of women with cervical cancer may be misdiagnosed by an HPV-only cervical screen. Adenocarcinoma verified as cervical in origin was detected in 169 women, of whom 45 of 169 women (26.6%) had negative HPV tests, 35 of 169 women (20.7%) had negative Pap tests, and 14 of 169 women (8.3%) had negative Co-Testing.

Given the average risk of the patient population included in the study, the results are broadly applicable to women in the age range studied, regardless of baseline risk for cervical cancer, authors said.

In this Quest Diagnostics Health Trends study, HPV/Pap Co-Testing identified more women whose cervical biopsy result revealed a finding of >CIN3 than HPV-only testing when offered as a primary screening test for cervical cancer. Co-Testing is better than either test alone, data that support current ACS recommendations for cervical cancer screening.

The American Cancer Society estimates that 12,360 women are diagnosed with cervical cancer each year (American Cancer Society, 2014). In this study, 19 percent of all cervical cancers were HPV-negative, meaning that 2,400 cervical cancers in the U.S. would be missed, including an even higher proportion of adenocarcinomas.

Authors report that the results of their study, as well as limitations of the study that led to FDA approval of an HPV-only primary test, including abnormally low cytology performance, lack of a Co-Testing comparator algorithm, the inclusion of women aged <30 years, requiring up to 3 follow-up visits, and no long-term follow-up, which raise concerns regarding the suitability of HPV-only testing as a primary cervical cancer screen, highlight the preeminence of Co-Testing approach in women ages 30 to 65 for detecting cervical cancer (FDA, 2014).

In another study, Zhou et al. (2016) investigated the clinical performance of the FDA-approved hrHPV test for the detection of High-Grade Cervicovaginal Lesions (Zhou et al., 2016).

They retrospectively reviewed more than 130,000 Papanicolaou (Pap) tests recorded in the laboratory information system database at Houston Methodist Hospital, Houston, Texas. Although, several investigators to that point considered HPV testing more sensitive than cytomorphology in detecting cervicovaginal dysplasia the results from this study indicated that hrHPV test alone was not superior to cytology in detecting high-grade cervicovaginal lesions (Gyllensten et al., 2012; Leinonen et al., 2012; Malila et al., 2013; Ogilvie et al., 2012; Rijkaart et al., 2012; Ronco et al., 2014; Wright et al., 2012). In a total of 1652 cases confirmed by biopsies, the sensitivities of the HPV and Pap tests in detecting any dysplastic or high-grade lesions on follow-up biopsies were similar with no statistically significant differences (80.8% vs 81.2% for any dysplastic lesions, $P = .86$; 91.3% vs 90.9% for high-grade lesions, $P = 1.0$).

Among the cases with biopsy-confirmed high-grade cervicovaginal lesions (CIN2/CIN3, vaginal intraepithelial neoplasia grade 2/3, adenocarcinoma in situ, or carcinoma; n = 253), the false-negative rates were 8.7% for the HPV test and 9.1% for cytology. Co-Testing with both cytological and HPV tests had a significantly lower false-negative rate (1.2%) in comparison with either HPV testing or cytology alone; this finding led the authors to the conclusion that, the two tests being complementary in detecting high-grade cervical lesions, cytology-HPV Co-Testing approach is the best strategy for screening women who are 30 years old or older because of the significant lower false-negative rates achieved.

It is important to note that in women with persistent HPV infections, the viral DNA may eventually integrate into the host genome; this can significantly reduce the viral load in cervical specimens. This is the underlying explanation why HPV is not always detected before in precancer lesions or even in cervical cancers. Several studies have concluded to this ascertainment. A recent study indicated that

only 91% of cervical squamous cell carcinomas were HPV-positive according to the Linear Array HPV genotyping test (Hopenhayn et al., 2014).

In another study, Zhao et al (2015) demonstrated that 9% to 25% of patients with squamous cell carcinoma had negative HPV test results (Zhao et al., 2009, 2015).

The data from the Kaiser Permanente (KPNC) study showed that Co-Testing in 330,000 women over five years definitively demonstrates that concurrent HPV testing and cytology can be feasibly implemented in routine clinical practice to provide powerful prevention of cervical cancer (Katki et al., 2011).

Zhou's et al. (2016) work was the second study conducted since the Food and Drug Administration (FDA) approved the Cobas HPV test as a primary screening method for cervical cancer, following the previous, aforementioned in this chapter, the study by Blatt et al. (2015). In this study, in contrast to the low sensitivity of the Pap test in detecting high-grade lesions (42.63%) reported in the ATHENA trial, Zhou et al. (2016) demonstrated that the sensitivity of the Pap test was 90.9% (Wright et al., 2012). Sensitivity performance of the Pap test in this study is comparable to the published data with liquid-based cytology (Belinson et al., 2001; Dudding & Crossley, 2013).

Several factors may be attribute to the difference in the findings between Zhou et al. study and the ATHENA trial. Optimal cytology reporting performance is crucial. Performance of the Pap test and Cobas HPV tests reflects the real-world practice versus that in study trials. Certainly, the fact that study by Zhou et al. was a large retrospective study rather than a controlled trial has a significant impact on results.

Another study conducted by Tao et al. demonstrated similar results. A relatively high negative rate in hrHPV testing in patients with cervical cancer compared to low rate when using both Pap cytology and hrHPV testing was found. In the current study, the rate of Co-Testing double-negative (Pap-negative/hrHPV-negative) findings was 3.9% (9 of 231 patients) in the 1-year period before a histologic diagnosis of cancer compared with a Pap cytology-negative rate of 15.5% (37 of 238 patients) and an hrHPV-negative rate of 15.5% (74 of 477 patients) (Tao et al., 2015).

Data from an earlier study examining real-life screening scenarios had already challenged the sensitivity of HPV testing alone in the detection of precancer and cancer, which was published in more formally conducted clinical trials. In the study of more than 1 million women, Gage and colleagues demonstrated that risk of developing CIN3+ disease within 3 years of screening was 29% lower in women who were cotest-negative, as compared with women who tested HPV-alone negative. Furthermore, among 405 cases of cervical cancer detected during the study, nearly 19% were HPV-alone negative compared with just over 12% of women who were cotest-negative (Gage et al., 2014).

Co-Testing has since been widely adopted and multiple FDA-approved testing platforms are now being used in the United States. Furthermore, the American Cancer Society (ACS), American Society for Colposcopy and Cervical Pathology (ASCCP), and American Society for Clinical Pathology (ASCP) in 2012 released updated screening guidelines that advocated cytology and HPV Co-Testing as the preferred screening option in women 30 and older (Saslow et al., 2012).

The USPSTF (U.S. Preventive Services Task Force) to update the 2012 recommendation on screening for cervical cancer reviewed the evidence on screening, with a focus on clinical trials and cohort studies that evaluated screening with high-risk human papilloma virus (hrHPV) testing alone or hrHPV and cytology together (Co-testing) compared with cervical cytology alone. Likewise, the USPSTF has incorporated in its Recommendation Statement the Co-Testing strategy for cervical screening in women aged 30 to 65 years. (US Preventive Services Task Force [USPSTF], 2018).

The challenge has always been to improve screening cost-effectiveness without compromising efficacy. The case in favor of primary HPV screening has been made largely on the basis of cost. The obvious

assumption is that adding the cost of an additional test would result in a higher financial burden to the screening program. The notion that screening with one test may be more cost-effective than two tests seems reasonable upon first consideration—but closer examination reveals this assumption to be wrong. Understanding the cost-benefit ratio of screening methods requires a thorough analysis of HPV assay technologies, what they detect, which molecules they are targeting in and how these factors influence the cost-effectiveness of cervical cancer screening.

ASSAYS FOR HPV DETECTION

Not all HPV assays are the same, and the first step in understanding their differences is to review the relationship between HPV and cervical cancer. Cervical cancer is predominantly caused by a small group of 14 genetically related high-risk (hr) HPV species, and more than 70% of cervical cancers are caused by the hrHPV 16 and 18 genotypes. However, the majority of hrHPV infections spontaneously regress. Only persistent hrHPV infections and expression of the E6 and E7 oncoproteins are associated with neoplastic transformation.

To cause neoplastic cervical disease, HPV, a double-stranded DNA virus, first enters cervical epithelial cells. Upon entering, the virus can either stay in its free episomal form or linearize and integrate into the DNA of the host cell (Einstein, 2002; Wang & Hildesheim, 2003). Following integration, HPV causes the malignant transformation of cervical cells via expression of the two oncogenic proteins: E6 and E7 (Baron et al., 2015).

Oncogenic protein E6 regulates degradation of tumor suppressor protein p53, which under normal conditions regulates cell growth and enables DNA repair enzymes to mend chromosomal damage (Ramakrishnan et al., 2015; Wang & Hildesheim, 2003).

Oncogenic protein E7 inhibits the retinoblastoma (Rb) protein, another important regulator of the cell cycle (Ramakrishnan et al., 2015; Wang & Hildesheim, 2003). When p53 and Rb are inactivated, chromosomal mutations and uncontrolled growth occur (Ramakrishnan et al., 2015; Wang & Hildesheim, 2003). Oncogenic proteins E6 and E7 not only cause damage individually, but they also have a synergistic effect that transforms the HPV-infected cell into a precancerous cell (Ramakrishnan et al., 2015). This process is typically slow, with progression of a high-grade lesion to cervical cancer taking approximately 10 years.

The hurdle that must be overcome to improve cervical cancer screening cost-effectiveness is distinguishing the minority of HPV infections or lesions prone to progression from the vast majority likely to regress. There is therefore, a need for straightforward and cost-effective detection strategies that are able to decisively identify those women in the population who are at risk of developing cervical cancer. Improving the ability to make this distinction would limit unnecessary follow-up costs, and harms from unnecessary over-treatment, that may be associated to obstetrical complications, not underestimating the burden from the needless anxiety in women.

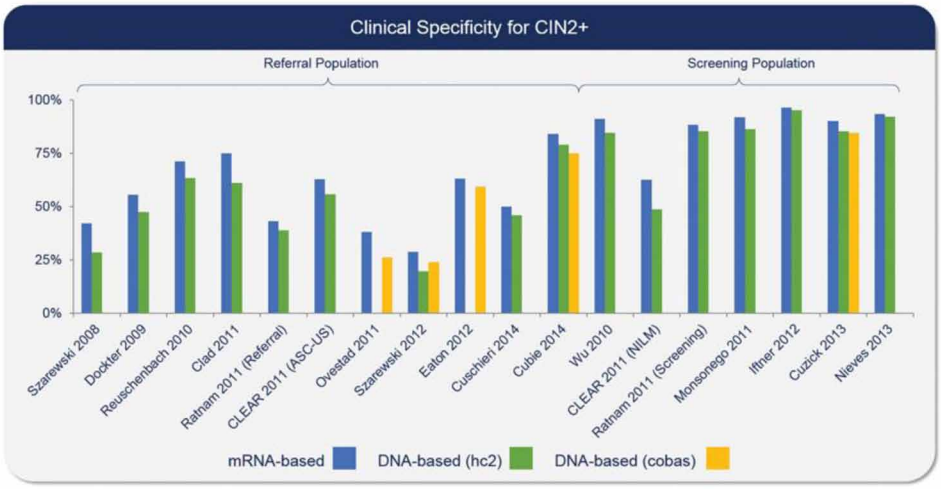
There are currently five nucleic acid-based HPV assays available in the U.S. for cervical cancer screening, approved by the FDA (Centers for Disease Control and Prevention, 2015; FDA, 2018). [31,32] Four of the assays, and more specifically the Hybrid Capture 2 High-Risk DNA test (Qiagen), Cervista HPV High-Risk DNA test (Hologic), Cobas 4500 PCR test (Roche) and Onclarity HPV Assay (Becton Dickinson) analyze HPV DNA; one assay, the Aptima analyzes HPV messenger RNA (mRNA). Aptima is the only FDA-approved test that detects HPV mRNA, and detects 14 hrHPV types. Aptima HPV

16/18/45 test is also FDA-cleared to triage its pooled Aptima HR HPV test further. By detecting HPV mRNA, as opposed to DNA, this latter test identifies expression of HPV E6 and E7 oncogenic proteins.

Comparing Specificity

Numerous studies have demonstrated that the mRNA-based hrHPV assay has higher clinical specificity for detection of cervical cancer lesions than DNA-based hrHPV assays (Haedicke & Iftner, 2016; Iftner et al., 2015; Luhn & Wentzensen, 2013). (Figure 1). The underlying explanation for improved specificity is detection of mRNA encoding E6 and E7 oncogenic proteins indicating lesion progression to invasive cancer. When E6 and E7 oncogenic proteins are detected, as opposed to HPV DNA detection indicating viral presence only, fewer false positive test results have been reported. First-generation hrHPV molecular tests used for adjunctive cervical cancer screening function by detecting viral genomic DNA in cellular samples from the uterine cervix. However, because, as noted earlier, the presence of hrHPV in the female genital tract is common and often transient in nature, and most cervical HPV infections resolve without becoming cancerous, hrHPV DNA-based test methods yield only moderate specificity for detection of high-grade cervical disease (Cuzick et al., 2006; Goodman et al., 2008; Koliopoulos et al., 2007; Moscicki et al., 2010a; Moscicki et al., 2010b; Münger et al., 2004). This leads to unnecessary follow-up and referral of patients to colposcopy, increasing the physical and emotional burdens on women and elevating health care costs.

Figure 1. Studies demonstrating higher clinical specificity with mRNA-based assay.



Consequently, poor specificity of hrHPV DNA-based test methods represents a significant limitation of the approach. Besides, hrHPV DNA-based test methods were the first molecular methods used for the detection of HPV virus, which have been developed with the advent of objective PCR technologies, together with scientific community's understanding of the role HPV plays in cervical cancer. Since then, technology advanced dramatically. mRNA-based hrHPV assays represent second-generation molecular tests. The significant performance superiority of an mRNA-based hrHPV assay is the attribute that

detection of viral mRNA, and in particular transcripts spanning the HPV E6/E7 region, would only be present in women with active productive or transforming infections, and would be generally absent in women who are HPV DNA positive because of a recent deposition of virus.

A recent study by Reid et al. (2015) demonstrated a 24% reduction in false positive test results with mRNA-based compared with DNA-based hrHPV assays (Reid et al., 2015). Expression of mRNA from viral E6 and E7 oncogenes is highly associated with the development of CIN (Sotlar et al., 2004; zur Hausen, 1994). Extensive investigation into the role of E6 and E7 oncoproteins in the human papillomavirus (HPV) life cycle has revealed that the expression of the corresponding oncogenes is necessary and sufficient for cell immortalization, neoplastic transformation and the development of invasive cancer (Klingelhutz et al., 1996; Liu et al., 2006; Schreiber et al., 2004). After 3 years of follow-up, women in this study who were HPV negative at baseline had very low risk for CIN2+ (<0.3%).

It is worth noting also that in this study results revealed that women with a NILM cytology result who also had a positive mRNA HPV result were approximately 24 times more likely to have CIN2+ disease after 3 years than women with a negative mRNA HPV result. This risk increased to approximately 68-forl for detection of CIN3+ disease.

Based on multiple clinical trials, HPV mRNA testing predicts the development of moderate to severe cervical dysplasia with similar sensitivity and improved specificity compared to HPV DNA testing methods. By utilizing mRNA testing, care paradigms can shift more selectively toward patients with active, oncogenic infections, and false-positive testing and unnecessary procedures can be avoided. This, in turn, can improve quality of life and treatment planning for these patients.

Consistent with the above conclusions, were the results from another clinical trial conducted by researchers from Department of Pathology and Genomic Medicine, BioReference Laboratories, Methodist Hospital Research Institute in Houston, and Weill Medical College of Cornell University in New York (Ge et al., 2019).

They analyzed HPV genotyping performance in risk stratification among cytology diagnosis categories in more than 4500 cases with cytology–HPV Co-Testing and biopsy follow-up. The clinical performance of different HPV assays, especially between assays targeting HPV L1-DNA and HPV E6/E7-mRNA, varies greatly. It is advocated by authors that the difference in clinical performance among the commercially available HPV assays may be attributable to the molecule that each HPV assay is targeting to, the mechanism to detect virus along with the HPV progression. The performance of E6/E7-mRNA HPV test genotyping in risk management was superior to HPV-DNA test due to its significantly higher specificity and positive predictive value in predicting high-grade squamous intraepithelial lesions or worse on biopsy. The mechanism may be related to the significant increase in E6/E7 expression following HPV DNA integration in high-grade squamous intraepithelial lesions or worse. They highlight the importance of carefully interpreting data from studies using different HPV testing methods and the need to incorporate HPV mRNA testing into the management guidelines and criteria.

Comparing Sensitivity

The Reid study compared the clinical performance of DNA-based hrHPV assays and an mRNA-based hrHPV assay using a cotest strategy for cervical cancer screening in a cohort of 10,860 women aged 30 years or older (Reid et al., 2015). The cumulative three-year absolute risk for CIN3 (cervical intraepithelial neoplasia) or higher was comparably low for either test for women with a negative result, indicating both tests provide a high negative predictive value. In contrast, cumulative absolute and relative risks

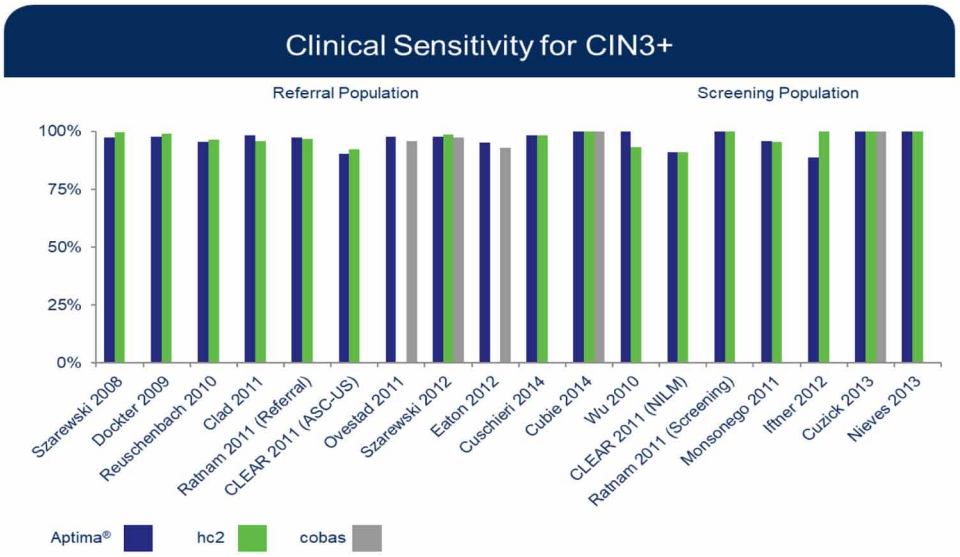
of CIN2+ and CIN3+ was consistent higher for mRNA-based hrHPV positive test than for DNA-based hrHPV positive test each year (Reid et al., 2015). More specifically, 6,3% of women with an mRNA HPV-positive result had CIN2+, whereas 5,1% of women with an HPV DNA test had CIN2+.

Together these data, and other studies, indicate that Co-Testing with mRNA-based compared with DNA-based hrHPV assays delivers equivalent clinical sensitivity, but mRNA-based testing was more specific for detection of CIN2 or worse (Haedicke & Iftner, 2016; Iftner et al., 2015; Luhn & Wentzensen, 2013).

As shown in the following figure (Figure 2), mRNA HPV testing has consistently shown equal sensitivity and superior specificity when compared to HPV DNA testing assays.

Figure 2 shows a summary of individual head-to-head studies assessing sensitivity for biopsy-confirmed CIN3+, while Figure 1 shows the comparative specificity for biopsy-confirmed CIN2+ for HPV DNA and mRNA assays.

Figure 2. Studies demonstrating clinical sensitivity with mRNA-based assay.



COMPARING COST-EFFECTIVENESS

The impact of the improved specificity on cost-effectiveness of cervical cancer screening was investigated in a study by Ting et al. [49] that compared costs and health outcomes between mRNA-based and DNA-based hrHPV assays in the context of current U.S. cervical cancer screening guidelines. Screening efficiency was examined using two different screening strategies: a) cotesting with HPV and liquid-based cytology in women 30 to 65 years; and b) triage of women with mild cervical cytological abnormalities in the U.S. (Ting et al., 2015). A Markov model for stochastic cost-effectiveness analysis was constructed using data from the Reid et al. study and another by Monsonego et al., both conducted in population-based settings (Castle et. al, 2015; Monsonego et al., 2011; Ting et al., 2015). The model followed a theoretical cohort

of women from age 12 to 100 years, not vaccinated for HPV, and assumed that at the beginning of the simulation that no woman was infected with HPV, or had CIN or cancer.

For both cotesting and triage screening protocols, mRNA-based hrHPV testing cost less than DNA-based hrHPV testing. Results indicated a 100% probability that DNA-based testing was not cost-effective, relative to mRNA-based testing, at the $100,000 per life-year saved threshold for triage, and a 55% probability that DNA-based testing was not cost-effective at the $100,000 per life-year saved threshold for cotesting. Based on the available evidence, mRNA testing for cotesting or ASC-US triage is likely to be more efficient than DNA testing under current US cervical cancer screening guidelines.

Felix et al. in another study presented the results of clinical-economic comparisons of Pap plus HPV mRNA testing including genotyping for HPV 16/18 (Co-Testing) versus DNA-based primary HPV testing with HPV 16/18 genotyping and reflex cytology (HPV primary) for cervical cancer screening (Felix et al., 2016). A health state transition (Markov) model with 1-year cycling was developed using epidemiologic, clinical, and economic data from healthcare databases and published literature. A hypothetical cohort of one million women receiving triennial cervical cancer screening was simulated from ages 30 to 70 years. Screening strategies compared HPV primary to Co-Testing. A 3-year interval for both strategies was employed as there is a known increase in the risk of invasive cervical cancer when extending the interval or Co-Testing to 5 years (Kinney et al., 2015). Use of the 3-year interval is not only within the recommended guidelines for screening outlined by the US Preventative Services Task Force (USPSTF) but it is also the most commonly adhered to strategy in the US (King et al., 2014; Kulasingan et al., 2013; Verilli et al., 2014).

Outcomes included: total and incremental differences in costs, invasive cervical cancer cases and deaths, number of colposcopies, and quality-adjusted life years for cost-effectiveness calculations.

Model results demonstrated that Co-Testing with the use of a highly specific HPV assay is not only clinically superior but also provides a cost-effective and potentially long-term cost-saving way of screening for cervical cancer compared to primary HPV screening. The model reveals that screening women with HPV testing alone would result in an additional 21 cases and an additional 20 deaths from cervical cancer per 100,000 women. It also predicts that the costs associated with screening and managing women using this strategy are higher than those using co-testing.

When projected the results to the one-million-woman cohort, the model predicts that using Co-Testing results in 2,141 fewer cases and 2,041 fewer deaths from cervical cancer, while achieving $39 million in savings when compared to screening using HPV testing alone.

Co-Testing also resulted in slightly fewer lifetime colposcopies per woman, fewer false positive colposcopies, and a higher number of true positive colposcopies.

If one applies the results of this model to the total screening population of the US, the model predicts that using HPV testing alone, rather than Co-Testing, would result in approximately 150,000 additional cases of cervical cancer and more than 100,000 cervical cancer deaths, while costing an additional $4.4 billion in health care costs over the 40-year screening period.

Consequently, results from Felix's study strongly support that Co-Testing remains the preferred approach for cervical screening in women aged 30 to 65, since this strategy, when compared with screening using HPV testing alone, decreases invasive cervical cancer cases and deaths and provides substantial long-term cost savings to the healthcare system.

A more recent study by Weston et al. examined the impact of using the m RNA high-risk human papilloma virus (HR-HPV) assay versus a DNA HR-HPV assay in a primary HPV cervical screening program (Weston et al., 2020). The study was designed on a hypothetical cohort followed for 3 years

through HPV primary cervical screening. The model simulated a cohort of 2 247 439 representing the number of women tested in the NHS Cervical Screening Program (CSP) in 2017–2018.

The rationale of this study was that a positive HR-HPV DNA test indicates the presence of DNA above certain concentration in cervical cells (Cook et al., 2018). However, as HPV infection is often transient and can be spontaneously cleared, the presence of this DNA does not necessarily indicate that a precancerous abnormality will develop (Stoler et al., 2013). The presence of HR-HPV E6/E7 mRNA in cervical cells has been shown to more accurately detect those at risk of developing CIN, and therefore at more at risk of developing cervical cancer, than the presence of HPV DNA (Arbyn et al., 2013; Cook et al., 2018).

The main primary outcome measures were total colposcopies and total costs for the cohort and secondary total HPV and cytology tests and number lost to follow-up (LTF).

In the population of 2.25 million women in the NHS CSP program, using an mRNA versus DNA HPV test saved an estimated £15.4 million, averted an estimated 28 009 unnecessary colposcopies, 90 605 unnecessary HR-HPV tests and 253 477 unnecessary cytology tests. There were also 9536 fewer women LTF for their colposcopy referral, and 114 988 fewer women LTF for HPV recall in years 2 and 3 for mRNA versus DNA testing.

The baseline results of this model suggested that using the Aptima mRNA assay versus Cobas 4800 HPV DNA assay in the new primary HPV screening algorithm in England is likely to result in a reduction in overall screening costs, unnecessary referral to colposcopy, unnecessary recall HR-HPV and cytology tests and reduced LTF. These reductions in resource use should not be associated with any subsequent reduction in identifying true positive women, as the sensitivity of the assays has consistently been shown to be similar (Dockter et al., 2009).

There is also expected to be an impact on women's quality of life. Cervical screening and colposcopy can have a negative impact on women's quality of life when they receive positive screening results or are referred to colposcopy (Waller et al., 2007).

By choosing the most specific test, the healthcare system can reduce the unnecessary stress and anxiety in women associated with unnecessary tests for false positives with no trade off in detecting CIN given that mRNA assays are as sensitive as DNA assays (Iftner et al., 2015).

Overall, results from the study suggest that using the Aptima mRNA HR-HPV assay is less expensive and avoids unnecessary HPV recall testing, cytology testing and colposcopies than using a DNA HR-HPV assay in the new primary HPV screening algorithm.

CONCLUSION

These studies show cervical cancer screening efficiency can be affected by the type of HPV assay used as well as the overall strategy. Results from these studies provide evidence that Co-Testing with an mRNA-based hrHPV assay is more likely to be cost-effective than DNA-based hrHPV testing, whether DNA-based hrHPV testing was used in Co-Testing or alone as a primary screening strategy.

The cost-benefit associated with the mRNA-based hrHPV assay observed in these analyses arises from the improved specificity of the mRNA-based assay that specifically detects expression of HPV oncogenic proteins, as opposed to DNA-based testing that reports only presence of the virus. The ability to detect expression of HPV oncogenic proteins E6/E7 favors the distinction between HPV infections that will progress to cervical cancer from those that will regress, leading to fewer cases where HPV nucleic

acids are detected but disease is not present. The information provided by an mRNA-based hrHPV assay result gives healthcare providers and patients greater assurance about whether or not there is a need for follow-up procedures. The improved specificity of mRNA-based hrHPV assays, together with improved sensitivity of mRNA-based hrHPV assay cotesting (mRNA-based hrHPV + LBC) compared with DNA-based hrHPV testing, suggest transitioning to DNA-based hrHPV testing alone as a primary screening would be not only less efficacious, but also more costly.

Moreover, Co-Testing has been successfully implemented into practice in the United States and recent data shows a continued decline in cervical cancer rates.

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Chapter 9
Is mRNA indeed Useful in Clinical Management of Cervical Pathology?

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ABSTRACT

Personalised medicine and precision medicine are being applied in more medical fields in the last years. The need for personalisation is especially pronounced in cervical pathology, since in the majority of cases an abnormal screening test does not necessarily imply high-grade lesion, regardless of whether the screening test is cytology or HPV testing. The chapter aims to summarize the exact added value that mRNA presents for management in clinical practice as well as highlight comparative advantages and disadvantages with other triage strategies.

INTRODCUTION

Personalised medicine and precision medicine are being applied in more and more medical fields in the last years. The need for personalisation is especially pronounced in cervical pathology, since in the majority of cases an abnormal screening test does not necessarily imply high-grade lesion, regardless of whether the screening test is cytology or HPV testing.

Deviation from the principles of personalised medicine leads unavoidably to overtreatment, with both clinical and psychological side effects. As far as the clinical side effects are concerned, CIN treatments have been associated with an increased risk of reproductive morbidity, such as miscarriage in

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the second trimester, preterm birth (PTB) (overall less than 37 weeks of gestation, but also more severe prematurity including less than 34 or 28 weeks of gestation) and perinatal mortality (Kyrgiou, 2006;Arby, 2008;Kyrgiou, 2014; Kyrgiou, 2015; Kyrgiou, 2016;Kyrgiou, 2017). This risk is more pronounced with more radical treatments and increasing cone depth. For example, relative risk (RR) of PTB is 1.54 (1.09, 2.18) for cone depth less than 10/12mm, compared to general population, but RR increases to 1.93 (1.62, 2.31) for cone depths more than 10/12mm, 2.77 (1.95, 3.93) for cone depths more than 15/17mm and 4.91 (2.06, 11.68) for cone depths more than 20mm (Kyrgiou, 2016). Psychological consequences should also not be neglected. Informing the patient that she needs treatment causes anxiety and panic, not only in the same patient but also in her family.

For this reason, CIN1 lesions should be managed conservatively, and only CIN2+ lesions should be treated, as a rule of thumb. In young women wishing further fertility, conservative management of CIN2 lesions is also acceptable (Massad, 2013), as long as colposcopy is satisfactory and patient is not expected to be lost to follow-up. Expectant management of CIN2 lesions is justified, because a high percentage of CIN2 lesions regress spontaneously, especially in younger women. According to a recent meta-analysis (BMJ, 2018), regression rate of CIN2 is 60% (57-63%) for women aged less than 30 years, and only 11% (5-19%) of CIN2 will progress to CIN3+ in this age group.

Although histology/biopsy is considered to be the gold standard in most medical fields, this is not very clear in cervical pathology. Sensitivity of colposcopically-directed punch biopsies (PBs) is not always high. According to a meta-analysis (Underwood, 2012), when cone histology was CIN3+, pre-treatment PBs had shown <CIN1 in 8.9% of cases, and <CIN2 in 19.9% of cases. In addition, PBs showing CIN2 are not informative of whether this lesion has a high likelihood of spontaneous regression in the future, similar to most CIN2 lesions (thus treatment is not necessary), or whether it might persist or progress (thus treatment might be warranted). For this reason, apart from PB results, more information is needed to help us in the personalised management.

A simple and free 'tool' that is available to everybody is the assessment of lifestyle risk (Table 1). Smoking (Collins, 2010), first sexual experience at a young age (Ruiz, 2012) and multiple sexual partners (Chan, 2003) are aggravating factors associated with a greater likelihood of an underlying high-grade lesion and lower likelihood of spontaneous regression. On the other hand, condom use (Munk, 20120) and HPV vaccination (especially before coitarche) (Paavonen, 2009) are protective factors.

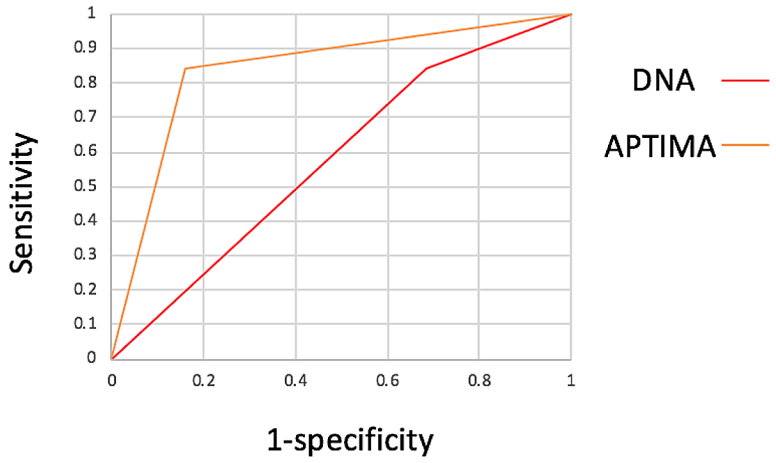
Table 1. Lifestyle risk assessment

	Low Risk	**Medium Risk**	**High Risk**
Smoking	No	Socially / <20 cigarettes	>20 cigarettes
Interval between menarche and coitarche	>6 years	3-6 years	<3 years
Number of sexual partners	<5	5-10	>10
Condom use	75-100%	50-75%	<50%
HPV vaccination	Yes, prior to coitarche	Yes, after coitarche	No

In the last years, risk stratification can also be performed through biomarkers. In contrast with cytology/ colposcopy/PBs informing us of the morphology of the cells, biomarkers provide valuable information

regarding what is going on at a molecular level. Two of the most frequently used biomarkers are HPV DNA test and HPV mRNA test (Aptima). HPV DNA test detects the existence of HPV. However, an HPV infection does not necessarily mean that this infection is 'active', i.e. that HPV oncoproteins E6/E7 are produced and carcinogenesis process has started. For this reason, HPV DNA test cannot distinguish between an 'active' and 'latent' HPV infection, and as a result it is positive not only in high-grade lesions, but also in low-grade lesions or in women without cervical pathology! In addition, some HPV DNA tests detect L1 gene, which might be lost when HPV DNA is integrated into host DNA in high-grade lesions and invasive cancer. Therefore, HPV DNA tests can miss as many as 20% of invasive cervical cancers (de Sanjose, 2010; Blatt, 2015)..

Figure 1. ROC curve for histological CIN2+



On the other hand, Aptima detects mRNA of the oncoproteins E6/E7. A positive mRNA test means that HPV infection is 'active' and oncogenic. A significant advantage of Aptima is its higher specificity: its positivity rates in uncomplicated HPV infections or low-grade lesions are much lower than HPV DNA test. At the same time, its sensitivity is equal to HPV DNA test and additionally, it does not miss cancers where L1 gene might have been deleted during genome integration. In other words, Aptima identifies only these women that are truly at risk of developing cervical cancer.

In order to calculate the efficacy of HPV DNA and mRNA tests, we performed a pragmatic study in women with abnormal cytology or history of abnormal cytology/treatment, who attended a colposcopy clinic participating in the Hellenic Cervical Pathology Academic (HeCPA) Group in 4 Greek cities (Ioannina, Athens, Thessaloniki, Patras). We recorded colposcopic impression, cytology result, HPV DNA (PCR: Array or Clart 3) or E6/E7 mRNA (Aptima) test, and lifestyle variables (smoking, interval between menarche and coitarche, number of sexual partners, condom use and HPV vaccination). If available, we also recorded histology result (either on PBs or on excised cone if treatment performed). Our aim was to estimate sensitivity, specificity and positive predictive value (PPV) of HPV tests for CIN2+ lesions.

For histologically-confirmed CIN2+, HPV DNA and mRNA tests had a similar sensitivity at 84.1%, but mRNA had greater specificity (83.9% vs 31.5%) (Figure 1). The same pattern was observed for cytological CIN2+ (mRNA vs DNA: 78.4% vs 84.2% for sensitivity; 79.6% vs 53.4% for specificity) (Figure 2).

Figure 3 depicts the percentage of positive HPV DNA and mRNA test according to histological diagnosis, and Figure 4 according to cytological diagnosis.

Figure 2. ROC Curve for cytological CIN2+

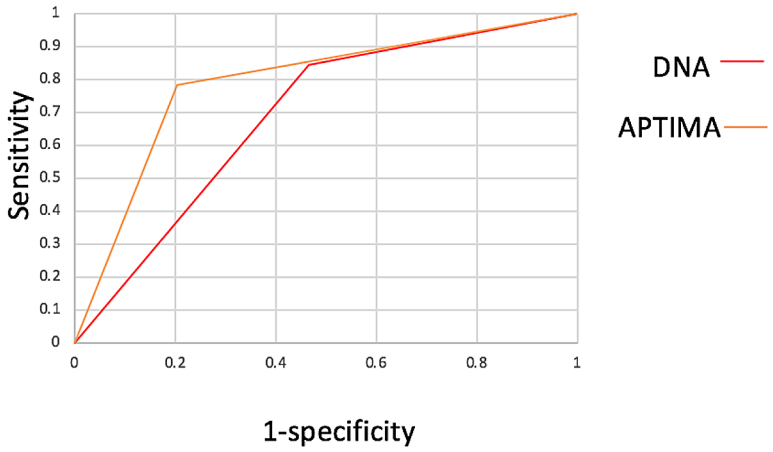
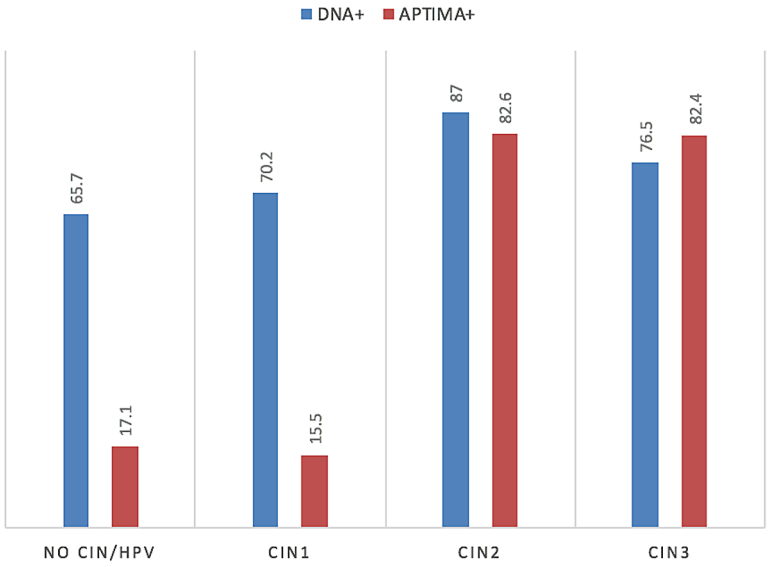


Figure 3. Positivity rates of HPV DNA and mRNA test according to histological diagnosis



In patients with abnormal cytology and colposcopy, we also calculated PPV. PPV of HPV mRNA for histological CIN2+ was 70% vs 35.7% for HPV DNA test. PPV of both positive HPV mRNA test and high-risk lifestyle was 98.3% (Figure 5). In other words, the conclusion is that if a patient with a high-risk lifestyle assessment attends a colposcopy clinic due to abnormal cytology and in whom colposcopy is

also abnormal and HPV mRNA test is positive, then the probability of an underlying high-grade lesion is almost 100% and treatment could be performed without the need for PBs. (NB: These conclusions cannot be applied to the general population, but to a highly specific subgroup of women who attend a colposcopy clinic due to abnormal cytology and in whom colposcopy is also abnormal).

Figure 4. Positivity rates of HPV DNA and mRNA test according to cytological diagnosis

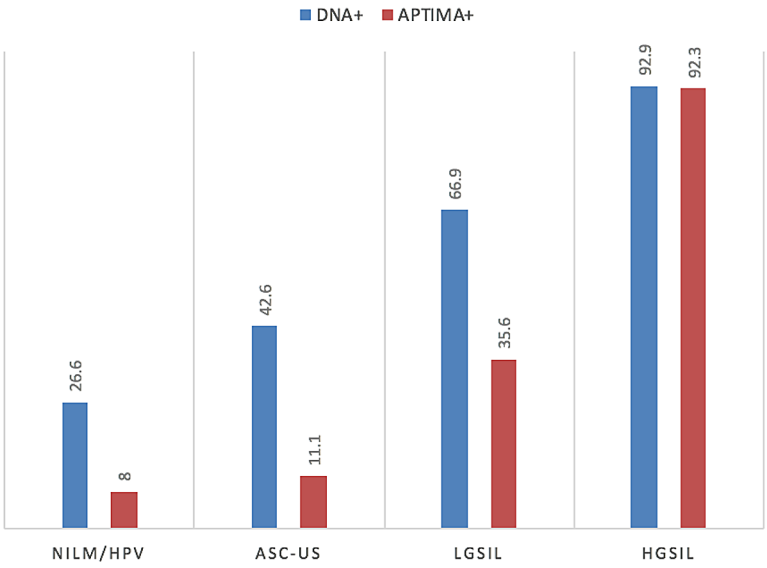
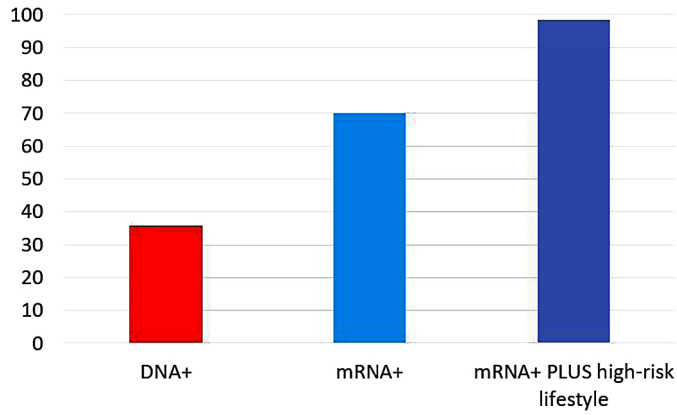


Figure 5. PPV for CIN2+ in women with abnormal cytology and colposcopy



The plans for the new version of ASCCP guidelines revolve around the need for personalisation. The aim of ASCCP is to adopt a 4-tier ranking for women attending cervical cancer screening programmes (Schiffman, 2017). In this suggested ranking, blue will denote a very low risk (i.e. no further action is needed), green will denote a low risk (i.e. triage or repeat cytology is needed), orange will denote medium risk (i.e. colposcopy is needed) and red will denote high risk (i.e. treatment is needed). This

risk stratification will take into consideration age, cytology, HPV testing, HPV vaccination status and history of screening test results. This 4-tier ranking is similar to a 3-tier ranking system which HeCPA group has implemented for women attending a colposcopy clinic because of abnormal screening test, where green denotes women at low risk, in whom the probability of an underlying high-grade lesion is low and return to general population screening is justified, orange denotes women at medium risk, in whom a more intensive surveillance is warranted, and orange denotes women at high risk who need treatment. Apart from the use of HPV mRNA test as triage test or even as screening test (in most parts of the UK, HPV mRNA will be now used as the primary screening test), HPV mRNA test is also useful as Test of Cure (ToC) at 6 months after treatment. Sensitivity of HPV DNA test as ToC is better than cytology and varies from 90.6 to 100%, while its specificity is not worse than cytology and varies from 63.8% to 93.1% (Mariani, 2016). There are not many studies yet investigating the role of HPV mRNA test as ToC, but our experience has shown that HPV mRNA is as sensitive as HPV DNA test, with better specificity though.

In addition to their good performance as ToC at 6 months, HPV tests might feature better sensitivity than cytology and colposcopy for detecting these rare cervical cancer cases who are being developed within many years after initial CIN treatment. In women with history of CIN treatment, the risk of invasive cervical cancer is 4-5 times higher than general population (Sourter, 1997). In the University Hospital of Ioannina, Greece, we have collected in the last 20 years 9 invasive squamous cervical cancer cases after previous CIN treatment. Interval between CIN treatment and diagnosis of cervical cancer varied from 7 to 17 years. The main and striking feature in all cases was that post-treatment follow-up was regular and normal, until cancer was diagnosed suddenly and unexpectedly on cytology or colposcopy. This could be explained by the crypt theory: Heavy cauterisation of the cervical crater during treatment might bury dysplastic cells (or cells currently not dysplastic but having been exposed to the same carcinogenic factors as the rest of the transformation zone) inside the crypts. These cells might subsequently progress to high-grade lesions or cancer, but cytology or colposcopy cannot detect them. It is only when the tumour reaches the external surface or the endocervical canal that they become accessible to cytology/colposcopy and can be detected. Cervical stenosis (a common side effect of CIN treatment) might delay the diagnosis of invasive cervical cancer even further.

HPV tests might probably have better sensitivity that cytology/colposcopy in detecting these rare cases of cancers after treatment, therefore a positive HPV DNA or mRNA test in women with history of previous CIN treatment should not be dismissed as non-important, even if cytology and colposcopy are normal. If the patient also reports symptoms suggestive of invasive cervical cancer (such as post-coital bleeding) and is >40-50 years of age, a repeat conisation could also be considered to exclude invasion inside the crypts.

To sum up, HPV mRNA test is a useful screening or triage test. If the lesion is proven or suspected to be serious and treatment is warranted, clinicians should try achieving the best oncological outcomes, without increasing significantly the risk of reproductive morbidity in subsequent pregnancies, i.e. treatment should be as radical as it should be (Arbyn, 2014). The balance between oncological and reproductive safety is fine and quite an art and requires a significant amount of experience. Finally, mRNA is also useful in detecting residual or recurrent disease after CIN treatment.

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Chapter 10
Non-Free Surgical Margins After LLETZ-LEEP:
Additional Intervention or Conservative Management?

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ABSTRACT

Large Loop Excision of the Transformation Zone (LLETZ) is thought to be the treatment of choice for the high-grade precancerous lesions. The cone is also the "gold standard" specimen for the diagnosis of the underlying cervical disease once it includes the entire area of carcinogenesis for the squamous epithelium (transformation zone). In most research studies, therapeutic success after conization is a term generally assigned for disease clearance, that is, absence of residual high grade/CIN2+ histology by the end of a reasonable follow-up period, aiming at risk reduction for future recurrence and development of invasion. Conversely, positive cone margins as a reflection of an incomplete excision may, to some extent, represent a negative prognostic factor. Therefore, margin status may also be regarded as an indicator for the quality of a clinical service. The chapter summarizes all current evidence regarding optimal treatment of positive margins after LEEP.

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INTRODUCTION

Among various options for the management of cervical precancerous lesions, Large Loop Excision of the Transformation Zone (LLETZ) is thought to be the treatment of choice for those labeled as High Grade. The cone is also the "gold standard" specimen for the diagnosis of the underlying cervical disease once it includes the entire area of carcinogenesis for the squamous epithelium (transformation zone).

In most research studies therapeutic success after conization is a term generally assigned for disease clearance i.e absence of residual High Grade / CIN2+ histology by the end of a reasonable follow-up period, aiming at risk reduction for future recurrence and development of invasion. Conversely, positive cone margins as a reflection of an incomplete excision may, to some extend, represent a negative prognostic factor. Therefore, margin status may also be regarded as an indicator for the quality of a clinical service.

In addition, there have been reports linking the cone size with the risk of preterm delivery. Consequently, balancing the risk between an iatrogenic complication (sizable cone bringing therapeutic success but contributing to a future preterm delivery) and a sub-optimal treatment (small "cervix-preserving" cone resulting to an incomplete excision) is of ultimate importance and also a major challenge for the clinician. *(Arbyn M. et al, 2017)*

THE IMPORTANCE OF POSITIVE MARGINS AND INDIVIDUALIZED MANAGEMENT

In case of positive margins the main question is whether this positivity truly reflects incomplete excision leading to residual disease. This residual disease may be important for two reasons. Firstly, since it is not included in the diagnosed specimen there is always an unknown risk to involve concurrent invasion. Secondly, this possible residual disease may also impose a threat for future development of such an invasion, if left untreated, as it occurs with any primary dysplastic disease.

It is well known from the natural history of HPV related lesions that the majority of the cases represent transient cellular changes that are restored back to normal after an ill-defined period of time ranging from a few months to 3-5 years thus leaving an intact epithelium. Conversely, a minority of the individuals affected by an oncogenic HPV type, will sustain a persistent infection and will follow an oncogenic pathway consisting of cellular transformation leading to carcinogenesis. Although there are no clearly defined causative factors leading to the oncogenic pathway, a number of identifiable parameters are linked statistically with the above disease progress, assisting us to formulate an estimate for the risk of the individual woman to develop invasion and therefore, to offer appropriate management.

Different histologic grades at a given time of diagnosis of the disease reflect different potential for disease progress or regression. A CIN2-3 lesion for example, is more related to persistent infection with E6/E7 expression and stimulation of cell proliferation and a higher risk to advance to neoplasia whereas a Low Grade lesion may merely be the expression of a transient infection with low oncogenic potential and a higher expectation for self-resolution.

Also, the fact that HPV of the lower genital tract is regarded as a common infection, affecting as much as 70 – 80% of the young female population in a typical western society, obviates the existence of "individual factors" or "host factors" for those few ones who will manifest cervical lesions and more so for those, even fewer ones, who will develop invasive disease, among the vast pool of infected subjects. At this point, systemic and local immunity seems to play a pivotal role. Known factors that alter im-

munity, such as, immunosuppressive diseases, medication, as well as hpv vaccination history are taken into account. Nevertheless, in the majority of cases of High Grade dysplasia there are no such clear, identifiable attributes but other immunity related paremeters have been statistically associated with precancerous lesions, namely smoking, dietary habits and lifestyle related to sexual behavior.

The type of hr-HPV also plays a significant role in the disease progress. HPV 16 for example, has an average length of persistence that is longer than most other high-risk types, and this may contribute to its higher cancer risk. This applies to a lesser extend, to other hr-hpv types. Other types (like type 18) seem to express a higher tropism for lesions extending to the glandular epithelium; therefore the type of hpv involved in a residual lesion is valuable information.

The above factors (Grade of the disease at the time of the initial diagnosis, HPV Type, and host factors) which, carry a prognostic role in the disease progress, are also prognostic factors for progression, in the case of residual disease after an excisional treatment.

Another group of factors that should be considered involves technical issues related to the excision procedure itself. Unfortunately, in some occasions the margin status is difficult to define or it is equivocal. This may occur in the case of excessive tissue thermal destruction by the energy used for cutting (electrical energy, laser beam) where the marginal tissue does not provide any information to the pathologist for the presence or absence of dysplastic changes. In other occasions, part of the epithelium at the cone borders is sloughed away from the main specimen thus limiting again pathologic interpretation as regards to marginal status. Another challenge related to treatment of the specimen or the resection technique is the actual anatomical definition of the margins themselves. This is the case where multiple specimens are produced either due to the need to assess the endocervical canal in higher depth as mandated by the clinical case scenario (ex. Glandular lesions) where the decision for a 2nd resection, deeper in the canal, is taken (top hut technique) or in other cases where, for example, the initially single fragile specimen looses its integrity and tears apart during storage or transport to the pathology. In all such cases proper orientation of the multiple parts is an issue in order to correctly reconstruct a "single" piece for the borders to be properly defined. Ideally, a single, properly treated cone, excised by a standard technique produces the right quality specimen but this is not always the case, as it occurs in the above examples, raising an ambiguity when describing the marginal status.

Overall, when planning management on positive margins the primary question is whether this positivity equals a complete therapeutic failure. In other words, the question is whether the risk of concurrent or future invasion still remains high enough to preclude expectant management for self – resolution.

Considering the natural history of the cervical precancerous lesions, the biology of carcinogenesis in relation to HPV type and host immunity, as discussed above, the answer would be based on the individual's prognostic factors related to its case scenario, the type of cone and woman's history. These can be summarized as below:

- The oncogenic potential of the treated precancerous lesion.
  - Grade of Lesion (CIN2, CIN3, extension to the endocervical glands, microinvasion – AdenoCa In Situ – AIS)
  - HPV type
  - Lesion size
  - Extend / number of positive margins sites
  - Topography of positive margins (endocervical or ectocervical)
- Host factors

- Age
- Immunosuppression (associated diseases, medication)
- History of precancerous lesion and treatment

- Specimen factors
  - Extension of thermal lesions
  - Fragmentation of the cone specimen

The decision on positive margins management (Expectant versus Surgical) is also influenced by the woman's perspective on family planning issues. The association of conization to cervical compromise raises a great challenge between risks for two major events, cancer development and premature delivery.

RISK FACTORS – THE EVIDENCE

The evidence for the role of the above factors on which to base the individualization of positive margins management derives mainly from retrospective studies and meta-analyses with a wide heterogeneity on comparison groups and primary endpoints. An attempt to produce prospective trials with cancer development as a primary endpoint would obviously raise serious ethical issues.

A recent retrospective study of 3582 women, explored the risk factors for persistent HSIL after Loop Electrosurgical Excision Procedure (LEEP). During follow-up 101 women expressed persistent High Grade disease and 9 women developed invasive cancer. Among various parameters examined between women with persistent disease and the non-persistent group were the dimensions of the cone specimen (width, length and circumference) the positivity of endocervical and ectocervical margins, age, cytology abnormality and positivity of hrHPV during the follow-up. After multivariate logistic analysis in was shown that positive margins, abnormal cytology during follow-up, positive hrHPV testing during follow-up and age above 50 were independent risk factors for persistent disease. Worthy to note is that positive endocervical margins were associated with a higher rate of persistence than positive ectocervical margins. The cone size itself (circumference, length and width) did not show any significant statistical difference between the persistent and non-persistent group (Chen L. et al, 2019). The above study shows the significance of the type of margins involved (endocervical) and age. The above information would easily prompt the decision towards repeat excision rather than expectant management, on positive margins of an older woman with a High Grade cone. Especially, if we consider that there is no family plan to compromise in the majority of this age group.

Another study shows the existence of residual disease in a series 232 women with CIS-positive margins who all underwent hysterectomy. In the majority of studies primary outcomes are usually related to disease development during follow-up, which undoubtedly has its clinical significance, and a statistical analysis is performed between free and positive margins groups. In such studies it is difficult to distinguish between residual or recurrent disease as the underline cause of an adverse outcome. The unique in the above study is that it directly addresses to the initial question; whether positive margins "equals" residual disease and what are the circumstances when this occurs, by providing a gold standard specimen (the remaining uterus), which does not allow much space for misinterpretation. The clinical parameters studied for their relationship with the existence of residual lesion in the uterine specimen after LEEP included age, LEEP method, histologic grade of the conized cervix, location of the positive margin after LEEP (mainly the distinction between endocervical and ectocervical), results of endocer-

vical curettage (ECC) when available and size of the conized specimen. After hysterectomy the factors with a significant statistical difference between patients with residual lesions and those with no residual lesion were age, excision method (CKC favoring less residual desease), proximal endocervical margin positivity and ECC positivity. When women with residual disease were sub-grouped to a higher and lower than microinvasive carcinoma (MIC) the histologic grade of the conized cervix statistically differed as well. Another important finding was that there were no residual invasive (MIC or advanced invasive cancer) lesions in women below the age of 50 who had High Grade lesion in the cone specimen. Therefore, since age is shown to be a key factor in the above study, conservative treatment with close follow-up appears to be a reasonable option for the younger age group especially when an available ECC is negative *(Chong GO. et al, 2017).*

Regarding the role of hrHPV testing, there is a systematic review and meta-analysis assessing the risk of therapeutic failure after excisional treatment of precancerous cervical lesions and its association with histological status of the cone margins. Therapeutic failure was defined as the occurrence of residual or recurrent CIN2+ disease during post conization follow-up. The study included 44446 cases. The inclusion criteria were the clear definition of the marginal status and the presence of follow-up including a) cytology or some type of HPV test between 3 and 9 months after treatment and b) further follow-up for at least 18 months including histologic confirmation for the presence of CIN2+

The positive margin rate was 23.1% (95% CI 20·4-25·9) overall. The above rate varied by treatment procedure (ranging from 17·8% [12·9-23·2] for laser conisation to 25·9% [22·3-29·6] for large loop excision of the transformation zone) and increased by the severity of the treated lesion. The risk of residual or recurrent CIN2+ was 6.6% (95% CI 4·9-8·4) and was increased by almost five-fold with positive resection margins (RR= 4.8 [95% CI= 3.2 – 7.2]) making positive margins a seemingly important predictor. Interestingly though, the pooled sensitivity and specificity for residual or recurrent CIN2+ lesion was 55.8% [95% CI= 45.8 – 65.5] and 84.4% [79.5 – 88.4] respectively which is inferior to the performance of post treatment hrHPV positivity (sensitivity 91% [95% CI= 82.3 – 95.5] and specificity 83.8% [77.7 – 88.7]) (Arbyn M. et al, 2017). On the other hand, in the group of women with free cone margins there was a risk of 3.7% to present with a CIN2+ histological lesion during follow-up whereas the rate of the treatment failure in the case of a negative hrHPV test post treatment was only 0.8% according to the pooled data of the above review.

Conclusively, the above meta-analysis has shown the important predicting value of positive cone margins for occurrence of treatment failure, nevertheless it does not seem to be the defining prognostic factor. Interestingly, hrHPV testing post treatment has shown a remarkably better performance as a predictor of treatment failure compared with the margins positivity. It is well known that HPV testing carries a high sensitivity and negative predictive value for the presence of High Grade disease in general. According to the results of the above study it seems to perform equally well in that area when it comes to the conized cervix making it a useful tool during follow-up for the decision making in the case of previous positive cone margins. Secondary but equally important messages of the above study is the association of treatment method and occurrence of CIN2+ histological disease during follow-up, favoring laser conization over Large Loop Excision of the Transformation Zone (LLETZ).

The importance of hrHPV test was also demonstrated in a pilot study where 352 women were tested with colposcopy and Pap smear at 6 months post-excisional treatment (either conization or LEEP procedure). The choice for the type of procedure was based on the accessibility of the transformation zone and the degree of the dysplasia. The advantage of this study was that is was a prospective one, which allowed for hrHPV test to be performed before and after treatment. These women had a follow-up for 5

years. Overall, 43 patients (12.2%) were considered as having recurrent disease. True recurrence 6 months after the initial procedure was revealed in 37 women (10.5%). The most important predictor of recurrence was the positive hrHPV test at 6 months post-op (OR= 38.8% [95% CI= 14.09 – 107.05]). The second was positive endocervical margins and the third was posiive pre-treatment HPV typing *(Laquevaque P. et al, 2010).* The results of the above study demonstrate the value of hrHPV testing as a predictor for the development of High Grade disease during follow-up. They therefore support its use as a valuable assessment tool in the decision making when dealing with positive cone margins. Conservative management may be therefore facilitated as a reasonable option in the cases with cone margin positivity. In agreement with other studies, it shows the important predictive value of endocervical margin positivity as a reminder for consideration in management.

The role of the site of margin involvement (ectocervical or endocervical) is shown in another retrospective study of 178 women aiming to identify predictors of recurrent / residual disease. Those women had LEEP for CIN3 or micro-invasive disease and follow-up at 6-12 months. Endocervical / ectocervical margin status, endocervical curettage (ECC) status, and maximum width of cervical intraepithelial neoplasia were assessed. The above study revealed a significant difference in the mean width of the cervical intraepithelial neoplasia between women with ectocervical margin involvement and those with clear margins (10.2 ± 3.1 mm vs 7.3 ± 3.5 mm, $P = 0.0002$). The odds ratios for recurrent / residual disease were 2.1 [95% CI= 0.5 – 8.4] for endocervical involvement, 3.2 [95% CI=1.3 – 7.9] for ectocervical involvement and 6.8 [95% CI=1.4 – 32.1] for ECC-positivity. As far as the age was concerned, analysis of the results demonstrated that, women with endocervical margin involvement or ECC positivity were significantly older while the opposite was true for those with ectocervical margin involvement, belonging to a much younger age group. Those differences above regarding age, localization of margin involvement and surface spread of the dysplastic disease make an indirect implication of different topographical disease pattern in different age groups which seems reasonable if we consider the differences in anatomy and maturity stage of the transformation zone as age advances. In addition, despite the fact that ectocervical margin involvement resulted in a higher degree of association with residual / recurrent disease as compared with the endocervical margin involvement (odds ratio= 3.5 over 2.1 respectively), the opposite was true between those groups, regarding the need for further treatment during follow-up. In line with the above is the fact that most ECC-positive patients (implying endocervical disease spread) underwent a second surgery while most patients with ectocervical involvement did not need further treatment as mentioned above *(Chikazawa K. et al, 2016)*. It seems like age represent an isolated predicting factor with clinical importance presumably due to a different biologic behavior of these HPV related dysplastic disorders in the cervix. This may shift the decision making towards a conservative management with close follow-up of those young women who present involved margins after an excisional treatment.

As far as the topography and extend of positive margins, there is another similar study of 376 women where the overall persistence/recurrence rate was 13%. The conditions studied as possible factors associated with persistent / recurrent disease included age, extent of dysplasia, endocervical glands involvement, positive margin status, degree of margin involvement and postcone endocervical curettage results. Positive cone margins were observed in 33% of women overall. 22% of these located in the endocervix, 8% were ectocervical while the remainder 3% involved both margins. In accordance with previous studies age was significantly associated with positivity using a cutoff of 35 years old. Widespread dysplasia, namely the presence of precancerous lesion in in more than 4 sections of the cone specimen, was also another important associated factor (p Value= 0.003). Concerning the relative risk for persistent / recurrent disease, that was much higher in the group of the involved margins and even higher in the subgroup of

positive margins with extensive disease as defined above. (Hazard ratio= 17, p Value<0.001 – for focal margin involvement and Hazard ration= 28, p Value<0.001 for extensive involvement). Age was also an independent factor (Hazard ratio= 1.18 for every 5 additional years, p Value=0.03) *(Shaco-Levy R. et al, 2014).* In the above study, apart from the significance of age and endocervical disease involvement as useful clinical information for further management, the disease load alone, whether it involves margins or merely presents in cone specimen in the form of multiple sections, also appears to be an indicator for a higher risk of persistence / recurrence. At this point, if it is reasonable to assume a possible relation between the colposcopic appearance and the histologic extend of the disease, the indirect implication would be that the colposcopic impression alone and especially the number of quadrants where the lesions extend might be another piece of information to add while planning management of women with positive cone margins.

Conclusively, while positive margins (especially endocervical) seem to be a strong risk factor for persistent or recurrent disease, they do not constitute an absolute indication for repeat excision, however they strongly suggest closer follow-up at least.

The only condition where positive for dysplastic disease cone margins is an almost absolute indication for repeat excisional treatment is at the presence of micro-invasive disease even if the latter is fully excised. This is incorporated in the British National Health Service Cervical Screening Program guidelines, stating that if the invasive disease is excised but Cervical Intraepithelial Neoplasia extends in the excision margin, then a repeat large loop excision of the transformation zone should be undertaken to exclude further invasive disease and to confirm excision of the dysplastic lesion *(NHSCSP Publication No 20, 2016).*

Despite the above, in everyday practice, there have been deviations from the above guideline predominantly by the rationale to spare fertility risks posed by a repeat excision.

In a retrospective study 17 such cases of conization with co-existance of MIC along with the CIN where identified. In one woman of this group neither the invasive lesion nor the CIN disease was fully excised (margin involvement for both) whereas in 5 cases margins where free for all type of lesions. In 11 women however, the micro-invasive disease was excised fully but intraepithelial neoplasia was present at the cone margin. That was the group of women where none of them opted for a repeat excision, contrary to the existing guideline *(NHSCSP Publication No 20, 2016).* All these 11 women had a negative follow-up, consisting of cervical cytology, for up to 4 years (mean duration= 2 years) *(Nicholson RC. et al, 2018)*. The above suggests that follow-up, even in this unfavorable clinical scenario, could be an alternative option obviously for those who want to minimize the risks of adverse obstetric outcomes in a gestation to come. A thorough in-depth consultation, informed consent and the woman's compliance to a strict follow-up are prerequisites in order to cautiously consider this conservative approach.

Nevertheless, despite all evidence favoring watchful expectant management in many cases of involved margins, one should always bare in mind the risk, however small, of invasion co-existence. This is demonstrated in a retrospective study of women with established High Grade lesion with positive margins in their cone specimen. The advantage of this study was that it was a group of women who underwent 2nd excisional treatment (either 2nd cone of Hysterectomy) within 6 months time, providing an almost co-current "gold standanrd" reference (2nd cone or cervical tissue of the uterine specimen) on which to study the relation between involved margins and true residual disease. Out of the 119 cases, there were 56 (47%) presented with residual HSIL disease in their subsequent surgical specimens, including 3 cases with Micro-Invasive Carcinoma (MIC) (stage 1A1) and 1 case with invasion (stage 1A2). Univariate analysis showed that age >35, menopausal state >5 years and involvement in multiple cone quadrants

were significantly associated with residual disease. In multivariate regression analysis it was shown that multiple quadrants involvement was also an independent risk factor (P = 0.001; OR= 3.701; 95% CI, 1.496-9.154). In almost half cases (the remainder 53%) the 2nd "reference" specimen (2nd cone or full cervix from the uterine specimen) was disease free despite margin involvement of the 1st cone *(Dou Y. et al)*. The above study share some features with a previously mentioned one *(Chong GO et al, 2017)* in the way that, in both, there is a histology gold standard reference in short period of time after conization (all women of both series underwent repeat conization or hysterectomy within 6 months post-op) and they lead to similar conclusions. In the later study, the reference to the number of positive margins as an independent risk factor in multivariate analysis adds an extra value to what previous studies have shown regarding the role of the topographical extend of the dysplastic lesion.

Although it seems that, when certain conditions are met, the option for follow-up is reasonably safe, we should always bare in mind of the risk for invasion co-existence in those women where the lesion has not been fully excised.

This is demonstrated in another study of 44 patients submitted to repeat cervical conization of total hysterectomy following a finding of affected endocervical margins in LEEP specimens. The risk factors analyzed in relation to the presence of residual lesions were age, smoking, cone depth, glandular involvement and the histopathology finding of cervical intraepithelial neoplasia. Out of the 23 women (52%) found with residual disease 1 case had had findings compatible with moderately differentiated invasive squamous call carcinoma and 2 patients were also diagnosed with invasive squamous cell carcinoma in the repeat conization specimen. Worthy to note that, those 2 patients had been diagnosed only with CIN 3 in their initial cone specimen. According to that study, in view of the high frequency of residual disease found when margins, especially the endocervical, are positive, and the 13% (2 out of 23 patients) with the co-existence of invasive disease, repeat conization would have been the option of choice instead of follow-up when trying to avoid a potentially negative outcome *(Antonio Chambo Filho et al, 2015)*. Not to mention that, those residual lesions in the endocervical canal are the most difficult to assess due to anatomical reasons and therefore their potential progression is likely to evade detection.

In concordance to the above studies, there seems to be a proportional increase of invasion rate found in a 2nd "reference specimen" when the endocervical: ectocervical involvement ratio of the 1st cone increases, in different study populations. So, the rate of co-current invasion may range between 10-15% in some studies *(Antonio Chambo Filho et al, 2015)*, justifying the option of a 2nd excisional treatment as the treatment of choice.

CONCLUSION

A CIN3 lesion involving the cone margins (or when the marginal state in not clearly defined) increases the risk of residual / recurrent disease but does not necessarily warrants routine 2nd excisional treatment provided that:

- There is no suspicion of glandular disease
- There is no suspicion for co-current invasion
- Age is <50 *(NHSCSP Publication No 20)*

In cone margin positivity and co-current Micro-Invasive Carcinoma (MIC), 2nd excision is the treatment of choice (regardless of MIC marginal status). Alternatively, watchful follow-up, in MIC-free margins only, might be an option *(Nicholson RC. et al, 2018)*, in selective cases of young women where the obstetric risk of a sizable cone is of particular importance for that woman. In those isolated cases, a thorough consultation, consent and compliance to a close follow-up are of ultimate importance. Initial follow-up should ideally take place in 4-6 months and consist of cytology, colposcopy, HPV testing and histology including ECC.

Overall, conservative management is a reasonable option in cases with favorable parameters such as:

- Women <35
- The margin involvement is focal or confined in a single quadrant
- CIN2- lesions
- The lesion involves ectocervical margins
- Presense of hrHPV negative test

2nd excision is the preferred option in cases where certain parameters are related with increased risk of residual / recurrence

- Women >50
- Extensive margin involvement / multiple quadrants involvement
- Endocervical margin involvement
- Positive ECC
- Presence of glandular disease

When applying those general principles, it is wise to recognize that the literature behind this, being mostly retrospective studies, has its limitations, which include the size of the sample investigated, sometimes leading to conflicting conclusions. The age boundaries presented, although highly indicative, are somehow arbitrary and should always be considered in combination with the other risk factors. Special attention should be taken in the follow-up option, acknowledging their difficulties in terms of patient compliance and also in their, sometimes compromised, ability to detect disease especially to those older patients with poor estrogenation in their lower genital tract, who carry a scarred tissue after a cone procedure, making access and proper assessment of the transformation zone and endocervical canal at least challenging if not impossible.

Also, despite the lack of evidence showing a measurable effect of immunocompomisation on the risk of residual / recurrent disease, it appears logical to regard it as an additional risk factor in the context of an HPV-related pathology where host immunity status plays a pivotal role in carcinogenesis. Full medical history of the patient, including lifestyle parameters (smoking, dietary habits, sexual behavior) and HPV vaccination, provide important complementary information for risk assessment.

Ideally, the management of positive margins is individualized, considering all the above individual parameters, obstetric history and expectations along with the woman's beliefs and priorities after a fully informative consultation.

The method most usually applied as a 2nd operation is a Loop Electrosurgical excision Procedure (LEEP) but knife conization or even hysterectomy are reasonable options. The final decision is guided by

the need for good assess and the ability to perform those operative maneuvers on the remaining cervical tissue in order to achieve complete removal of the residual disease.

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Chapter 11
Early-Stage Cervical Cancer: Is There a Place for Conservative Treatment?

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ABSTRACT

Recent advances in screening and early diagnosis have decreased cervical cancer incidence and mortality rate in high-resource settings. The postponement of childbearing and the young age of women at diagnosis produced new challenges in the management of this disease. In recent years, attention has been directed to assessing more conservative procedures that can reduce treatment-related morbidity, without compromising oncologic safety and reproductive potential. Fertility sparing surgery (FSS) procedures, including cervical conization, simple or radical trachelectomy with pelvic nodes dissection or sentinel lymph node assessment, and neoadjuvant chemotherapy followed by conization, have shown encouraging results. In this chapter, the authors discuss the role of conservative surgery in the management of early-stage cervical cancer focusing on obstetrical and oncological outcomes.

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INTRODUCTION

Epidemiology, Etiology and Prevention

In 2018, approximately 570,000 women developed cervical cancer and 311,000 women died from it. Worldwide, cervical cancer was the fourth most common cancer and also the fourth leading cause of cancer death among women (Arbyn et al., 2020).

Markers of sexual activity, such as a younger age at first intercourse and a higher number of sexual partners, are consistently the most important risk factor for cervical cancer, which lead to research for sexually transmissible microbial agents as the cause. There is overwhelming evidence, both biologic and epidemiologic, that cervical infection by certain Human Papilloma Virus (HPV) types is a precursor event in the genesis of cervical cancer. HPV is a DNA virus capable of inducing malignant transformation of epithelial cells and causing cervical, anal, vulvar, penile and some oral cancers. HPV types are classified according to their oncogenic potential based on the frequency of the association with cancer and squamous intraepithelial lesions. There are over 60 types which infect the anogenital mucosa, of which 12 types (HPV-16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59) are designated as high-risk HPV, and an additional 13 types are considered "probable" high-risk HPV (HPV-26, 30, 34, 53, 66, 67, 68, 69, 70, 73,82, 85, 97). The low-risk types cause subclinical infections or clinically visible benign lesions known as flat and acuminate condylomas. Over 80% of sexually active individuals will be infected by a genital HPV at some point in their lifetime. The majority of genital HPV infections are asymptomatic and clear within 1-2 years without consequences when immune function is normal. Persistent infection by a high-risk HPV is a necessary cause of cervical cancer, detected in 99.7% of cervical neoplasia (squamous and adenocarcinoma). Prevention of cervical cancer is possible through vaccines (primary prevention) and also screening with cervical cytology (secondary prevention), because progression from infection to cancer is usually slow, in the order of decade (De Pokomandy & Mayrand, 2017).

Primary Prevention: HPV Vaccines

Ever since HPV was identified as the necessary cause of cervical cancer and other tumors, intense research and development activities focused on the development, testing and licensure of HPV vaccines. As of 2015, three HPV vaccines are commercially available: a bivalent vaccine (Cervarix™) targeting types 16 and 18; a quadrivalent vaccine (Gardasil™) targeting types 16, 18 and also 6 and 11 responsible for most genital lesions; a nonavalent vaccine (Gardasil-9™) targeting the quadrivalent types plus 31, 33, 45, 52, 58. These vaccines utilize virus-like particles comprised from the L1 capsid protein of HPV to induce seroconversion, and are usually given in three separate injections over a 6 month period. The vaccines are associated with frequent local reaction, but generalized or severe reactions are rare. Recent data of literatures show early decreases of infections by vaccine-targeted HPV types, condylomas, abnormal cervical cytology results and cervical HSIL (High grade Squamous Intraepithelial Neoplasia) at the population. Some decrease was also seen in unvaccinated individuals from the vaccine program eligible age groups, indicating some herd immunity. However, as with any new intervention, some aspects are still to be clarified. There is a theoretical risk of a gradual change in the distribution of HPV types in vaccinated population due to empty niches when HPV 16 and 18 are eliminated. Type-specific immunity conferred by vaccination may also wane over time and the duration of protection is unknown.

Finally, HPV vaccine prices make it currently impossible to implement large-scale vaccination programs in resource-poor countries (De Pokomandy & Mayrand, 2017).

Secondary Prevention: Cervical Cytology and HPV DNA – Testing

Cervical cytology (Pap test) can detect cellular changes typical of cervical cancer, high-grade squamous intraepithelial lesion (HSIL) or HPV infection. Women with abnormal screening cytology then undergo diagnostic evaluation by colposcopy. Histological examination of colposcopy-directed biopsies of such lesions confirms the diagnosis. This procedure is the primary reason of reduction in cervical cancer mortality in most high-income countries. However, Pap test is based on subjective interpretation of morphologic alterations and also depends on the correct sampling of cervical cells. In the last years, liquid-based cytology has improved the efficiency of smear processing, but did not overcome the limitations of poor test sensitivity and reproducibility.

There is a considerable interest in the use of HPV DNA testing as a cervical cancer screening tool. An important advantage of this procedure is that it is amenable to automation. Moreover, the HPV DNA testing is more reproducible, more sensitive and has a higher negative predictive value compared to Pap test (De Pokomandy & Mayrand, 2017).

Management of Early Stage Cervical Cancer

Thanks to mass screening many women are diagnosed at an early stage and at a relatively young age. In most women in western countries pregnancy is delayed until late age and the young age in which some of them are diagnosed with cervical cancer produced new challenges in the management of this disease, with a high demand for fertility-sparing surgery. To be eligible for fertility-sparing treatment of cervical cancer women should satisfy two main criteria: desire for future fertility and low oncologic risk.

In 2018 the FIGO (International Federation of Gynecology and Obstetrics) Committee for Gynecologic Oncology has revised the staging classification of carcinoma of the cervix. Stage IA: lateral extension measurement was removed. Stage IB now has three subgroups: IB1 - invasive carcinoma $\geq$5 mm and <2 cm in greatest diameter; IB2 - invasive carcinoma 2-4 cm; IB3 - tumor > 4 cm. Imaging or pathology findings may be used to assess retroperitoneal lymph nodes; if metastatic, the case is assigned stage IIIC: IIIC1 - only pelvic lymph nodes involvement; IIIC2 - para-aortic lymph nodes involvement (Bhatla et al., 2019). However, the most of the recent data reported in this chapter refers to the previous FIGO cervical cancer staging published in 2009.

Early-stage cervical cancer includes disease that is confined to the cervix, measuring $\leq$ 4 cm, with no apparent spread to adjacent structures or distant organs. The standard treatment for women diagnosed with early-stage cervical cancer is simple hysterectomy for microinvasive disease (stage IA1) with no involvement of lympho-vascular space invasion (LVSI) or radical hysterectomy with removal of uterus, cervix, parametrial tissue, upper vagina and pelvic lymphadenectomy from stage IA2 to IB2. However, abdominal radical trachelectomy (ART) or vaginal radical trachelectomy (VRT) with pelvic lymph nodes dissection or sentinel lymph node assessment has been proposed for women desiring future fertility.

Many data have demonstrated the feasibility of radical trachelectomy and a retrospective study conducted by Dargent et al. in 1994 confirmed the oncological safety of this surgical approach followed by a recurrence rate of 4% (Dargent et al., 1994). In addition, Xu et al. (2011) confirmed that oncologic outcomes of radical hysterectomy and radical trachelectomy are equivalent. Similar to radical

hysterectomy, radical trachelectomy requires removal of the parametria. However, previous studies have shown that approximately 60% of women undergoing radical trachelectomy have no residual disease in the surgical specimen, suggesting that perhaps those women could have been treated with less radical surgery (Schmeler et al., 2011). Moreover, radical trachelectomy may be associated with significant morbidity: lower urinary tract dysfunction, sexual dysfunction, and colorectal motility disorders associated with autonomic nerve damage (Plante et al., 2011). For this reason, mostly in women with early stage cervical cancer desiring fertility preservation, less radical surgical options have been investigated: conization, simple trachelectomy with sentinel lymph node assessment and neoadjuvant chemotherapy followed by conization.

Rationale for Conservative Management of Cervical Cancer

The natural history of cervical cancer is well known. The tumor spreads laterally to the parametria and downwards to the vagina but rarely upward in the uterine body. For this reason, the uterine body, the fallopian tubes and the ovaries can be spared in most small tumors confined to the cervix, thus preserving the possibility of a future pregnancy. However, conservative surgery must be suggested exclusively to women who desire to preserve their reproductive potential and who have a low risk of recurrence.

Various risk factors affecting prognosis in early cervical cancer have been identified: tumor size, histological subtype, lympho-vascular space invasion (LVSI), depth of stromal invasion, parametrial infiltration, lymph node involvement, status of resection margins (Festi & Landoni, 2017).

Tumor Size

Tumor size is one of the most important criteria when considering the indication for and the type of fertility-sparing surgery. The volume of the tumor has an independent impact on the prediction of nodal status and on survival. According to the 2018 Guidelines of European Society of Gynecological Oncology, every woman with a desire for future pregnancy and histologically proven squamous cell carcinoma or usual-type (HPV-related) adenocarcinoma of the cervix with largest diameter equal to or less than 2 cm, should be counseled about the possibility of fertility-sparing treatment (Cervical Cancer Guideline [ESGO], 2018). Preoperative imaging is crucial to assess major tumor characteristics. Magnetic Resonance Imaging (MRI) is the best technique in this context because it accurately shows tumor size, depth of stromal invasion, and distance between the upper margin of the tumor and the internal cervical *os*. In the hands of experienced radiologists, MRI can also help to preoperatively identify high-risk patients who are not candidates to fertility-sparing surgery and who require radical hysterectomy (Lakhman et al., 2013).

Histological Subtype

For early stage disease, the difference in recurrence and mortality between squamous cervical carcinoma and cervical adenocarcinoma seems negligible, and both subtypes may be deemed eligible for fertility preservation. However, rapid recurrence was observed in some series of fertility-sparing surgery that included neuroendocrine tumors of the cervix (Agarwal et al., 2011).

Lympho-Vascular Space Invasion

Lympho-vascular space invasion (LVSI) is a negative prognostic factor for recurrence and nodal metastasis, however LVSI alone not necessarily preclude the possibility of fertility-sparing management. A review by Beiner et al. (2007) found that 28% of patients undergoing radical vaginal trachelectomy had LVSI but only 5% had nodal metastases.

Depth of Stromal Invasion

The invasion of less than half the thickness of the cervical stroma seems to represent the necessary condition to perform a trachelectomy with at least 5 mm of free margin and therefore safe from an oncological point of view. Moreover, preservation of part of the cervical stroma lowers the risk for cervical incompetence, ascending infection, premature rupture of membranes and premature delivery (Kinney et al., 1995).

Parametrial Infiltration

Parametrial removal is important in early cervical cancer to prevent local recurrence and to obtain a free margin. Involvement of parametria correlate with lymph node status, tumor size, depth of stromal invasion, stage, LVSI, grade and residual tumor in the surgical specimen (Schmeler et al., 2011). Several retrospective studies have shown very low rates of parametrial involvement in women with early-stage cervical cancer with favorable pathologic characteristics who have undergone radical hysterectomy. These studies suggest that these women could be managed in a more conservative way.

Covens et al. (2002) reported the incidence of parametrial involvement in 842 women with stage IA1 through IB1 cervical cancer who underwent radical hysterectomy. This study had the goal to determine the incidence of factors predictive for parametrial involvement and to identify a population at low risk for pathologic parametrial involvement. Thirty-three women (4%) had pathologic parametrial involvement, eight in the parametrial lymph nodes and 25 in the parametrial tissue (none had both). Compared with women without parametrial involvement, women with parametrial involvement were older (42 vs. 40 years, $P < 0.04$), had larger tumors (median, 2.2 vs. 1.8 cm, $P < 0.04$), had a higher incidence of LVSI (85% vs. 45%, $P = 0.0004$), were more likely to have grade 2 or 3 tumors (95% vs. 65%, $P = 0.001$), had larger depth of stromal invasion (median, 18 vs. 5 mm, $P < 0.001$), and were more likely to have pelvic lymph node metastases (44% vs. 5%, $P < 0.0001$). The incidence of parametrial involvement in 536 women with negative lymph nodes, tumor size 2 cm or smaller, and stromal invasion 10 mm or less was 0.6%.

Wright et al. (2007) tried to determine factors predictive of parametrial tumor spread and to define a subset of women at low risk for parametrial disease. A total of 594 women with invasive cervical cancer who underwent radical hysterectomy were retrospectively reviewed. Parametrial metastases were documented in 64 patients (10.8%). Factors associated with parametrial disease were high-risk histology, advanced grade, deep stromal invasion, LVSI, large tumor size, advanced stage, uterine body or vaginal involvement, and pelvic or para-aortic lymph node metastases. A subgroup analysis was performed to identify patients at low risk for parametrial spread. The authors noted that in women with negative lymph nodes, no LVSI and tumors smaller than 2 cm, the incidence of parametrial disease was only 0.4%.

Lymph Node Assessment

The involvement of the lymph nodes is the most relevant prognostic factor in cervical cancer and its presence determines the choice of the subsequent adjuvant treatment. In the absence of grossly positive lymph nodes visible at pre-operative computerized tomography (CT) or magnetic resonance imaging (MRI), lymph nodes assessment must be obtained by surgery. Currently, sentinel lymph node detection can be done without additional pelvic lymphadenectomy in stage IA1, while this procedure has not been validated in patients with stage IA2 with presence of LVSI, IB1 or IIA1. However, it can be done in combination with systematic pelvic lymphadenectomy.

For decreasing the need for pelvic lymphadenectomy in patients with early stage cervical cancer, the 2015 NCCN Guidelines for Cervical Cancer suggest sentinel lymph node (SLN) biopsy. SLN procedure has been used in tumors up to 4 cm in size, but the best detection rates and mapping results are obtained in tumors less than 2 cm in size. This technique utilizes a direct injection with dye or radiocolloid Technetium-99 (^{99}Tc) into the cervix, usually at 2 or 4 points. The SLN are identified at the time of surgery with direct visualization of colored dye or fluorescent camera if indocyanine green (ICG) is used, or by a gamma probe if ^{99}Tc is used (Cervical Cancer, Version 2.2015 [JNCCN], 2015, pp. 395-404).

Cervical injection of indocyanine green or the combination of blue dye with radiocolloid (^{99m}Tc) are both acceptable methods for SLN detection. Detection rates are 93.5% when combining blue dye and radiocolloid, 95.5% when using fluorescent dye and near-infrared fluorescence imaging, and only 74.4% when using blue dye alone.

SLNs are commonly located medial to the external iliac vessels, ventral to the hypogastric vessels, or in the superior part of the obturator space. SLNs usually undergo ultra-staging by pathologists, which allows for higher detection of micro metastasis that may alter post-operative management (Angeles et al., 2018).

The 2019 NCCN Guidelines for Cervical Cancer (Cervical Cancer, Version 3.2019 [JNCCN], 2019, pp. 64-84) report principles of evaluation and surgical staging based on the revised 2018 FIGO staging and recommend adherence to the SLN algorithm, produced by Cormier et al. (2011). The SLN mapping algorithm requires the performance of a side-specific nodal dissection in cases of failed mapping and removal of any suspicious or grossly enlarged nodes regardless of mapping (Cormier et al., 2011).

The most relevant studies aiming to evaluate the role of SLN in cervical cancer were the French SENTICOL trials. The SENTICOL I identified the SLN using radiocolloid and blue dye injection and estimated the sensitivity and the negative predictive value (NPV) of the SLN biopsy to assess lymphatic involvement using complete histologic pelvic lymphadenectomy as gold standard, SLN biopsy showed sensitivity of 92.0% and NPV of 98.2% (Lécuru et al., 2011). The SENTICOL II trial was designed to evaluate short and mid-term morbidity of pelvic lymphadenectomy (Mathevet et al., 2017). After a negative result of intraoperative assessment of frozen-sectioned SLN, patients were randomized to standard full pelvic lymphadenectomy or exclusive SLN biopsy. Results showed that the SLN biopsy group had less lymphatic complications, less neurological symptoms, and better quality of life. Definitive validation of SLN detection as an isolated lymphatic assessment method for early stage cervical cancer will be carried out in the SENTICOL III (NCT 03386734). In this trial, disease-free survival (DFS) and health-related quality of life will be evaluated as co-primary objectives. The SENTICOL III trial is currently ongoing.

For SLN it is recommended that both intraoperative and final pathology be reviewed by a pathologist specializing in gynecologic diseases and that ultra-staging be performed. However, frozen section is not universally practiced due to the concerns regarding false negatives and loss of tissue for permanent

pathological processing. A range of false negative rates for intra-operative frozen section in early cervical cancer has been reported. For stage IA2-IB1, Panici et al. (2005) reported a false negative rate of 4.2%. Gortzak et al. (2010) examined the use of SLN procedure among 81 women with early cervical cancer (stage IA-IB1). This study reported a false negative rate of 21.4% (3/14 negative sentinel nodes). Two of the three cases had micro metastases < 2 mm in size that were found only after ultra-staging.

In case of intraoperatively proven lymph node involvement, fertility sparing surgery should be abandoned and the woman referred to definitive chemoradiotherapy (Cervical Cancer Guideline [ESGO], 2018).

Surgical Margins

Little prospective data exist as to the optimal surgical margin for trachelectomy specimen. A retrospective review by McCann et al. (2013) found that for patients with stage 1A2 – 2A cervical cancer undergoing radical hysterectomy, close surgical margins (defined as margins ≤ 5 mm), while not an independent risk factor for recurrence, were associated with other intermediate and high risk features, including lymph node positivity, parametrial involvement, increased size of primary lesion, increased depth of stromal invasion and LVSI. In a recent review based on extrapolation of data on recurrence following radical hysterectomy, Willows et al. (2016) show that optimal surgical margins after fertility-sparing management are at least 5 mm.

Fertility-Sparing Surgery Procedures

Conization

Conization involves using a knife (cold-knife), Loop Electrosurgical Excision Procedure (LEEP) / Large Loop Excision of the Transformation Zone (LLETZ) or laser, to cut out the area of the cervix around the cervical *os*, removing the entire transformation zone and much of the endocervical canal. The cold-knife cone uses a regular surgical blade to remove a conical area from the surface of the cervix into the cervical canal. This procedure has the advantage of removing a single surgical specimen, without "burned", thus facilitating evaluation of the margins for complete management of the disease. LEEP is now the most common means of conization, since it is faster and easier and has fewer immediate complications than laser or cold-knife cones (Tulunay & Ozgul, 2017).

Simple Trachelectomy

Simple trachelectomy involves amputation of the cervix with an incision 7-10 mm above the tumor, then removal of the endocervical canal by use of the loop electrosurgical excision procedure with a small loop electrode. Individual sutures to the outer edge created by the small loop re-approximate the vaginal edge circumferentially. Cerclage is not performed (Rob et al., 2011).

Vaginal Radical Trachelectomy (Dargent's Procedure)

With the feasibility to perform laparoscopic pelvic lymph node dissection safely, combination of laparoscopic lymphadenectomy with radical vaginal trachelectomy was developed and published by Daniel

Dargent et al. (1994). The technique consists of three steps: laparoscopic pelvic lymphadenectomy and preparation for the vaginal part; radical vaginal resection; laparoscopic control of hemostasis.

The surgeon needs to be experienced in laparoscopy, first learning laparoscopic lymphadenectomy and eventually paracervical lymph-node dissection with or without SLN identification. The extent of laparoscopic surgery varies from school to school. The second phase of the procedure requires experience in vaginal surgery, because identifying and mobilizing the ureter is difficult in vaginal surgery; this is necessary for the safe resection of the parametrium bilaterally. Radicality of the resection of the parametria is limited by the goal of preserving the uterine artery by ligating only the vaginal branch of this artery. The cervix should be transected about 1 cm above the endocervical tumor margin and a maximum of 1 cm caudally from the internal cervical orifice (Rob et al, 2011).

Abdominal Radical Trachelectomy

The intent of the radical abdominal trachelectomy is to resect the cervix, 1-2 cm of the upper vagina, parametrium, and paracolpos in a similar manner to a type III radical abdominal hysterectomy but sparing the uterine fundus or corpus. The procedure is begun by developing the para-vesical and pararectal spaces and dissecting the bladder caudal to the mid-vagina. The round ligaments are divided, and large Kelly clamps are placed on the medial round ligaments to manipulate the uterus. Care is taken not to destroy the proximal part of the fallopian tubes or the utero-ovarian pedicles. The infundibulo pelvic ligaments with ovarian blood supply are kept intact. Care is also taken not to injure the fallopian tubes or disrupt the utero-ovarian ligament. The uterine vessels are then ligated and divided at their origin from the hypogastric vessels. The parametria and paracolpos with uterine vessels are mobilized medially with the specimen, and a complete ureterolysis is performed similar to a type III radical abdominal hysterectomy. The posterior peritoneum is incised and the uterosacral ligament divided; similarly, the parametria and paracolpos are divided. Using a vaginal cylinder, the desired length of vaginectomy is performed, and the specimen is completely separated from the vagina and placed in the mid-pelvis, keeping its attachment to the utero-ovarian ligaments. The lower uterine segment is then estimated, and clamps are placed at the level of the internal os. Using a knife, the radical trachelectomy is completed by separating the fundus from the isthmus or upper endocervix at approximately 5 mm below the level of the internal os, if possible. The uterine fundus with preserved attachments to the utero-ovarian ligaments is placed in the superior part of the pelvis. The specimen, consisting of radical trachelectomy and parametria with suture marking the vaginal cuff at 12 o'clock, is sent for frozen section evaluation of its endocervical margin. The uterine fundus is inspected, and curettage of the endometrial cavity is performed as well as a shave disc margin on the remaining cervical tissue, which is sent for frozen section analysis. This is performed to ensure that the reconstructed uterus to vagina is disease-free. A frozen section analysis is also obtained on the distal vaginal margin, if clinically indicated. If all frozen sections tested are benign and at least a 5-mm clear margin is obtained on the endocervical edge, a permanent cerclage with #0 Ethibond may be placed prior to the reconstruction. The uterus is reconstructed to the upper vagina with 6 to 8 #2-0 absorbable sutures (Abu-Rustum et al., 2006).

Laparoscopic approach has been used as a standard surgical treatment of early cervical cancer in many centers. Besides lymphadenectomy, laparoscopy is used for ureterolysis, first part of bladder dissection and transaction of uterine vessels, cardinal and uterosacral ligaments. Vaginal procedure includes colpotomy, cervix amputation, dissection of posterior paracolpium and suture of uterus to vagina (Cibula et al., 2005).

In the last years, the robotic approach was introduced in clinical practice. The robotic approach to radical trachelectomy may circumvent some of the disadvantages of either radical vaginal trachelectomy or radical abdominal trachelectomy. The robotic system has the advantages of improved visualization due to 3-dimensional optics; improved tissue manipulation due to flexibility of the instruments; improved fine dissection; and minimal invasion resulting in decreased adjacent tissue trauma and adhesions, diminished operative pain, shorter postoperative hospitalization, and better cosmesis. With the Da Vinci system, the uterine vessels can be dissected from the hypogastric artery to the corpus. At the corpus, the ascending branch of the uterine artery can be maintained with cauterization of the descending branches to the cervix. The vaginal cuff is sutured to the residual cervix or lower uterine segment using absorbable sutures that can be either tied or secured with Lapra-Ty. The permanent cerclage requires an instrument tie that is easily accomplished with the robot (Burnett et al., 2009).

Obstetrical Outcomes

The ESGO guidelines (2018) for the management of patients with cervical cancer recommended a consultation at a fertility center before starting fertility-sparing treatment (FST). However, any pregnancy following FST should be considered a high-risk pregnancy and delivery should be performed in a perinatal center (Cervical Cancer Guideline [ESGO], 2018).

In systematic review Bentivegna et al. (2016) analyzed the fertility results, obstetric outcomes and management of infertility in patient with stage I cervical cancer undergoing different FSS procedures: conization/simple trachelectomy, vaginal radical trachelectomy, abdominal radical trachelectomy by laparotomy, abdominal radical trachelectomy minimally invasive (pure laparoscopic or robot assisted laparoscopy) and NACT followed by cone resection, simple trachelectomy or radical trachelectomy. The overall fertility, live birth, and prematurity rates for these procedures were, respectively, 55%, 70%, and 38%. No difference was observed in life birth rates according to the FSS procedures ($P = 0.17$), but pregnancy rates and prematurity rates were both significantly different ($P < 0.001$). Particularly, the pregnancy rate (determined in series with complete data on the total number of patients attempting to become pregnant and the number of them succeeding) was 56% for cone resection/simple trachelectomy, 57% for VRT (Dargent's procedure), 44% for laparotomic RT and 65% for minimally invasive RT. The live birth rate (determined in series with complete data about the total number of pregnancies and the number of live births) for these procedures were, respectively 74%, 67%, 68%, 78%. The prematurity rate (determined in series with complete data about the number of live birth deliveries and the number of premature deliveries) was 15%, 39%, 57%, 50% for conization/simple trachelectomy, VRT, laparotomy RT, minimally invasive RT, respectively. It is clear that in conization/simple trachelectomy the cervical resection and radicality is more limited than with the other procedures and the rate of postoperative morbidity exerting an impact on subsequent fertility is low. In abdominal laparotomic RT, used for extending the radicality of surgery in patients with less favorable prognostic factors (tumor > 2 cm), the fertility rate was low: 44% vs. 57% and 65% ($P < 0.001$) in patients treated with a vaginal or a minimally invasive RT, respectively. This lower rate after laparotomic RT could be due to uterine artery ligation, frequently performed with this approach. Nevertheless, the subgroup analysis conducted by the authors of the review showed that uterine artery preservation or ligation had no impact on the fertility rate. This shows that the preservation of the infundibulo-pelvic and ovarian vessels in these young patients could be sufficient to adequately supply the arterial vascular network of the uterine corpus and thus achieve a pregnancy. Unfortunately, some patients desiring a pregnancy had become infertile as a result of FSS.

The main cause of infertility was related to a cervical factor: the lack of cervical mucus to facilitate sperm migration, a potentially increased latent subclinical endometritis, and/or cervical stenosis. In RT procedure the most common complications likely to impact fertility were cervical stenosis and/or cervical erosion. The use of different tools (catheter, intrauterine device, Smit sleeves) to prevent stenosis seems to decrease the complication rate. The report of fertility results and obstetric outcomes in patients undergoing neoadjuvant chemotherapy (NACT) followed by conservative surgery shows promising results. Two surgical procedures were used: a simple trachelectomy/cone resection (31%) and a radical trachelectomy (69%). When a radical trachelectomy was performed after NACT, all the teams used a prophylactic cerclage at the end of the procedure. FSS procedure was abandoned or not retained for oncologic reasons in 8% of patients. Cervical stenoses were observed in 8% of patients. Among patients who had at least one pregnancy, 48% and 38% of patients had respectively undergone a simple cervical resection and a radical trachelectomy. The prematurity rate was lower compared with that observed after vaginal or abdominal radical trachelectomy (15% versus 39% and 57% respectively, $p < 0.001$). Eighty-two per cent of preterm deliveries were related to preterm premature rupture of membrane (pPROM).

Pareja et al. (2015) identified 14 reports concerning the use of NACT in patients with early-stage (FIGO stages IB1-IIA) cervical cancer interested in future fertility. A total of 8 patients did not preserve fertility and among the remaining 65 patients (89%) who preserved fertility after NACT, 20 pregnancies were reported (30.7%), with 16 deliveries (6 preterm and 10 at term), 2 ongoing pregnancies, 1 ectopic pregnancy, and 3 miscarriages (some women delivered more than one baby).

The pathogenesis of fetal losses was probably related to the shortened uterine cervical length. In the second trimester, fetal losses and premature delivery were also related to premature rupture of membrane (PROM), mainly due to subclinical or clinical chorioamniotitis. Several procedures or precautions aimed at decreasing this risk were reported and two specific surgical procedures were described to try to reconstruct cervical competency: the prophylactic cerclage after removal of the cervix and before the utero-isthmic anastomosis, and the Saling's procedure. The Saling's procedure consists of a closure of the cervical ostia using vaginal mucosa, done around 14 WG under general anesthesia to decrease the risk of vaginal bacteria contaminating the amniotic fluid (Saling, 1981). Some authors believe that this procedure increases the rate of stenosis or cervical erosion. In the Mathevet et al. experience (2003) the use of this procedure after vaginal RT reduced the risk of fetal loss from 50% to 22%.

Currently, 2018 ESGO guidelines recommend prophylactic cerclage after removal of the cervix and before the utero-isthmic anastomosis (Cervical Cancer Guideline [ESGO], 2018).

Following simple or radical trachelectomy with its inherent placement of a permanent cerclage, delivery can be performed only by caesarean section. Routine hysterectomy following fertility sparing surgery and finished family planning is not generally recommended because it does not seem to increase oncologic safety despite limited available data. Secondary hysterectomy should only be performed in women with recurrent clinical symptoms such as dysmenorrhea, dyspareunia, vaginal discharge, irregular bleeding or repeated cervical stenosis (Fokom & Schmeler, 2019).

If the first objective of fertility sparing surgery is offering a safe surgery to a well-selected group of women, on the other hand, Quality of Life (QOL) cannot be a secondary endpoint anymore. In a multicenter retrospective study Fanfani et al. (2014) analyzed the QOL in terms of sexual and reproductive outcomes in patients suffering from early stage cervical cancer, submitted to an excisional cone as fertility-sparing treatment. Of 30 women identified for this study, 23 (76.7%) provided signed informed consent and completed the questionnaire. Four patients (13.3%) were submitted to a radical hysterectomy after fertility-sparing conization and 3 women (10%) declined. Of the 30 women, 4 (13.3%) were submitted

to neoadjuvant chemotherapy and 1 (3.3%) to three cycles of platinum-based adjuvant chemotherapy. The questionnaire included socio demographic characteristics, medical and cancer history, and assessment of specific dimensions of physical, psychological, reproductive and sexual functions. After surgery, all women had regular menstrual cycles. One woman (4.4%) had trouble in lubricating, 3 (13%) had anxiety about performance, 6 (26.1%) complained of dyspareunia which was resolved within 3 months. Overall, 11 (48%) reported concerns about a future pregnancy, of whom 7 (30%) had a fear of possible inability to conceive, 1 (4.4%) to maintain the pregnancy, 2 (8.7%) to have a recurrence of tumor during pregnancy and 1 (4.4%) had the fear of possible negative impact of cancer history on the baby. Sixteen women (70%) had an immediate psychological and physical recovery, 4 (17%) after 3 months and 2 (9%) after 12 months. No patient wrote to have concerns about choosing this fertility-sparing treatment.

Oncological Outcomes

Oncologic safety can be assessed in terms of clinical-pathologic risk factors for recurrence. These include lymph node assessment, tumor size, histological subtype, depth of stromal invasion, presence of LVSI, parametrial involvement and feasibility of achieving tumor-free margins.

In patients with LVSI and tumors 2 cm or smaller, two strategies for fertility-sparing surgery are relevant: Dargent's procedure and abdominal radical trachelectomy. The choice between abdominal radical trachelectomy and vaginal radical trachelectomy for patients with stage IB1 tumors smaller than 2 cm and with LVSI, therefore, should include the surgical expertise of the team. In patients with stage IB1 tumors larger than 2 cm, Dargent's procedure is contraindicated because of the high risk of recurrent disease. Consequently, two main strategies are deemed feasible: neoadjuvant chemotherapy and abdominal radical trachelectomy. However, these procedures should be assessed in terms of morbidity and fertility results. After neoadjuvant chemotherapy, some patients have related grade 3 hematological or renal morbidity. After abdominal radical trachelectomy, especially laparotomic radical procedure, morbidity is more frequent and severe: peritonitis, tubo-ovarian abscesses, ureteral injuries, vaginal dehiscence, uterine necrosis were reported. In women with tumors of 2-4 cm, the oncological results (recurrence and positive margins) and fertility outcomes were similar for neoadjuvant chemotherapy and abdominal radical trachelectomy (Bentivegna et al., 2016).

Cao et al. (2013) performed a matched case-control study comparing surgical approaches in 126 patients undergoing radical trachelectomy. They found no significant differences between VRT and ART for mean operating time, perioperative complications or postoperative complications. Although VRT resulted in higher pregnancy rates (35.5% vs 8.8%) and live birth rates (23.3% vs 8.8%), it also resulted in higher rates of recurrence (9.8% vs 0%) and death from disease (2.8% vs 0%).

In a recent article Bogani et al. (2019) evaluated the long-term obstetric and oncologic outcomes of 32 young women (aged < 40 years) with early cervical cancer (stage IA2, IB1 and IB2) undergoing to cervical conization and laparoscopic pelvic node assessment, by systematic pelvic lymphadenectomy (N = 30; 94%) or SLN mapping (N = 2; 6%). Median follow-up time was 75 months (range 12-184 months). As for reproductive outcomes, 11 (69%) out of 16 women who attempted to conceive got pregnant. No recurrent disease was diagnosed among patients undergoing conservative treatment; while 2 out of 6 patients having definitive surgical or radiotherapy treatments developed recurrent disease. Five-year disease free and overall survivals were 94% and 97%, respectively. This preliminary data show that in patient with small volume disease (< 2 cm) cervical conization would be effective, however trachelectomy should be the preferred treatment modality for patients with large cervical cancer (> 2 cm). Nodal

assessment is useful to understand the need of more aggressive treatments. In selected patients with negative nodes, conization seems to offer good local control rate, decreasing radicality and morbidity without compromising oncological outcomes.

Willows et al. (2016) identified oncological outcomes of 1312 patients eligible for fertility sparing management of early cervical cancer in a review of large case series of radical trachelectomy. After accounting for adjuvant treatments, 91% successfully preserved their fertility. The crude recurrence and mortality rates in this group were 4.5 and 1.7%, respectively. For 2-4 cm FIGO stage IB1 and IIA disease, NACT was shown to reduce nodal metastases, parametrial infiltration, and overall tumor size. Literature review identified 80 cases of tumor $\geq$ 2 cm stage IB1-IIA eligible for NACT prior to fertility-sparing surgery. The crude recurrence rate was 6.3% and one patient died from her recurrent disease. The use of NACT has resulted in at least 36 pregnancies with a 72.2% live birth rate. The timing of nodal assessment respect to NACT was not standardized.

A study by Landoni et al. (2007) reported the safety and feasibility of NACT followed by conization (chemo-conization treatment) in 11 young women (8 stage IB1 < 3 cm and 3 stage IA2), with favorable tumor characteristics and desire to preserve fertility. As a first step, all patients underwent laparoscopic bilateral pelvic lymph nodes dissection. The patients with tumor diameter less than 2 cm with negative nodes received deep laser conization aiming to achieve clear margins of excision. The patients with tumor diameter more than 2 cm and less than 3 cm and negative nodes underwent three courses of neoadjuvant chemotherapy with paclitaxel, ifosfamide, cisplatin (TIP) for squamous carcinoma or paclitaxel, epirubicin, cisplatin (TEP) for adenocarcinoma, followed by laser conization for appropriate reduction of tumor diameter. All patients were free of recurrence of disease after a mean follow-up of 20 months. Three pregnancies, both resulting in full term babies, occurred during the follow-up period.

Similar results have been obtained by Maneo et al. (2008) in nulliparous women aged 40 years or younger, with stage IB1 cervical tumor (carcinoma or adenocarcinoma), tumor size less than 3 cm, no uterine body involvement and no lymph node metastasis evaluated by MRI and by positron-emission tomography (PET), that were enrolled into a trial of conservative management employing neoadjuvant chemotherapy and surgery. The chemotherapy consisted of three courses of cisplatin 75 mg/m^2, paclitaxel 175 mg/m^2 and ifosfamide 5 g/m^2 (TIP) or epirubicin 80 mg/m^2 (TEP) instead of ifosfamide for adenocarcinoma, every 3 weeks. After evaluation of the clinical response to chemotherapy, patients underwent cold-knife cervical conization and complete pelvic lymphadenectomy. No invasive relapses have been evidenced. A 56% of patients who underwent conization attempted to conceive: this rate is comparable to patients treated by trachelectomy.

A study by Vercellino et al. (2012) showed higher rates of recurrence among a subset of women with positive nodes, in whom fertility-sparing surgery was aborted, compared to women with negative nodes that went on to have NACT and VRT.

These data suggest that nodal assessment prior to NACT identifies a high-risk group of women in whom fertility preservation should be avoided. Conversely, some authors contend that the use of NACT prior to lymph node assessment may result in fewer nodal metastases, and thus a higher number of women eligible for fertility-sparing surgery (Eiriksson & Covens, 2012).

Early Cervical Cancer in Pregnancy

Pregnancy does not appear to accelerate the natural history of the tumor or increase the incidence of metastatic disease, although the survival rate of patients diagnosed during pregnancy seems somewhat

higher than in women who are not pregnant, probably because of early diagnosis. On the contrary, when there is a late diagnosis during pregnancy there is apparently a worse prognosis, partly due to therapeutic limits in these specific cases (L. Charkviani et al., 2003). Therefore, a Pap test should be always performed as part of the regular checkup for a woman during her first outpatient visit for pregnancy. The therapeutic management depends on the week of pregnancy, the FIGO stage, the size of the lesion, the desire of the woman to save pregnancy.

Women with stage FIGO IA1- IB1 squamous cell carcinoma with less than 2 cm tumor size and no LVSI may be candidates for conservative treatment during gestation with conization or simple trachelectomy, completing the treatment 6-8 weeks after having given birth. During pregnancy a simple trachelectomy is not exempt of maternal-fetal complications. Surgery is preferably performed during the second trimester of pregnancy and only in patients with strong colposcopy or pathologic evidence of incipient invasive cancer. When conization is practiced during the first trimester, abortion occurs in 33% of cases. After conservative treatment of cervical cancer during pregnancy, delivery can be vaginal. Cesarean section is reserved for cases in which the tumor stage is higher than IA2. In these cases a radical hysterectomy and bilateral pelvic lymphadenectomy can be done during the same surgery (Moreno-Luna et al., 2016).

In all cases, the treatment options involve an important ethical, emotional and social dilemma for the women and for the medical team. The psychological support of the women is important. The management has to be discussed by a multidisciplinary team of obstetricians, neonatologists, gynecological oncologists, medical oncologists, and pathologists.

Preservation of the Hormonal Function in Young Women

In 2018, ESGO Guidelines have analyzed ovary-sparing procedures that have been suggested for women with early stage cervical cancer who not desire to preserve fertility but want to preserve ovarian function to avoid long-term morbidity due to premature menopause (Cervical Cancer Guideline [ESGO], 2018).

Ovarian Preservation

In a systematic review including 5 studies, Jiao et al. (2016) evaluated the safety of ovarian preservation according to the histological type. The incidence of ovarian metastasis of women with early-stage adenocarcinoma and squamous cell carcinoma were 2% and 0.4%, respectively (OR = 5.27; 95% CI = 2.14-13.45).

In another review based on data from six studies, Touhami et al. (2015) observed that at least one of the following risk factors was present in 97% of women with ovarian metastasis from adenocarcinoma of the cervix: age > 45 years, FIGO stage > IB, positive lymph nodes, deep stromal invasion, LVSI, uterine *corpus* invasion, parametrial invasion or tumor size > 4 cm. All included FIGO stage IB adenocarcinomas had an incidence of ovarian metastases under 4%.

Ovarian Transposition

A study of Morice et al. (2000) evaluated the safety of ovarian transposition (OT) to the paracolic gutters during radical hysterectomy with lymphadenectomy in women younger than 40 years presenting with a small invasive cervical carcinoma (<3 cm) treated by a radio-surgical combination. The rates of preservation of ovarian function were 100% for patients treated exclusively by surgery, 90% for patients

treated by postoperative vaginal brachytherapy, and 60% for patients treated by postoperative external radiation therapy and vaginal brachytherapy. The authors confirmed that in these selected cases the risk of ovarian metastases is low.

However, available data about the efficacy of ovarian transposition for preserving ovarian function in cervical cancer patients are limited, notably due to the very small number of patients included in the majority of studies, the wide variation in the type of ovarian transposition technique (bilateral robotic OT, unilateral laparoscopic OT, unilateral laparoscopic OT with contralateral oophorectomy, bilateral laparoscopic OT, unilateral OT via laparotomy, bilateral OT via laparotomy), and the absence of data describing the type of postoperative radiation treatments (vaginal brachytherapy, external radiation therapy, external radiation therapy and vaginal brachytherapy).

The available data investigating the potential risk factors related to the recurrence of cervical cancer following ovarian transposition are also too limited to define a pattern of risk factors (Cervical Cancer Guideline [ESGO], 2018).

CONCLUSION

Over the past two decades, with the widespread use of cervical cancer screening programs in high-resource settings, a growing number of women are diagnosed with early-stage disease. Moreover, there has been an increase in early-stage cervical cancers diagnosed in young women who are still of childbearing age and who often request to preserve their fertility. In recent years, attention has been directed to assessing more conservative procedures that can reduce treatment morbidity, without compromising oncologic safety and reproductive potential. Treatment of early stage cervical cancer has evolved over the years with gradual shift from radical surgery to more conservative techniques. In selected patients with early stage cervical cancer, in presence of favorable prognostic features (tumor size < 2 cm; no lymph node metastases) and low risk of parametrial spread, conservative procedures can be proposed.

Radical vaginal or abdominal trachelectomy seem to be safe and feasible procedures, with low morbidity, low recurrence and low mortality rates. However, obstetrical outcomes are unfavorable when compared with other, less invasive, conservative procedures, such as conization or simple trachelectomy. These techniques, associated with pelvic nodes dissection or sentinel lymph node assessment, are now considered valid approaches with acceptable oncological outcomes.

In selected women with more advanced disease (tumor size from 2 to 4 cm), a fertility sparing surgery is feasible but should be preceded by neoadjuvant chemotherapy (chemo-conization). The potential negative effects of neoadjuvant chemotherapy on ovarian function, especially when using alkylating agents, should be considered in patients with an immediate desire of pregnancy. However, literature data prove that chemo-conization is associated with more favorable obstetrical outcomes in comparison with other more invasive procedures.

The management of pregnancies achieved by women who underwent fertility sparing treatments for early cervical cancer should be standardized and delegated to reference centers, involving gynecologic oncologists, reproductive endocrinologists, maternal-fetal medicine specialists and psychologists. However, a natural fertility and childbearing could be unachievable for some young women with cervical cancer. In these cases, advances in assisted reproductive technologies may still make pregnancy and parenthood possible.

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Chapter 12
Cervical and Vulvar Cancer in Early Stages: What Is the State-of-the-Art Treatment?

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ABSTRACT

Cervical and vulvar cancer represent two clinical entities whose diagnosis and management are often challenging. They are frequently diagnosed in the early stages, therefore leaving chances for optimal treatment and prognosis. The aim of this chapter is to answer two oncological issues concerning early stage cervical and vulvar cancer. First, is still room for surgical treatment for early stage cervical cancer or should we suggest chemoradiotherapy instead? Second, when is a limited surgical intervention sufficient for early stage vulvar cancer?

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INTRODUCTION

The aim of this chapter is to answer two oncological issues concerning early stage cervical and vulvar cancer. First, if there is still room for surgical treatment for early stage cervical cancer or should we suggest chemoradiotherapy instead. Second, when is a limited surgical intervention sufficient for early stage vulvar cancer.

EARLY STAGE CERVICAL CANCER

Introduction

Cervical cancer is the third most common cancer that occurs in women after breast and colon cancer, with approximately 527,624 new cases and 265,653 deaths in 2012 (Ferlay, 2013). Concerning the five-year survival of European women with diagnosed cervical cancer, this was about 62% in 2000-2007 (Sant, 2015).

Cervix can be easily visualized and sampled or treated with little or no anesthesia. This has helped to better understand the natural history of cervical cancer along with the development of simple outpatient techniques of screening and prevention. The known factors that raise the risk of developing cervical cancer are human papilloma virus (HPV), low socio-economic status, smoking, marrying before the age of 18 years, young age at first sexual intercourse, multiple sexual partners, and multiple childbirths (Paul, 2011). Cervical cancer originates in the cells lining the cervix, mainly the lower part of the uterus known as the uterine cervix. There are mainly two types of cells covering the cervix, the glandular cells and the squamous cells which meet at a place called the transformation zone and this is the place where cervical cancer commonly originates. The location of the transformation zone changes with age. Normal cells become precancerous and subsequently turn cancerous and do not transform into cancer cells abruptly initially (American Cancer Society, 2015). Persistent infection with certain HPV types and especially with high-risk types has been documented as a causative factor for the development of cervical cancer (Walboomers, 1999). A study that evaluated the HPV infection in 10,575 histologically confirmed cases of invasive cancer from 38 countries in Asia, Europe, Latin America, Caribbean, North America, Oceania and Sub-Saharan Africa over a period of 60 years, found that 85% (8,977) of the cases were HPV DNA positive. HPV 16, 18 and 45 were the three most common types found in 61%, 10%, and 6% of the cases, respectively (de Sanjose, 2010).

The histopathologic types of cervical cancer are:

1. Squamous cell carcinoma (keratinizing; non-keratinizing; papillary, bas-aloid, warty, verrucous, squamotransitional, lymphoepithelioma-like)
2. Adenocarcinoma (endocervical; mucinous, villoglandular, endometrioid)
3. Clear cell adenocarcinoma
4. Serous carcinoma
5. Adenosquamous carcinoma
6. Glassy cell carcinoma
7. Adenoid cystic carcinoma
8. Adenoid basal carcinoma

9. Small cell carcinoma
10. Undifferentiated carcinoma (Bhalta, 2018)

Cervical cancer can be divided into three groups:

1. **Early Stage:** Cervical carcinoma confined to the uterus. Tumors up to 4 cm. (FIGO IA-IB1).
2. Local advanced Cervical Cancer (LACC), tumors that grow locally larger than 4 cm or with primary parametrial invation (FIGO stage IB2-IIB). and
3. Advanced-stage cervical cancer, with tumors predominantly comprising pelvic structures or distant metastatic tumors (FIGO stage IIIA-IVB).

Although radiotherapy and radical surgery are equally effective for early stages, the latter strategy is generally accepted as a standard of care. On the other hand, concomitant chemoradiotherapy is used as first-line therapy for patients with advanced stage disease (FIGO stage IIIA-IVB) (Minig, 2014).

In general, the benefits of surgical treatment include: 1) the emotional satisfaction that the tumor has been removed, 2) the accuracy of the surgical staging, 3) the ability to maintain ovaries, 4) preventing the development of secondary endometrial cancer 5) complication that may occur are more easily treated . On the other hand, radiotherapy, in addition to being the treatment of choice for more advanced cancers, excels because it is applicable to most patients regardless of age or medical condition. In particular, patients with co-existing medical conditions who are not candidates for surgery can be successfully treated with radiotherapy or chemoradiotherapy (Photopulos, 1990).

In 1999, based on five randomized trials (RCTs), the National Cancer Institute recommends concomitant chemoradiotherapy rather than only radiatiotherapy for women with cervical cancer. This has led to the revision of the treatment of many women with cervical cancer (Keys, 1999; Morris, 1999; Peters, 2000; Rose, 1999; Whitney, 1999).

Therapeutic Approach (FIGO 2014)

Most guidelines are still based on previous 2014 FIGO staging system:

- Stage IA1 (stromal invasion with a maximum depth of 5mm and a horizontal spread up to 7mm)

According to the European Community of Gynecologic Oncologists (ESMO), the treatment for patients with stage 1A disease should be individualized according to age, desire to maintain fertility, and the presence or absence of lymphovascular invasion (LVSI). Conization can be considered a definitive treatment as hysterectomy does not improve the outcome. Staging of lymph nodes is not indicated in IA1 patients with negative LVSI, but may be performed in patients with IA1 and positive LVSI. Sentinel lymph node biopsy is an accepted method in cases of LVSI (+). Radical hysterectomy is contraindicated and represents overtreatment for these patients (Landoni, 2017).

According to NCCN, modified radical hysterectomy is recommended in patients with IA1 and LVSI (+). Also, postoperative pelvic radiotherapy (with or without concomitant chemotherapy with cisplatin) is a Category 1 recommendation for women with stage IA and negative lymph nodes after surgery, who have high risk of cervical cancer (large tumor, deep invasion and / or LVSI (+) (Cidula, 2018).

- Stage IA2 (stromal invasion of more than 3mm and not more than 5mm, with a horizontal spread of 7mm or less)

According to the European Community of Gynecologic Oncologists (ESMO), in patients with stage IA disease, conization or simple hysterectomy is an appropriate treatment. Parametrectomy is not recommended. Staging of lymph nodes may be considered in patients with LVSI (-), but should be performed in patients with LVSI (+).Sentinel lymph node biopsy seems to be an acceptable staging method.

In patients undergoing simple hysterectomy with LVSI (+) stage IA2, chemoradiotherapy is recommended in cases of suspected residual tumor or positive lymph nodes. Otherwise, in the absence of imaging findings, only radiotherapy is recommended (Landoni, 2017).

According to NCCN, modified radical hysterectomy is recommended in patients with IA2. Pelvic radiotherapy and brachytherapy are suggested as an alternative therapeutic approach (Cibula, 2018).

- Stage IB1 (Cancer limited to the uterus and clinically visible lesion 4.0 cm or less)
- Stage IIA1 (cancer invades beyond the uterus, but not the pelvic wall or lower vagina, clinically visible lesion of 4.0 cm or less is greater)

The treatment strategy should aim at avoiding a combination of radical surgery and radiotherapy due to the high morbidity after combined therapy.

In case of negative lymph nodes on imaging:

Radical surgery by a gynecologic oncologist is the preferred treatment method. Pelvic lymphadenectomy or sentinel lymph node biopsy is also recommended.

In case of intraoperative detection of lymph node involvement further lymphadenectomy and radical hysterectomy should be avoided. In these cases, paraaortic lymphadenectomy may be considered for staging.

In case of positive lymph nodes on imaging:

In patients with positive pelvic lymph nodes on imaging, chemoradiotherapy is recommended. Aortic lymphadenectomy, at least up to the lower mesenteric artery, may be performed for staging in case of negative aortic lymph nodes on imaging.

Following radical surgery, chemoradiotherapy is indicated in the following patient groups:

- Macro- or micro-metastases to the pelvic lymph nodes
- Positive surgical margins
- Parametrial involvement
- Stage IIB (Parametrial involvement)
- Stage III (Tumor extending to the pelvic wall and / or involving the lower third of the vagina and / or causing hydronephrosis
- Stage IV (The tumor invades the bladder or rectal mucosa and / or extends beyond the true pelvis)
- Stage IVB (distant metastases)

Chemoradiotherapy and brachytherapy are recommended.

Radiotherapy is administered in four to six cycles (1.8-2 Gy), with one of the following cisplatin-based chemotherapy regimens:

Cisplatin 40 mg / m2 IV once a week (up to 70 mg / week) or

Cisplatin 50-75 mg / m2 IV on day 1 with intravenous infusion of 1000 mg / m2 5-fluorouracil (5-FU) on days 2-5 and days 30-33 (total dose 4000 mg / m2 in each cycle) or

Cisplatin 50-75 mg / m2 IV on day 1 plus 5-FU 1000 mg / m2 continuous intravenous infusion for 24 hours on days 1-4 (total dose 4000 mg / m2 each cycle) every 3 weeks for a total of three to four cycles . (Landoni, 2017;Cibula, 2018; National Comprehensive Cancer Network, 2016; Chuang, 2016)

In 2018, the International Federation of Gynecology and Obstetrics (FIGO) recently revised the staging system for cervical cancer [table 1]. One major change in comparison to 2014 FIGO staging is that a new stage IB3 was added, including all tumors greater than 4 cm (former stage IB2).By this change the former stage IB1 was divided into stage IB1 (tumors < 2 cm) and IB2 (tumors > 2 cm but smaller than 4 cm). In addition, all tumors with LN metastases were included into the new, formerly not existing stage IIIC. Nodal metastases limited to the pelvic LN are classified into stage IIIC1. Furthermore, tumors with positive paraaortic LN are now classified into stage IIIC2. Under the revised system, radiographic and/or histological findings are allowed to assign stage IIIC disease. Stage IIIC1 is appointed when only pelvic LN metastasis is detected, while stage IIIC2 is designated when para-aortic LN metastasis is documented by either method. As a result, the revised FIGO staging system now incorporates imaging into the system The aim of these changes was to provide more accurate prognostic groups and thereby help trigger more adequate treatment decisions. In addition, the cervical cancer classification is now more harmonized with the staging systems of endometrial and ovarian cancer. The new FIGO classification for cervical cancer reflects the strong impact of lymph node metastases on survival and contributes to the improvement with regard to risk stratification. (Berek, 2019)

Table 1.

I The carcinoma is strictly confined to the cervix (extension to the uterine corpus should be disregarded)
IA Invasive carcinoma that can be diagnosed only by microscopy, with maximum depth of invasion <5 mm
IA1 Measured stromal invasion <3 mm in depth
IA2 Measured stromal invasion ≥3 mm and <5 mm in depth
IB Invasive carcinoma with measured deepest invasion ≥5 mm (greater than stage IA), lesion limited to the cervix uteri
IB1 Invasive carcinoma ≥5 mm depth of stromal invasion, and <2 cm in greatest dimension
IB2 Invasive carcinoma ≥2 cm and <4 cm in greatest dimension
IB3 Invasive carcinoma ≥4 cm in greatest dimension
II The carcinoma invades beyond the uterus, but has not extended onto the lower third of the vagina or to the pelvic wall
IIA Involvement limited to the upper two-thirds of the vagina without parametrial involvement
IIA1 Invasive carcinoma <4 cm in greatest dimension
IIA2 Invasive carcinoma ≥4 cm in greatest dimension
IIB With parametrial involvement but not up to the pelvic wall
III The carcinoma involves the lower third of the vagina and/or extends to the pelvic wall and/or causes hydronephrosis or nonfunctioning kidney and/or involves pelvic and/or para-aortic LNs
IIIA The carcinoma involves the lower third of the vagina, with no extension to the pelvic wall
IIIB Extension to the pelvic wall and/or hydronephrosis or nonfunctioning kidney (unless known to be due to another cause)
IIIC Involvement of pelvic and/or para-aortic LNs, irrespective of tumor size and extent (with r and p notations)
IIIC1 Pelvic LN metastasis only
IIIC2 Para-aortic LN metastasis
IV The carcinoma has extended beyond the true pelvis or has involved (biopsy proven) the mucosa of the bladder or rectum. (a bullous edema, as such, does not permit a case to be allotted to stage IV)
IVA Spread to adjacent pelvic organs
IVB Spread to distant organs
When in doubt, the lower staging should be assigned.

Treatment Approach (FIGO 2018)

The addition of stage IB3 will contribute to the improvement of the patients triaging between surgery and radiotherapy. Patients with large stage IB tumors are best managed with chemoradiotherapy, and dual-modality therapy is discouraged in patients with cervical cancer (Bhatla, 2018). In a trial by Landoni et al. dual modality therapy was required in 54% of patients who had tumors <4 cm, and 84% of those with tumors >4 cm. The combination of surgery and radiotherapy was associated with greater morbidity resulted compared with radiotherapy or surgery alone (Landoni, 1997). Patients with positive para-aortic nodes are typically managed with concurrent chemoradiotherapy, and these patients would be staged as stage IIIC2 in the new system. One study demonstrates greater than 35% disease-specific survival in this population (Kidd, 2010). Some patients with supraclavicular-only LN metastasis have been shown to achieve long-term disease-free survival. Recent data indicate that some patients who receive external beam radiotherapy and chemotherapy for limited oligo-metastatic disease may also have a prolonged disease-free survival (Zighelboim, 2006). Furthermore, according to the National Comprehensive Cancer Network guidelines, fertility-sparing trachelectomy is an acceptable operation for patients with stage IB1 disease, but not for those with stage IB2 disease (National Comprehensive Cancer Network, 2018). Laparoscopic radical hysterectomy is associated with poorer survival compared to the laparotomy approach in stage IB1–IB2 disease, although stage IB3 disease with tumor size larger than 4 cm was not examined in their studies (Melamed, 2018; Ramirez, 2018) Subanalyses of their study show that stage IB1 disease may not differ in survival rates compared with a minimally-invasive procedure.

CONCLUSION

- Treatment planning should be on an interdisciplinary basis (oncology board).
- Patients should carefully consider the treatment options and possible alternatives.
- Treatment should be carried out by a specialized team
- In locally advanced cervical cancer (IB2 and higher (except for IIA1) or in early-stage disease with suspected lymph nodes on magnetic resonance imaging, PET / CT or abdominal / thoracic CT is recommended for evaluation of lymphadenepathy or distant metastases).
- PET-CT is the preferred option for chemoradiotherapy planning
- Surgery is the preferred treatment option in stage IA 1, IA 2
- Chemotherapy is the treatment of choice in stages IB2,IB3, IIA2, III and IV
- Chemoradiotherapy is an alternative treatment with equally good results compared to surgical treatment for stages IB1 and IIIA
- Patients with coexisting medical conditions who are not candidates for surgery can be successfully treated with radiation or chemoradiotherapy

EARLY STAGE VULVAR CANCER

Introduction

The vulva is the external part of the female genitalia. The vulvar structures extend inferiorly from the pubic arch and include:

- **Mons Pubis:** This is the rounded area in front of the pubic bones. Mons pubis becomes covered with hair at puberty. It includes the skin folds under the pubic hair that protect the opening of the vagina and the urethra. The urethra is the tube that carries urine out of the body.
- **Labia majora**: The outer folds of skin on each side of the vulva.
- **Labia Minora:** The inner folds of skin on each side of the vulva.
- **Prepuce or Hood of the Clitoris:** This is made by the top of the inner folds of the vulva where the labia minora meet.
- **Clitoris:** This is below the prepuce. It's a sensitive piece of tissue that swells with blood when stimulated.
- **Fourchette:** This is where the labia minora meet at the bottom of the inner folds of the vulva.
- **Perineum:** The area between the fourchette and the anus. (Yeung, 2016)

The internal and external pudendal arteries are responsible for the blood supply. The ilioinguinal and genitofemoral nerve innervates the anterior part of the vulva, while the posterior part is innervated by the perineal branch of the posterior cutaneous nerve. The majority of the vulva is drained by lymphatics that pass laterally to the superficial inguinal lymph nodes. The clitoris and anterior labia minora may also drain directly to the deep inguinal or internal iliac lymph nodes (Way, 1948).

Vulva cancer is a rare condition and accounts for about 4% of all gynecological cancers. It affects predominantly elderly women as two-thirds of cases occur in women over 60 years (Judson, 2006). The most common histological type is squamous cell carcinoma (95%), whereas the other histological types are extremely rare The other histological types are: melanoma, adenocarcinoma, sarcoma, and basal cell carcinoma. Surgical treatment appears to be the only curative treatment option in the early stages of the disease. Surgical treatment is often associated with considerable morbidities and psychosexual issues (Alkatout, 2015). The risk of developing vulvar carcinoma is related to different behavioral, reproductive, hormonal, and genetic aspects. Factors that raise the risk include other genital cancers, chronic inflammatory diseases of the vulva, smoking, history of genital warts, and vulvar intraepithelial neoplasia. Paget's disease of the vulva is a rare disease, with an incidence varying between <1% and 2% of vulvar malignancies (Jones, 2011).

Precancerous conditions of the vulva are changes to vulvar cells that can lead to cancer. These conditions are not yet cancer. But if they aren't treated, there is a chance that these abnormal changes may become vulvar cancer. Vulvar intraepithelial neoplasia (VIN) means changes to the epithelial cells in the surface layer of skin that covers the vulva. Squamous VIN was traditionally classified into three grades (VIN I, II, III) similarly with cervical intraepithelial neoplasia (CIN). The grade of VIN expresses how deep the abnormal cells go into the top layer of the skin that covers the vulva. VIN 1 means that the depth of abnormal cells is less than one-third of the top layer of vulvar skin. VIN 2 means that the depth of abnormal cells is less than two-thirds of the top layer of vulvar skin. VIN 3 means that the depth of abnormal cells is more than two-thirds of the top layer of vulvar skin. Some women have no symptoms

of VIN and are diagnosed when having tests for other health problems. The signs and symptoms of VIN may include: mild to severe itching or burning on the vulva, soreness, burning or severe tingling in the vulva that can become worse when urinating, changes to the vulvar skin such as red, white or discoloured areas, warty appearance or areas of thick skin discomfort or pain during sex. Tests used to diagnose VIN may include: exam of the vulva, vagina, cervix and anus, colposcopy, biopsy. In 2004, the International Society for the Study of Vulvar Disease (ISSVD) introduced a new classification for precancerous lesions of the vulva that are precursors of squamous cell carcinoma. There are two different types, which differ in their etiology, pathogenicity and clinical significance (Sideri, 2005).

The first form, called usual type, is associated with infection with some high-risk HPV types and involves high-grade lesions (VIN 2 -3). VIN1 lesions were excluded from the classification as these are often due to HPV 6 and 11 which do not develop into vulvar cancer and VIN classes 2 and 3 were merged into one class, now called usual VIN lesion (uVIN). UVIN lesions are usually multifocal and often coexist with intraepithelial cervical, vaginal and rectal lesions. The progression of uVIN lesion in carcinoma is low, ranging from 10-12%. The risk of developing invasive cancer is very low in patients under the age of 35 as opposed to women over 45. In women who develop vulvar cancer, HPV 16, 18, and 33 are most commonly found (Sideri, 2004; De Vuyst, 2009; Heller, 2007; Jones, 2010, 2005). Immunization with the quadrivalent or 9-valent human papillomavirus vaccine, which is effective against human papillomavirus genotypes 6, 11, 16, and 18, and 6, 11, 16, 18, 31, 33, 45, 52, and 58, respectively, has been shown to decrease the risk of vulvar high-grade squamous intraepithelial lesion (HSIL) (VIN usual type) and should be recommended. The bivalent HPV vaccine (subtype 16, 18) has not been studied for vulvar HSIL (VIN usual type) prevention (Jones, 2005)

The second form, called differentiated VIN type (dVIN) which represents the HPV-negative sequence of vulvar carcinogenesis, is associated with chronic inflammatory skin conditions, such as squamous cell hyperplasia, sclerosis, and chronic lichen. It is more common in postmenopausal women with a mean age of 68 years and most of the time is single-focal. The differentiated type of VIN is HPV-independent and is often caused by p53 mutations. These are high-grade lesions, and similarly in the first form there is no longer a classification of the grade. (Heller, 2007; Del Pino, 2013,Carlson, 1998)

The rationale for changing the terminology in 2015 was to unify the nomenclature of HPV-associated squamous lesions of the lower genital tract. The ISSVD recommends the terms low-grade squamous intraepithelial lesion of the vulva (vulvar LSIL) and high-grade squamous intraepithelial lesion of the vulva (vulvar HSIL) for histopathologic diagnoses of productive HPV infections, which includes external genital warts and precancer, respectively. The 2015 terminology is similar to the World Health Organization's classification and to the Lower Anogenital Tract Squamous Terminology (commonly known as the LAST Project) classification that is used by the American Society for Colposcopy and Cervical Pathology and has been adopted by the College. Based on the 2015 ISSVD terminology of vulvar squamous intraepithelial lesions, usual type VIN is now classified as vulvar HSIL, and differentiated VIN remains the same. Flat lesions associated with basal atypia and koilocytic changes (formerly termed VIN 1) are considered LSIL (condyloma or HPV effect) in the current 2015 ISSVD classification system . Other intraepithelial vulvar neoplasms, such as Paget disease and melanoma in situ, are rare. (Bornstein, 2016)

Precancerous lesions of vulva and early stages of vulvar cancer are uncommon and as a result there are no standard screening programs. Detection is based on visual assessment and biopsy. The appearance of vulvar HSIL (VIN usual type) can vary. Lesions may be flat or elevated and their color can vary from white to gray or from red to brown to black. Biopsy is indicated for visible lesions for which definitive diagnosis cannot be made on clinical grounds. Furthermore, a biopsy is needed for visible lesions with

presumed clinical diagnosis that is not responding to usual therapy, for lesions with atypical vascular patterns, or for lesions that rapidly change in color, or size. Biopsy should be performed in postmenopausal women with apparent genital warts and in women of all ages with suspected condyloma in whom topical therapies have failed. Although information regarding the evaluation of women with immunocompromised conditions and HPV-related disease is limited, human immunodeficiency virus (HIV)-seropositive patients and patients on immunosuppression after organ transplant may need biopsy of lesions when the level of suspicion is lower. Colposcopy can be also useful in determining the extent of disease if lesions are not clearly visible in women with persistent focal vulvar pruritus and pain with no gross lesions, and women who remain symptomatic despite appropriate treatment for presumed vulvo-vaginitis.

The technique of colposcopy of the vulva is similar to the usual colposcopy examinations of the cervix. Colposcopy can be achieved using a micromanipular device, which has depth gauge that enables the execution of high-power density without accidental defocusing. It is necessary that all parts of the vulva are examined: labia majora and minora, vestibule, clitoris, terminal urethra, perineum, perianal regia, and anus up to its muco-cutaneous junction. It should be performed after applying 3–5% acetic acid to the vulva for several minutes as keratinization requires longer acetic acid application for effect. The colposcopical image of different vulvar lesions depends on the features of the tissue examined. The thickness of the epithelium and the vascularity of the underlying stroma are the most important . Thickness of the skin affects the opacity and it varies among persons. Thickness of the skin also varies in between different areas of the vulva. Skin of hair-bearing parts is thicker than the skin of other areas of the vulva. Its prominent surface keratin layer does not provide a clear view of the underlying blood vessels. Pigmentation can also obscure blood vessels. Therefore vascular aberrations such as punctations and mosaic patterns are less marked and less reliable than with colposcopy of the cervix. They are less common and can be practically seen only on the non-hair-bearing areas wich include the inner portions of the labia minora where the keratin layer is thinner. Thus, leukoplakia and acetowhite epithelium are the most frequent colposcopical manifestations of vulvar pathology. Stromal changes that influence colposcopical appearance are usually due to the increase in vascularity. This increase may be part of an inflammation, an immune response or the neovascularisation of neoplasia. In these cases, the colour of the skin will become red. The vascularisation may also be decreased or stroma may undergo fibrotic changes, which result in whitish colouring of the skin (Kesic, n.d) .

THERAPEUTIC PROTOCOLS

Precancerous Lesions

Treatment is recommended for all women with vulvar HSIL in order to prevent development of invasive vulvar cancer while protecting usual vulvar anatomy and its function. Treatment includes surgical resection, laser ablation or topical imiquimod therapy. Women with complete response to treatment and no new lesions at re-examinations scheduled in 6 and 12 months after initial treatment should be monitored annually.

Wide local resection is the preferred initial intervention. The goal is to achieve 0.5-1 cm free surgical margins, but these limits can be altered to prevent injury of clitoris, urethra, anus or other noble structures. Women with injuries in gentle areas should be referred to a specialist to avoid disturbance

of their psycho-sexual function. Women with free surgical margins have a significantly lower risk of relapse than women who do not have free surgical margins.

Simple vulvectomy is another method that involves removing the entire vulva jointly with perineal and subcutaneous skin tissue. It is used to treat multifocal or extensive lesions of both benign and premalignant skin conditions of the vulva.

Skinning vulvectomy is rarely required, although it may be useful in cases of confluent multifocal lesions. The method of removing only the top layer of the affected vulvar skin tissue without taking away the subcutaneous skin tissue is called a skinning vulvectomy.

Carbon dioxide laser ablation is acceptable for the treatment of vulvar HSIL (common type of VIN) when there is no suspicion of cancer. Laser ablation permits treatment of VIN in an outpatient or day-surgery setting under local anesthesia and it eliminates cosmetic disfigurement. It can be used for individual, multifocal, or confluent lesions, although the risk of recurrence may be higher than after surgical resection. In hair-bearing areas, laser procedures must ablate hair follicles, which can contain vulvar HSIL (VIN usual type) and extend into the subcutaneous fat for 3 mm or more. Consequently, large vulvar HSIL (VIN usual type) lesions over hair-bearing areas may be preferentially treated with surgical excision. Ablation over skin that does not bear hair should extend through the dermis (up to 2 mm). 750–1,250 W/cm2 power density is considered appropriate to avoid deep injury. Therefore, laser ablation of vulva HSIL doesn't permit histologic evaluation of the excised tissue and detection of possible occult early invasion. (American College of Obstetricians and Gynecologists, 2016; van der Meijden, 2016)

Another alternative method is to apply topical imiquimod 5%. Topical imiquimod treatment is convenient, self-administered, and less invasive than surgery. Imiquimod is an immune response-modifying agent currently FDA approved for the topical treatment of actinic keratosis, superficial basal cell carcinoma, and external genital warts. Classified as an immune response-modifying drug, imiquimod enhances local skin immune responses by activating toll-like receptor-7 and -8 on macrophages and dendritic cells, which induces the release of pro-inflammatory T-helper cell type 1 cytokines (interferon-α, interleukin-2, interleukin-12) and upregulates cell-mediated immunity. In a review of three clinical trials, the frequency of application of imiquimod 5% cream ranged from two to three times weekly, with some studies employing slow frequency escalation . The duration of treatment lasted 16 weeks in all studies, and follow up ranged from 2 months to more than 7 years. The results of these studies demonstrated complete response rates ranging from 30 to 81%, partial response from 9.5 to 38%, and no response from 9 to 30%. Side effects resulting from the application of imiquimod to the lesions include inflammation with mild to medium erosions or erythema. (Grimes, 2016). Overall, the recurrence rates after treatment range from 9% to 50%. Among the therapeutic methods the lowest relapse rates are observed with surgical removal. Although surgery remains the treatment mainstay, vulvar disfigurement and loss of sexual function must be considered. (American College of Obstetricians and Gynecologists, 2016; van der Meijden, 2016; Jeong-Min, 2015)

Early Stages of Vulvar Cancer (Stage I-II)

In any patient suspected for vulvar cancer, diagnosis should be established by a punch/incision biopsy. Excision biopsy should be avoided for initial diagnosis, as this may obstruct further treatment planning. In patients with multiple vulvar lesions, all lesions should be biopsied separately with clear documentation of mapping. All patients with vulvar cancer should be referred to a Gynaecological oncology centre and treated by a multidisciplinary gynaecological oncology team. Preoperative work-up should at least

include clear documentation of clinical exam size of lesion, distance to the midline/clitoris/anus/vagina/urethra and palpation of lymph nodes. Evaluation of the cervix/vagina/anus is also recommended. (European Society of Gynaecological Oncology, 2016)

There is no role for diagnostic imaging in the primary detection and characterization of vulvar cancer. However, imaging (MR) may play a role in evaluation of the local extent of disease in advanced cases, especially if urethral invasion is suspected, as well as in the evaluation of lymphadenopathy (US, CT, MRI) and distant metastatic disease (CT and PET CT). Using the ultrasound, vulvar cancer appears as a soft tissue mass with internal vascularity. On CT, vulvar cancer appears as a nonspecific soft tissue mass, and on MRI, the tumor shows intermediate signal intensity on T1W and high signal intensity on T2W sequences. Further staging with CT thorax/abdomen and pelvis is recommended where there is a clinical suspicion of, or proven nodal) metastatic disease and/or advanced stage disease. (Alkatout, 2015)

Early stages of vulvar cancer include Stages I and II:

I Tumor confined to the vulva
IA Lesions ≤2 cm in size, confined to the vulva or perineum and with stromal invasion < 1.0 mm, no nodal metastasis
IB Lesions >2 cm in size or with stromal invasion >1.0 mm, confined to the vulva or perineum with negative nodes
II Tumor of any size with extension to adjacent perineal structures (1/3 lower urethra, 1/3 lower vagina, anus) with negative nodes.

Depending on the size and extent of the primary tumor, radical local resection or radical vulvectomy may be required. There seems to be no difference in the two methods concerning survival and recurrence rates. The target is to preserve 1-2 cm of free surgical margins. The European Society of Gynecologic Oncologists (ESGO) recommends radical local resection versus radical vulvectomy and free surgical margins of at least 1 cm. Adjuvant radiotherapy should start as soon as possible, preferably within 6 weeks of surgical treatment when needed. When invasive disease extends to the pathological excision margins of the primary tumour, and further surgical excision is not possible, postoperative radiotherapy should be performed. In case of close but clear pathological margins, postoperative vulvar radiotherapy may be considered to reduce the frequency of local recurrences. There is no consensus for the threshold of pathological margin distance below which adjuvant radiotherapy should be advised (Koh, 2017; European Society of Gynaecological Oncology, 2016)

In some cases of extensive vulvar cancer, plastic surgery is recommended for covering the defect. The multidisciplinary team working with plastic surgery colleagues enhances the spectrum of available operative therapy using local fasciocutaneous skin-flaps for minor cosmetic defects. In cases of more severe wounds extending over larger areas of the vulva and its surrounding regions, regional myocutaneous skin-flaps lead to good results. (Weikel, 2005)

Stage IA

For IA stage, inguinofemoral lymphadenectomy is not recommended as the risk of metastasis is negligible. (Hacker, 1981; Hampl, 2009)

Metastasis to the inguinofemoral lymph nodes is directly related to the depth of invation. When stromal invasion is between 1.1-3.0 mm, the chance of metastasis to the inguinofemoral lymph nodes is 7-8% and for 3mm the chance of metastasis is 26-34%. (Homesley, 1993)

Stage IB, II

Unilateral or bilateral inguinofemoral lymphadenectomy is recommended. In patients with unifocal cancers of < 4 cm, without suspicious groin nodes, the sentinel lymph node procedure is recommended. Where metastatic disease is identified in the sentinel lymph node, inguinofemoral lymphadenectomy in the groin with the metastatic sentinel lymph nodeis recommended. For tumours ≥ 4 cm and/or in case of multifocal invasive disease, inguinofemoral lymphadenectomy by separate incisions is recommended. In lateral tumours (medial border > 1 cm from midline), ipsilateral inguinofemoral lymphadenectomy is recommended. Contralateral inguinofemoral lymphadenectomy may be performed when ipsilateral nodes show metastatic disease. When lymphadenectomy is indicated, superficial and deep femoral nodes should be removed. Preservation of the saphenous vein is recommended. (European Society of Gynaecological Oncology, 2016)

The prognosis of patients with vulvar cancer is quite good when convenient treatment is provided in a timely manner. Inguinal and/or femoral node involvement is the most significant prognostic factor for survival in patients with vulvar cancer. Extracapsular growth of lymph node metastases, two or more affected lymph nodes, and more than 50% replacement of lymph nodes by tumor are predictors of poor survival. The overall 5-year survival rate ranges from 70% to 93% for patients with negative nodes and from 25% to 41% for those with positive nodes. Other prognostic factors include stage, capillary lymphatic space invasion, and older age. Recurrent lesions in the lymph nodes, as well as in distant sites, are not amenable to surgery or radiotherapy. They are difficult to treat, and the 5-year survival rate is generally less than 5%. (Alkatout, 2015)

CONCLUSION

Precancerous lesions of vulva and early stages of vulvar cancer are uncommon and as a result there are no standard screening programs. The precancerous lesions are often overlooked and are treated as nonspecific dermatologic conditions. Often the patients seek multiple opinions from different specialists for symptom relief. Therefore, the gynecologists, dermatologists, and other healthcare providers in this field should be familiar of the clinical features and detection of the different premalignant vulvar lesions in order to arrive at the correct diagnosis and proper management (Premalatha, 2019). There are two types of intraepithelial neoplasia (VIN):

1. The usual type of VIN and
2. The differentiated type of VIN
    a. In every patient suspected of having cancer of the vulva, the diagnosis should be documented by biopsy. Complete resection of the lesion for initial diagnosis should be avoided, as this may impede further planning of treatment.
    b. Treatment is recommended for all women with vulvar HSIL with surgical resection, laser ablation, or topical imiquimod therapy.

c. Among the methods of treatment for vulvar HSIL, lower recurrence rates are observed with surgical resection.
d. Depending on the size and extent of the primary tumor in vulvar cancer, radical local resection or radical vulvectomy is recommended. The target is to preserve at least 1 cm of free surgical margins.
e. Stage IA does not require groin inguinofemoral lymphadenectomy.
f. The prognosis of patients with vulvar cancer is quite good when convenient treatment is provided in a timely manner.

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Section 5
Ovarian Pathology

Chapter 13
Is There a Role for Laparoscopy in Ovarian Cancer?

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ABSTRACT

During 1960s and 1970s, the first laparoscopic procedures concerned the treatment of benign diseases. Today the indications have significantly increased even in ovarian borderline tumours and in ovarian cancer. Furthermore, the role of diagnostic laparoscopy remains apparent in the overall therapeutic setting of advanced ovarian cancer as well. The chapter aims to summarize current evidence regarding potential role of laparoscopy in ovarian cancer treatment as well as indicate potential difficulties its usage may pose.

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BACKGROUND

During the 1960s and 1970s the first laparoscopic procedures concerned the treatment of benign diseases. Today the indications have significantly increased even in borderline ovarian tumours and in ovarian cancer.

Laparoscopic Treatment of Borderline Ovarian Tumours

Nowadays, borderline ovarian tumors (BOTs) represent a separate entity in the group of epithelial ovarian cancers. BOTs we recognized by the International Federation of Gynecology and Obstetrics (FIGO) in 1961 and by the World Health Organization (WHO) in 1973. Currently, three definitions are used for these tumors: borderline tumor, tumor of low malignant potential, and atypical proliferative tumor (Fischerova, Zikan, Dundr, & Cibula, 2012). In the literature, the first reference to this group of tumors was made by Taylor (1929), who already considered them as tumor lesions and whose clinical and histopathological characteristics straddled those of benign and malignant tumors.

BOTs account for 15%–20% of all epithelial ovarian tumors, occurring in 1.8–4.8 out of 100,000 women per year (Lenhard et al., 2009). Although a recent decreasing trend of ovarian neoplasms has been registered globally, the percentage of BOTs among ovarian neoplasms is on the rise. This is thought to result from a more precise pathologic diagnosis of BOTs and from changes in the risk factors associated with BOTs, compared to previous years (Seong, Kim, Kim, & Song, 2015).

Borderline tumors have been identified in all epithelial subtypes, including endometrioid, clear cell, Brenner (transitional cells) and mixed epithelial tumors. The most common histotypes are serous (53.3%) and mucinous (42.5%) (Du Bois, Ewald-Riegler, & Du Bois, 2009; Seidman et al., 2004). Borderline ovarian tumors are generally characterized by an increased epithelial proliferation accompanied by nuclear atypia, usually from light to moderate, usually, and by a slightly increased mitotic activity (Fischerova et al., 2012; Hart & Norris, 1973).

In general, BOTs are considered tumors with good prognosis. The three factors which better correlate with the percentage of long-term survival are represented by FIGO stage, histotype and patient's age (Kaern, Tropé, Kristensen, Abeler, & Pettersen, 1993b).

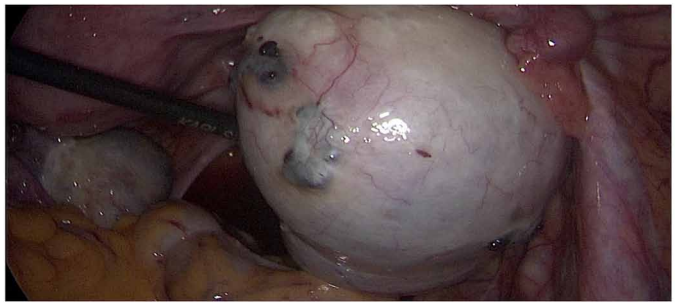
According to a recent classification, 90% of **serous BOTs** have a typical aspect (unilocular cyst with thin septa inside) and 10%–15% of them have a micropapillary aspect. These latter are generally bilateral and occur more often with residual disease after surgery and with a high rate of invasive implants (Vang et al., 2017; Prat & De Nictolis, 2002). The extra-ovarian disease is referred to as "implant." In serous BOTs, ranging from 20% to 40% of cases, implants are mainly located on the omental or peritoneal surface. In most cases (88%), they are non-invasive implants. Invasive implants occur less frequently (12%), showing a destructive invasion of the tissue underneath. Lymph node involvement was documented in 20%–30% of cases in which lymph node dissection had been performed. Unlike invasive cancer, the clinical meaning of lymph node involvement in BOT is not properly defined, since there is not a clear difference of survival between positive and negative lymph node diagnoses, suggesting how the lymph node spread and involvement more likely occur using in the peritoneal way rather than through lymphatic vessels (Ushijima et al., 2015; Fadare et al., 2008). Prognosis of serous BOTs is excellent (survival of 98% after 5 years) in patients with stage I cancer who had a complete surgical staging. Additionally, patients with advanced tumor stage and non-invasive implants reported 90% of survival after 5 years (Sherman et al., 2004). However, patients with invasive implants registered only 66% of survival after 5 years. There is no proven benefit of chemotherapy for late-stage patients. Long-term follow-up is necessary,

and there is a small risk of transformation to high-grade serous carcinoma. Surgery to maintain fertility has to be considered for younger patients, although a high risk of recurrence exists in case of invasive implants (Ushijima et al., 2015).

Mucinous BOTs represent about 30%–50% of all BOTs, and they are less likely to be bilateral (7%). There are two histological subtypes: intestinal type (85%–90%) and endocervical type (from 10% to 15%), with different clinical and pathological features. The intestinal type occurs in old age, is frequently unilateral with large multilocular cysts, is associated with pseudomyxoma peritonei, which represents a metastasis of malignant tumors of the gastrointestinal tract, more frequently of the appendix, and presents a good prognosis. The endocervical type occurs in younger women and more often in bilateral form compared to the intestinal type (from 20% to 30%). This type presents as a unilocular cystic tumor and a more advanced stage; it is correlated with implants or lymph node metastasis, and mortality rate can reach 50% according to its stage (Seong et al., 2015). Prognosis of mucinous BOTs is excellent in stage I tumors. However, 9% of intestinal mucinous BOTs reappear within 5 years, and 13% within 10 years, as mucinous carcinoma. Additionally, benign mucinous adenomas rarely reappears after cystectomy or intraoperative rupture of the cyst. Cystectomy is the only unfavorable prognostic factor. More than 80% of invasive mucinous carcinomas contain areas of intestinal mucinous BOT and intraepithelial carcinoma as precursor lesions (Ushijima et al., 2015).

In Figure 1 is represented a laparoscopic view of mucinous BOT

Figure 1.



The first step of laparoscopy (LPS) is the macroscopic evaluation of ovarian tumefaction. In case extemporaneous histologic examination confirms the diagnosis of BOT, staging is recommended. Therefore, an intraoperative exploration of the whole abdominal cavity should be performed, with peritoneal washing, omentectomy, multiple peritoneal biopsies and complete removal of all suspected macroscopic lesions. For the removal of primary tumor, bilateral adnexectomy is recommended in combination with hysterectomy.

Lymphadenectomy is not suggested since the rates of recurrence and survival for patients with positive or negative lymph nodes are similar (Kaern, Tropé, & Abeler, 1993a; Seidman & Kurman, 2000).

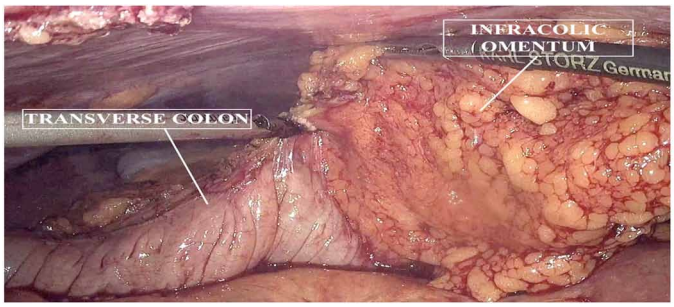
Another indication of laparoscopic surgery is the staging of cases not staged previously when the definitive histologic examination has confirmed the diagnosis after the first surgery. During the extemporaneous histologic examination, there is a tendency to underrate the diagnosis of BOT as a benign tumor (from 24.1% to 30.6%) rather than overrating it as a malignant tumor (from 6.6% to 9.9%) (Fischerova

et al., 2012). Therefore, in all cases of surgically treated ovarian lesions, an accurate exploration of the abdominal cavity and the resection of all macroscopic lesions seem to be usefull, and in many cases this approach avoids surgical restaging (Fischerova et al., 2012). There is a great debate on the prognostic benefit of a complete staging if macroscopic exploration is normal and if omentectomy, hysterectomy and appendectomy should be performed in this situation. Since only 15% of unilateral tumors are associated with an extra-ovarian disease, complete staging is probably not necessary for a unilateral ovarian tumor, unless suspected peritoneal lesions or micropapillary patterns are observed. Nonetheless, an accurate intraoperative exploration cannot be omitted (Seidman, Cho, & Ronnett, 2011). It should be noted that 56% of bilateral tumors are associated with extra-ovarian disease. Borderline micropapillary tumors are often present bilaterally and with invasive implants; therefore, complete staging is recommended to sample the largest number of implants (Seidman et al., 2011; Chang, Ryu, KI Chang, Yoo, & Yoon, 2008).

The omentum is the most likely site for invasive implants. Consequently, surgeons have to remove enough omental tissue so the pathologist can distinguish between invasive and non-invasive implants. Recent studies have demonstrated recurrence in 4 patients out 45, in whom omentectomy was not performed, revealing the presence of residual hidden tumors that were left in situ (Tropé, Davidson, Paulsen, Abeler, & Kaern, 2009).

In Figure 2 is represented a laparoscopic infracolic omentectomy.

Figure 2.



Some authors have questioned the role of hysterectomy when peritoneal implants are not present on the surface of uterine serosa. In fact, a low rate of uterine involvement has been observed among patients with BOTs treated with hysterectomy and bilateral adnexectomy (2%) (Fischerova et al., 2012). When the extemporaneous histologic examination leads to diagnosis of a mucinous ovarian tumor, especially in the context of pseudomyxoma peritonei, it is necessary to perform an appendectomy so as not to erroneously confuse the diagnosis of appendiceal mucinous neoplasm (Bradley, Stewart, Russell, Levine, & Geisinger, 2006). Otherwise, performing an appendectomy seems to be optional at the moment of surgery. No histologic evidence of appendiceal involvement has been found in 57 patients with ovarian malignancies appearing at the initial stage, including 15 BOTs, in a recent case series from the MD Anderson Cancer Center (Ramirez, Slomovitz, McQuinn, Levenback, & Coleman, 2006).

In another two studies, the type of surgical approach (laparoscopy vs laparotomy) did not seem to influence the progression-free interval and the recurrence rate (Fauvet, Boccara, Dufournet, Poncelet, & Daraï, 2005a; Romagnolo, Gadducci, Sartori, Zola, & Maggino, 2006). Additionally, recent studies

have demonstrated that laparoscopic surgical staging of early-stage ovarian tumors is as safe and effective compared to laparotomy (LPT) (Ghezzi et al., 2007). Furthermore, the laparoscopic approach has the advantage of a lower risk of morbidity and adherence compared to the open approach. Nonetheless, it is still important to consider that LPS may imply a higher risk of tumor rupture and the possibility, albeit rare, of metastasis in the access sites to the abdominal cavity (Deffieux et al., 2005).

Conservative Surgery

Conservative surgery consists of sparing the uterus, along with one or both ovaries, during surgical staging. Since BOTs are relatively common among young women and have an optimal prognosis, preserving fertility is often a problem (Tinelli, Tinelli, Tinelli, Cicinelli, & Malvasi, 2006). It is essential to consider that the median age at diagnosis is 40 years, where 27% of patients are younger than 40 years of age compared with about 60 years for women with invasive carcinoma (Kramer & Greene, 2004). In this regard, in addition to the possible negative impact of surgery on fertility, it is important to underline that, regardless of surgical treatment, infertility is a condition that can be often observed in women with BOT because of the pathology itself, appearing before diagnosis in 10%–35% of these patients (Fauvet et al., 2005b; Gotlieb et al., 1998). Although conservative surgical treatment could be associated with a reduction in fertility, due to damage of healthy ovarian tissue or to the appearance on adherences involving the tubes, a large number of studies demonstrate that about 1/3 of patients who undergo this procedure are later able to have a pregnancy, without influencing the tumor pathology negatively (Fauvet et al., 2005b; Morice et al., 2001; Beiner, Gotlieb, Davidson, Kopolovic, & Ben-Baruch, 2001). The literature describes conservative surgery as relatively safe and effective for patients with BOT (Zanetta et al., 2001; Uzan et al., 2010). The recurrence rate after radical surgery is approximately 5%, while after conservative surgery it is higher, ranging from 10% to 20%. Generally, recurrence does not appear as invasive cancer, but as BOT often in the ovary saved during surgery. Recurrence outside ovaries appears in 20% of late-stage BOTs (FIGO stage I and III), compared to 2% of cases at FIGO stage I (Seong et al., 2015).

Cystectomy is associated with a higher rate of recurrence (up to 31%). For this reason, it should be performed only in the case of patients with bilateral tumors and/or with a single residual ovary. The exception to this rule is represented by very young patients for whom an attempt to preserve the most considerable quantity of ovarian tissue is performed. In these cases, possible recurrence can be promptly revealed by an accurate follow-up, performed optimally through transvaginal ultrasound. However, extensive sampling of the resection margins of the removed ovarian cyst is essential. Factors predicting recurrence after cystectomy are resection margins containing tumor cells, multifocal intra-ovarian tumor, or rupture of the intraoperative cyst. Cystectomy is not safe in patients undergoing conservative treatment for mucinous BOTs because of an increased risk of recurrence in the form of invasive carcinoma (Fischerova et al., 2012; Morris et al., 2000).

If recurrence of the residual ovary occurs, further conservative management may be offered to those patients who are planning future pregnancies. This treatment has to be reserved to patients without invasive implants who are young ($\leq$ 40 years) and wish to preserve their fertility and undergo long-term follow-up. However, if invasive disease is observed, at the moment of clinical recurrence a complete debulking is recommended without saving fertility. Removal of the ovary conserved after patients have completed their fertility plans depends on different factors, such as the histologic subtype, FIGO stage of disease, type of conservative surgery, and patient's wishes. Based on the fact that most of recurrent diseases are borderline, easily treatable and have an excellent prognosis, various groups suggest that

the systematic removal of the remaining ovary is not mandatory after pregnancy, provided that patients may have a regular follow-up (Burger, Prinssen, Baak, Wagenaar, & Kenemans, 2000). However, the psychological impact caused by the wait for recurrence is remarkable, and the risk of developing invasive ovarian tumors persists. Therefore, other authors recommend a definitive surgery after completion of family planning. It is possible to avoid concurrent hysterectomy since solitary recurrences have not been detected in the uterus, to obtain low morbidity correlated with adnexectomy (Fischerova et al., 2012).

There is heated debate on the need to perform a second operation to restage those tumors which were diagnosed as benign during surgery, and as BOT by definitive histologic examination. According to many authors, surgical restaging does not influence the survival rate of patients (Trillsch et al., 2010). Since about 39% of BOTs metastasize into the omentum, and about 9% manifest with invasive implants, restaging procedure is suggested if the abdominal cavity and peritoneal surfaces were not adequately examined during the first surgery (Zapardiel et al., 2010). In particular, micropapillary serous BOTs are associated with extra-ovarian disease, invasive implants and lymph node involvement; therefore a restaging procedure may be necessary (Seong et al., 2015; Fauvet et al., 2004; Camatte et al., 2004).

Since BOT recurrences may also appear 15 years after the surgical operation, a follow-up should be performed in the long-term. This indication is imperative for patients treated with conservative surgery, with a focus on the preserved ovary. The recommendation is to perform a 3 months follow-up for the first 2 years after surgery, every 6 months for the next 3 years, and annually for the rest of the patient's life. Follow-up visits consist of clinical evaluation, transvaginal ultrasound, and detection of serum CA-125 (Tropé et al., 2009; Cadron et al., 2007).

Laparoscopic Treatment of Ovarian Carcinoma

Ovarian cancer is not a single disease. In the ovary there could be several distinct tumors with singular clinical and pathological characteristics. About 90% of ovarian tumors are carcinoma (malignant epithelial tumors), and based on histopathology, immunohistochemistry and molecular genetic analysis, five main types have been distinguished: high-grade serous carcinoma (HGSC [70%]), endometrial carcinoma (EC [10%]), clear cell carcinoma (CCC [10%]), mucinous carcinoma (MC [3%]) and low-grade serous carcinoma (LGSC [< 5%]). Malignant germ cell tumors (dysgerminoma, yolk sac tumors and immature teratoma [3% of ovarian tumors]), as well as potentially malignant cord-stromal tumors (1%–2%, mainly granulosa cell tumors), are considerably less common (Mutch & Prat, 2014). Ovarian tumors represent ¼ of malignancies affecting the female genital tract, but they are the fifth most common cause of death for cancer in women. Only in 20%–25% of patients is the disease diagnosed in its early stage. An accurate evaluation of the spread of the disease through surgical staging is essential to guarantee the right treatment and optimal survival (Gallotta et al., 2014).

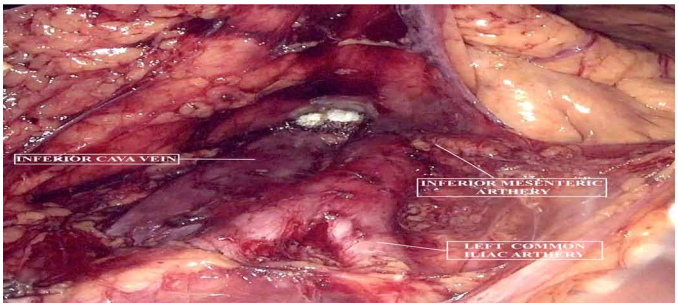
The traditional approach for the staging of apparent early-stage ovarian carcinoma includes LPT with an extended incision of the median line, which is exhibited in the whole peritoneal cavity. According to the guidelines of the International Federation of Gynecology and Obstetrics (FIGO), the best practices include total abdominal hysterectomy, bilateral adnexectomy, omentectomy and appendectomy, especially in case the appendix is macroscopically involved, and the histotype of the lesion is mucinous.

Additionally, in the absence of macroscopically visible peritoneal nodules, multiple biopsies have to be performed at the level of those peritoneal surfaces that are more likely to be implants of malignancy for circulation characteristics of peritoneal fluid (bilaterally paracolic gutters, Douglas, bladder, right

hemidiaphragm, mesenteric root, and pelvic and lumbar aortic lymphadenectomy) (Gallotta et al., 2014; Associazione Italiana Oncologia Medica [AIOM], 2016).

Pelvic and lomboaortic lymphadenectomy should always be performed like in Figure 3 where is represented an extraperitoneal laparoscopic para-aortic lymph node dissection.

Figure 3.



In young patients wishing to have children, in the presence of apparent early-stage ovarian carcinoma (IA G1-2, not clear cell), a conservative approach preserving the uterus and contralateral ovary is a possible option. In these cases, it is recommended to accurately explore the residual ovary, on which superficial biopsies can be done on suspected areas, and perform a hysteroscopy with endometrial biopsy, whose positivity allows to classify stage IIA tumors apparently confined in the gonad. In the case of endometrioid carcinoma of the ovary, hysteroscopy may also highlight the possible presence of a synchronous endometrial carcinoma. In any case, conservative surgery has to be associated with peritoneal and retroperitoneal intensive staging (AIOM, 2016).

Role of LPS in Early-Stage Ovarian Tumor

The first example in the literature of the use of LPS in ovarian tumors was that of Querleu and Le Blanc (1994). Later, many researchers have evaluated the feasibility and efficacy of laparoscopic staging of apparent early-stage ovarian malignancies (ESOMs), thus confirming the use of minimally invasive approaches in selected patients. (Tozzi, Köhler, Ferrara, & Schneider, 2004; Colomer, Jimenez, & Bover Barcelo, 2008; Chi et al., 2005). Most retrospective series report survival percentages of about 90%, which is the same rate observed in patients staged with LPT (Heitz, Harter, & du Bois, 2013). However, minimally invasive surgical techniques are not usually performed in early-stage ovarian tumors, perhaps because of persistent doubts on the efficacy in identifying the hidden metastatic disease. In particular, the following criticisms have been raised: an insufficient exploration of the abdominal cavity, lymphadenectomy with a lower number of lymph nodes, possible risk of metastasis at the level of laparoscopic accesses, risk of spread of tumor cells caused by the abdominal pressure of CO2, risk of rupture of the tumor mass and lack of tactile sensation (Gallotta et al., 2014; Vergote et al., 2001).

Nonetheless, in the last decades, the increasing expansion of laparoscopic surgery, supported by the improvements in technology, has revolutionized the surgical management of patients with gynecological cancer thanks to the recognized benefits of minimally invasive surgery in terms of reduction

of morbidities and recovery time after surgery. However, unlike what has been documented for uterine tumors, routine use of the laparoscopic approach for ovarian malignancies seems to be limited, despite the encouraging results in the literature. A study by Ghezzi et al. (2007) described an increasing use of LPS for ESOM from 7% to 90%. In this context, the largest multicenter, retrospective study about the practicability and results of laparoscopic staging of ESOMs is that by Gallotta et al. (2014). Thanks to the considerable size of the sample collected in this study, it was also possible to make a separately analyze 150 patients undergoing immediate laparoscopic staging and 150 patients undergoing delayed laparoscopic staging after accidental diagnosis of ESOM. This study reports a recurrence rate of 8.3%, a disease progression-free survival after 3 years of 85.1% and overall survival of 93.6%; these results are similar to those of the meta-analysis of Park et al., 2013. Therefore, these data confirm in a wide series of patients that laparoscopic staging of ESOMs is feasible, safe, and provides results of survival comparable to those obtained with the LPT (Gallotta et al., 2014). In a retrospective study by Zivanovic et al. (2008) on 1,694 patients with laparoscopically treated ovarian tumor, only 1.8% of them developed metastasis at the level of laparoscopic accesses. This risk was further reducible through the correct selection of patients and the safe use of endobags and topical cancer-killing agents, such as povidone-iodine (Hoffstetter, Ortega, Chiang, Paik, & Beart, 2001). Furthermore, it has been proven that the development of these lesions does not affect patient survival (Vergote, Marquette, Amant, Berteloot, & Neven, 2005). The National Comprehensive Cancer Network (NCCN, 2014), in its guidelines of 2014, supported use of the minimally invasive approach for ESOM performed by expert surgeons with a focus on the correct selection of patients.

Role of LPS in Advanced-Stage Ovarian Tumor

Most advanced epithelial ovarian cancers (AEOCs) are diagnosed at the late stage of the disease when wide intra-peritoneal spread has already occurred (Fagotti et al., 2013b).

At present, primary cytoreductive surgery, followed by adjuvant chemotherapy, represents the most commonly used treatment in this group of patients (Vizzielli et al., 2016). For a long time, the preferred surgical approach was the open one. However, especially in the last years, the literature has shown a tendency to compare surgical outcomes and the feasibility of the laparoscopic approach rather than the LPT in patients with AEOC (Nezhat et al., 2010). In this regard, the main criticisms against a minimally invasive approach in this field are as follows: problematic management of heavy haemorrhages, risk of insufficient resection of the omentum, and the problematic treatment of diaphragmatic metastases (Liang et al., 2017). Considering that residual tumor (RT) after primary surgery is one of the most important prognostic factors in patients with AEOC, it is clear that an accurate evaluation of these aspects is essential. In a recent study by Liang et al., (2017), the results in terms of intraoperative complications, progression-free survival (PFS) and overall survival (OS) have been compared in two groups affected by AEOC, treated with LPT (N=68) or with LPS (N=64). The results of the study proved that, compared to the open approach, LPS reduced operating time, intraoperative blood loss, and led to shorter recovery time. No difference has been observed as regards intraoperative and postoperative complications and patient PFS and OS. Furthermore, the same authors underline that lymphadenectomy is simple with LPS, since, with this technique, areas such as those next to the abdominal aorta and vena cava are more visible and easily accessible. This latter aspect is widely supported in the literature by various studies, demonstrating the same number of removed lymph nodes using the two techniques (Favero et al., 2015). Also, in terms of residual disease after primary surgery, the two techniques seem to be comparable

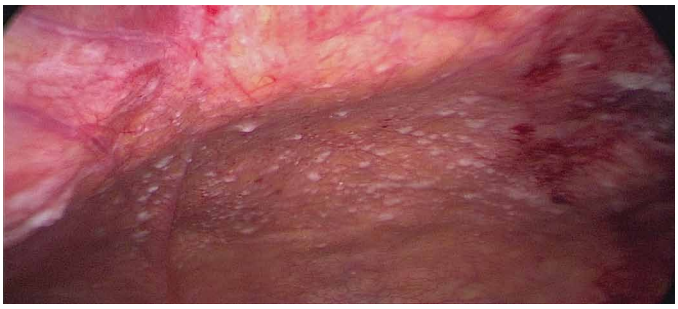
concerning their results, as described in the study by Ceccaroni et al. (2018). They highlighted another important aspect in the group of patients undergoing LPS: a shorter time interval from surgery to the start of chemotherapy compared to those treated with LPT. This is due to a shorter time to recover and to a faster return to their normal daily life, which has always characterized the minimally invasive approach. In terms of results, LPS is also comparable also to robotics, benefitting from a lower cost of the surgical procedure (C.H. Chen, Chiu, H.H. Chen, Chan, & Liu, 2016).

Although, as mentioned above, primary surgical cytoreduction is the most common approach, a certain percentage of women, between 25% and 90%, are unsuitable for optimal cytoreduction after explorative LPT and to be subsequent treatment with neoadjuvant chemotherapy (Eisenkop, Friedman, & Wang, 1998; Bristow, Tomacruz, Armstrong, Trimble, & Montz, 2002). In order to identify patients preoperatively with unresectable tumors who could be exempted from an unnecessary explorative LPT, different approaches have been adopted including evaluation of CA-125 and radiological evaluation of the spread of the tumor. Nonetheless, the accuracy of these parameters has been unsatisfactory and limited by the retrospective nature of the studies and the highly variable rates of optimal cytoreduction in different series of patients (Fagotti et al., 2008; Chesnais et al., 2017).

LPS is well known to offer a direct and enlarged view of the peritoneal cavity and a better view of the upper abdomen. Additionally, it allows a pathologic evaluation of the disease without an open surgery procedure, with a shorter operating time and better results in terms of postoperative morbidity.

In 2008 the group Università Cattolica del Sacro Cuore established a predictive and quantitative model providing each patient with a score, considering different sites of disease evaluated laparoscopically, to predict the opportunity of obtaining an optimal cytoreduction (Fagotti et al., 2008).

Figure 4.



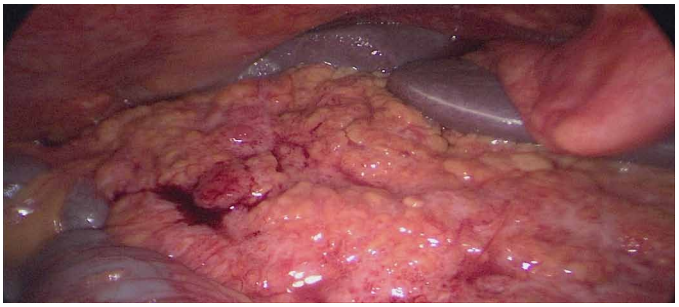
This model considered seven parameters (Fagotti et al., 2008, 2013b):

1. peritoneal carcinosis, with massive and/or miliary involvement (score 2);
2. infiltrating carcinomatosis and/or nodules into most of the diaphragmatic surface (score 2);
3. large infiltrating nodules and/or involvement of the root of the mesentery, supposed based on limited movements of the different intestinal segments (score 2);
4. spread of the tumor along with the omentum up to the greater curvature of the stomach (score 2);
5. possible intestinal resection (excluding recto-sigmoid resection) and/or presence of miliary carcinomatosis widespread on the intestinal loops (score 2);

6. clear neoplastic involvement of the gastric wall (score 2);
7. superficial lesions of the liver exceeding 2 cm (score 2).

In Figure 4 is represented a laparoscopic view of OC' s peritoneal implants.
In Figure 5 is represented an omental cake in laparoscopic view.

Figure 5.



The sum of the scores of these parameters gives the predictive index value (PIV), which is the specific laparoscopic score for each patient. As regards the performances of this model, it has been confirmed that, to a PIV cut-off of 8, the percentage of inappropriate laparotomic explorations is 0%, while the percentage of unnecessary explorations is 40.5% (Fagotti et al., 2008). It has been demonstrated that the threshold value of 8 is the limit for an optimal cytoreduction. Additionally, women have been divided into two different groups: high tumor load (HTL) in case of PIV ^{3} 8 and mild-low tumor load (LTL) in the case of PIV < 8 (Fagotti et al., 2013b). Through this laparoscopic model, the spread of intra-abdominal disease is evaluated in cases of primary AEOCs, so as to guide the management of these patients towards primary debulking surgery (PDS), followed by chemotherapy, or towards neoadjuvant chemotherapy (NACT), followed by interval debulking surgery (IDS) (Hoffstetter et al., 2001). Furthermore, it has been demonstrated that LPS is a valid technique to recognize total or partial responders of NACT to be subjected to IDS or to opt for second-line therapy (Fagotti et al., 2010). The same working group then confirmed, through the MITO study, the optimal reproducibility of this model when it was also applied outside of specialized reference centers (Fagotti et al., 2013a).

In 2010, the randomized study EORTC-NCIC generated broad debate across the gynecological oncology community, as regards the best treatment option to be offered to patients with AEOC. In fact, the study demonstrated that NACT followed by IDS significantly reduced postoperative morbidity, while maintaining survival rates similar to those of PDS (European Organization for Research and Treatment of Cancer, & NCIC Clinical Trials Group, 2010).

In 2013, the group of Fagotti et al. analyzed the PFS and OS of women with AEOC treated with LPS as an ordinary procedure in managing AEOC for a 5-year period (Fagotti et al., 2013b). The study confirmed that RT was essential in predicting survival. Median PFS reported in patients without RT to PDS was 25 months (IC 95% 15.1–34.8), which is inside the interval (24.0–25.9 months) shown in the contemporary literature (Fagotti et al., 2013b). However, an important discovery emerged from these data: comparable survival percentages in women who were not subjected to a complete cytoreduction to PDS

and in patients treated with NACT followed by IDS. It seems that in case absent RT cannot be obtained at PDS, primary radical cytoreduction rather than NACT/IDS should be suggested based on the clinical subject's capacity to withstand an aggressive surgery. In this context, LPS seems to be an appropriate instrument to define the spread of intra-abdominal cancer and, consequently, the feasibility of surgery. The results of this study are also in contrast with the EORTC study, in which PFS is similar in PDS and NACT/IDS groups, regardless of RT. While maintaining similar patient pre-operative characteristics, the highest rate of absent RT to PDS in the 2013 study concerning that obtained in the EORTC group (62.1% vs 19.4%) may easily justify the improvement in patient survival. In conclusion, the present data show a very innovative aspect in the complex management of AEOC, that the group with absent residual tumor is better than any group subjected to NACT. In other words, the use of LPS in tertiary reference centers as a triage instrument with a scoring system is a new approach for the management of AEOC, which seems to not have a negative impact in terms of survival. On the other hand, since it is eminently feasible and safe, identifying the treatment may be useful and avoids useless laparotomies and surgical complications. Based on these results, a randomized trial on PDS vs NACT (Identifier ClinicalTrials.gov: NCT01461850) has been analyzed, recruiting only patients with laparoscopic HTL (PIV ^{3} 8) (Fagotti et al., 2016). The SCORPION study has proved that treatment with NACT/IDS should be preferred to treatment with PDS in patients with HTL (laparoscopic PIV of ^{3} 8 and £12) while the measurements of the questionnaire on the quality of life (QoL) did not show differences between the two groups at the end of the treatment (Fagotti et al., 2016).

More recently, LPS has been proposed as a possible instrument for cytoreductive surgery in patients with AEOC after NACT to extend to these patients the benefits of this approach in terms of surgical impact and rapid recovery. Based on these pioneering experiences, it has been suggested that minimally invasive interval debulking surgery (MI-IDS) could be considered safe and feasible in patients with a complete clinical response. To confirm this hypothesis, a study from 2016 compared patients subjected to MI-IDS with a balanced population treated with standard LPT (Gueli Alletti et al., 2016b). Together with the MISSION trial (Gueli Alletti et al., 2016a), this study suggests that the laparoscopic/robotic approach could represent an alternative and feasible surgical method to perform IDS in this specific subgroup of patients, with no impact on PFS. The positive evidence in measuring the quality of life further supports this conclusion (Gueli Alletti et al., 2016a-b).

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Chapter 14
Surgical Prevention in Ovarian Cancer:
What Is the Optimal Strategy?

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ABSTRACT

Ovarian cancer is the second most common malignant disease of the female genital tract, but the first in mortality because it is usually diagnosed at an advanced stage. Options for early detection, diagnosis, and treatment are limited. Prevention of ovarian cancer relates to primary prevention by avoiding factors that are epidemiologically associated with an increased incidence of ovarian cancer and the adoption of protective habits. These include interventions to exclude the fallopian tubes and ovaries. Secondary prevention is related to early diagnosis. The chapter aims to summarize current evidence on prevention of ovarian cancer as well as role of surgery to prevent advanced-stage disease.

INTRODUCTION

Ovarian cancer is the second most common malignant disease of the female genital tract, but the first in mortality because it is usually diagnosed at an advanced stage. Options for early detection, diagnosis and treatment are limited. The outcome is not good because the disease is often diagnosed late. Ovarian cancer is composed of several subtypes with distinct biological and molecular properties (even within the same histological subtype), and there is inconsistency in availability of and access to treatment. Upfront treatment largely relies on

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debulking surgery to no residual disease and platinum-based chemotherapy with the addition of novel targeted agents (Cortesi, 2013).

Epithelial Ovarian Cancer Subtypes

In recent years, many of the pathogenetic mechanisms of ovarian carcinogenesis have been understood and it is now realized that ovarian epithelial cancer is not a single clinical entity (Gilks, 2008) (Table 1).

The most common histological type (> 70%) is the High grade serous type (HG-serous), which is typically diagnosed at an advanced stage, having peritoneal metastases and poor prognosis. The second most common types (about 10%) are the endometriod and clear cell type, which are usually less localized and associated with endometriosis. There are also the low grade - serous tumor (4%), which is of different origin from the high grade serous type. Low grade tumors are platinum resistant and are associated with borderline malignancies. Even more rare (less than 4%) is the mucous cystadenocarcinoma that is usually localized and has different origins.

Prevention of Ovarian Cancer

Prevention of ovarian cancer relates to primary prevention by avoiding factors that are epidemiologically associated with an increased incidence of ovarian cancer and by the adoption of protective strategies (Table 2).

These include interventions to excise the fallopian tubes and ovaries. Secondary prevention is related to early diagnosis with preventive examinations (specific tumor markers and vaginal ultrasound) in order to diagnose the disease at an early stage and have a good outcome (Table 3).

Ovarian cancer develops in a high-risk population with hereditary ovarian cancer and in a population with normal risk (Temkin, 2017).

Ovarian Carcinogenesis and the Role of the Fallopian Tubes

Epidemiological studies have repeatedly shown that women who have undergone sterilization with tubal ligation, salpingectomy or hysterectomy with or without tubal ligation have been less likely to develop ovarian cancer. It appears that the disruption of the communication of the ovarian surface with the fallopian tubes, uterus, and lower genital tract has a protective effect on the appearance of ovarian cancer. The reduction in the incidence of HG serous carcinoma is approximately 97% after hysterectomy and salpingoophorectomy, 80% after bilateral salpingectomy, and approximately 20% after ligation of the fallopian tubes (Rice, 2014; Gaitskell and Coffey 2016; Gaitskell and Green, 2016).

The epidemiological findings may be explained by the observation of the pathology specimens and molecular studies in epithelial ovarian cancer. Recent data from the histology of the fallopian tubes from women with hereditary cancer that have been removed prophylactically, show that there are preinvasive forms of neoplasia, such as serous tubal intraepithelial carcinoma (STIC) that is characterized by p53 mutation, that precedes serous type cancer and leads to ovarian malignancy. 75% of women with HG ovarian or peritoneal cancer have also cancer lesions in the fallopian tubes and in 40-60% of these of STIC lesions can be found if the fallopian tube is examined with a specific protocol (Kindelberger, 2007).

STIC has also been found in a small portion of women who have been sterilized with salpingectomy or have undergone salpingectomy at the time of other surgery for benign reasons. These were younger

than the average age that ovarian cancer appears and it can be assumed were likely to develop ovarian cancer in the future (Piver, 1993). Small single lesions that histochemically show presence of Tp53 (p53 signature) without disorder of architecture which is present in STIC, are found in the fallopian tubes in up to 50% of healthy women, suggesting that mutation at one point in p53 is not sufficient for carcinogenesis (Mehra, 2011). Female carriers of the BRCA1 and BRCA2 mutant genes have a 40-60% and 20-30% risk respectively of developing ovarian cancer. If they udergo preventive salpingoophorectomy, the risk is reduced by at least 80% and in about 1-6% of them tiny cancer lesions or STIC can be found in the fallopian tubes (Powell, 2011).

Epidemiological studies suggest that tubal ligation significantly reduces the incidence of endometrioid and clear cell carcinomas, which are associated with the presence of endometriosis, which is caused by the passage of endometrial cells through the fallopian tubes, or endosalpingosis (Garett, 2013). Some endometriotic lesions were found to have mutations of genes (PTEN, ARID1A, PIK3CA, KRAS, and PPP2R1A) that contribute to carcinogenesis and exhibit clonality. These lesions may be responsible for the subsequent development of cancer as precursors (Anglesio, 2015). One Swedish study found that women who underwent surgery for endometriosis or had unilateral salpingoophorectomy for endometriosis were 70% - 80% less likely to develop ovarian cancer (Melin, 2013). It is also known that the irritation of the tubes with talc powder or pelvic inflammatory disease increases the risk of ovarian cancer with mechanisms that remain unclear.

According to epidemiological data and proposed theories on ovarian carcinogenesis, salpingectomy with or without excision of the ovaries seems to play an important role in the primary prevention of ovarian cancer. It is mainly recommended for the high-risk population for hereditary ovarian cancer (risk reducing bilateral salpingo-ophorectomy RRBSO) and for the general population as opportunistic salpingectomy with or without oophorectomy (opportunistic salpingectomy, OS). (Table 2).

Hereditary Ovarian Cancer

The most important predisposing factor for ovarian cancer is genetic predisposition and this occurs in 18-24% of the cases (Walker, 2015). Genetic mutations are more common in HG-serous cancer (type II) while endometriosis and hormonal factors are more common in type I (Table 3).

Although the most common mutations are the BRCA1 / 2 genes mutations (15-20%), there are some other genes involved. BRCA1 / 2 tumor suppressor genes are transmitted in a dominant fashion and encode proteins that have a regulatory role in homologous recombination of the DNA. The risk for ovarian cancer for BRCA1 carriers is 20-45% and for BRCA2 is 10-20%, while both predispose to higher breast cancer rates (40-75%).The family history of these women is indicative, but about 50% of the women with ovarian cancer with no hereditary history are positive for BRCA mutations . This fact reinforces the view that all women with ovarian cancer should be screened for the presence of mutations of these genes and if they are positive, then the family should be tested (Alsop, 2012).

Another syndrome that predisposes to ovarian cancer at a frequency of 8-12% (although it is more often associated with colorectal cancer and endometrial cancer) is the Lynch syndrome, in which the MMR (mismatch repair) genes are mutated. They act by removing DNA breakpoints by recognizing insertions and deletions and repairing mismatched base pairs. The presence of one of the EPCAM, MLH1, MSH2, MSH6, MLH3, MLH3, PMS2 mutated genes predisposes to a cumulative incidence of ovarian cancer up to the age of 70 years at 24% for MSH2, 20% for MLH1, and 1% for MSH6 (Bonadona, 2011).

In these cases endometrioid and clear cell carcinomas (type I) are found more often. Other mutations account for 3.8% of hereditary cancers.

The identification of the women with a hereditary predisposition can be made on the basis of a family history (bilateral breast cancer, history of male breast cancer, early ovarian cancer or breast and ovarian cancer in the same individual) . If the woman is found positive, the rest of the family should also be tested. In general, population control and face-to-face counseling is not efficient, as most of the physicians are insufficiently informed, and the number of the geneticists for counseling is inadequate (D'Andrea, 2016). Another problem is how detailed this examination will be as the cost increases. In the Jewish Ascenazy group where BRCA1 / 2 mutations are frequent (2.5%, as opposed to that of general population which is 0.002-0.006%), population control is economically advantageous.

As for Lynch Syndrome, the finding microsatellite instability (MSI) in the uterine cancer lesion with histochemistry might guide genetic investigation (Kbari, 2019).

Other Important Predisposing Factors

In a meta-analysis of 23,000 women from 13 patient-control trials with a history of endometriosis, the relative risk (OR) for clear cell carcinoma was 3.05 (95% CI: 2.43-3.84), for endometrioid carcinoma was 2.04 (95% CI: 1.67-2.48) and for LG Serum was 2.11 (95% CI: 1.39-3.20) (Pearce, 2012). In the OMEGA study, which monitors long-term infertile women who have followed assisted reproductive methods, the group of women with endometriosis, as a cause of infertility, had a four-fold increased risk of ovarian cancer (OR 4.1, 95% CI,1.6-10.7) (Buis, 2013).

Hormone factors (Table 1) which predispose to ovarian cancer include estrogen replacement therapy in women after hysterectomy (increase of 18-27% per five years of use). Pregnancy has a protective effect. With one pregnancy the reduction is 40% and after 5 pregnancies 80% (protection mainly from endometrial carcinoma).Studies in subfertile populations were not conclusive with the exemption of endometriosis (Cortesi, 2013).

Non-Surgical Methods for Ovarian Cancer Prevention

General population. There are two widely used methods for ovarian cancer prevention, the measurement of the tumor marker Ca125 and vaginal ultrasound alone or in combination. Wit For the population which is at normal risk (about 1.2 per 100,000), studies with large numbers of annual controls over successive years have been carried out with disappointing results (Screening for Ovarian Cancer, 2018). The largest study (UKTOPS) with more than 200,000 women over 11.1 years showed no difference in mortality from ovarian, fallopian and peritoneal cancer (0.35% in the control group versus 0.32% in the group monitored with vaginal ultrasound and 0.32% in the group monitored with Ca125 / ROCA (Menon, 2019). A second study with approximately 70,000 women (PLCO study) for 6 years showed no difference in mortality between the control group (0.29%) and the group monitored with ultrasound and Ca125 with 0.34% mortality (OR, 1.18 [95% CI: 0.82-1.71]) (Buys, 2011). These strategies pose risks because they may lead to unnecessary operations. In the UKTOCS study it was estimated that 2.9 operations would be needed to find one cancer if Ca125 was used in sequential measurements according to a special program developed (ROCA, Risk of Ovarian Cancer Algorithm) by this group, and if only ultrasound was used this ratio was 1: 35.2 .When the combination of Ca125 / ROCA with ultrasound was used the ratio was 1: 16.5. Finally, unnecessary surgery was required in 0.97% of the Ca125 participants

and 3.25% of the ultrasound participants in the UKTOCS study. Correspondingly, this rate was 3.17% in the PLCO study using Ca125 in combination with ultrasound. Complications of surgery were reported in 15% of these women (Pearce, 2012).

Women with high risk for ovarian cancer: There are only prospective cohort studies and these are generally not encouraging. As a result most authorities recommend other preventive methods such as administration of contraceptives or surgery. The largest study was carried out in England (UKFOCSS) according to the protocols mentioned above (UK TOCS) in 3563 women with hereditary ovarian cancer who refused salpingoophorectomy. The sensitivity of the test was 81-87% and its positive predictive value was 25.5. The ratio for cancer diagnosis was 1: 4 and 30.8% were in stages I and II. If the intervals were greater than one year the odds for advanced stage were greater (85.7% vs. 26.1%), which makes the authors recommend screening every 4 months and not every year (Rosenthal, 2013). In another study in 888 women with BRCA1 or BRCA2 mutation, 10 cancers were identified, 8 of which were stage III and 3 of them occurred in less than a year after the previous screening (Hermsen, 2007).

Surgical Prevention of Ovarian Cancer

In the high-risk group of women, risk-reducing bilateral salpingoophorectomy (RRBSO) is the most effective method of prevention. This can be done laparoscopically safely, as a one-day operation. In a meta- analysis in 2009, the risk reduction of ovarian / fallopian tube / peritoneal cancer was > 80% (Rebbek, 2009).

It is recommended that RRBSO should be performed at the age of 35-40 (especially in cases of BRCA1 mutations) or when they have completed their family. The average age that women with BRCA1 mutations develop ovarian cancer is the early 40s, 10% of them develop ovarian cancer at the age of 50 years. Only 2-3% of women with BRCA2 mutations develop cancer before the age of 50, so surgery is recommended at the age of 40-45 years (Elective and risk-reducing salpingo-oophorectomy, 2008). The risk reduction, as mentioned, is not complete and there is a risk of developing peritoneal cancer, which reaches 3.9% for BRCA1 and 1.9% for BRCA2 at 20 years, so long-term follow-up is required. Breast cancer mortality is reduced by 50% in this population. In women with BRIP1, RAD51C, RAD51D and Lynch Syndrome, surgery is recommended at the age of 45–50 years.

Hysterectomy should also be performed for Lynch Syndrome. The risk of endometrial cancer was studied by Shu et al in 1083 women that carried BRCA mutations. No increased risk for endometrioid endometrial carcinoma or sarcoma was found after stratifying by subtype. Five serous and/or serous-like (serous/serous-like) endometrial carcinomas were observed (4 BRCA1+ and 1 BRCA2+) 7.2 to 12.9 years after RRSO (BRCA1: 0.18 expected [O:E ratio, 22.2; 95% CI, 6.1-56.9; P < .001]; BRCA2: 0.16 expected [O:E ratio, 6.4; 95% CI, 0.2-35.5; P = .15]) It is concluded that although the overall risk for uterine cancer after RRSO was not increased, the risk for serous/serous-like endometrial carcinoma was increased in BRCA1+ women. Given the fact that uterine serous carcinoma carries a bad prognosis this increased risk for a rare disease should be discussed with the patients.

Salpingoophorectomy should be done with excision of the ovarian side 2cm above the upper pole of ovary at the infudilopelvic ligament and of the fallopian tube on its origin near the cornua.

About 30% of women with BRCA1 / 2 mutations choose not to have salpingoophorectomy to avoid the hormonal effects of castration. In these cases, salpingectomy may be performed initially to be followed by oophorectomy at the age of 50 years (BS / DO, bilateral salpingectomy / delayed oophorectomy). This approach seems attractive and many prospective studies are ongoing (Hereditary Breast

and Ovarian Cancer Syndrome, 2017) . Chemoprophylaxis with oral contraceptives has been proposed for these women and in a meta-analysis of 18 studies with 1503 women with BRCA1 / 2 mutations it appeared to reduce the risk by approximately 50% [RR] 0.50, 95% CI: 0.33-0.75 or by 5% for each year of administration. No Increased incidence of breast cancer was found in this study (Iodice, 2010). Data is available only for the combined contraceptive pill and not for the patches or the ring.

In low-risk risk women for ovarian cancer oophorectomy is not recommended for hormonal reasons. On the other hand, removal of the fallopian tubes is recommended to be during other operations for benign reasons. These surgeries are usually performed many years before the 6th decade when ovarian cancer is usually developed. Such a procedure (opportunistic salpingectomy, OS) seems attractive and has been increasingly adopted in recent years as a recommendation by all organizations. Its widespread application was started in Canada (British Columbia) in 2008 resulting in an increase in salpingectomy during hysterectomy from 8% to 75% (without decreasing the salpingoophorectomy rates) and during sterilization from 0.5% to 48% (Mc Alpine, 2014). A prospective study has been launched in Canada since 2010, but the results of this study will be available in 10-20 years. It is recommended to investigate its application in laparoscopic cholecystectomies and urogynecological procedures. This strategy is also applied in other countries, resulting in an increase of 70-400% of salpingectomies during open, laparoscopic and vaginal hysterectomies in the US (Mikhail, 2016) . This type of additional surgery did not appear to have complications. There is a known reduction in ovarian function after a hysterectomy, but it seems that salpingectomy does not make it worse. In addition, tubal ligation for sterilization does not appear to affect ovarian function and reserves (Venturella, 2017).

Oophorectomy During Hysterectomy in Order to Prevent Ovarian Cancer

Oophorectomy leads to menopause with an immediate decrease in estradiol by 80% and testosterone by 50% (Lowder, 2010). Women who were undergone bilateral oophorectomy before their menopause present double risk (95% CI: 1.14–3.53) to develop immediate or long term complications from the procedure (hemorrhage, pelvic pain, sleep disorders, urinary incontinence, activity restriction, orgasm disorders) (Carlson, 1994) .

Also, women whose ovaries were preserved during hysterectomy showed menopausal symptoms and FSH> 40 IU / L 3.7 years earlier than those who did not have a hysterectomy (Farquhar, 2005) .The preservation of one ovary did not confer any advantage (4,4 years earlier).

The long-term impact of oophorectomy is an increase in mortality in general and perhaps an increased risk of mental disorders and dementia. Women who have had bilateral oophorectomy, and especially those before the age of 45, overall live less than those who have had unilateral or no oophorectomy at all. In the Nurses Health Study of 29,380 women, whether pre- or post-menopausal at the time of surgery, it was found that the risk of death from cardiovascular disease and cancer (lung and colon) was increased despite the significant reduction in the risk of breast and ovarian cancer (Parker, 2009). The WHI study confirmed this finding with a 40% increase in cardiovascular disease (OR: 1.41, 95% CI: 1.09–1.83) and, in those who were under 45 years and did not receive hormone replacement, by 84% (OR: 1.84, 95% CI: 1.27–2.68) (Rivera, 2009; Howard, 2005; Kotsopoulos, 2018). With these data, in an hypothetical group of 10,000 women aged 50-54 who had bilateral oophorectomy, in 80 years of age there would be 47 fewer deaths from ovarian cancer, 838 more deaths from cardiovascular disease and 158 more hip fractures (Carlson, 1994).

Estrogen administration after RR salpingoophorectomy did not increase the incidence of breast cancer in women with BRCA1. The incidence was 10.7% in those who did not use hormone therapy and 10.3% in those who did use it (P = 0.86).

The administration of estrogen alone has 10% lower risk in causing breast cancer in comparison to the administration of progesterone and estrogen (12% with estrogen versus 22% with combination) (Kotsopoulos, 2018) . In a population with a median age of 63 years, estrogen administration for 7.2 years did not increase the incidence of breast cancer in the WHI study (Level A) (Anderson, 2004). Therefore younger women undergoing oophorectomy during an hysterectomy can safely receive estrogen replacement therapy only without an increase in the risk of breast cancer, although there are no randomized studies.

The risk for a second operation due to ovarian pathology is higher if only one ovary is maintained (7.6% vs. 3.6%). It is usually due to the onset of pain or mass within the first 5 years after hysterectomy and most commonly occurs in women with endometriosis, pelvic inflammation or concomitant chronic pelvic pain (Elective and Risk Reducing Salpingo-Oophorectomy, 2008).

In women with hereditary breast / ovarian cancer the risk for cancer is so high that oophorectomy is required. In the general population, however, oophorectomy prior to menopause or the age of 51 is not recommended, although some studies raise the limit to 65 years (Carlson, 1994). The subject should be discussed in details with the patient after a good history is obtained.

CONCLUSION

The fallopian tube is strongly related to the development of ovarian cancer either through intrinsic pathology in type I tumors or as a means of communication of the ovarian surface and pelvic peritoneum with inflammatory and irritative factors in type II tumors. Preventive salpingectomy and oophorectomy is strongly recommended for female mutation carriers. In those who do not wish to undergo surgery, contraceptives are effective and safe against carcinogenesis. Furthermore, monitoring with tumor marker markers and ultrasound should be performed very often on these women, but is not so effective. Alternatively, these high risk women could undergo only salpingectomy initially and then oophorectomy after menopause, although there is no data on the degree of prophylaxis. Opportunistic salpingectomy in the general population at the time of hysterectomy or other surgery has many theoretical benefits that have been epidemiologically proven, however prospective studies are needed.

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APPENDIX

Table 1. Types of epithelial ovarian cancer, origin and genes involved in carcinogenesis

Epithelial Ovarian Cancer					
	Type I			Type II	
	Clear cell	**Endometrioid**	**Mucous**	**Serous Low Grade**	**Serous High Grade**
incidence	12%	11%	3%	3%	70%
Associated Mutations	PIK3CA ARIDIA PPP2RIA ZNF217	CTNNBI PTEN PIK3A ARIDIA	KRAS	KRAS BRAF ERBB2 PIK3CA	P53 BRCA1 BARCA2
Origin STIC OOK Endometriosis Beningn tumors	- X X -	- X X -	- X X -	- X X X	X - - -

(Temkin, 2017)

Table 2. Protective and aggravating factors for ovarian cancer

Protective Factors	RR	95% CI	Aggravating Factors	RR	95% CI
hormonal contraception	0,73	(0.70-0.76)	Early menarche, late menopause	1,74 1,61	1.74 (1.28-2.18) 1.61 (1.15-2.08)
Green Tee	O,66	(0.54-0.80)	White race	1,35	1.35 (1.08-1.50
Multiparity ≥ 4	0,40	(0.30-0.50)	BMI>25	1,33	1.33 (1.05-1.68)
breastfeeding	0,98/μήνα	(0.97-1.00)	Oestrogen in hormone replacement therapy	1,20	1.20 (0.98-1.32)
sterilization	0,33	(0.16-0.64)	Endometriosis	1,43	1.43 (1.19-1.71)
hysterectomy	0,67	0,45-1,00	BRCA1	42,4	(15-119.6)
			BRCA2	20,6	(7.75-57.2)
			MMR	19	(5.0-30.0)
			Exposure to calcium		(1.37-2.28)

(Cortesi, 2013)

Table 3. Prevention of ovarian cancer

Noninvasive	Cancer markers (Ca 125) Alone or in combination with vaginal ultrasound/ doppler
Surgical	Bilateral Salpingoophorectomy:(BSO) with or without hysterectomy At high risk women for reducing the risk of ovarian cancer RiskReducingBilateralSalpingoophorectomy(RRBSO) In women at high risk for ovarian cancer, first salpingectomy and delayed oophorectomy RRS/DO (RiskReducingSalpingectomy/DelayedOophorectomy Opportunistic salpingectomy or salpingoophorectomy in the general population at the time of hysterectomy or other surgery (opportunistic BSO) Salpingectomy for sterilization without oophorectomy Ligation of fallopian tubes for elective sterilization

Chapter 15
Postmenopausal Ovarian Cyst: To Intervene or Follow Up?

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ABSTRACT

Ovarian masses (tumors) are very often in gynaecological daily practice. Almost 5%-10% of the women worldwide receive operative procedures for ovarian pathology. The risk related to ovarian cancer is increased from 3d to 8th decade of woman's life. However, in 80% of the ovarian pathology, the etiology will be of benign origin (cystic, solid, or mixed). The accurate follow-up of patients with adnexal pathology may contribute the early diagnosis of the disease and the improvement of prognosis in a case of malignancy. Optimal management of cysts in postmenopausal women remains challenging. The chapter aims to summarize current clinical evidence regarding diagnosis and treatment of such a pathology.

INTRODUCTION

Ovarian masses (cystic, solid or mixed) are often in Gynaecological daily practice. Almost 5%-15% of the women worldwide receive operative procedure for ovarian pathology (Dorum, Blom, Ekerhovd, & Granberg, 2005). However, the 80% of the ovarian masses is of benign origin. In addition, the risk related to ovarian cancer increasing from the 3^{d} to 8th decade of woman's life. The accurate follow-up of adnexal pathology may contribute to the patient's early diagnosis of ovarian cancer and the prognosis as well.

Ovarian mass can be cystic (clear liquid, clear round margin), cystic mass with additional solid part in the internal area of the cyst (mixed type), or solid ovarian mass. Functional cystic masses are more often in premenopausal period and the etiology of those cysts is the hormonal status of the women during the menstrual cycle. Almost 40% of them are diagnosed by transvaginal ultrasonography (TVUS), duo to routine Gynaecological examination. More often functional cysts are unilateral and the maximal diameter is not more than 4-5cm.

In postmenopausal period ovarian cysts are less common. Although, the majority of those tumors in this group of women is of benign origin, ovarian cancer (incidence 6.0-11.4/100.000) could not be excluded, especially in case of mixed type (solid & cystic) masses (Ferlay et al., 2013).

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Histopathology

Ovarian tumors are classified according to the histological nature as:

1. Epithelial ovarian tumors
2. Germ cell tumors
3. Sex cord tumors.

Epithelial ovarian masses (cystic, solid or mixed) are the most common almost 90% of the ovarian tumors (Bristow et al., 2015). The formers are further classified according to the clinical behavior as:

- Benign tumors
- Malignant tumors
- Borderline tumors.

Furthermore, the epithelial masses are classified according to the histological type as: serous, mucinous, clear cell, endometrioid, Brener and mixed epithelial tumors (Table 1). Serous and mucinous ovarian masses are the commoner types.

Risk Factors and Family history

Risk factors related to ovarian pathology are established. Pathologic history and life style of women with ovarian mass might be important for the investigation of such cases. The most common risk and protective factors are presented below:

On the other hand, family history is critical to define women who are at increased risk for ovarian cancer (Bankhead, Kehoe, & Austoker, 2005). The risk may consider high for ovarian cancer in case of first degree relatives (mother, father, sister, and daughter), affected from cancer within the family, such as:

- Two or more women first degree relatives with history of ovarian cancer.
- One first degree relative with ovarian cancer at any age and second first degree relative with breast cancer at age less than 50 years.
- One first degree relative with ovarian cancer at any age and two relatives with breast cancer (connected with first degree relationship), under the age of 60 years.
- Three or more family member with colon cancer or two with colon and one with stomach, endometrial, ovarian, urinary tract, small bowel cancer within two generations (one of those relatives must be of first degree under the age of 50 years).
- One relative with both breast and ovarian cancer.

Furthermore, genetic alterations and gene mutations is very important to individualize women at high risk for ovarian cancer. Individuals with history of hereditary neoplasmatic syndrome must be under close follow-up, as well as woman with known carrier of gene mutation such as:

Table 1. Histopathology and clinical behavior of Epithelial Ovarian Tumors according the WHO classification

Epithelial Ovarian Tumors
Serous *Benign* *Malignant* *Borderline*
Mucinous *Benign* *Malignant* *Borderline*
Endometrioid *Benign* *Malignant* *Borderline*
Clear cell "Mesonephroid" *Benign* *Malignant* *Borderline*
Brenner *Benign* *Malignant* *Borderline*
Mixed Epithelial tumors *Benign* *Malignant* *Borderline*
Undifferentiated - Unclassified tumors

Table 2.

Risk Factors	Protective Factors
Age > 50 years	Breastfeeding
Obesity	Long use of pills Early pregnancy (< 26 years)
Diet high in fat	
Early menstruation	Diet high in fruit, milk, vegetables
Nulliparity	Multiparity
Delayed menopausal	

- BRCA 1 & BRCA 2 positive increases the relative risk for breast and ovarian cancer (40% for ovarian cancer when BRCA 1 is positive, 10% when BRCA 2 is positive, while the risk could be as high as 60% in case of BRAC 1-2 positive, compare to ∼2% of incidence of ovarian cancer in female population).
- MLH1, MLH3, MSH2, MSH6, TGFRBR2, PMS1 & PMS2 genetic alterations connected with Lynch II syndrome (hereditary no-polyposis colorectal cancer) increase also the risk for breast, ovarian, endometrial and thyroid cancer.

- PTEN alteration is connected mainly with thyroid and endometrial cancer and less often with ovarian cancer.
- MUTYH mutation is connected with Familial Adenomatous Polyposis.
- STK11 mutation which is related to Peutz-Jeghers syndrome.

Finally, women with Turner syndrome must be checked for the recessive Y chromosome (XY mosaic), because the presence of recessive Y may contribute to the development of ovarian tumors such as gonadoplastoma or dysgerminoma.

Clinical Characteristics

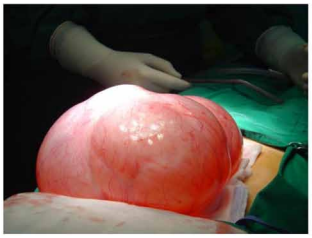
Although, clinical examination is of poor sensitivity (between 10% to 50%) in detection of ovarian mass and even less in prediction of ovarian malignancy, pelvic examination of a palpable mass is important especially in case of infiltration of the cystic mass to the other pelvic organs such as bladder and rectum (Padilla, Radosevich & Milad, 2005).

Cystic-adenoma of serous type is more often unilateral, asymptomatic, although some patients may complain for pelvic or abdominal pain, depending on the diameter of the cystic mass. Patients with serous cystic-adenocarcinoma are also asymptomatic, however the clinical characteristics defer from those of serous cystic-adenoma (mobility, nodularity, ascites). The maximal diameter of both type of serous cysts (benign or malignant) can be reach 30-40cm (Figure 1a), however more common 8-10cm. In 30% of cases the cystic masses can be bilateral.

Mucinous cystic mass (the second more common epithelial ovarian mass), are smaller than serous cyst, while bilateral localization is less common than serous cyst (10%) (Figure 1b). The clinical behavior of mucinous doesn't defer than serous cysts, although more silence (smaller volume). In case of diagnosis of mucinous cystic, the exploration of gastrointestinal tract is recommended especially in case of bilateral position, which increases the possibility of gastrointestinal origin of such tumors. Careful, palpation of the entire tract is recommended, especially of small and gross intestine, while appendectomy may be an option.

Endometrioid ovarian cyst is even less common, while in 20% of cases previous history of endmetriosis is documented. Coexistence of endometrial carcinoma reaches 30% of patients with the endometrioid ovarian adenocarcinoma. The rest of the ovarian cysts are very rare (less than 5%).

Figure 1. a) Ovarian serous cystic-adenoma, b) ovarian mucinous cystic-adenocarcinoma.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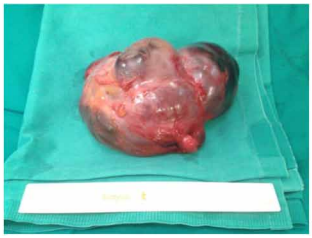
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Diagnosis

Clinical diagnosis of the ovarian cysts is not always feasible, because of the silence behavior of the cyst, especially in case of a small cystic volume. However, abdominal and pelvic examination is critical in the diagnosis of palpable ovarian cysts, especially in case of infiltration with other pelvic or abdominal organs. Although the asymptomatic nature of the ovarian cysts, abdominal tenderness and pelvic pain may characterize ovarian masses of 8cm, while in case of diameter > 8cm, abdominal distention, loss of appetite and increased urinary urgency are the main clinical symptoms, especially in case of invasive epithelial masses.

Ca-125

The cancer antigen Ca-125 has a critical role in the diagnosis of ovarian cancer with sensitivity almost 78%, however with very low specificity (Bast et al., 1983). It is widely used with a cut-off level of 35IU/ml (Bast et al., 1983; Zorn et al., 2009). Using the threshold of 30IU/ml the sensitivity of the antigen concerning the diagnosis of ovarian malignancy reaches the 81% with a specificity of 75% (Jacobs et al., 1990). The accuracy of the Ca-125 is higher in epithelial ovarian cystic masses and for women in postmenopausal life, however it's specificity is lower in case of mucinous ovarian tumors.

The accuracy of the antigen Ca 125 is influenced due to the high false positive rate, because of benign gynaecological conditions such as: multiple myomas, endometriosis, adenomyosis, pelvic inflammation, ovarian cystic torsion, etc (Gadducci et al., 1992). This is also true for many pathologic conditions such as: tuberculosis, hepatitis, pleuritis, peritonitis, appendicitis, etc (Grover, Koh, Weideman, & Quinn, 1992; Jacobs et al., 1989).

CEA, Ca 19-9, AFP, Inhibin B, HE4

Other biomarkers such as CEA, Ca 19-9, AFP, Inhibin B, HE4 and many others are used for the accurate diagnosis of ovarian pathology, especially in postmenopausal period, as well as for the prognosis in case of ovarian malignancy. However, the poor accuracy of those markers makes the daily use of them inconclusive.

The carcino embrionic antigen (CEA), is the second more accepted tumor marker in the diagnosis of ovarian pathology. CEA is glycoprotein normally produced in the gastrointestinal tract, however may be also elevated in heavy smokers (Sajit et al., 2007). The CEA blood test is not reliable for the early diagnosis or the prognosis of cancer. CEA is mainly used for the postoperative monitoring of colorectal carcinoma (after surgical intervention with or without adjuvant treatment) (Goldstein & Mitchell, 2005). CEA levels are also raised in pancreatic, gastric and lung carcinoma. Its contribution to ovarian mass is restricted, mainly used in case of gastrointestinal carcinoma with ovarian infiltration or in patients of advanced ovarian cancer with nodal disease.

The tetrasaccharide Ca 19-9 is a tumor marker useful in the management of pancreatic cancer, especially in cases with relapse. It may also elevated in patients with colorectal cancer, hepato-cellular and ovarian carcinoma, however with high rate of false positive and negative results (Locker et al., 2006).

Alfa-fetoprotein (AFP) and the Inhibin B are tumor markers mainly used in special types of ovarian masses such as: sex cord and germ cell respectively. Similarly, the accuracy of the former biomarkers is low.

The Human Epididymis Protein 4 (HE4) is also a glycoprotein found in epididymal epithelium, which may be increased in ovarian, lung, bladder, breast and endometrial cancer. HE4 presents false positive results in case of benign lesion, however of lower rate compared to Ca 125 (Urban et al., 2012). A retrospective data showed that the sensitivity of HE4 to distinguish benign from malignant ovarian masses was 73% compared to 43% of Ca 125 (Moore et al., 2008). Using both markers (Ca 125 & HE4) the former sensitivity has increased to 76%. However, another prospective data showed improved specificity using both biomarkers, although with less sensitivity concerning the differential diagnosis of the adnexal mass (Moore et al., 2009). According the former study, for the postmenopausal population the sensitivity and specificity is as high as 92% and 75% respectively. In conclusion, HE4 is a promising biomarker, although there is not enough data to support the wide use of HE4 in the management of the ovarian pathology, or the substitution of the Ca 125 with HE4 glycoprotein (Moore et al., 2009)

Trans-Vaginal Ultrasonography (TVUS)

Trans-vaginal ultrasonography is a useful tool for the investigation of the ovarian masses (cystic or solid). There are different ultrasonographic models related to the diagnosis and the prediction of malignancy of the adnexal (ovary or fallopian tube) pathology. Until now there is no perfect model to predict precisely the risk of malignancy. However the sensitivity of TVUS ranges between 82% and 91%, according the different diagnostic models. The most popular models worldwide related to prediction of ovarian cancer, is the RMI (Risk of Malignancy Index) (Jacobs et al., 1990) and the IOTA model (International Ovarian Tumour Analysis) (Timmerman et al., 2010). The RMI model presents a sensitivity of 83% and specificity of 89% (cut-off point 200) for postmenopausal women, while the IOTA model presents a sensitivity 95% and specificity 91% for the same group of women.

Trans-Abdominal Ultrasonography (TAUS) and Doppler Ultrasonography

Trans-abdominal ultrasonography is a useful tool in case of pelvic mass of extra-ovarian origin, or in case of gross cystic mass (more than 15cm). The contribution of TAUS in such cases is critical especially in case of differential diagnosis of pelvic masses, as well as for the investigation of the precise origin of cystic or solid pelvic mass.

Doppler ultrasonography and power Doppler may also improve the specificity of ultrasound especially for the suspicious ovarian cyst of postmenopausal women (Vuento et al., 1995). In addition 3D power Doppler may contribute to the differential diagnosis of postmenopausal patients with ovarian mass with complex morphology or with equivocal central blood vascularization (Alcazar & Rodriquez, 2009; Guerriero et al., 2007). However, the formers are not the first line diagnostic approach because of the expensive equipments which are required and the high level experience which is demanded from the operator.

RMI Model

The RMI model was first introduced by Jacobs et al., (1990) as diagnostic tool in ovarian malignancy of menopausal women, using the entity of gynaecological ultrasound and Ca 125, giving the name of RMI I. Thereafter, the model was revised three times as: RMI II (Tingulstad et al., 1996), RMI III (Tingulstad et al., 1999) and RMI IV (Torres et al., 2002). There was no real improvement of the sensi-

tivity and specificity compared to the primary model (RMI I), which remains the most utilized in daily practice of all RMI models. According to the RMI I three factors are involved in the final score of the former index such as: Ultrasound score (U), Menopausal status (M) and Ca125 value (Ca125) (Table 2). The ultrasonographic features which are included in the Ultrasound score are the multilocularity of the cystic mass, the existence of the solid part, the bilateral adnexal pathology, the presents of ascites and the peritoneal metastasis. Every feature is scored with 1 point. In case of no features the ultrasound score is 0 (U=0), while in case of one pathologic feature the ultrasound score is 1 (U=1). However, in case of ultrasonographic characteristics between 2 to 5, the Ultrasound score is allocated with 3 points (U=3), which is the maximum score related to the "U" factor. Concerning the Menopausal status, the premenopausal patient is scored with 1 point, while the postmenopausal patients are allocated with 3 points. Finally, Ca 125 value is included in the RMI score with the units which are given in IU/ml by the blood sample of the patients, that could be between zero or thousands of units. The multiplication of the three factors involved in the RMI model, gives the final score of the adnexal pathology. However, it is difficult to correlate the absolute risk of malignancy with the final score of the RMI model. According the results of the RMI analysis related to evaluation of the model, score of less than 25 has a risk of malignancy no more than 3%, a scoring between 25 and 250 has a risk almost 20%, while in case of RMI score more than 250 the risk of malignancy reaches the 75% (Davies, Jacobs, Woolas, Fish, & Oram, 1993). Previous reports showed that the RMI is an effective diagnostic model for patients with ovarian malignancy (Hakansson et al., 2012). A systematic review using the RMI model, with a cut-off point of 200, showed sensitivity of 78% (95% CI, 71-85%), while the specificity reached 87% (95% CI, 83-91%) (Geomini, Kruitwagen, Bremer, Cnossen, & Mol, 2009). Using a scoring system with threshold of 250 units the specificity is increased in 90%, however with less sensitivity, almost 70% (National Institute for Health and Care Excellence, 2011).

Table 3. Risk of Malignant Index (RMI) is the multiplication between **U** *(***U***ltrasound score of the different sonographic characteristics),* **M** *(***M***enopausal status) and* **Ca125** *value. Increased risk for malignancy may consider value > 200*

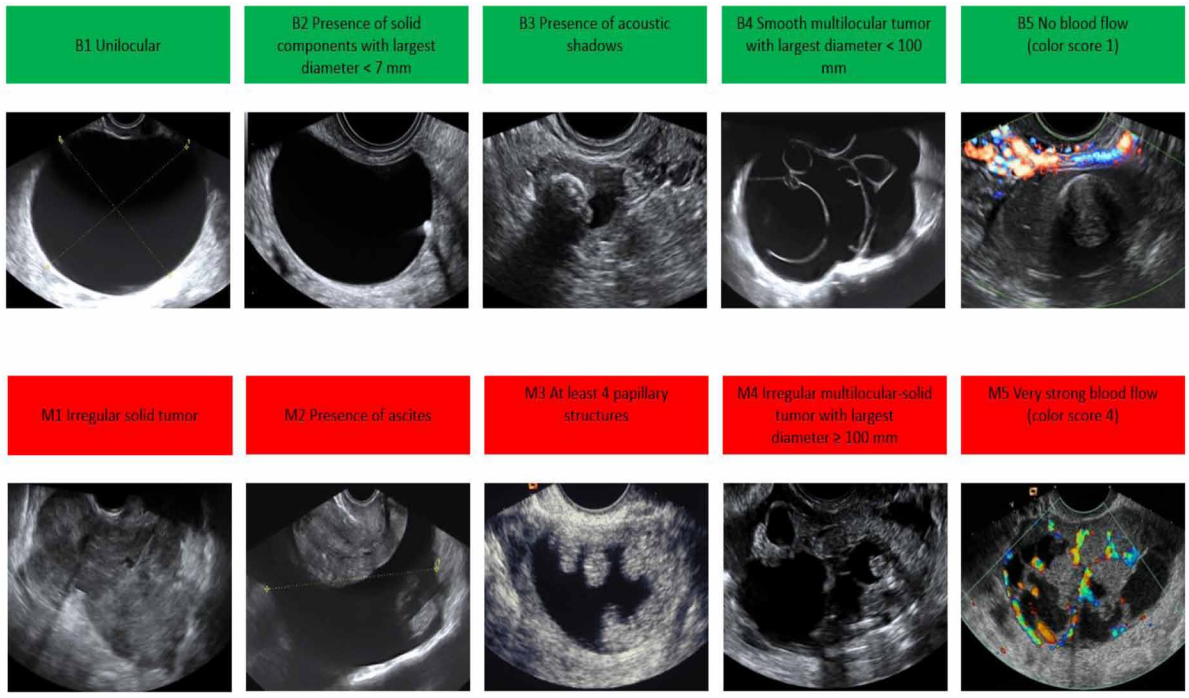
RMI I= U x M x Ca125		
U	Multilocular	1
	Solid	1
	Metastasis	1
	Ascites	1
	Bilateral	1
M	Pre-menopausal	1
	Post-menopausal	3
Ca 125		Value (IU/ml)

IOTA-ADNEXA Model

The IOTA group has introduced the simple rules (ultrasound-based) in 2008 for the investigation of ovarian cancer (Timmerman et al., 2008). According this model, using simple ultrasound characteristics by

TVUS gray-scale and Doppler ultrasonography, might predict the risk of the ovarian malignancy (Figure 2). Using the morphological characteristics (B-rules & M-rules) by the ultrasound, the sensitivity and the specificity to distinguish benign from malignant ovarian mass is 95% and 91% respectively. In case of only benign features (B-rules) according the IOTA group the mass is classified as benign. In case of one or more malignant features (M-rules), such as: irregular solid tumor or multilocular solid tumor, presence of ascites, blood flow and papillary structures, the ovarian mass, is classified as malignancy and further management is undertaken by Oncological group. In case of mixed rules (both B-rules and M-rules) the IOTA prediction is inconclusive and further investigation is need by experienced ultrasonographer using more advanced model such as LR1, LR2 or IOTA-ADNEXA model. The logistic regression model 1 and 2 (LR1 and LR2) and the IOTA ADNEXA model using the ultrasound findings of the adnexal pathology (B & M-rules), in addition to further epidemiologic characteristics of patients (menopausal status, Ca 125, reference center, etc), may be reach an excellent diagnostic performance, in case of the inconclusive ovarian masses, with a sensitivity and specificity of 90% and 93% respectively (Kaijer et al., 2013; Timmerman et al., 2010).

Figure 2. International Ovarian Tumour Analysis (IOTA), benign morphologic characteristics (B-rules) and malignant characteristics (M-rules), according the ultrasonographic grey-scale evaluation of adnexal pathology
(Timmerman et al., 2008).



CT

Computerized tomography (CT) is a useful tool in the diagnosis of peritoneal disease in case of ovarian cancer or in the detection of retroperitoneal metastatic disease. However, there is no clear evidence to establish the superiority of CT compared to TVUS concerning the diagnostic accuracy between benign and malignant adnexal mass (Buist et al., 1994).

MRI

Magnetic resonance imaging (MRI) can be used as a second line examination, especially in case of differential diagnosis of ovarian masses in which the ultrasonography was inconclusive. MRI presents better diagnostic accuracy than CT or Doppler ultrasonography for the inconclusive ovarian cystic masses previous investigated by TVUS. The same it is also true for tumor of extra ovarian origin. However, CT scan could be offer better accuracy comparing to MRI, concerning the investigation of peritoneal spread and retroperitoneal metastatic disease (Thomassin-Naggara et al., 2009). On the other hand, MRI might improve the differential diagnosis of complex ovarian lesions compared to CT scan (Anthoulakis & Nikoloudis, 2014).

Management of Ovarian Cyst in Postmenopausal Period

The therapeutic approach of patients with ovarian cysts in postmenopausal period is a challenge, although the rate of ovarian malignancy of such cases is low (Levine et al., 1992). Additionally, the suspicious ovarian masses, according the preoperative investigation, make the decision of therapeutic approach of those patients even more equivocal, compare to simple ovarian cysts.

Simple Ovarian Cyst

An asymptomatic ovarian cyst in postmenopausal period, with unsuspicious ultrasonographic characteristics (simple cyst, unilocular, less than 5cm of maxim diameter), without pathologic vascularization and normal Ca 125 score, can be managed conservatively. Close observation is recommended for the next 1-2 years (every 4-6 months), by ultrasound and Ca 125, using the prognostic models related to ovarian pathology such as: IOTA model or RMI or both of them. In case of stable ultrasonographic, unsuspicious features and with normal Ca 125 score after 2 years of observation, the close follow up may be interrupted. In large cancer screening trial among women over the age of 55 years, with one simple ovarian cyst (not more than 5cm), after one year screening, 32% of such cysts resolved, while 54.4% remained stable (Greenlee et al., 2010). The rest of the initial simple cyst (13.6%) chanced characteristics, although conversion to solid mass was 0.5% and complex cyst 5.3% after one year of screening (Greenlee et al., 2010). The author concluded it might be safe for postmenopausal women to be managed conservatively, in case of simple ovarian cysts.

The aspiration of such cysts of postmenopausal women is contraindicated, because of the almost 30% of the recurrence of such cysts in the next 1-2 years after the aspiration, as well as the low diagnostic accuracy (25%) to distinguish benign and malignant ovarian mass (Ganjei, Dickinson, Harrison, Nassiri, & Lu, 1996; Moran et al., 1993). In addition, even though the rate of malignancy of such cysts is

very low, the probability of spillage cannot be excluded in case of final diagnosis of ovarian carcinoma, changing by this the stage of the disease and the patient's prognosis (Vergote et al., 2001).

Although, the risk of malignancy of such cysts is extremely low, the surgical approach is an option in case of unchanged ovarian pathology, especially in postmenopausal period, after a follow up of two years. Furthermore, the patient's anxiety is another reason for surgical intervention. In the former patients, laparoscopic removal of the ovarian cyst or the *en bloc* removal of the adnexa (salpingo-oophorectomy) with peritoneal cytology is the optimal therapeutic approach (National Institute for Health and Care Excellence, 2011; Scottish Intercollegiate Guidelines Network, 2013). The use of laparoscopic endo-bag to externalize the ovarian cyst or the adnexa is the oncologic standard to eliminate the spillage of the cystic liquid. Frozen section is obligatory in such cases, even if the limitations of the method is quite high, with false negative results more than 10%, especially for gross cystic mass (Geomini et al., 2005). The patient must be informed for further radical operation with full staging (total hysterectomy, bilateral adnexectomy, pelvic & paraortic lymphadenectomy, infracolic omentectomy, biopsies from suspicious areas) in case of positive frozen (Trimbos et al., 2003). Completion of the procedure laparoscopically is an option, following the previous oncologic rules, or conversion to laparotomy (Tozzi & Schneiderb, 2005). In case of benign lesion according the result of the frozen section, further surgical procedure such as: controlateral adnexectomy or even more hysterectomy, must be discussed preoperatively with the patients (Scottish Intercollegiate Guidelines Network, 2013). However, an optimal intervention in such cases (benign frozen), it could be the bilateral adnexectomy without hysterectomy.

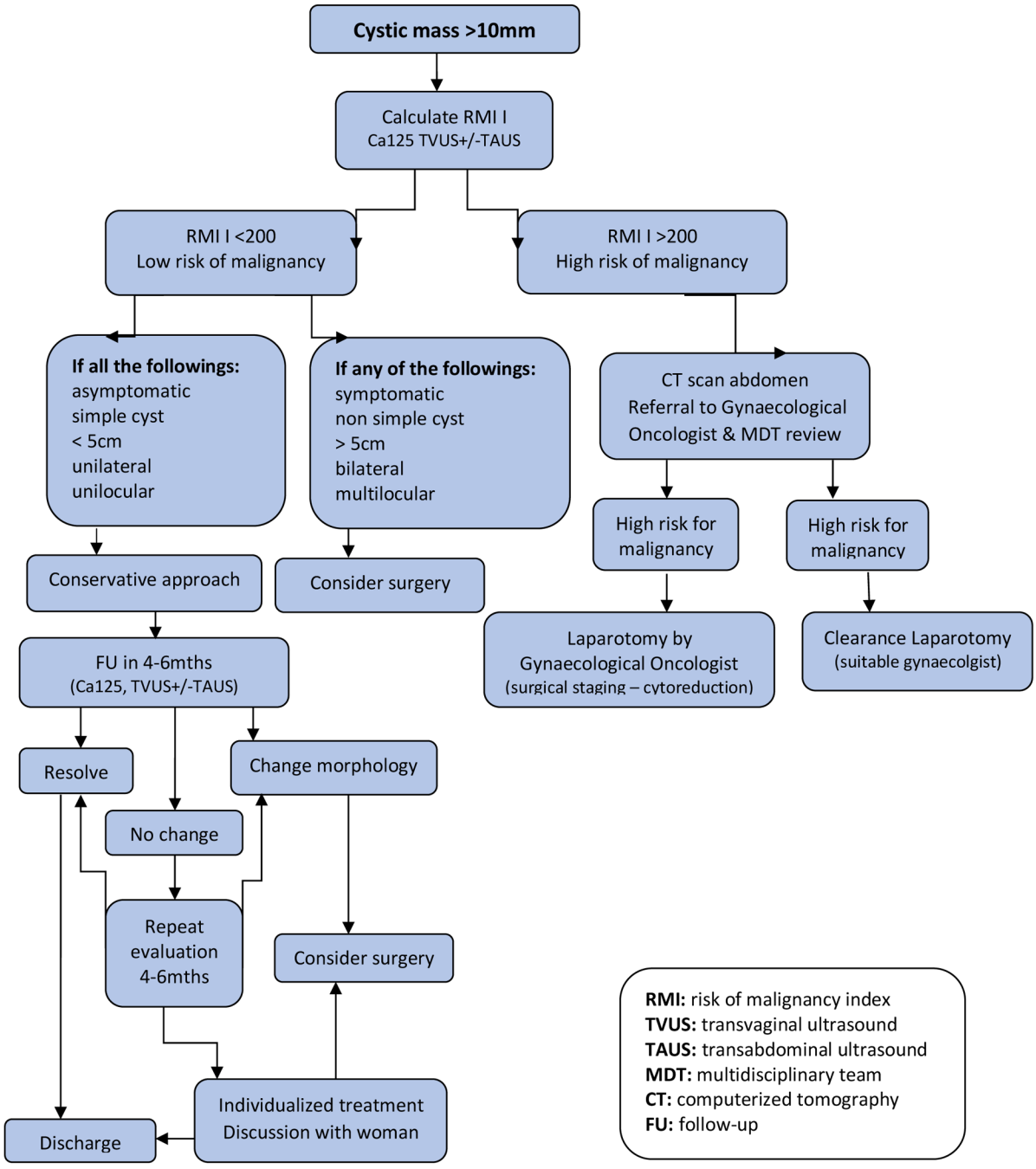
An algorithm of the management of ovarian cystic masses during the postmenopausal life is presented below using the RMI scoring system (Table 3) (Royal College of Obstetricians & Gynaecologists, 2016)

Suspicious Ovarian Mass

Patients of high risk of malignancy according the RMI (>200 score), or the IOTA-ADNEX model (>10% malignant risk) it is preferable to be managed by Gynaecologists specialized in Gynaecological Oncology, offering the best practice concerning the therapeutic approach and the prognosis of patients with final diagnosis of ovarian cancer (Vernooij et al., 2009). Those patients must be surgically treated via laparotomy, with medial vertical incision (initially below to the umbilicus), however with possibility of the extension of the incision above to the umbilicus, for a complete surgical staging (previously noted), in case of positive frozen section (Querleu et al., 2017). Guided biopsy or aspiration of the suspicious ovarian mass could be performed only in case of advanced ovarian cancer to confirm the diagnosis. Laparoscopic intervention with inspection of the peritoneal cavity and guided biopsy of the suspicious masses is also an attractive approach (Angioli et al., 2006; Leblanc, Sonoda, Narducci, Ferron, & Querleu, 2006).

Thereafter, optimal debulking (whether possible) in case of patients who are appropriate for radical operation (cytoreduction) according their pathologic status or neoadjuvant chemotherapy (following by interval debulking), can be organized. Previous reports showed no difference of patient's prognosis, however with even better peritoneal debulking after neoadjuvant chemotherapy (Vergote et al., 2010).

Figure 3. Management of ovarian cysts in postmenopausal women
(Royal College of Obstetricians & Gynaecologists, 2016)



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Chapter 16
Borderline Ovarian Tumors: What Is the Optimal Therapeutic Strategy?

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ABSTRACT

Borderline ovarian tumors (BOTs) are a specific subgroup of ovarian tumors and are characterized by cell proliferation and nuclear atypia without invasion or stromal invasion. They are usually more present in younger people than the invasive ovarian cancer and are diagnosed at an early stage and thus have a better prognosis. Histologically, borderline tumors are divided into serous (50%), mucosal (46%), and mixed (4%). The serous tumors are bilateral in 30% of the cases and are accompanied by infiltrations outside the ovary in 35% of the cases. These infiltrations may be non-invasive or invasive depending on their microscopic appearance and may affect treatment. Surgery is the approach of choice, and laparoscopic surgery, with the undeniable advantages it offers today, is the "gold standard." All the surgical steps required to properly treat borderline tumors, at both diagnostic and therapeutic levels, can be safely and successfully be applied laparoscopically. Manipulations during surgery should be limited, and biopsies for rapid biopsy should be done within an endoscopic bag.

INTRODUCTION

Borderline ovarian tumors (BOT) are epithelial neoplasms that present upregulated cellular proliferation and slight nuclear atypia, but with no evidence of destructive stromal invasion (Silverberg et al., 2004). They were first described by Tailor and his associates in 1929 and then FIGO recognized the entity of borderline ovarian tumors in 1971. Two years after, in 1973, the World Health Organization (WHO) followed with their recognition (Serov, Scully, & Sobin, 1973) and then finally borderline ovarian tumors were fully categorized in the WHO Classification in 2014, which is the one currently taken

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into consideration (Hauptmann, Friedrich, Redline, & Avril, 2017). Currently, three terminologies are used to describe them across the literature: borderline tumors, tumors of low malignant potential and atypical proliferative tumors (Sutton, 2001). Borderline ovarian tumors represent 10 – 20% of all ovarian epithelial tumors (Lenhard et al., 2009) and can occur approximately to 1.8 – 4.8 per 100.000 women each year, with a constantly increasing percentage among ovarian malignancies in the last decades, across the whole world (Bjørge, Engeland, Hansen, & Tropé, 1997; HEINTZ et al., 2006; Skírnisdóttir, Garmo, Wilander, & Holmberg, 2008). The median age of diagnosis is 45 years old, but sadly one third of them is under the age of 40 years old. This fact makes fertility preservation a very serious topic of discussion among health care workers and patients (Sherman, Berman, et al., 2004; Sherman, Mink, et al., 2004), especially because almost 80% of the cases are diagnosed at an early stage (FIGO Stage I) (Andreas du Bois et al., 2013).

HISTOLOGY

Borderline ovarian tumors are characterized by the presence of nuclear atypia, mitotic activity $\geq$ 10% of the tumor cells and microscopic papillary projections (Acs, 2005), while microinvasion of the stroma can be present (foci $<$ 3mm in the longest dimension and $\leq$ 10mm^2 in surface) (Nam, 2010). Six histological subtypes have been recognized, based on the epithelial cell type: serous, mucinous and other less common (endometroid, clear cell, seromucinous, borderline Brenner tumor). Moreover, there are studies that indicate that histological distribution depends also on the geographical region: serous subtype is most common in Western countries, while in Korea-Japan mucinous borderline ovarian tumors are more common (Song et al., 2013).

Serous is the most common subtype among borderline ovarian tumors (50 – 55%) (R. Kurman, Carcangiu, & Herrington, 2014) and recent analyses have shown that they present similar molecular and genetic alterations with low – grade serous carcinomas (LGSC), which is very important during differential diagnosis in the frozen section and the final histology report (R. J. Kurman & Shih, 2010; Matsuo et al., 2020). They are uni- or multilocular cysts with or without epithelial proliferation on the outer surface of the tumor and almost one third of them are bilateral (Hauptmann et al., 2017). Moreover, microinvasion is associated with adverse effects on the prognosis of the patients and higher recurrence rates of the tumor (Andreas du Bois et al., 2013), but in contrary there are studies in the literature which support that there is no association between microinvasion and recurrence rate or even survival (Prat & De Nictolis, 2002). Micropapillary variant is present in 5 – 15% of serous borderline ovarian tumors and is described as an intermediate entity between borderline ovarian tumors and low – grade serous carcinomas (R. J. Kurman & Shih, 2010). Like microinvasion, the micropapillary pattern alone is not an independent prognostic factor, but it is frequently present at advance stages, especially when invasive peritoneal disease is present (Hannibal et al., 2014). While some studies found a higher recurrence risk (Shih et al., 2011), others did not confirm these results, opposing the same recurrence risk independently from micropapillary variant (Andreas du Bois et al., 2013). Furthermore, approximately 30% of serous borderline ovarian tumors present peritoneal implants, either non-invasive or invasive foci. According to the latest data, these peritoneal implants are now considered as low – grade serous carcinoma from the WHO Classification in 2014 and should be closely described in the histology report.

The second most common subtype of borderline ovarian tumors is mucinous (35 – 45%) (R. Kurman et al., 2014). These tumors are usually large, unilateral, cystic, with a smooth ovarian surface and

multiple inner cystic spaces. (Hauptmann et al., 2017). It is very important that secondary involvement of the ovaries should be excluded and the most frequent site that the tumor can arise is the appendix (Jeffrey D. Seidman, Kurman, & Ronnett, 2003). Like serous borderline ovarian tumors microinvasive foci displaying high – grade nuclear atypia should be always regarded as microinvasion.

Furthermore, less common histological subtypes of borderline ovarian tumors are borderline Brenner tumors, who are thought to arise from benign Brenner tumors. They are usually > 10cm and have a predominating epithelial proliferation (Hauptmann et al., 2017). Another subtype is seromucinous borderline ovarian tumors (5 – 7% of all borderline ovarian tumors) (R. Kurman et al., 2014), also known as mullerian mucinous borderline ovarian tumors (prior known as endocervical-type mucinous). They are usually presented to younger women as unilocular cysts of 8 – 10cm with multiple intracystic papillae (Shappell, Riopel, Smith Sehdev, Ronnett, & Kurman, 2002). 40% are bilateral, 20% have peritoneal implants or lymph node involvement and often they co-exist with endometriosis-related cancers. On the other hand, endometroid borderline ovarian tumors (2 – 3% of all BOTs) have a higher incidence of endometriosis-related cancers and co-exist in 63% with endometriosis and in 39% with endometrial hyperplasia or carcinoma. Therefore when fertility-sparing surgery is offered, endometrial curettage should be performed to all patients, in order to be able to continue with the family planning (Hauptmann et al., 2017). The least common borderline ovarian tumor is the clear cell subtype (1%) and usually appear to postmenopausal women as solid tumors with small unilateral cysts (Hauptmann et al., 2017). Last but not least, BRCA mutations occur only in 4.3% of the patients in early stage borderline ovarian tumors, in contrast to invasive ovarian cancer, where is much higher (24.2%) (Gotlieb et al., 2005).

Frozen section for the identification of borderline ovarian tumors is a controversial issue, which has caused debates among physicians. The main reason is its low accuracy to differentiate them from either benign or malignant cases (45 – 87%) (Seong, Kim, Kim, & Song, 2015). 20 – 30% of cases diagnosed as borderline ovarian tumors with frozen section are ultimately determined as invasive ovarian cancer and, surprisingly, 5% as benign ovarian tumors, in the final pathology (Burger, Prinssen, Baak, Wagenaar, & Kenemans, 2000). Moreover, cases that were identified as borderline ovarian tumors are truly misdiagnosed, meaning that a review of the slides showed a different diagnosis than the first one. These results were presented in many studies, like one from the AGO Study Group with over 1000 patients. All of them showed the same data after the second-look histology: 6.6 – 9.9% and 24.1 – 30.6% to invasive ovarian cancer and to benign ovarian tumors, respectively (Andreas du Bois et al., 2013; Tempfer, Polterauer, Bentz, Reinthaller, & Hefler, 2007)

CLINICAL PRESENTATION – DIAGNOSIS

As in invasive ovarian cancer, borderline ovarian tumors are very hard to detect, especially in the early stages. This is the reason why the diagnosis is often delayed. Almost one third of the patients are asymptomatic and 50 – 60% present abdominal distention or pelvic pain, with ascitic fluid to be uncommon (Solmaz Hasdemir & Guvena, 2016). Clinical examination should always be performed, but it can be useful only in large tumors and to assess the mobility of the uterus and the pelvic mass. On the other hand, tumor markers are considered sensitive in discriminating benign and malignant lesions (Timmerman et al., 2007), but in most case CA 125 is normal or slightly increased, mostly in the serous subtype, while CA 19-9 and CEA are likely to increase in the mucinous subtype (Ayhan, Guven, Guven, & Kucukali, 2007). In large tumors It is useful to calculate the ratio of CA 125/CEA to identify the origin of the pelvic

mass (adnexal or gastrointestinal), because a result > 20 favors the origin to be form the female genital tract. In addition, high preoperative serum values of CA 125 are associated with advanced stages of the disease (Kolwijck, Thomas, Bulten, & Massuger, 2009).

The ultimate goal is to preoperative diagnose borderline ovarian tumors, which is fairly hard, or at least characterize the tumors as suspicious. This is very important in order to carefully plan the surgical approach and also the type of the procedure. But sometimes preoperative diagnosis is difficult, because the ultrasonographical features might overlap with those of either benign masses or invasive ovarian cancer, so unfortunately the diagnosis is intraoperative, during frozen section (Solmaz Hasdemir & Guvena, 2016). Transvaginal ultrasound is the exam of choice, due to its high accuracy (91-95%) (Solmaz Hasdemir & Guvena, 2016) and the characteristic features are cysts with papillae, septae (49-63%) and solid parts (78% in serous subtype and 40% in mucinous) (Fischerova, Zikan, Dundr, & Cibula, 2012). However, sometimes cyst papillae are hard to detect, especially when the cyst is > 5cm, because of its large inner surface and also the fact that small papillae < 2 – 3mm can be missed by ultrasound (Exacoustos et al., 2005). Pados et al. proposed a series of ultrasonographic criteria that can help to categorize cysts as benign or suspicious (Pados et al., 2012) (Table 1). Magnetic Resonance Imaging (MRI) does not seem to significantly alter the preoperative accuracy and has a high cost (Kim, 2019), while Computed Tomography (CT) is used for detecting peritoneal implants and also does not significantly increase the accuracy (Pados et al., 2012; Solmaz Hasdemir & Guvena, 2016; Yang et al., 2020) . A large meta-analysis confirms the aforementioned data that ultrasound + colored doppler is the best diagnostic method to evaluate adnexal masses (Table 2), because it is a cheap, fast, noninvasive and easily endured from the patient examination (Kinkel, Hricak, Lu, Tsuda, & Filly, 2000).

Moreover, in 2014 a diagnostic test, called IOTA – ADNEX model, was presented in order to evaluate the potential malignancy in women before surgery for adnexal masses (Van Calster et al., 2014). For the development of the test 24 centers, from 10 countries, participated in the study and in total 5909 cases were evaluated. The test is based on 9 parameters, 3 clinical (C) and 6 from the ultrasound (U):

1. Patients age (C)
2. CA 125 (C)
3. Type of center performing the test (oncological or not) (C)
4. Maximum diameter of the tumor (U)
5. Ratio of the solid part of the tumor (U)
6. Over 10 cystic spaces in the tumor (U)
7. Number of pupillary projections (0, 1, 2, 3, >3) (U)
8. Presence of acoustic shadow (U)
9. Presence of ascites (not just free fluid in the douglas space) (U)

The test has a sensitivity of 97% and a specificity of 71%. However, the most important feature is that it does not provide only information about the adnexal mass being benign or malignant, but it gives multiple results concerning the possible percentage of benign ovarian tumor, borderline ovarian tumor and ovarian invasive cancer. The model is accessible free online: www.iotagroup.org/adnexmodel.

Table 1. Ultrasonographic evaluation of ovarian tumors

	Benign	Suspicious
Size	≤ 8mm	> 8mm
Septum thickness	≤ 3mm	> 3mm
Cyst wall thickness	≤ 3mm	> 3mm
Papillary excrescences projection	≤ 3mm	> 3mm
Solid part	Absent	Present
Free fluid	Absent	Present
Doppler RI	> 0.42	< 0.42

Table 2. Imaging techniques for adnexal masses

Examination	Sensitivity	Specificity	Diagnostic Accuracy
Ultrasound	88%	83%	82%
Colored Doppler	71%	67%	68%
Ultrasound + Colored Doppler	**88%**	**97%**	**95%**
3D Doppler	93.3%	100%	95.6%
CT	90%	85%	87%
MRI	100%	98%	99%
PET-CT	67%	79%	77%

THERAPY

The treatment of choice for borderline ovarian tumors is surgery. Careful inspection of the entire peritoneal cavity, specifically inside the pelvis (uterus, tubes, ovaries, bladder, douglas, sigmoid-rectum, pelvic wall), at the medium (right-left gutter, small bowel, large bowel, both bowel mesentery, omentum, appendix) and upper abdomen (right-left diaphragm, liver, spleen, stomach, pancreas, lesser omentum) is crucial (Solmaz Hasdemir & Guvena, 2016) (Figure 1). In cases that the patient has completed their family planning, the staging surgery includes total hysterectomy, bilateral salpingo – oophorectomy, radical omentectomy, peritoneal washing with cytology and resection of all macroscopically visible peritoneal disease (Benedet, Bender, Jones, Ngan, & Pecorelli, 2000; Trope, Kristensen, & Makar, 2000). The requirement of systemic pelvic and paraaortic lymph node dissection has been a controversial issue in the past years, because lymph node involvement ranges from 21 – 29%. However, some studies have shown that recurrence and survival rates are not affected from the lymph node status (Camatte et al., 2004). So, lymph node dissection can be omitted in these patients, but possible bulky (enlarged) lymph nodes should be removed during cytoreductive surgery (Coumbos et al., 2009). Appendicectomy should always be performed in mucinous borderline ovarian tumors, in order to exclude the possibility of ovarian metastases from mucinous tumors of the appendix (Cadron et al., 2007). Another important issue that has been a point of controversy in the later years is the need of a restaging surgery after the discovery

of a borderline ovarian tumor in the final histology report of the initial surgery. A meta-analysis suggest that restaging does not alter recurrence rates (A. Chevrot, Héquet, Fauconnier, & Huchon, 2020)

On the other hand, fertility – preserving surgery is considered in most borderline ovarian tumor cases, because they appear in significantly younger patients than invasive ovarian cancer. A variety of fertility-sparing surgeries have been proposed, based on the organs of the female genital system that are being preserved (Buonomo & Peccatori, 2020). Preservation of the uterus and at least one ovary is considered as an acceptable standard of care from many authors, but the surgery plan should be thoroughly discussed preoperatively with the patient and in a multidisciplinary meeting (A du Bois, Trillsch, Mahner, Heitz, & Harter, 2016). Generally, two types of conservative surgery can be offered to these patients: unilateral salpingo – oophorectomy (USO) and unilateral ovarian cystectomy with or without contralateral ovarian cystectomy (this should be strongly considered when the tumor is bilateral) (Solmaz Hasdemir & Guvena, 2016). Cystectomy could be offered instead of unilateral salpingo – oophorectomy (Daraï et al., 2013), but it is not recommended in mucinous borderline ovarian tumors, due to the fact that they have a high frequency of invasive lesions during recurrences, and also in bilateral massive borderline ovarian tumors, where the preservation of ovarian tissue is not feasible and essentially no functional ovarian tissue is left after the surgery. In this case, the surgeon should at least preserve the uterus, in order to offer to patient the chance for In Vitro Fertilization (IVF) with oocyte donation (Vasconcelos & de Sousa Mendes, 2015). Many studies confirm that preservation of fertility is a viable option in younger patients with early stage borderline ovarian tumors (Seong et al., 2015). However, this type of surgery should be careful offered in advanced stages, especially when peritoneal invasive implants are present (Alvarez & Vazquez-Vicente, 2015). Surely, a question arises about the remaining ovary and uterus after the completion of family planning, but it appears to be acceptable to wait until a recurrence develop and then perform a secondary debulking surgery, removing also the remaining female genital system. It is of high importance, when a relapse is detected, that fertility – sparing surgery should be avoided within secondary surgery when peritoneal implants are present (Cadron et al., 2007; Tinelli, Tinelli, Tinelli, Cicinelli, & Malvasi, 2006). Nevertheless, when the phycological impact of an imminent relapse is overwhelming for the patient, removal of the remaining genital system could be offered (A du Bois et al., 2016).

Traditionally, borderline ovarian tumors were treated with laparotomy and midline incisions. However, in the last years laparoscopy seems to be the preferred surgical approach for borderline ovarian tumors (A du Bois et al., 2016). This is in accordance with the surgical approach for benign adnexal masses in women in the reproductive age (Pados, Tsolakidis, & Bontis, 2006). Many studies have extensively described the advantages of laparoscopy compared to laparotomy. Specifically, well-known advantages of laparoscopy are less morbidity, shorter hospital stay (Seong et al., 2015) and intraabdominal adhesions. The last advantage, adhesions, has been established in the later years as one of the main reasons for postoperative complications, in the short term, and for infertility, in the long term (Pados, Venetis, Almaloglou, & Tarlatzis, 2010). On the other hand, there are some negatives when trying to manage borderline ovarian tumors with laparoscopy. The main disadvantages of laparoscopy are port site metastases (Furukawa, Nishioka, Noguchi, Kajihara, & Horie, 2014), increased risk of cyst rapture (33.9% vs. 12.4%) and incomplete staging (Fauvet, Boccara, Dufournet, Poncelet, & Daraï, 2005). Surprisingly, studies with large series of patients and long follow-up periods showed that, the aforementioned disadvantages had no significant impact to the recurrence rate and overall survival of the patients, when compared to laparotomy (Andreas du Bois et al., 2013). Those disadvantages of laparoscopy could be eliminated by the use of endoscopic bag and careful preoperative diagnosis, because the problem is not

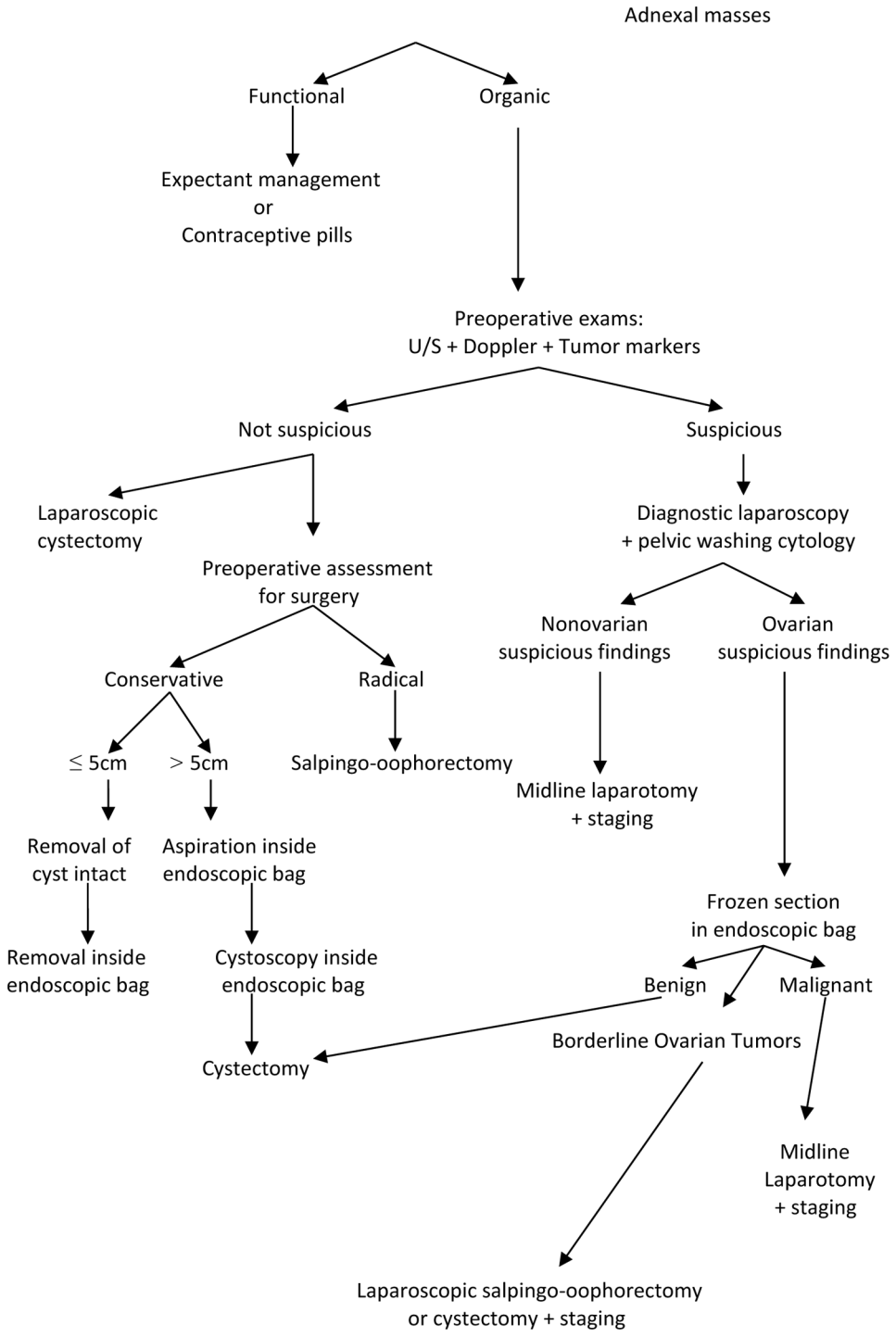
on the surgical approach of choice, but the ignorance of the surgeon that a possible ovarian malignancy (Pados et al., 2012). With a clear protocol for laparoscopic management of adnexal masses (Figure 2), the rate of unexpected borderline ovarian tumors, during laparoscopy, is very low (Table 3) (Pados et al., 2012). However, the presence of a skilled gynecology – oncology specialist with endoscopic experience is vital in order to achieve the best oncological result and also maintain an acceptable fertility capacity, when fertility – sparing is needed.

Table 3. Frequency of malignancy during laparoscopy for "benign" adnexal tumors

Authors	Year	Patients – Cysts	Borderline – Invasive	Percentage (%)
Lehmann et al	1991	969 – 1016	36 (B + Ca)	2.0
Nezhat et al	1992	1011 – 1209	4Ca	0
Cristalli et al	1992	100	3B	3.0
Canis et al	1992	652	4B + 6Ca	1.8
Audebert	1994	700	8B + 17Ca	3.57
Nicoloso et al	1995	5307	60B + 18Ca	1.47
Wallwiener et al	1996	100	2B + 1Ca	3.0
Sadik et al	1996	220	1B + 1Ca	0.9
Guglielmina	1997	803	25B + 9Ca	4.2
Malik et al	1998	292 – 316	11 (B + Ca)	3.5
Mettler et al	2005	493	2B + 4Ca	1.2
Pados et al	2010	1332 – 1838	8B	0.6

Furthermore, there is no scientific proof that adjuvant therapy (chemotherapy, radiotherapy or endocrine therapy) alters the prognosis of borderline ovarian tumors, even in advanced stages with peritoneal invasive implants (Morice et al., 2003; C. Tropé, Kaern, Vergote, Kristensen, & Abeler, 1993). There are studies in the literature with small series of patients and in specific histological subtypes that show some benefit with systemic therapy (Stambough, Muscal, Edwards, & Dietrich, 2020), but further larger studies are needed. The adverse effects outweigh the possible benefits of the systemic treatment, because borderline ovarian tumors generally have low proliferation rates and traditionally cytotoxic drugs are thought to be ineffective in these cases. Therefore, current guidelines do not recommend any adjuvant treatment for borderline ovarian tumors, and any systemic treatment should be given only within clinical trial, after careful discussion with the patient (Cadron et al., 2007).

Figure 1. Protocol for Laparoscopic management of adnexal masses



FOLLOW UP – RECURRENCE

All studies agree that a long follow-up period is very important for borderline ovarian tumors. Follow-up of these patients is every 3 months for the first 2 years and every 6 months for the next 3 years. Afterwards, follow-up examinations every year for at least 15 years from the initial diagnosis (Patrono et al., 2013). Some authors state that patients with borderline ovarian tumors, especially serous histology, should have a minimum follow-up of 10 years to evaluate recurrences and a follow-up of 20 years to evaluate survival (Silva, Gershenson, Malpica, & Deavers, 2006). This is proposed, because the most frequent tumor found in the recurrence is a low – grade serous carcinoma, so there is no rapid progression of the disease. Physical examination, ultrasonography and tumor markers should be performed every time during follow-up, especially when fertility – sparing surgery was offered and also periodically MRI or CT scans should be performed to evaluate the whole abdominal cavity (Solmaz Hasdemir & Guvena, 2016), in order to timely identify recurrences.

Overall, recurrence rates of borderline ovarian tumors are estimated between 3 – 10% (Ayhan, Guvendag Guven, Guven, & Kucukali, 2005; Lenhard et al., 2009). 37% of the relapses are diagnosed in the first 2 years, 31% between year 2 – 5 and 32% > 5 years from the initial diagnosis (from which 10% occurs more than 10 years after surgery) (Andreas du Bois et al., 2013). All studies in the literature conclude that the recurrence rates are much higher when fertility – sparing surgery is offered, instead of radical cytoreduction (10 – 20% vs. 5%) (Cadron et al., 2007; Chan et al., 2003; Lenhard et al., 2009; Morice, 2006; Morice et al., 2003; Suh-Burgmann, 2006) and that the type of conservative surgery plays a significant role (higher rates of 10-42% are presented in patients undergoing cystectomy compared to unilateral salpingo – oophorectomy) (Daraï et al., 2013). However, this higher recurrence rates did not have a statistically significant negative impact on disease-free or overall survival of the patients, according to studies with large series of patients and long follow-up periods (Andreas du Bois et al., 2013; Palomba et al., 2007; Yinon et al., 2007).

Moreover, it is of high value to address the infertility issue of these patients and to assess in detail their management after fertility – sparing surgery for borderline ovarian tumors (Audrey Chevrot et al., 2020). As stated in the literature the rate of spontaneous pregnancy after conservative surgery for borderline ovarian tumors is 32 – 65% and those rates are even higher in the cystectomy group, in patients < 40 years old and in non – serous histological subtypes (mainly mucinous) (Alvarez & Vazquez-Vicente, 2015; Daraï et al., 2013). Ovarian stimulation for in vitro fertilization should be avoided, because of the increased risk of ovarian malignancies, during these process, but in vitro fertilization with natural cycles should be discussed and offered to these patients (van Leeuwen et al., 2011). Also, attempting pregnancy without in vitro fertilization is recommended (Seong et al., 2015). The findings of some studies in the literature suggest that any other treatment for infertility should be delayed for at least one or two years after the initial diagnosis, for two main reasons: first, due to the chance of spontaneous pregnancy and secondly due to the higher risk of recurrence in the first two years from the surgery (Alvarez & Vazquez-Vicente, 2015; C. G. Tropé, Kaern, & Davidson, 2012).

Most authors conclude that borderline ovarian tumors relapse mostly in the remaining ovary (Solmaz Hasdemir & Guvena, 2016) and that extra – ovarian relapses occur in approximately 20% of advanced stages (FIGO Stage II or III), instead of 2% in early stages (FIGO Stage I) (Andreas du Bois et al., 2013). Moreover, borderline ovarian tumors can develop recurrent disease in the form of invasive ovarian cancer (A du Bois et al., 2016) and 20% of all patients with a relapse will ultimately suffer from invasive ovarian cancer (Andreas du Bois et al., 2013). Mucinous borderline ovarian tumors are most likely to recur as

an invasive carcinoma, with a mean time interval to progression to carcinoma of 33 months, compared to 75 months of serous borderline ovarian tumors (Solmaz Hasdemir & Guvena, 2016). Treatment of recurrences depends on the site and the histological type of the relapse: when borderline ovarian tumors relapses in the remaining ovary by the same histological subtype, a second fertility – sparing surgery could be discussed in some specific cases, always after a multidisciplinary meeting, but when the relapse is extra – ovarian and especially in the form of invasive carcinoma, cytoreductive surgery should be performed (Seong et al., 2015).

PROGNOSIS

The prognosis of borderline ovarian tumors is generally excellent. 5 and 10 year survival rates for early stage borderline ovarian tumors (FIGO Stage I) are 99% and 97%, respectively (Audrey Chevrot et al., 2020; Solmaz Hasdemir & Guvena, 2016). On the other hand, 5 year survival rates for advanced borderline ovarian tumors (FIGO Stage II and III) are less favorable (65 – 87%) (C. Tropé, Davidson, Paulsen, Abeler, & Kaern, 2009). The main prognostic factors at the time of diagnosis, described in the early literature, are FIGO Stage, presence of peritoneal implants (especially in cases with invasive foci), microinvasion and micropapillary pattern (Solmaz Hasdemir & Guvena, 2016). However, later studies showed that there is no significant prognostic impact from microinvasion or micropapillary pattern of the borderline ovarian tumors (Andreas du Bois et al., 2013; Prat & De Nictolis, 2002; J D Seidman & Kurman, 2000). When a recurrence occurs, the main prognostic independent factor is the need for a complete cytoreductive surgery, with no residual disease at the end of it. This has a determinant impact on the overall survival of the patients, during either primary or secondary surgery (mortality rate of 60% in suboptimal compared to 12% in complete debulking surgeries) (Crispens et al., 2002).

The prognosis can be completely different based on the time that the borderline ovarian tumor is diagnosed according to surgery (Pados et al., 2012): 1) The malignancy is macroscopically evident in the diagnostic phase of the laparoscopy and therefore no operative maneuvers are performed on the cyst – tumor of the ovary, with no adverse effect on the prognosis of the patient, 2) The malignancy is macroscopically evident during the operative phase of the laparoscopy, when the ovarian cyst wall is opened and the stage of the patient is upgraded from IA to IC_1, because of the cyst rapture (this is the reason that all studies suggest that always an endoscopic bag should be used), 3) There is no macroscopic evidence of malignancy during the whole laparoscopy and the frozen section was either not performed or was false negative, so the results for a borderline ovarian tumor comes with the delay of the final pathology (this scenario has the worse prognosis for the patient).

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Chapter 17
Cystic Masses During Pregnancy:
What Is the Optimal Management?

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ABSTRACT

The prevalence of cystic masses in pregnancy varies from 0.1 to 2.4% and approximately 1 to 6% of these masses are malignant. The clinical presentation of cystic masses in pregnancy varies widely. The majority of cystic masses identified in pregnancy are benign simple cysts less than 5mm in diameter. Malignant neoplasms may be developed, and it is of paramount importance for the attending physician to be able to identify them. Ultrasonography is an excellent tool for the detection of cystic masses and for the discrimination between benign and malignant masses. IOTA group has proposed simple ultrasound rules in order to distinguish between benign and malignant cystic masses. In some cases where there is uncertainty about the type of mass, the MRI has high diagnostic value. Tumor markers that used in epithelial and nonepithelial cancers in nonpregnant women are difficult to interpret in pregnancy, because they are involved in biological functions associated with fetal development, differentiation, and maturation.

PREVALENCE

The prevalence of cystic masses in pregnancy varies from 0.1 to 2.4% and approximately one to 6 percent of these masses are malignant (Schmeler KM et al. 2005, Smith LH et al. 2001, Webb KE et al. 2015, Aggarwal P et al. 2011 and Giuntoli RL et al. 2006).

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Cystic Masses During Pregnancy

The majority of the ovarian masses diagnosed during pregnancy are benign simple cysts with diameter less than 5cm. Most of them are functional ovarian cysts, follicular or luteal, which are part of the normal ovarian function. Approximately 70 per cent of all cystic masses diagnosed in the first trimester of pregnancy, resolve in the early second trimester without any intervention, as part of the natural history of the functional cysts (Giuntoli RL et al. 2006).

In addition, simple cysts in the first trimester with diameter ranging between 1cm and 3 cm, are independent of the gestational age (Perkins KY et al. 1997). However, it is apparent that the size of the cyst at diagnosis is inversely correlated to the probability of the cyst to resolve in the first trimester. Only six per cent of the cysts with diameter less than 6 cm persist in the second trimester, while 39 per cent of those with diameter greater than 6 cm persist in the second trimester (Di Saia PJ et al. 2002). The majority of the persisting cysts with diameter greater than 6 cm are mature teratomas (Schmeler KM et al. 2005). In addition, the ovarian cystic masses that present during pregnancy, have similar characteristics with functional cysts of non-pregnant women of reproductive age (Goffinet F. 2001).

Two distinct cystic masses in pregnancy are the luteomas and the theca lutein cysts. Both cystic masses tend to resolve spontaneously as pregnancy progresses and there is no need for surgical intervention. Surgical intervention is required only in the case of complications.

Luteomas comprise 0.7 per cent of the cystic masses during the pregnancy. The size of luteomas varies from 1cm to 20 cm, usually they are well demarcated and one third of them are located bilaterally.

Theca lutein cyst may present in pregnancy in case of pathologically increased levels of human chorionic gonadotropin (hCG). In fact, theca lutein cysts are luteinized follicle cysts that form as a result of overstimulation from high human chorionic gonadotropin (hCG) levels or hypersensitivity to hCG. Women with gestational trophoblastic disease, multiple gestation, ovulation induction, or a pregnancy complicated by fetal hydrops are likely to represent theca lutein cysts. They usually present as bilateral multiseptated cystic adnexal masses. As the majority of the cystic masses in pregnancy, theca lutein cysts resolve spontaneously with the completion of the pregnancy and there is no need for surgical intervention. Only cysts that cause obstruction and complications may need to be surgically addressed (Goffinet F. 2001).

However, one of the following tumors may develop during the pregnancy and it is of paramount importance for the clinician to be able to recognize and differentiate these tumors from the benign cystic mass lesions.

Malignant Neoplasms

Epithelial ovarian tumors comprise approximately one-half of all ovarian malignancies in pregnant women, germ cell ovarian malignancies make up approximately one-third, and stromal tumors and a variety of other tumor types (eg, sarcomas, metastatic tumors) account for the remainder.

Epithelial Ovarian Tumors

Approximately half of the epithelial ovarian tumors detected in pregnancy are of low malignant potential (formerly called “borderline”), and the other half are invasive (Palmer J et al. 2009). Epithelial ovarian

tumors of low malignant potential diagnosed in pregnancy may exhibit atypical characteristics suggestive of invasive cancer such as nuclear enlargement, anisocytosis, and multifocal microinvasion.

Germ Cell Tumors

Approximately 75 per cent of the malignant ovarian germ cell tumors in pregnancy are dysgerminomas; endodermal sinus tumors, immature teratomas, and mixed germ cell tumors comprise the remainder (Bakri YN et al. 2000). Most germ cell tumors are grossly limited to one adnexa, but lymphatic spread to pelvic or para-aortic nodes occurs, most commonly in dysgerminoma (Kumar S et al. 2008). Dysgerminomas are bilateral in 10 to 15 percent of cases; other germ cell tumors are almost always unilateral.

Sex Cord-Stromal Tumors

Approximately 50 percent of all pregnancy-associated stromal tumors are granulosa cell tumors, one-third are Sertoli-Leydig cell tumors, and the remainder are unclassified stromal tumors (Young RH et al. 1984). Most of these tumors are limited to one ovary at the time of diagnosis. Prior to the routine use of prenatal ultrasound, approximately one fifth of these lesions presented with intraperitoneal hemorrhage and/or hemorrhagic shock, but this has become less common with earlier diagnosis.

Between 10 and 15 percent of stromal tumors secrete androgens and produce virilization. Although estrogen secretion also occurs, symptoms of a hyperestrogenic state are masked by the already high estrogen concentration associated with pregnancy.

Pregnancy-related histologic changes in these tumors include a disorderly arrangement of cells, increased edema, and unusually large numbers of lutein or Leydig cells (Young RH et al. 1984).

Presentation

The clinical presentation of cystic masses in pregnancy varies widely. They may cause no symptoms, or they may lead to abdominal pain, lumbar pain, constipation, abdominal distension, even acute abdomen. The majority of cystic masses become apparent and identified in the first half of the pregnancy as accidental findings during routine prenatal sonographic assessment. Cystic masses that have not been identified during pregnancy, are usually identified during the labour by caesarian section (Schmeler KM et al. 2005, Perkins KY et al. 1997, Di Saia PJ et al 2002, Goffinet F. 2001 and Palmer J et al. 2009).

Nonspecific Symptoms

Symptoms and signs that precede the diagnosis of ovarian cancer include abdominal or back pain, constipation, abdominal swelling, and urinary symptoms (Goff BA et al. 2004, Goff BA et al. 2007). Since these symptoms are almost universally present in normal pregnancies, their presence is unlikely to trigger a diagnostic evaluation.

Palpable Mass

In some women, a suspicious finding, such as a palpable adnexal mass or posterior cul-de-sac mass or nodularity, may be identified during a routine antenatal physical examination and subsequently evaluated by ultrasound.

Acute Abdominal Pain

In a few patients, acute abdominal pain due to torsion of the adnexa prompts the diagnostic evaluation. Adnexal torsion occurs in approximately 5 percent of pregnant women with an adnexal mass (benign or malignant) (Schmeler KM et al. 2005). In one review, adnexal masses between 6 and 8 cm in diameter had a significantly higher rate of torsion (22 percent) than either smaller or larger masses (Yen CF et al. 2009). Sixty percent of the torsions occurred between the 10th and 17th week of gestation; only 6 percent occurred after 20 weeks.

EVALUATION

Ultrasound

Ultrasonography is an excellent tool for the detection of cystic masses and for the discrimination between benign and malignant masses. International Ovarian Tumor Analysis (IOTA) group has proposed simple ultrasound rules in order to distinguish between benign and malignant cystic masses (Timmerman et al. 2010). In order to develop the sonographic criteria, the International Ovarian Tumor Analysis group conducted a multicenter study. Nine centers were participated in the study from five different countries: University Hospital Malmö (Sweden), University Hospital Leuven (Belgium), Universita del Sacro Cuore Rome (Italy), Dipartimento di Scienze Cliniche, Sacco University of Milan (Italy), Hôpital Boucicaut Paris (France), Centre Medical des Pyramides, Maurepas (France), King's College Hospital London (United Kingdom), Istituto di Scienze Biomediche Ospedale, San Gerado Universita di Milano, Monza (Italy), and Universita degli Studi di Napoli, Naples (Italy). The following inclusion criteria were used: patients presenting with at least one overt persistent adnexal mass who were assessed by a principal investigator at one of the participating centers were eligible for inclusion in the study. Data from the apparent worse case mass were used for this study. Patients were excluded from study for the following reasons: pregnancy or refusal of transvaginal sonography, surgery more than 120 days after sonographic assessment, disagreement in the classification (malignant or benign) between the original pathology report and the report of an expert reviewer, or incomplete submission of the data. A standardized sonographic procedure was used at all centers. Gray scale and color doppler images were used to obtain over 40 morphologic and blood flow end points to characterize each adnexal mass. These criteria have been illustrated, described and defined (Timmerman et al. 2010). When intratumoral blood flow velocity waveforms were not detected, the peak systolic velocity, time averaged maximum velocity, the pulsatility index, and the resistance index were coded as 2.0 cm/sec, 1 cm/sec, 3.0 cm/sec, and 1.0 cm/sec, respectively, for use in mathematical modeling. The presence or absence of pain during the examination was recorded. Finally, the investigator gave a subjective assessment of whether the mass was likely to be malignant or benign. The final outcome measures of the study were the histologic diagnosis and, in the cases of malignancy,

the surgical stage. Surgery was performed in the case of a mass classified as persistent (ie, still present 6 to 12 weeks after the initial scan). In cases of symptomatic masses, suspected malignancy, or at the patient's request, surgery was performed more quickly, either by laparoscopy or laparotomy according to the surgeon's judgment. All excised tissues were sampled for histologic examination at the local center. Tumors were classified according to the criteria recommended by the International Federation of Gynecology and Obstetrics (Timmerman et al. 2000). The degree of differentiation of malignant tumors was recorded. The pathologic samples from approximately 10% of the patients were randomly selected for peer review.

Finally, the IOTA group concluded in a simple model comprised of five sonographic criteria (including shape, size, solidity, and results of colour doppler examination) that are used to predict a malignant tumour (M features) or a benign tumour (B features). If one or more M features were present in the absence of a B feature, the mass was classified as malignant. If one or more B features were present in the absence of an M feature, it was classified as benign. If both M features and B features were present, or if none of the features was present, the simple rules were inconclusive. In the B features belong, the presence of unilocular cyst, the presence of solid cyst under 7mm, the presence of acoustic shadowing, the presence of smooth multilocular tumor less than 100mm in diameter and the absence of blood flow. In the M features belong, the presence of irregular solid mass, the presence of ascites, the presence of at least 4 papillary structures, the presence of irregular multilocular solid tumor with diameter greater than 100mm and the presence of strong blood flow (table 1).

MRI

In most cases the sonographic evaluation is sufficient for the evaluation of the cystic mass. However, in some cases where the is uncertainty about the type of mass, the MRI has high diagnostic value, due to its high sensitivity and due to the fact that it does not expose patients to radiation (Goff BA et al. 2004, Thomassin-Naggara I et al. 2017, Telischak NA et al. 2008). Nonetheless, Gadolinium-based contrast material should generally be avoided in pregnancy because fetal safety has not been established.

Tumor Markers

Although serum tumor markers are routinely drawn during the assessment of a pelvic mass in nonpregnant women, this approach is not suggested during pregnancy. Pregnancy-associated pelvic masses are infrequently malignant, and the interpretation of these tumor markers varies with gestational age and comorbid conditions. Several of the tumor markers used to follow epithelial and nonepithelial cancers in nonpregnant women are difficult to interpret in pregnancy because oncofetal antigens (eg, alpha-fetoprotein (AFP), human chorionic gonadotropin (hCG), carcinoembryonic antigen (CEA), cancer antigen 125 (CA 125)) are involved in biological functions associated with fetal development, differentiation, and maturation. The levels are normally elevated during gestation and fluctuate with gestational age, or they may be abnormally elevated due to abnormal placentation or fetal abnormalities (eg, preeclampsia, Down syndrome, open neural tube defect) (Goff BA et al. 2004).

Fine Needle Aspiration

Previous studies had investigated the use of fine needle aspiration in ovarian cystic masses during pregnancy (Mooney J et al. 1997, Wang PH et al. 1999, Lee GH et al. 2004). The method is safe as the rate of complications ranges from zero to two per cent (Leiserowitz GS et al. 2006). However, this method is not recommended as the rate of the cystic mass relapse varies from 30% to 50% (Wang PH et al. 1999, Lee GH et al. 2004, Bernhard LM et al. 1999). In addition, the sensitivity of the cytological examination of the aspirated fluid for the detection of malignancy is 25 per cent with 73 per cent false positives (Whitecar et al. 1999). In case of malignancy, fine needle aspiration may contribute to the dissemination of the cancer cells and therefore, this technique should not be performed (Yakasai IA et al. 2012, American College of Obstetricians and Gynecologists ACOG Practice Bulletin. Management of adnexal masses.).

Operation

According to widely accepted guidelines about the management of pelvic mass during pregnancy, pregnant women with asymptomatic mass during the first trimester characterized by the presence of irregular solid mass, the presence of ascites, the presence of papillary structures, the presence of irregular multilocular solid tumor with diameter greater than 100mm and the presence of string blood flow, should be operated in order to remove the mass (Schmeler KM et al. 2005, Aggarwal P et al. 2011, Vergote I et al. 2001, Knudsen UB et al 2004, Yen CF et al. 2009, Wang PH et al. 1999, Lee GS et al. 2004, Leiserowitz GS et al. 2006, Bernhard LM et al, 2006). The immediate period after the first trimester is considered as the best time for an elective surgery for the removal of a mass during pregnancy. This is based on the fact that after the first trimester almost all the functional cysts will have been resolved. In addition, in the same period the organogenesis has also been completed, therefore the probability of fetal teratogenesis due to administration of medications is low.

Early Stage Ovarian Cancer (Borderline and Invasive)

The incidence of a malignant adnexal mass during pregnancy is reported between four and eight in 100000 pregnancies (Amant F et al. 2010). Most frequently reported are the non-epithelial tumours (germ-cell and sex-cord) followed by ovarian tumours of low malignant potential (LMP, e.g. borderline tumours) and epithelial ovarian cancers (Morice P et al. 2012). As stated above, diagnosis is usually made by routine prenatal ultrasound examination. The presence of ascites, peritoneal seeding or an omental cake indicates advanced disease. Of all malignant tumours of the ovary ten percent are metastases of other organs, mainly gastrointestinal or breast tumours. They are usually solid and bilateral (Glanc P et al. 2008). When the probability of malignancy is high or if there is a high risk of developing complications (rupture, torsion) surgery is indicated.

For early stage ovarian cancer, stage I and II according to the International Federation of Gynecology and Obstetrics (FIGO), standard surgical procedure consisting of hysterectomy, bilateral adnexectomy, omentectomy, cytology, biopsies and lymphadenectomy (Prat J. 2014). For early stage disease, fertility- and pregnancy preserving treatment may be considered. In these selected cases surgery includes removal of the adnexa and surgical staging (cytology, peritoneal biopsies, omentectomy and appendectomy in mucinous tumours). In unilateral borderline tumours, a laparoscopic procedure without spilling is pos-

sible. For invasive epithelial ovarian carcinoma, grade I and diagnosed at FIGO stage Ia, fertility- and pregnancy preserving management can also be performed (Prat J. 2014). Restaging after delivery may be considered because of occult extra-ovarian disease, which may not be assessed adequately during pregnancy (Amant F et al. 2010, Morice P et al. 2012). Non-epithelial tumours (germ-cell and sex-cord stromal tumours), which frequently present as bulky masses, are over 90% diagnosed at FIGO stage Ia and therefore are also treated by a resection and surgical staging (Mancari R et al. 2014). For high-grade stage I and any stage II disease, standard adjuvant chemotherapy (carboplatin-paclitaxel) can be considered.

More specifically, according to FIGO,

Stage I: Tumor confined to ovaries or fallopian tube(s)
T1-N0-M0
IA: Tumor limited to 1 ovary (capsule intact) or fallopian tube; no tumor on ovarian or fallopian tube surface; no malignant cells in the ascites or peritoneal washings
T1a-N0-M0
IB: Tumor limited to both ovaries (capsules intact) or fallopian tubes; no tumor on ovarian or fallopian tube surface; no malignant cells in the ascites or peritoneal washings
T1b-N0-M0
IC: Tumor limited to 1 or both ovaries or fallopian tubes, with any of the following:
IC1: Surgical spill
T1c1-N0-M0
IC2: Capsule ruptured before surgery or tumor on ovarian or fallopian tube surface
T1c2-N0-M0
IC3: Malignant cells in the ascites or peritoneal washings
T1c3-N0-M0

Comment

Stage I ovarian or fallopian tube cancer is confined to the ovaries or the fallopian tubes and peritoneal fluid/washings. Tumor rupture or surface involvement by tumor cells warrants a stage of IC. It is not possible to have stage I peritoneal cancer.

Controversial Issues

Bilateral involvement (stage IB). Independent contralateral primary tumor versus implants or metastases

Stage IB is relatively uncommon, occurring in only 1%–5% of stage I cases (Heintz AP et al 2006, Yemlnova AV et al. 2008). Occasionally, a large stage IB ovarian tumor is associated with a contralateral normal-size ovary exhibiting small and superficial foci of tumor, suggesting that the latter are metastatic. Among stage I tumors with bilateral involvement, one-third have this appearance (Seidman JD et al. 2010).

Surface involvement of the ovary or fallopian tube should be considered present only when tumor cells are exposed to the peritoneal cavity. It is characterized by exophytic papillary tumor on the surface of the ovary or fallopian tube or on the outer surface of a cystic neoplasm replacing these organs; rarely, a smooth ovarian tumor surface will be shown to have an exposed layer of neoplastic epithelium. Assessment of surface involvement requires careful gross examination.

Limited evidence suggests that dense adhesions of an apparent stage I tumor requiring sharp dissection (or when dissection results in tumor rupture) result in outcomes equivalent to tumors in stage II (Dembo AJ et al. 1990, Ozols RF et al. 2005). At present, however, it is not clear whether upstaging based on dense adhesions is warranted. A recent study suggests that it is not (Seidman JD et al. 2010).

In several series of stage I tumors, multivariate analyses identified degree of differentiation as the most powerful prognostic indicator of disease-free survival (Dembo AJ et al. 1990), (Ahmed FY et al. 1996, Vergote I et al. 2001). With the exception of ECs and MCs, the histologic grade is implicit in the tumor type (i.e. HGSC, LGSC, CCC (the vast majority are high-grade tumors)). Currently, grade 3 ECs are considered to be the same as HGSCs. Most MCs involving the ovary are metastatic from the gastrointestinal tract and some might appear well differentiated (G1).

It is controversial whereas rupture during surgery worsen prognosis in the absence of excrescences, ascites, or positive washings. Some studies found that intraoperative capsule rupture portends a higher risk of disease recurrence (Vergote I et al. 2001, Bakkum-Gamez JN et al 2009), others did not (Seidman JD et al. 2010, Dembo AJ et al. 1990, Ahmed FY et al. 1996, Chan JK et al. 2008, Obermair A et al. 2007). In a multivariable analysis, capsule rupture and positive cytologic washings remained independent predictors of worse disease-free survival (Bakkum-Gamez JN et al 2009). Rupture should be avoided during primary surgery of malignant ovarian tumors confined to the ovaries. Data from several studies suggest that stage I CCC is more frequently stage IC compared with other cell types (Seidman JD et al. 2010), possibly because of an increased risk of rupture (Timmers PJ et al. 2009).

In multivariable analysis, capsule rupture and positive cytologic washings remained independent predictors of worse disease-free survival (Bakkum-Gamez JN et al 2009).

RECOMMENDATIONS

Histologic type, which in most cases includes grade, should be recorded.

All individual subsets of stage IC disease should be recorded.

Dense adhesions with histologically proven tumor cells justify upgrading to stage II.

If rupture is noted, peritoneal washing and cytology study are indicated.

Stage II: Tumor involves 1 or both ovaries or fallopian tubes with pelvic extension (below pelvic brim) or primary peritoneal cancer

T2-N0-M0

IIA: Extension and/or implants on uterus and/or fallopian tubes and/or ovaries

T2a-N0-M0

IIB: Extension to other pelvic intraperitoneal tissues

T2b-N0-M0

Comment

Stage II ovarian cancer is still difficult to define. It comprises a small and heterogeneous group making up less than 10% of ovarian cancers. It is defined as extension or metastasis to extraovarian/extratubal pelvic organs and may include curable tumors that have directly extended to adjacent organs but have not yet metastasized, as well as tumors that have seeded the pelvic peritoneum by metastasis and, therefore, have a poor prognosis. Of note, the sigmoid colon is within the pelvis, and therefore sigmoid involvement only is considered stage II. The Committee felt that subdividing this small category further into IIB1 and IIB2 (i.e. microscopic and macroscopic pelvic peritoneal metastases) was not based on evidence/biology. All stage II disease is treated with adjuvant chemotherapy, so subclassification is not essential. Also, the old substage IIC (i.e. IIA or IIB but with tumor on surface, capsule ruptured, or ascites or positive peritoneal washing) was considered redundant and eliminated.

Controversial Issues

Is it biologically justified to separate the pelvic from the extrapelvic peritoneum? Is disease outside the ovary but below the pelvic brim so much better that it warrants a separate stage?

Biologically, this is stage III disease and it is only because of the anatomic location in the pelvis that it is designated stage II. Some investigators claim that the peritoneum is an anatomic unit and that pelvic involvement and extrapelvic involvement are prognostically similar. Thus, they suggest defining as stage III all cases with peritoneal involvement including uterine serosa (as is done for stage IIIA endometrial carcinoma of the uterus). Most Committee members felt that there was a clear division of stage II and III disease in terms of survival, and therefore the subdivision of IIA and IIB remains.

RECOMMENDATIONS

To separate direct extension from metastases.

Advanced stage ovarian cancer (borderline and invasive)

When there is a high probability of advanced stage ovarian cancer, further imaging besides ultrasound is required to evaluate the stage. As stated above, in pregnant women the use of MRI after the first trimester is considered safe and allows accurate evaluation of the mass and its possible spread. In case of higher stage disease in borderline tumours, adnexectomy/biopsy during pregnancy is aimed for, followed by completion of surgery after delivery. Since chemotherapy is not effective for borderline disease and given the indolent nature, an otherwise conservative approach during pregnancy is advised. Similar, the performance of complete cytoreductive surgery for advanced stage invasive (FIGO stage III) ovarian cancer is not possible during pregnancy. In most reported cases of advanced invasive disease, patients chose to terminate pregnancy when diagnosis has been made early in the first trimester of pregnancy (Mancari R et al. 2014). When the patient wants to proceed the pregnancy, neoadjuvant chemotherapy (carboplatin and paclitaxel) until fetal maturity and complete cytoreductive surgery after delivery is recommended from midpregnancy onwards (Amant F et al. 2010). However, experience is limited and the proposed approach still has an experimental character. A vaginal delivery is aimed for.

According to FIGO

Stage III: Tumor involves 1 or both ovaries or fallopian tubes, or primary peritoneal cancer, with cytologically or histologically confirmed spread to the peritoneum outside the pelvis and/or metastasis to the retroperitoneal lymph nodes

T1/T2-N1-M0
IIIA1: Positive retroperitoneal lymph nodes only (cytologically or histologically proven):
IIIA1(i) Metastasis up to 10 mm in greatest dimension
IIIA1(ii) Metastasis more than 10 mm in greatest dimension
IIIA2: Microscopic extrapelvic (above the pelvic brim) peritoneal involvement with or without positive retroperitoneal lymph nodes
T3a2-N0/N1-M0
IIIB: Macroscopic peritoneal metastasis beyond the pelvis up to 2 cm in greatest dimension, with or without metastasis to the retroperitoneal lymph nodes
T3b-N0/N1-M0
IIIC: Macroscopic peritoneal metastasis beyond the pelvis more than 2 cm in greatest dimension, with or without metastasis to the retroperitoneal lymph nodes (includes extension of tumor to capsule of liver and spleen without parenchymal involvement of either organ)
T3c-N0/N1-M0

Comment

Most ovarian cancers are HGSCs that usually present in stage III, with the vast majority (84%) stage IIIC (Heintz AP et al. 2006). These tumors characteristically spread along peritoneal surfaces involving both pelvic and abdominal peritoneum including the omentum, surfaces of the small and large bowel, mesentery, paracolic gutters, diaphragm, and peritoneal surfaces of the liver and spleen. A finding of ascites occurs in two-thirds of cases. Lymph node metastases are found in the majority of patients who undergo node sampling or dissection and in up to 78% of advanced-stage patients (Harter P et al. 2007). Approximately 9% of patients with tumors that otherwise appear to be stage I have lymph node metastases; the corresponding figures for stages II, III, and IV are 36%, 55%, and 88%, respectively (Ayhan A et al. 2008). Rarely, inguinal or supraclavicular (stage IV) node metastases will be the presenting manifestation of ovarian carcinoma (Euscher ED et al. 2004).

Less than 10% of ovarian carcinomas extend beyond the pelvis with exclusively retroperitoneal lymph node involvement. Evidence in the literature indicates that these cases have a better prognosis than that of tumors with abdominal peritoneal involvement (Onda T et al. 1998, Kanazawa K et al. 1999, Panici PB et al. 2005, Cliby WA et al. 2006, Ferrandina G et al. 2007, Baek SJ et al. 2008). The new staging includes a revision of stage III patients and assignment to stage IIIA1 based on spread to the retroperitoneal lymph nodes without intraperitoneal dissemination. Stage IIIA1 is further subdivided into IIIA1(i) (metastasis $\leq$ 10 mm in greatest dimension) and IIIA1(ii) (metastasis $>$ 10 mm in greatest dimension), even if there are no retrospective data supporting quantification of the size of metastasis in IIIA1. Involvement of retroperitoneal lymph nodes must be proven cytologically or histologically.

Controversial Issues

Serous borderline tumors and LGSCs may develop in retroperitoneal and cervical lymph nodes from endosalpingiosis, often in association with serous borderline tumors of the ovary and with favorable prognosis (Prat J et al. 2002, Djordjevic B et al. 2012). In none of the reported case series was a histopathologic distinction made between HGSC and LGSC.

It was suggested that upward nodal involvement (e.g. mediastinal nodes) should be included but, for now, the Committee felt that the stated limitation was appropriate.

Regarding the amount of peritoneal involvement, it was claimed that stage III tumors should be divided into microscopic and macroscopic, and if the latter measurement (in centimeters) should be given. Further distinction should be made between single small lesions within the omentum (< 2 cm) and diffuse peritoneal disease including the upper abdomen and diaphragm.

Specific mention should be given to bowel infiltration (transmural with mucosal involvement) and umbilical deposit (currently IVB); however, some consider that involvement of the umbilicus should be IIIC rather than IV as it represents peritoneal extension into the urachal remnant. Similarly, isolated parenchymal liver metastasis and splenic parenchymal metastasis are susceptible to cytoreductive surgery and, according to some investigators, should be IIIC, although this was not adopted by the Committee (i.e. transmural bowel infiltration, umbilical deposit, and parenchymal metastases in the liver and spleen or elsewhere such as lung and bone are assigned to stage IVB).

RECOMMENDATIONS

To classify IIIA1 cases histologically.

To compare outcome of stage IIIA1(i) and IIIA1(ii) cases.

To compare outcome of stage IIIA1 and IIIA2 cases.

Stage IV: Distant metastasis excluding peritoneal metastases
Stage IVA: Pleural effusion with positive cytology
Stage IVB: Parenchymal metastases and metastases to extra-abdominal organs (including inguinal lymph nodes and lymph nodes outside of the abdominal cavity)

Any T, any N, M1

Comment

Stage IV is defined as distant metastasis and includes patients with parenchymal liver/splenic metastases and extra-abdominal metastases; 12%–21% of patients present with stage IV disease (Heintz AP et al. 2006). Extension of tumor from omentum to spleen or liver (stage IIIC) should be differentiated from isolated parenchymal metastases (stage IVB).

Notes

The primary site (i.e. ovary, fallopian tube, or peritoneum) should be designated where possible. In some cases, it might not be possible to delineate the primary site clearly; such cases should be listed as "undesignated."

The histologic type should be recorded.

The staging includes a revision of stage III patients; assignment to stage IIIA1 is based on spread to the retroperitoneal lymph nodes without intraperitoneal dissemination because an analysis of these patients indicates that their survival is significantly better than that of patients with intraperitoneal dissemination.

Involvement of retroperitoneal lymph nodes must be proven cytologically or histologically.

Extension of tumor from omentum to spleen or liver (stage IIIC) should be differentiated from isolated parenchymal metastases (stage IVB).

RECOMMENDATION FOR FUTURE CONSIDERATION

Splenectomy seems to take care of isolated metastases in a better way than partial hepatectomy. In future, isolated splenic metastasis may be considered stage IIIC rather than stage IV, whereas parenchymal liver metastasis would remain stage IVB.

In case that operation is needed, open surgery and laparoscopic are both feasible. Laparoscopy is associated with a longer operative duration but better surgical outcomes than the laparotomy for the surgical management of ovarian masses during the second trimester of pregnancy. If a malignancy is suspected, a laparotomy should be performed. A Pfannenstiel incision should be avoided, as it would not provide sufficient exposure. The vertical midline incision should be adequate to minimize the need to manipulate the gravid uterus while obtaining exposure to the adnexal mass.

Immediately after entry into the peritoneal cavity, peritoneal washings should be obtained for staging purposes in case the mass is malignant. The opposite adnexa should be carefully inspected and palpated for a contralateral adnexal mass. Contralateral ovarian biopsy is recommended if the ovary appears to be involved, but routine biopsy or wedge resection of a normal-appearing contralateral ovary is unwarranted.

The most common findings at surgery are persistent corpus luteal functional cysts, benign dermoid cysts, and serous or mucinous cystadenomas. If the preoperative imaging and intraoperative gross findings are both consistent with a benign diagnosis, it is reasonable to attempt a cystectomy rather than perform a salpingo-oophorectomy. If the mass is larger than 10 cm, it may not be technically feasible to perform an ovarian cystectomy. If the mass is solid, has surface excrescences, is associated with ascites, or has other features suggesting malignancy, then ipsilateral salpingo-oophorectomy is appropriate. The mass should be sent for frozen section and the pathologist informed of the concurrent pregnancy. Resection of the contralateral ovary should not be performed unless bilateral disease is identified; this decision must await the frozen section analysis. All suspicious lesions should be biopsied.

If the pathologist confirms a malignant tumor at frozen section, the surgeon should be prepared to complete an adequate surgical staging procedure, and a gynecologic oncologist should be consulted. Hysterectomy is not performed if preservation of the pregnancy is desired, and the surgeon must individualize each case, weighing the pros and cons of staging versus potential risk to the mother and fetus. In certain malignant germ cell tumors of the ovary (eg, endodermal sinus tumors), lymph node dissection may be omitted, as the patient will require chemotherapy based on the histopathology alone.

Adequate surgical staging is of particular importance for stage I cancers (ie, those that are limited to the ovary), as many, but not all, of these neoplasms are adequately treated with surgery alone. In such cases, the need for postoperative adjuvant chemotherapy is determined by the histologic tumor type. Surgical staging (eg, sampling of lymph nodes) is less critical in the setting of obvious advanced disease (eg, stage IIIB/C disease), as these tumors (with the exception of tumors of low malignant potential) will require chemotherapy.

If a metastatic ovarian cancer is identified, cytoreduction should be attempted. The extent of surgical cytoreduction involves individual judgment, balancing the extent of surgery with the expected benefit. It is rare that removal of the gravid uterus is required for maximal cytoreductive surgery at the initial surgery because it is possible, if necessary, to return for secondary cytoreduction following chemotherapy and successful completion of the pregnancy. This management strategy is not thought to adversely impact survival, although, as a general rule, survival is poor for women who have late-stage disease.

Despite the importance of early surgical debulking to outcomes in ovarian cancer, the surgeon should keep in mind the sensitivity of these tumors to platinum-based chemotherapy when aggressive resection of metastatic disease is considered. With modern platinum-based adjuvant chemotherapy, approximately 70 percent of patients who present with advanced disease will respond to chemotherapy, even if they have residual disease remaining after cytoreductive surgery.

In pregnancy, the hazard of overly aggressive surgery and delay in starting chemotherapy can be illustrated by a case report of a patient with a yolk sac tumor that was resected at 19 weeks of gestation (Rajendran S et al. 1999). Chemotherapy was delayed because of the pregnancy and at 32 weeks of gestation, tumor recurrence necessitated a cesarean-hysterectomy and bowel resection with colostomy. Three weeks later, the colostomy was taken down and another suprahepatic tumor mass was resected. The patient was then given bleomycin, etoposide, and cisplatin (BEP) for four cycles, but the course was complicated by a fecal fistula that developed at the colostomy site.

For women with advanced-stage ovarian cancer diagnosed before delivery, hysterectomy and secondary cytoreductive surgery are reasonable postpartum to remove persistent disease. This surgery can be performed following vaginal delivery or in conjunction with cesarean delivery. This approach has been taken by a few investigators who reported managing advanced epithelial ovarian cancer (EOC) cases during pregnancy (Mendez LE et al. 2003, Picone O et al. 2004, Sood AK et al. 2001, Ferrandina G et al. 2005). In four case reports, two patients had persistent disease involving the adnexa (Mendez LE et al. 2003, Picone O et al. 2004), two cases involved the bowel (Picone O et al. 2004, Sood AK et al. 2001), and one case also involved the pelvic peritoneum, omentum, and appendix (Picone O et al. 2004).

PROGNOSIS

There is no evidence that pregnancy worsens the prognosis of ovarian tumors compared with nonpregnant patients matched for tumor histology, stage, and grade (Grimm D et al. 2014). Approximately 75 percent of invasive ovarian malignancies in pregnant women are early-stage disease. Due to the favorable mix of stage, grade, and histology, the five-year survival rate for ovarian tumors associated with pregnancy is between 72 and 90 percent. The presence of ascites at diagnosis implies advanced disease and poor prognosis (Zhao XY et al. 2006). Although one cohort study found that postpartum lactating women diagnosed with ovarian cancer had a poorer prognosis than women diagnosed before or during

pregnancy, the number of cases was small (Stensheim H et al. 2009). This finding needs to be confirmed in larger studies.

The decision to continue or terminate a pregnancy when ovarian cancer is diagnosed in the first trimester should be individualized and made by a fully informed woman in collaboration with her clinician. Early termination of pregnancy does not improve the outcome of ovarian cancer. In addition to the usual reasons for pregnancy termination, some factors that should be considered in women with ovarian cancer include:

- Whether she is willing to assume a possible risk of fetal toxicity or complications from ovarian cancer treatment during pregnancy.
- Her prognosis and ability to care for her offspring.

The effect of ovarian cancer treatment on future fertility.

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Chapter 18
Ovarian Cancer as Random Finding in Laparoscopy: Optimal Management and Medicolegal Issues

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ABSTRACT

Laparoscopy can be used for almost all gynecological procedures and is considered as the indicated method for specific procedures. This is especially true for adnexal surgery. Of course, while it is considered a method of choice for the treatment of benign ovarian tumors, the same does not apply to malignant ones, although treatment of ovarian cancer either at an early or even at a more advanced stage is feasible with laparoscopy. Finding malignancy, when not suspected, during laparoscopic treatment of an ovarian cyst is a situation raising several issues, depending on whether the identification of malignancy is intra- or post-operative, which involve inadequate surgical staging, peritoneal spread of cancer cells, intraoperative rupture of a malignant ovarian cystic tumor, and port site metastasis. This chapter analyzes the possible adverse events related to the use of laparoscopy in the treatment of adnexal masses considered as benign but turn out to be malignant, and how they can be mitigated with careful preoperative patient selection and with adequate surgical experience.

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INTRODUCTION

Laparoscopy is a minimally invasive technique consisting a surgical approach that is now daily practice in gynecology for the treatment of both simple and complex diagnostic and therapeutic problems. Laparoscopy, i.e. the visualization of the peritoneal cavity, was developed during the 20th century, when the basic principles of the method were gradually implemented, and it was a change in paradigm for surgery in general (Lane, 2018; Misro, 2015; Nano, 2012; Spaner & Warnock, 1997; Teixeira, 2020). Air insufflation in the peritoneal cavity was first used by Kelling (Kelling, 1902; Schollmeyer, Soyinka, Schollmeyer, & Meinhold-Heerlein, 2007) to treat intraperitoneal hemorrhage in dogs and, during the same year, the first peritoneal cavity examination was performed on a pregnant woman by Ott (Himal, 2002; Von Ott, 1901). Subsequently, following the initial experimental implementation of the above methods, specialized tools and techniques were developed, including the use of carbon dioxide, the development of a specially designed needle for the induction of pneumoperitoneum, by Verres in 1937 (Veress, 1961), and later, the development of automated systems for carbon dioxide insufflation and monitoring of intraperitoneal pressure, for irrigation and aspiration as well as for electrocoagulation with the significant contribution of Kurt Semm (Himal, 2002; Semm, 1983a, 1983b). A medical doctor who had a pivotal role in the development of laparoscopy was Raul Palmer (Litynski, 1997b), who, among others, studied the use of carbon dioxide in laparoscopy, and standardized the insufflation method advocating that the intraabdominal pressure should not exceed 25 mmHg, and that the insufflation speed should not exceed 500 cc per minute (Palmer, 1947). Palmer's work established safety rules for laparoscopy which are the basis of modern minimally invasive surgery.

During the last decades of the 20th century, laparoscopy has gained significant grounds over the classical surgical approach in the treatment of gynecological diseases (Lim, 2017; Litynski, 1997a). Furthermore, gynecology was among the medical specialties that adopted the new method very quickly, as the benefits, regarding better quality of the post - operative course combined with improved cost of hospitalization for women were greatly appreciated (Lundorff, Thorburn, Hahlin, Kallfelt, & Lindblom, 1991; Magos, Baumann, & Turnbull, 1988; Rademaker, Einarsson, Huirne, Gu, & Cohen, 2019).

Indeed, it was quickly shown that when a procedure was performed with minimally invasive techniques it required shorter duration of post-operative hospitalization and a shorter recovery time after hospital discharge compared to the use of the standard surgical techniques (Lundorff et al., 1991; Magos et al., 1988). Moreover, post-operative pain, post-operative morbidity and the cosmetic result regarding surgical wounds were improved in case of laparoscopy compared to laparotomy (Nguyen et al., 2011; Stocchi, Nelson, Young-Fadok, Larson, & Ilstrup, 2000). These beneficial effects are independent of the kind of the surgical procedure performed on the patient. In addition, concerning the overall health care cost affecting a state's annual budget and therefore the whole society, laparoscopy also seemed a well-balanced, cost effective process with a substantial economic gain (Levine 1985). Cost effectiveness is very important in the design of a state's health care policy since the implementation of this basic principle permits a rationalized allocation of the budget available for policies related to the prevention and treatment of diseases, affecting the whole population regardless of sex, age or other demographic parameters (Bartha, 2018; Behera & Dash, 2019; Gupta & Ranjan, 2019; Izadi, Bahadori, Teymourzadeh, Yaghoubi, & Ravangard, 2019; Lomas, Martin, & Claxton, 2019). Altogether, these reasons have led to a widespread worldwide adoption of minimally invasive techniques among surgeons involved in the surgical treatment of gynecological benign as well as malignant diseases.

Among gynecologists there has always been a tendency to act, regarding the treatment of a disease, as less invasively as possible, since apart from the treatment of a condition the gynecologist has to offer consultation taking under consideration both the preservation of good health for their female patients, and the need to preserve a patients' fertility, when there is a desire for that (Bogani et al., 2019; Gingold, Gueye, & Falcone, 2018; Gomel, 2019; C. Nezhat, Roman, Rambhatla, & Nezhat, 2020).

Laparoscopy can now be used for almost all gynecological procedures, either malignant (Falcetta et al., 2016; Galaal, Donkers, Bryant, & Lopes, 2018; Matsuo, Chen, et al., 2019; Wang, Deng, Xu, Zhang, & Liang, 2015) or benign (Ades, Dobromilsky, Cheung, & Umstad, 2015; Jokinen, Heino, Karipohja, Gissler, & Hurskainen, 2017; Kundu et al., 2018; Linder et al., 2018; Panici et al., 2007; Sandberg, Twijnstra, Driessen, & Jansen, 2017; Zhu, Wong, & Bai, 2000) and is considered as the indicated method for specific procedures. This is especially true for adnexal surgery. Of course, while it is considered a method of choice for the treatment of benign ovarian tumors, the same does not apply to malignant tumors. However, studies have shown that treatment of ovarian cancer either at an early or even at a more advanced stage is feasible with the use of minimally invasive surgery (Liu, Nagarsheth, & Nezhat, 2009; F. R. Nezhat et al., 2010; H. J. Park et al., 2013). There are, nonetheless, some risks involved in the implementation of laparoscopy in such cases that may lead to overriding of the basic principles of oncological surgery. These are the risks of inadequate surgical staging of cancer (Desfeux et al., 2005; Desfeux et al., 2006; Lecuru et al., 2006; Lecuru et al., 2004; J. Y. Park et al., 2008), peritoneal spread of cancer cells due to the pneumoperitoneum (Abu-Rustum et al., 2003; Koster, Melchert, & Volz, 1996; Qijun, Jiang, & Chongshu, 2018; Zhang et al., 2015), intraoperative rupture of a malignant ovarian cystic tumor (Bakkum-Gamez et al., 2009; Higashi et al., 2011; Matsuo, Machida, et al., 2019; Sjovall, Nilsson, & Einhorn, 1994; Suh et al., 2015; Vergote et al., 2001; Yousef, Pucci, & Emil, 2016), and metastasis to the main or the ancillary trocars (Ataseven et al., 2016; Lago et al., 2019; O'Sullivan, Shireen, Swafani, & Curtain, 2016; Shin, Lee, Kim, Nam, & Park, 2018; Wilkinson-Ryan, Pham, Sergent, Tafe, & Berwin, 2019), used for the scope or the laparoscopic surgical instruments respectively, during minimally invasive surgery (Liu et al., 2009).

Inadequate surgical staging of ovarian cancer can occur during a laparoscopic approach to ovarian surgery but adequate staging is feasible and depends on the experience of the gynecologic – oncologist (Desfeux et al., 2006). Concerning laparoscopic staging for ovarian cancer there are contradicting reports; earlier reports have shown poor results regarding proper staging in case of stage I ovarian cancer (Lecuru et al., 2004), whereas other relatively more recent reports presented results showing similar surgical staging adequacy and accuracy between laparoscopy and laparotomy for early-stage ovarian and fallopian tubal cancer (J. Y. Park et al., 2008; Suh et al., 2015). Indeed, in a recent systematic review comparing surgical ovarian cancer staging with either laparoscopy or laparotomy, no differences were found in survival, so laparoscopy should be an acceptable method for ovarian cancer staging that additionally has less surgical morbidity and faster recovery, providing the necessary conditions for the timely onset of adjuvant chemotherapy (Bogani et al., 2017).

The rupture of an ovarian cyst during surgical dissection is a complication that can occur both during laparoscopy or laparotomy. There are studies that support higher rates of rupture with laparoscopy, but this is not universally accepted. Recent systematic reviews have shown no statistically significant difference in the likelihood of ovarian cyst rupture between the two different surgical approaches (laparoscopy or laparotomy). [Odds ratio (OR) 1.38, 95% CI 0.52 – 3.38)] (Bogani et al., 2017). Regarding the rupture of an ovarian tumor during surgery, there are reports associating the histologic type of the ovarian cancer with the risk for intraoperative rupture of the tumor. A quite recent retrospective observational study in

Japan, which examined 15,163 women with stage IA-IC1 epithelial ovarian cancer (table 1) who underwent primary surgical treatment, showed that clear cell carcinoma of the ovary had the highest risk of intraoperative capsule rupture (57.3%), followed by the endometrioid carcinoma (48.8%), the serous carcinoma (41.8%), and the mucinous carcinoma (32.0%) (Matsuo, Machida, et al., 2019). The question, though, would be if intraoperative rupture of an ovarian tumor could interfere with overall survival and furthermore, if adjuvant chemotherapy would improve overall survival in case of intraoperative rupture. The abovementioned study by Matsuo et al showed clearly that survival of women whose ovarian tumors had ruptured during surgery was similar between those who received postoperative chemotherapy and those who did not (Matsuo, Machida, et al., 2019).

Concerning the effect of carbon dioxide, the gas used, almost universally during the past decades, for pneumoperitoneum in laparoscopy, it has been shown in earlier experimental studies that it may affect the growth of cancer cells (Koster et al., 1996; Volz, Koster, Spacek, & Paweletz, 1999). This has been further confirmed in more recent experimental studies showing even a positive correlation of the duration of pneumoperitoneum with the promotion of the proliferation and metastasis of human ovarian cancer in nude mice (Zhang et al., 2015). However, there are conflicting results (Lecuru et al., 2002) and an adverse effect of pneumoperitoneum on laparoscopic management of ovarian cancer in humans has not been fully confirmed. (Abu-Rustum et al., 2003). This discrepancy between animal models and in vivo studies in female patients has been partially attributed to a hypothesis that the volume of tumor cells injected in the animals is quite large, leading to bias. So, attempts have been made to rationalize the process and mimic real – life conditions more accurately by designing novel mouse models (Qijun et al., 2018).

Metastasis at the site of the trocars' placement after laparoscopic surgery in women with ovarian cancer is another risk. Metastasis at the trocar entry site is a medium-term, relatively common complication in women with epithelial ovarian cancer and most often occurs in case of ascites, infiltrated lymph nodes or when the stage is advanced (Ataseven et al., 2016; Heitz et al., 2010). In general, for all surgically treated malignancies with minimally invasive techniques, the incidence of this complication varies from 1-2% (Ramirez, Wolf, & Levenback, 2003); however, in case of diagnostic laparoscopy in advanced ovarian cancer the reported incidence of port site metastasis is higher and varies significantly from 17 to 47% (Ataseven et al., 2016; Vergote, Marquette, Amant, Berteloot, & Neven, 2005). There are various hypotheses regarding the pathogenesis of these metastases such as the entrapment of cancer cells in the surgical wound associated with the use of laparoscopic surgical instruments, the chimney effect, in which the outflow of carbon dioxide through the trocars entrains cancer cells, or the effect of pneumoperitoneum on local immunity (Ramirez et al., 2003). In order to minimize the risk of port site metastasis it has been suggested to perform the resection of the port site during primary ovarian cancer cytoreductive surgery in case diagnostic laparoscopy was performed prior to laparotomy (O'Sullivan et al., 2016). This strategy, however, has not proven to be beneficial in terms of survival and conferred higher wound complication rates, therefore, it is considered controversial and other authors recommend not to use it (Lago et al., 2019).

The abovementioned potential complications from the implementation of minimally invasive surgery for the treatment of ovarian cancer makes it imperative that careful pre-operative evaluation of an adnexal tumor is conducted so that its surgical approach is optimal. The basic element of pre-operative evaluation of an adnexal tumor involves mainly whether the tumor is benign or malignant. In most cases an adnexal tumor is a random finding or a finding within the framework of screening. Organized screening for ovarian cancer prevention has not yet proved to be cost-effective so there are not organized

screening programs for this disease. There is, however, opportunistic screening, conducted mainly with transvaginal ultrasound, which can lead to the detection of findings requiring further evaluation. Ultrasound examination can identify specific characteristics of an ovarian tumor suggesting malignancy such as the size of the tumor being larger than 10 cm in diameter, the presence of papillary projections or solid components, irregular shape, concurrent ascites or increased flow in doppler velocimetry with ultrasound. (American College of & Gynecologists' Committee on Practice, 2016).

Moreover, the abovementioned ultrasound findings combined or not with biochemical markers have been used for the development of specially designed mathematical models aiming to classify an ovarian mass depending on its malignant potential. A systematic review and meta-analysis, recently published, investigated the diagnostic accuracy of 19 such models regarding preoperative evaluation of ovarian masses. All the models were classified, utilizing Receiver Operating Characteristics (ROC) analysis, according to the optimal combination of sensitivity and specificity regarding the characterization of an ovarian mass as malignant or not. The models showing the highest sensitivity and specificity were the simple rules IOTA model and the logistic regression 2 IOTA model. (Kaijser et al., 2014). IOTA is a scientific group studying ovarian tumors and has carried out a multi-center study regarding ovarian tumor differential diagnosis. The simple rules IOTA model suggests that there are 10 simple rules/characteristics according to which an ovarian tumor can be classified as benign or malignant. Five characteristics are considered "benign" and five are considered "malignant". The "benign" characteristics are the following: the presence of a unilocular cyst, the presence of solid components in the cyst smaller than 7 mm in diameter, the presence of acoustic shadows, largest diameter smaller than 10 cm in case of a multilocular tumor, and absence of color flow in doppler ultrasound evaluation. Characteristics considered as malignant are: the presence of an irregular solid tumor, the presence of ascites, the presence of at least four papillary structures, a diameter larger than 10 cm in case of a multilocular tumor, and the presence of very strong blood flow in doppler ultrasound evaluation (Timmerman et al., 2010).

The second mathematical model, showing good diagnostic accuracy, is a more sophisticated one than the simple rules model and can be implemented using specially designed software. It is a model based on logistic regression, evaluating six different parameters, age and five ultrasound findings of the investigated ovarian tumor. These are the maximum diameter of the largest solid part of the tumor, the presence of irregular surface on the inner wall of the tumor or cyst, the presence of papillary projections with detectable blood flow in doppler ultrasound, the presence of acoustic shadow, and the presence of ascites (Timmerman et al., 2005).

All predictive models used to differentiate benign from malignant ovarian masses have an error rate. This is true for both of the above models that exhibit the optimum combination of sensitivity and specificity. For example, the diagnostic accuracy of the models deteriorates when the ovarian tumor under investigation is too small (smaller than 4 cm) or too large (larger than 12 cm) (Timmerman et al., 2005). It is, thus, expected that, in some cases, due to the probability of false negative outcomes, tumors, which according to preoperative evaluation are considered as benign, may actually prove to be, either intraoperatively or post – operatively, malignant. (Muzii, Angioli, Zullo, & Panici, 2005). This, of course, is not a very common phenomenon. A retrospective study examining 1,128 adnexal cysts that were surgically removed from 884 patients in Japan without any preoperative suspicion of malignancy based on either imaging or biochemical parameters showed that the incidence of malignancy in the final biopsy was 1.2% for cysts (14/1,128) or 1.5% for patients from whom these cysts were removed (13/884) (Matsushita, Watanabe, Yokoi, & Wakatsuki, 2014). In six of these thirteen cases, the final histologic result was a diagnosis of ovarian cancer (one case of mucinous carcinoma, one case of endometrioid

carcinoma, one case of granulosa cell carcinoma, and three cases of carcinoid). In the remaining seven cases where the result was not benign, a borderline malignancy was found (in five cases histology reported a mucosal tumor and in the other two a serous one). (Matsushita et al., 2014).

The rate of the diagnosis of malignancy in the final histologic evaluation in the case of an ovarian mass initially evaluated as benign and treated laparoscopically varies according to references in the literature by 11 - 19% in studies without careful preoperative evaluation and by 0 - 2.5% in studies where, preoperative assessment of the likelihood of malignancy before deciding how to surgically approach an ovarian tumor was thorough (Matsushita et al., 2014; Muzii et al., 2005). This, again, demonstrates the importance of careful pre-operative evaluation.

Further treatment of patients after a final histologic diagnosis of an ovarian cyst depends primarily on whether it is a borderline tumor or ovarian cancer. According to the World Health Organization and its classification for ovarian cancers, the borderline malignancy is defined as that epithelial ovarian tumor that exhibits atypical proliferation of epithelial cells without destructive stromal infiltration (Heintz et al., 2006). Therefore, in the case of a borderline tumor, complete staging should be followed, including peritoneal lavage for cytologic examination, peritoneal biopsies from the area of the paracolic gutters, omentectomy, appendectomy and, in the case of mucosal borderline tumor, bilateral salpingooophorectomy, if fertility sparing is not desirable. Hysterectomy as well as pelvic and paraaortic lymphadenectomy are not necessary in the case of borderline tumors. Staging of borderline tumors is an important prognostic factor that primarily determines the likelihood of recurrence. Thus, as estimated by the largest cohort of borderline tumors to date according to a multicenter study in Germany, the risk of recurrence, when the borderline tumor is stage II or III by FIGO, is 2.43 times higher than stage I (du Bois et al., 2013). Consequently, the finding of borderline malignancy as a random finding in the final histological diagnosis raises the discussion with the patient about the trade-off between maintaining fertility and the risk of recurrence. If the patient wishes to maintain her fertility, depending on her age of course, the uterus and one ovary (with the adjacent tube) should be preserved, since the ovary with the tumor must be removed. In this case, the patient is informed of the risks of incomplete staging and treatment and assumes them by giving clear and signed consent.

In cases where malignancy is suspected during laparoscopic ovarian cystectomy, the surgeon's choice is to proceed immediately to appropriate staging or to interrupt the operation and proceed to staging at a second subsequent operation. A prerequisite for the first option is that the discussion about potential malignancy has been pre-operatively done and the patient has agreed to this approach, and of course that there is the necessary surgical experience to complete the procedure either laparoscopically or by laparotomy after conversion of laparoscopy in open surgery. However, the safest option is to perform the staging during subsequent operation because intraoperative biopsy may be different from the final one and the presence of invasion in the latter changes the staging and treatment modalities.

In the case of invasive ovarian cancer in the final biopsy the staging is more complicated as it involves washings form the pelvis, the paracolic gutters and the diaphragmatic area, total hysterectomy with bilateral salpingo oophorectomy, biopsies from the parietal peritoneum of the lateral pelvic wall, the pouch of Douglas and the vesico-uterine pouch, as well as from the visceral peritoneum of the rectum and the bladder, omentectomy, biopsies from the paracolic gutters, and the diaphragm, and pelvic and para-aortic lymphadenectomy (Hoskins, 1993). Therefore, given the severity of the surgery required for staging and the fact that there is not a serious pre-operative suspicion of malignancy, it is preferable to have a second staging operation if invasive ovarian cancer is found during the initial operation, in order

to provide the patient with sufficient information about their options regarding radicality of the surgery taking under consideration the desire to preserve fertility.

Fertility preservation in women with ovarian cancer is a matter that has been of particular concern to the scientific community for the last two decades, mainly due to the delay in first pregnancy being attributed to social and economic reasons, as well as due to the fact that approximately 10% of ovarian cancers occur in women below 40 years old. (Duska et al., 1999). Thus, fertility preservation today is considered a viable option for women with ovarian cancer under very specific conditions. First, it should be emphasized that preserving fertility is associated with maintaining the uterus and one ovary in patients with ovarian cancer. So, staging should be done as described previously with the exception of these organs. The possibility of preserving fertility has been studied by many scientific groups worldwide. In 2016, a systematic review was published with the aim of investigating the oncological safety of fertility preservation in case of ovarian cancer. The review included 1,150 patients with primary epithelial ovarian cancer and 139 with recurrent disease reported by 21 scientific groups. It was found that fertility preservation is a safe process from an oncological point of view when the stage is IA or IC1 (FIGO) and grade is not 3 (Bentivegna et al., 2016). Stage IA refers to cancer limited in one ovary or fallopian tube with intact capsule, without tumor in the surface and without cancer cells being detected in peritoneal washings fluid. Stage IC1 refers to cancer in one or both ovaries implicated by intraoperative spill of the content of the tumor in the peritoneal cavity (Javadi, Ganeshan, Qayyum, Iyer, & Bhosale, 2016) (Table 1).

In the laparoscopic approach of a seemingly benign ovarian cyst that eventually proves to be malignant there is always the risk of rupture which may be greater than laparotomy. This rupture of the cyst in case of malignancy substantially changes the stage of the disease, when the tumor is restricted in the ovary, from IA to IC1 by FIGO. However, the question arises whether this change in stage is predictive of the course of the disease. An earlier study on prognostic factors for early stage ovarian cancer, which included 1,545 women with invasive ovarian cancer stage I, found that when a cystic rupture during surgical removal in case of malignancy occurred, there was a 1.64-fold decrease in disease-free survival [hazard ratio: 1,64, (1,07 – 2,51)] (Vergote et al., 2001). Similarly, a newer Norwegian prospective study of 279 women with stage I ovarian cancer found a statistically significant difference ($p < 0.05$) in survival without relapse after five years of follow-up in women with intraoperative spill in case of malignancy (79%) compared to women with ovarian cancer stage IA or IB without rupture (91%) (Paulsen, Kaern, & Trope, 2011).

Consequently, it is advised to avoid cyst rupture during laparoscopy, by taking certain precautions. The first would be careful patient selection for the laparoscopic approach regarding the removal of an ovarian cyst. In case it is decided to opt for laparoscopy, the following strategy is suggested: the distinction between diagnosis and treatment. This strategy initially involves an inspection of the peritoneal cavity and testing on peritoneal washings. In case of a suspicion of malignancy intraoperatively, then it would be more proper to postpone surgical treatment and refer the woman to a specialized gynecological oncology department, and get the woman's consent for the indicated treatment. In case of no macroscopically identified signs of malignancy, the removal of the cyst can be done while avoiding cyst rupture and using an endobag for retrieving the specimen (Muzii et al., 2005).

If malignancy is suspected while attempting to remove the ovarian cyst or is documented in biopsy during the operation then rupture of the cyst is considered to increase the stage of the disease from IA to IC. This is not safe from an oncological point of view. In case of malignancy documented at the final biopsy, without any previous signs, then it is important not to delay re-operation for complete surgical

staging (Muzii et al., 2005). The time interval, considered safe, for re-operation is 16 days. (Lehner, Wenzl, Heinzl, Husslein, & Sevelda, 1998).

As a conclusion, there are potential adverse events related to the use of laparoscopy in the treatment of adnexal masses, but these can be mitigated with careful preoperative patient selection and with adequate surgical experience.

Table 1. Ovarian cancer staging (FIGO)

FIGO Stage	Stage Description
IA	Tumor limited to one ovary, capsule intact, no tumor on surface, negative washings.
IB	Tumor involves both ovaries, capsule intact, no tumor on surface, negative washings.
IC1	Tumor limited to one or both ovaries, surgical spill
IC2	Tumor limited to one or both ovaries, capsule rupture before surgery or tumor on ovarian surface.
IC3	Tumor limited to one or both ovaries, malignant cells in the ascites or peritoneal washings.
IIA	Extension and/or implant on uterus and/or Fallopian tubes
IIB	Extension to other pelvic intraperitoneal tissues
IIIA	Positive retroperitoneal lymph nodes and/or microscopic metastasis beyond the pelvis
IIIA1 (i)	Positive retroperitoneal lymph nodes only (Metastasis £ 10 mm)
IIIA1 (ii)	Positive retroperitoneal lymph nodes only (Metastasis > 10 mm)
IIIA2	Microscopic, extrapelvic (above the brim) peritoneal involvement with or without positive retroperitoneal lymph nodes
IIIB	Macroscopic, extrapelvic, peritoneal, metastasis £ 2 cm with or without positive retroperitoneal lymph nodes. Includes extension to capsule of liver/spleen.
IIIC	Macroscopic, extrapelvic, peritoneal metastasis > 2 cm with or without positive retroperitoneal lymph nodes. Includes extension to capsule of liver/spleen.
IVA	Pleural effusion with positive cytology
IVB	Hepatic and/or splenic parenchymal metastasis, metastasis to extraabdominal organs (including inguinal lymph nodes and lymph nodes outside of the abdominal cavity)

(Zeppernick & Meinhold-Heerlein, 2014)

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Chapter 19
Should All Endometriotic Cysts Be Removed?
How, Why, When?

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ABSTRACT

Endometriosis is a chronic condition that affects 5-10% of women of reproductive age. It is characterized by the presence of endometrial tissue outside the uterus, which induces a chronic inflammatory reaction and formation of scar tissue and adhesions, resulting in the deformation of the female pelvis anatomy. Twenty-five to fifty percent of women with infertility suffer from endometriosis, while 30-50% of infertile women are diagnosed with the disease. Endometrioma is a benign cyst of the ovary that contains ectopic endometrial tissue and is a common cause of endometriosis. There are some gray areas regarding clinical decisions and endometriotic cysts. The chapter aims to present current evidence regarding optimal management of endometriotic cysts.

INTRODUCTION

Endometriosis is a chronic condition that affects 5-10% of women in reproductive age (Giudice & Kao, 2004; Nickkho Amiry, Savant, Majumder, O'sagie & Akhtar, 2018). It is characterized by the presence of endometrial tissue outside the uterus, which induces a chronic inflammatory reaction and formation of scar tissue and adhesions, resulting in the deformation of the female pelvis anatomy (Kennedy et al, 2005; Nickkho Amiry et al, 2018). Endometriosis is associated with a long list of gynaecological symptoms (dysmenorrhoea, non-cyclical pelvic pain, deep dyspareunia, infertility and fatigue in the presence of any of the above) and non-gynaecological cyclical symptoms (dyschezia, dysuria, haematuria and rectal bleeding, shoulder pain) (Dunselman et al,2014). 25-50% of women with infertility suffer from

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endometriosis, while 30-50% of infertile women are dignosed with the disease (Macer & Taylor, 2012; Nickkho Amiry et al, 2018). There are some high risk factors strongly associated with presence of endometriosis in women, such as increased exposure to menstruation (i.e. earlier menarche, shorter menstrual cycles and nulliparity) and low body mass index(BMI) (Kvaskoff et al, 2015; Missmer & Cramer, 2003; Vigano et al, 2012). Additionally, data from some modern studies support that some genetic and environmental factors may contribute to the development of the disease (Kvaskoff et al, 2015; Porpora et al, 2013; Rahmioglou et al, 2014). Endometrioma is a benign cyst of the ovary that contains ectopic endometrial tissue and is a common cause of endometriosis (17-44%) (Alborzi, Keramati, Younesi, Samsami & Dadras, 2014; Brosens, Puttemans, Gordts, Campo & Benagiano, 2013; Hughesdon, 1957; Nickkho Amiry et al, 2018). They are probably the most commonly diagnosed form of the disease due to the relative case and accuracy of the ultrasonographic diagnosis (Saridogan et al, 2017). Most endometriomas are pseudocysts and their pathogenesis differs from other benign ovarian cysts (Brosens et al, 2013; Hughesdon, 1957; Nickkho Amiry et al, 2018). The present chapter aims to clarify some gray areas regarding clinical decisions and endometriotic cysts. How significant is actually the size of the cyst, should they removed in order to improve fecundity rates or artificial reproductive treatment (ART)? Lastly is there really a risk of malignancy to justify surgical removal in all cases?

ENDOMETRIOMA AND INFERTILITY

The mechanism by which fertility is affected in women suffering from endometriosis involves an increase in oxidative stress in healthy ovarian tissue resulting in a decrease in the ovarian reserve (Nickkho Amiry et al, 2018; Sanchez et al, 2014). Presence of endometrioma can also afflict fertility by invoking tubo-ovarian anatomy (Hamdan, Dunselman, Li & Cheong, 2015). Endometriomas often coexist with deep endometriosis (Saridogan et al, 2017). Pharmaceutical treatment of ovarian suppression with gonadotropine releasing hormone (GNRH) analogues or combined contraceptive pill, although it may cause diminution of the endometriomas' size and remission of disease symptoms, such as dysmenorrhoea and dyspareunia, it does not appear to improve female infertility (Garcia-Velasco & Somigliana, 2009; Nickkho Amiry et al, 2018). However, modern studies have shown that pharmaceutical ovarian suppression before an assisted reproduction cycle increases the likelihood of a successful pregnancy afterwards (Collinet et al, 2018). The majority of the modern studies have focused on the effectiveness of surgical treatment in improving the infertility of women with endometriosis. The mainstay of management for endometrioma, when treatment is required, is surgical treatment (Saridogan et al, 2017). For women in reproductive age who wish to conceive, surgical treatment should be conservative in order to preserve the normal ovarian tissue and blood supply (Nickkho Amiry et al, 2018; Saridogan et al, 2017). Methods of conservative surgical treatment include cystectomy(excision of the cyst capsule), drainage of the cyst content and ablation by laser or plasma energy, drainage of the cyst content and electro-coagulation, combined technique(both excision of the cyst wall and ablation) and three step approach, with three month administration of GnRH analogue between two laparoscopic surgeries, for treatment of large endometriomas (Saridogan et al, 2017). As a proposed surgical treatment of endometrioma, cystectomy prevails in relation to drainage of the cyst's content and electrocoagulation of the cyst's wall capsule (Carmona, Martinez-Zamora, Rabanal, Martinez-Roman & Balasch, 2011; Dunselman et al, 2014; Hart, Hickey, Maouris & Buckett, 2008). Surgical teatement should be considered for endometriomas larger than 3cm in the mean diameter (Dunselman et al, 2014; Hart et al, 2008). Cystectomy appears to out-

weigh the improvement in pain symptoms such as endometriosis associated dysmenorrhoea, dyspareunia and non menstrual pelvic pain as well as increasing the likelihood of spontaneous conception (Hart et al, 2008). In addition it reduces the likelihood of recurrence of endometrioma compared to drainage and electrocoagulation of the endometrioma wall (Carmona et al, 2011). Laparoscopy is an ideal tool for the diagnosis and treatment of endometriosis, while, laparotomy is rarely indicated for treatment of benign ovarian endometrioma (Saridogan et al, 2017; Yeung, Shwayder & Pasic, 2009). Laparotomy and laparoscopy are equally effective in the treatment of endometriosis associated pain, but laparoscopic surgery is usually associated with less pain, shorter hospital stay and quicker recovery as well as better cosmetic outcome, hence it is usually preferred to open surgery (Dunselman et al, 2014). A systematic review and meta-analysis by Niccko-Amiry et al (2018) included the results of a total of 28 studies, 10 of which compared the results of the surgical treatment for endometrioma to no surgical intervention followed by assisted reproduction. The results of the meta-analysis indicated that there was no significant difference in rates of successful pregnancies [OR 0.88(95% CI 0.60,1.29)] and clinical pregnancies [OR 1.08(95% CI 0.80-1.45)] per assisted reproduction cycle between women who had surgically treated endometriomas and those who had not undergone a surgical treatment (Nickkho Amiry et al, 2018). Surgery for endometrioma showed to favour live birth rate per cycle, but this was not statistically significant [OR 0.75 (95% CI 0.54,1.06)](Nickkho Amiry et al, 2018). The secondary outcomes of the meta-analysis showed no statistical difference in the number of oocytes retrieved [mean difference - 0.43(95% CI-1.67,0.80)], the total number of embryos created per cycle [mean difference 0.06 95% CI - 0.21 to 0.33)], the gonadotropin ampoules used per cycle [mean difference 1.31 (95% CI(-3.87,6.50)] and the total gonadotropin dose per cycle[mean difference 244.81(95% CI – 525.43 to 1015.06)] between the two groups (Nickkho Amiry et al, 2018). Furthermore, it seems that there is no prevalent technique of conservative surgical treatment of endometrioma when it comes to assisted reproduction outcomes (Hamdan et al, 2015; Nickkho Amiry et al, 2018). Pregnancy rates and number of oocytes retrieved during in vitro fertilization (IVF) where similar between women who underwent transvaginal aspiration and those who underwent conservative cystectomy no matter the technique used.(cystectomy followed by electrocoagulation or suturing, laser or plasma ablation etc.) (Hamdan et al, 2015; Nickkho Amiry et al, 2018). As it has been recommended by the study of Garcia-Velasco & Somigliana (2009) indications for surgical removal of an endometrioma prior to an assisted reproduction cycle are the difficulty in accessing the ovarian follicles due to the location of the cyst and when the size of the cyst is larger than 4-5 cm in the mean diameter, the rapid increase in cyst size, the presence of suspicious ultrasonographic features, such as papillary projections, intense symptomatology of the disease as well as the increased risk of the cyst's rupture. However, in each surgical treatment of an endometrioma, the need for preserving the blood supply of both the ovaries and the ovarian reserve is emphasized (Garcia-Velasco & Somigliana, 2009). Minimizing intervention and preservation of the healthy ovarian tissue is of outmost importance (Tang et al, 2013). In addition there are recent studies, which imply that the surgical removal of an endometrioma before the onset of an assisted reproduction cycle reduces or may even eradicate the ability of the ovary to respond to gonadotropin medication and produce follicles (Somigliana et al, 2003). Post-operative reduction of the ovarian reserve is associated with lower levels of serum Anti-Mullerian hormone, reduction of the antral follicle count on ultrasound, lower number of oocytes retrieved and greater risk for failure of controlled ovarian hyperstimulation during an assisted reproduction cycle (Hamdan et al, 2015; Nickkho Amiry et al, 2018; Saridogan et al, 2017; Younis, Shapso, Fleming, Ben-Shlomo & Izhaki, 2019). Furthermore, other studies have demonstrated that surgical removal of bilateral endometriomas causes a remarkable reduction in the concentration of the

serological index of anti-mullerian hormone and a decrease in the number of follicles in the ovary (Muzzi et al, 2014; Somigliana et al, 2012). It is more than obvious that careful selection of infertile women with endometriomas for surgical treatment prior to assisted reproduction should be appropriately designed according to patient personalized needs, as surgical treatment does not appear to increase the chances of successful pregnancy (Collinet et al, 2018; Dunselman et al, 2014; Nickkho Amiry et al, 2018). This choice should be made after evaluating the potential benefit compared to the reduction of the ovarian reserve and the successful ovarian stimulation, that any surgery causes (Nickkho Amiry et al, 2018). As an exception to the rule, surgical treatment of endometrioma prior to artificial reproductive treatment should be considered in order to improve endometriosis associated pain and the accessibility of follicles, when there is rapid growth of the cyst and potential for rupture during pregnancy or when there are suspicious for malignancy ultrasonographic features (Dunselman et al, 2014; Nickkho Amiry et al, 2018). In case of potential malignancy or recurrence of large endometrioma, even oophorectomy should be considered and discussed with the woman (Saridogan et al, 2017). Recurrence of endometrioma after conservative surgical treatment seems to be age related (Seo, Lee, Yoon & Choi, 2017). The risk is ~ 4-fold greater for women aged 20-29 years old and ~ 2-fold greater for women aged 30-39 years old compared to those aged over 40 years old (Seo et al, 2017). In any case, the main goal of an intervention in infertile women with endometriosis should be the best possible outcome in treating infertility (Collinet et al, 2018; Dunselman et al, 2014; Nickkho Amiry et al, 2018).

ENDOMETRIOMA AND OVARIAN CANCER

Although endometriosis is a benign disease, there are several data implying relationship to certain cancers (Kvaskoff et al, 2015). The disease presents some features observed in malignant tumors such as abnormal tissue growth in ectopic position, dysfunction of affected organs and genetic background (Garry, 2001). Several epidemiological studies have linked endometriosis to ovarian cancer as well as non-gynecological cancers such as melanoma and non-Hodgkin's lymphoma (Brinton, Gridley, Persson, Baron & Bergqvist, 1997; Brinton et al, 2004; Brinton et al, 2005; Kobayashi et al, 2007; Melin, Sparen & Bergqvist, 2007; Melin, Sparen, Persson & Bergqvist, 2006; Modugno et al, 2004; Ness et al, 2002; Ness et al, 2000; Pearce et al, 2012; Rossing, Cushing-Haugen, Wicklund, Doherty & Weiss, 2008). Ovarian cancer has the highest correlation with endometriosis. This correlation was already demonstrated by Sampson in 1925. Since then it has been confirmed in a large percentage of cases with ovarian cancer (Heidemann, Hartwell, Heidemann & Jochumsen, 2014; Somigliana et al, 2006). Overall, the association of endometriosis with the increased risk of ovarian cancer has been confirmed in 20 modern epidemiological studies since 1997 (Kvaskoff et al, 2015). In a large pooled study by Ness et al (2002) it appeared that the risk of ovarian cancer occurring in women with endometriosis was 1.73%. The pooled study by Pearce et al (2012) revealed that the risk of development of invasive ovarian cancer in women with endometriosis comes up to 1.46%, while the results of the same study revealed twice the risk of endometrioid or low grade serum ovarian cancer and threefold the risk of developing clear cell ovarian cancer for these women. In contrast, the risk of mucosal cancer, high grade serum and borderline malignancy tumors of the ovary does not seem to increase when there is a case history of endometriosis (Pearce et al, 2012). Endometriosis is associated with low grade ovarian cancer, diagnosed at early stages, with good prognosis as well as good 5-year survival rate which is around 90% (Pearce et al, 2012). As for other forms of gynecological cancer, modern studies present controversial results and do

not indicate a clear correlation of endometriosis with an increased risk of breast, endometrial and cervical cancer (Kvaskoff et al, 2015). The risk of developing ovarian cancer in the general population is 1.40%, while in women with endometriosis, it is 1.90% (Vercellini et al, 2018). This risk is particularly high in women with chronic endometriotic cyst, who have not received pharmaceutical treatment for ovarian suppression (Vercellini et al, 2018). Several authors describe ovarian endometriosis in the presence of histological atypia as a precancerous condition that precedes the onset of ovarian malignancy, as it is a condition presenting similar genetic mutations in the PTEN, KRAS, ARID1A, CTNNB1 genes with those seen in histological types of ovarian cancer associated with endometriosis (endometriotic, clear cell) (Mangili et al, 2012; Vercellini et al, 2018). At the same time, it has been shown that the ovarian microenvironment may foster the malignant transformation of endometriosis, as the ovarian layer produces steroid hormones which may favor oncogenesis in endometriotic cysts (Blanco et al, 2017; Cochrane et al, 2017; Karnezis, Cho, Gilks, Pearce & Huntsman, 2017; Vercellini et al, 2018). On the other hand, the development of malignancy in non ovarian endometriotic lessions is quite rare (Karnezis et al, 2017; Vercellini et al, 2018). Cellular atypia seems to be an intermediate precursor of typical endometriosis and ovarian cancer (Karnezis et al, 2017; Vercellini et al, 2018). Based on the presence of cellular atypia, endometriosis is characterized as a high or low risk for developing ovarian cancer (Karnezis et al 2017; Vercellini et al, 2018). In most cases, both endometrial and clear cell ovarian cancer will develop within an endometriotic cyst of the ovary and will be confined within it for a long time, while, diagnosis as well as surgical treatment will be performed as long as Stage I disease is present (Kurman & Shih, 2016; Vercellini et al, 2018). Furthermore, modern molecular, epidemiological and histopathological studies, support that endometrioid carcinomas of the ovary seem to be low grade tumors and most of them coexist with endometrioid carcinoma of the endometrium constituting a disease of common origin and contemporary manifestation in two different anatomical positions (Anglesio et al, 2016; Vercellini et al, 2018). In women with endometriotic cyst who are not treated, the risk of ovarian cancer is 1.9% and the risk of death from the disease is 1.31% (Vercellini et al, 2018). Regarding the early diagnosis and surgical treatment of suspected for malignant transformation endometriotic cysts, modern studies describe certain characteristics that increase the suspicion of malignancy (Vercellini et al, 2018). Exacoustos, Manganaro & Zupi (2014) describe a typical benign endometrioma as a unilocular or multilocular cyst, with low-level echogenic fluid content, with no solid parts, or papillations with blood flow, and which is diagnosed in a woman at premenopausal age. In postmenopausal women, though, the ultrasound features of endometriotic cysts may differ, as they are usually non-echogenic or mixed echogenic multilocular cysts (Exacoustos, Manganaro & Zupi, 2014). The study by Guerriero et al (2016) confirmed that endometriotic cysts in perimenopausal age are usually multilocular, low-level echogenicity is less frequent, and papillations or solid parts are more likely to be present. The maximum diameter of the endometriotic cyst does not depend on age (Guerreiro et al, 2016). The study of Nezhat, Apostol, Nezhat & Pejovic (2015) notes that any increase in the size of an endometriotic cyst in the postmenopausal period or during hormone therapy of ovarian suppression in the premenopausal period, modification of ultrasonographic features or the appearance of mural nodules are strong indications for surgical treatment of an endometrioma. At the same time, the rapid worsening of symptoms such as dysmenorrhoea and dyspareunia reinforce suspicion of malignant transformation (Vercellini et al, 2018). Other independent prognostic factors of ovarian cancer are the age over 45 years and the endometrioma's size more than 8 cm (Kobayashi et al., 2008). Malignant ovarian tumors that develop in the endometriotic cyst mostly present solid parts with vascularization in the ultrasound (Exacoustos et al, 2014; Vercellini et al, 2018). In older women with endometriotic cyst, the presence

of mural nodules is more likely to be associated with malignancy and in combination with a rapid increase in tumor size, these two are the most reliable predictors of early detection of malignant transformation (Tanase, Kawaguchi, Takahama & Kobayashi, 2017; Taniguchi et al., 2014). All patients with ovarian cancer within the endometriotic cyst were over 40 years of age and nearly 67% of those were detected with papillations in the cyst during preoperative ultrasonography (Kuo et al, 2017; Vercellini et al, 2018). The ultrasonographic evaluation of suspicious endometriomas by gynecologists or radiologists specialized in oncology may increase the sensitivity of imaging methods to detect suspicious malignant endometriomas requiring surgical treatment (Glang et al,2017; Vercellini et al, 2018). Early diagnosis of endometriomas with cellular atypia, which is a precancerous condition, cannot be performed on the basis of the aforementioned ultrasound features that characterize lesions with already malignant transformation, as these characteristics are not a common reference in both situations (Guerriero et al, 2016; Vercellini et al, 2018). Unfortunately, so far trials which tested if screening programs for ovarian cancer can decrease the diseases' mortality did not come up to satisfying results (Buyss et al, 2011; Pinsky et al, 2016). Data from Prostate, Lung, Colorectal and Ovarian (PLCO) cancer trial showed that a screaning program for ovarian cancer, based on ultrasonography and testing of serological biomarkers, not only failed to benefit mortality but it also increased morbidity, due to extensive surgical intervension (Buyss et al, 2011; Pinsky et al, 2016). In young women wishing to be pregnant, the presence of typical benign endometriomas with a diameter of less than 5 cm is not evidence of surgical treatment due to the risk of ovarian reserve harm, as a result of surgical intervention in healthy ovarian tissue (Muzzi et al, 2017; Vercellini et al, 2018). In women less than 45 years of age, who do not want a future pregnancy, it is recommended to remove endometriomas by maintaining the ovaries as any premature iatrogenic hypoestrogenism will increase the risk of cardiovascular events (Parker et al, 2009; Vercellini et al, 2018). As women approach menopause, both the reproductive and hormonal benefits of the presence of the ovaries are deducted; with the result that oophorectomy is preferred in the presence of endometrioma (Thomsen et al, 2017). Recent studies have shown that surgical treatment reduces the risk of developing ovarian cancer by half in women with endometrioma, with the data supporting salpingo-oophorectomy as the most appropriate surgical treatment (Melin et al, 2013; Rossing et al, 2008). However, the data from these studies remain under discussion due to the small number of cases (Melin et al, 2013; Rossing et al, 2008).

MANAGEMENT OF ENDOMETRIOMA IN PERIMENOPAUSAL WOMEN

The World Health Organisation (WHO) defines as perimenopause a period of 2-8 years preceding menopause and 1 year following woman's final menses and the age of 45 years old is considered to be the lowest limit of the perimenopausal period (Vercellini et al, 2018). Two alternative approaches have prevailed in the management of women with benign small-sized endometriomas in perimenopausal age (Vercellini et al, 2018). The first describes the removal of the ovaries with the endometriotic cyst in combination with bilateral salpingectomy, particularly in women with chronic endometrioma, who have not received oral contraceptive tablets or progesterone, in women with denovo growth of endometrioma during pharmaceutical treatment, and in women with endometrioma relapse (Kuo et al, 2017; Tanase et al, 2017; Taniguchi et al, 2014; Vercellini et al, 2018). All the above are situations of increased malignancy risk and evidence for surgical treatment (Haraguchi et al., 2016). The second alternative describes the close monitoring and progesterone treatment under the condition of immediate surgery, in case of

suspected ultrasonographic features of the endometriotic cyst, increased size of the cyst or increased serological indexes of Ca-125 and HE4 (Kurman & Shih, 2016; Prat, 2017; Vercellini et al, 2018). The theory of close monitoring is based on the fact that ovarian malignant tumors that develop into endometriotic cysts remain in them for a long time (Vercellini et al, 2018). At the same time, regular monitoring of women with endometriosis without suspected malignant features has an implementation, when surgery is considered as a high risk choice, due to previous surgeries, adhesions or other concomitant diseases that increase the risk of cardiovascular complications (Vercellini et al, 2018). With regard to women with endometriomas and coexisting deep endometriosis, the decision to remove deeper affected areas in the case of surgical removal should be made according to the symptomatology of the disease, as the likelihood of malignant transformation is very low (Vercellini et al, 2018). A lot of research has been carried out in recent years on the usefulness of bilateral salpingo-oophorectomy as a preventative surgical treatment in perimenopausal women with a history of endometriosis, but without the presence of endometrioma in any of the ovaries (Vercellini et al, 2018). Various models based on risk factors for developing ovarian cancer as well as economic analysis were used to estimate the reduction of ovarian cancer risk and the cost-effectiveness of salpingo-oophorectomy both in high-risk women and women with a low risk of developing ovarian cancer (Manchada, Legood, Pearce & Menon, 2015; Pearce et al, 2015). So far, the data are not sufficient to provide guidelines suggesting surgical treatment as a systematic preventative measure in perimenopausal women with a history of endometriosis (Guerriero et al, 2016; Haraguchi et al, 2016; National Institute for Health and Care Excellence, 2017; Pearce et al, 2012). Preventative surgical treatment should be recommended for women at increased risk for ovarian cancer, such as those with a family history of ovarian malignancy, a history of infertility and nulliparity, history of surgery for endometriosis with atypia in histological examination and maintenance of the ovary in the context of a desire for childbearing as well as those with a known history of endometriosis without the use of pharmaceutical treatment, as a means of suppressing hormone function of the ovary (Pearce et al, 2015; Vercellini et al, 2018). The chronic use of contraceptive pills for ovarian hormonal suppression in premenopausal women has shown that if it continues for more than 10 years, it reduces the risk of developing ovarian cancer by 80% (Modugno et al, 2004).

CONLUSION

Regarding fertility treatment in a disease so diverse like endometriosis a personalized approach should be considered according to the patient's needs, history, age other fertility factors, social and economic status, religion. Proper surgical treatment will enhance fecundity in a lot of cases, while routinely removal of endometrioma before ART cannot be justified just to improve assisted reproductive outcome. Preservation of healthy ovarian tissue is of outmost importance and thus should be taken into account before counseling for an operation, and choosing the appropriate technique. Avoiding surgical treatment to infertile women with endometriomas, who wish to conceive, seems to be the ideal approach, as long as other serious indications for surgery are not present. Size of endometrioma less than 3 cm should not be routinely surgically removed before ART, unless there are other symptoms like pain is present. It seems that the presence of endometriosis increases the risk of ovarian cancer in women up to 1.9%, while for histological cancer-related subtypes, such as endometrioid and clear cell carcinoma, the risk is doubled and tripled respectively. At the same time, the risk of cellular atypia in endometriotic ovarian cysts, a condition described as precancerous, amounts to 1-3%. Screening of the general population in

order to detect asymptomatic endometriomas is not likely to reduce ovarian cancers' specific mortality. Therefore, counseling for women in the perimenopausal age over 45 years with typical benign endometriomas less than 5 cm, should include the alternatives of both surgical treatment and conservative progesterone therapy in combination with regular monitoring. Since women prefer surgical treatment, it is recommended to remove the ovaries suffering from endometriosis in combination with bilateral salpingectomy, which significantly reduces the risk of ovarian cancer. For women with a history of endometriosis, with no active disease in their ovaries, the majority should be directed to conservative progesterone treatment and regular monitoring unless there are factors in their history that rank them in a high risk group for developing ovarian malignancy. In this case, bilateral saplingo-oophorectomy is recommended as a means of preventing malignancy. Therefore, overall, endometriosis patients may be at higher risk of cancer, but the paucity of carefully-conducted studies makes it difficult to quantify this risk precisely. We need more well-designed research with validated and detailed data, particularly on subtypes, in order to minimize bias and produce clear answers.

LIST OF ABBREVIATIONS

1. ART = artificial reproductive treatment
2. GNRH = gonadotropine releasing hormone
3. IVF = in vitro fertilisation
4. ICSI = intracytoplasmic sperm injection
5. BMI = body mass index
6. WHO = World Health Organisation
7. PLCO = Prostate, Lung, Colorectal and Ovarian

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Section 6
Endometrial Pathology

Chapter 20
Uterine Leiomyoma or Sarcoma?
What Should I Do?

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ABSTRACT

Uterine leiomyomas are benign neoplasms derived from the smooth muscle cells of the myometrium. In contrast, uterine sarcomas are rare tumors, with a prevalence of 3-7 per 100,000 women, originating from myometrial cells or endometrial connective tissue. Uterine sarcomas and especially leiomyosarcomas are more aggressive than uterine epithelial neoplasms. The differential diagnosis between leiomyoma and uterine sarcoma preoperatively remains challenging for the clinical practitioner in order to determine optimal treatment. The chapter aims to summarize current evidence regarding differential diagnosis and optimal management of these two challenging clinical entities.

INTRODUCTION

Differentiating leiomyomas from sarcomas, is nowadays more essential than ever, given that conservative therapies for leiomyomas tend to gain ground over hysterectomy and, more significantly, that the trend to perform minimal invasive procedures instead of classical surgical management requires the best preoperative evaluation in the interest of patients' safety.

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Leiomyomas are benign monoclonal tumors, with a prevalence as high as 25% in women of reproductive age, although their true incidence remains unclear due to the fact that a significant number of cases continue to be undiagnosed, whereas, the possibility for a woman to be diagnosed with a fibroid during her lifetime is estimated near 70%, and this percentage is even higher in black women. The term "leiomyoma" reveals the origin of this tumor from soft muscle myometrial cells (Bulum, 2013; Downes, 2010; Hosh, 2016; Vlahos, 2017; Wysowski, 2002).

On the other hand, sarcomas are rare malignant tumors, arising from myometrial smooth muscle cells and their neighboring connecting tissue. Their prevalence is estimated 3-7/100000, while leiomyosarcomas constitute the 60-70% of cases. These malignant uterine neoplasms are rare in women under 40 years old, and their biological behavior is more aggressive in comparison to epithelial uterine malignant tumors.

Sarcomas have been recently histologically classified by World Health Organization (WHO) according their differentiation and the origin of neoplastic cells replacing the older classification (Oliva 2014, Prat 2009)

Table 1. Classification of sarcomas according to WHO

Smooth Muscle Tumor of Uncertain Malignant Potential
Leiomyosarcoma
• Epitheleioid leiomyosarcoma • myxoid leiomyosarcoma
Endometrial Stroma and Related Tumors
• endometrial stromal nodule • low grade endometrial stromal sarcoma • high- grade endometrial stromal sarcoma • undifferentiated uterine sarcoma • uterine tumor resembling ovarian sex cord tumor
Miscellaneous Mesenchymal Tumors
• rhabdomyosarcoma • perivascular epithelioid cell tumor ■ benign ■ malignant
Others
• adenomyoma • atypical polypoid adenomyoma • adenofibroma • adenosarcoma • carcinosarcoma

Uterine sarcomas are commonly divided into two subgroups: "homologous" refer to those containing exclusively uterine tissues, such as endometrial stroma, smooth muscle, vascular tissue, and they are the most frequently reported. "Heterologous" sarcomas, are rare tumors containing extrauterine elements (rhabdomyosarcoma, liposarcoma).

Uterine carcinosarcoma was traditionally classified into sarcomas, and was broadly known as Mixed Malignant Mullerian Tumor, however, its origin from monoclonal cells with mainly epithelial characteristics, led to its recent classification into carcinomas (Kurman, 2014).

Smooth uterine muscle of uncertain malignant potential (STUMPs) refers to a special category of uterine tumors indicating that they cannot be clearly diagnosed as benign or malignant. It is a matter of debate whether this special subgroup should be managed and followed-up as sarcomas, especially in pre-menopausal women with fertility desire, taking into consideration their benign behavior when compared to leiomyosarcomas. However, recurrence even delayed, is estimated between 8.7% and 11%. Given the lack of consensus regarding the malignant potential, diagnostic criteria, gold-standard treatment and follow-up, often the optimal type of surgery is based on immunohistochemistry in order to investigate the overexpression of p16 and p53, thus, to identify the patients at increased risk of recurrence (Dall'Asta, 2014).

Differentiating leiomyomas from sarcomas remains a clinical challenge due to their similar clinical manifestations and imaging features. This differential diagnosis is essential for clinicians because current therapeutical approaches for leiomyomas could have a detrimental effect in case of misdiagnosis, given that:

- conservative strategies for fibroid treatment, such as medication or uterine artery embolization, not only are unsuitable for sarcomas treatment, but, more significantly, could further delay diagnosis and treatment, and result to disease progress, regarding sarcomas
- using techniques that disseminate tissues in order to preserve uterus, such as myomectomy and intraperitoneal fibroid morcellation during laparoscopy could lead to a worse prognosis, in case of sarcomas.

Clinical Manifestations

Premenopausal abnormal uterine bleeding and postmenopausal bleeding could be present in both leiomyomas and sarcomas, while unpleasant smell of blood is often described by patients suffering from malignancies, but it is not a pathognomonic finding. Other symptoms arising from tumor growth, such as abdominal distention, constipation, urinary disorders and pelvic pain are not diagnostic as they are common in both situations. Furthermore, symptoms of progressed and metastatic disease which are not described in case of leiomyoma, are not helpful for clinicians in early stage, where differential diagnosis plays the most vital role (Nordal, 1997).

Clinical Examination

Clinical examination can reveal a palpable pelvic mass, but this finding is also present in both leiomyomas and sarcomas, whereas, signs and symptoms from metastases have a poor diagnostic value, as their appearance indicate an already progressed disease. The size, as well as the consistency of the mass, could be helpful in some cases.

Regarding the tumor size, it is important to evaluate changes, such as rapid growth, although both slow growth of sarcomas and quick growth of fibroids have been described.

Risk Factors

Since clinical manifestations are not diagnostic, estimating risk factors based on patients' characteristics and history can be a reliable tool for clinicians to distinguish patients with higher possibility of malignancy.

- **Age:** Although sarcomas are extremely rare in patients under 40 years old and are more frequently found after 60 years, young age does not exclude the possibility of malignancy. Generally, diagnosing a pelvic mass in a postmenopausal woman which did not exist previously, or continuing growth of a known pelvic mass, after menopause, raise suspicions for sarcoma if the patient does not receive Hormonal Replacement Therapy (HRT). Otherwise, HRT should be interrupted, and the tumor growth should be reevaluated (Hosh, 2016).
- **Race:** black women are at a higher risk for sarcomas.
- **Tamoxifen Use:** Long-term use of tamoxifen (five years or more) has been associated with an increased risk for uterine sarcoma, with an incidence as high as 17 per 100,000 (Wickerham, 2002). In these women, sarcomas usually present after two to five years from the initial tamoxifen use.
- **Pelvic Radiation**: Pelvic radiation is mainly associated with an increased risk of developing carcinosarcoma, which is not any more classified as sarcoma, although other types of sarcomas have been reported, as well (Mark, 1996).
- **Other Factors:** Hereditary leiomyomatosis and renal cell carcinoma (HLRCC) syndrome is a rare autosomal dominant syndrome in which patients present cutaneous and uterine leiomyomas and an aggressive type of renal cell cancer. An increased risk for uterine sarcomas has been described as well, although, hysterectomy already performed for uterine myomas could cover their true incidence. A personal history of retinoblastoma may also increase the risk for sarcoma of the uterus as well as for different locations (Mark, 1996; Yu, 2009).

IMAGING FINDINGS

Ultrasound

In some cases, ultrasonography can aid differential diagnosis between fibroids and sarcomas. Typically, fibroids present as well-defined masses which do not invade into the neighboring myometrium, surrounded by a hypoechogenic circumference. The mass could be iso- hyper- or hypoechogenic. Cystic degeneration areas may appear as hypoechogenic lesions and lead to misdiagnosis, given that this is a typical finding in sarcomas, although, in fibroids, they content some hyperechogenic remnants, moving under the pressure of transducer. Calcifications can also be observed in postmenopausal women or after pregnancy (Botsis, 1998).

In contrast, sarcomas usually present as uterine masses of mixed echogenity, with undefined borders, infiltrating the myometrium. Hypoechogenic areas often represent central necrosis. Abnormal vascularization with low resistance index and increased peak systolic velocity is also observed. Although these findings are typical ultrasound features for sarcomas, they can be found in fibroids as well, thus, they are not considered to be pathognomonic (Amant, 2009).

Magnetic Resonance Imaging (MRI)

MRI is a powerful tool for clinicians to differentiate leiomyomas from sarcomas, as it offers the greatest sensitivity in diagnosis of sarcomas among all imaging methods.

Calcifications represent areas of necrosis and are consistently observed in sarcomas, while in fibroids they are usually absent, whereas, hemorrhage is also frequently appeared in sarcomas.

Additionally, after gadolinium administration, enhancement of signal is more intense in sarcomas, although it can be noticed in fibroids, as well.

Diffusion weighted MRI can distinguish malignant lesions and should be offered in difficult cases, especially in those presenting with intense signal in T2-weighted sequence (Santos, 2015).

Leiomyomasarcoma, the most common among uterine sarcomas, presents in MRI as large, infiltrating endometrial mass, hypointense on T1-weighted images and of intermediate to high intensity on T2-weighted images, with indistinct margins. Heterogeneity, rapid growth, central hyperintensity on T2 images, indicating central necrosis, and early heterogenous enhancement after gadolinium administration are common findings in leiomyosarcomas. However, leiomyomas frequently present with high signal on T2-weighted images due to degeneration, thus, the combination of indistinct margins with necrosis in rapid growing masses should be considered as malignancy indications. Finally, several studies have shown that diffusion weighted MRI can decrease the possibility of misdiagnosis, in case of leiomyosarcomas, therefore, it should be offered in patients with single mass, hyperintense on T2 images (Rha, 2003; Tamai, 2008; Wu, 2011).

Endometrial stromal sarcomas are rare tumors which represent the 10% of uterine malignancy with mesenchymal component, most commonly seen in women 40-55 years, and they are associated with tamoxifen and estrogen use (D' Angelo, 2010; Shah, 2012).

In MRI, Endometrial Stromal Sarcomas appear as polypoid endometrial lesion with low signal in T1-weighted sequence and high intensity on T2 images, but, more significantly, as they usually invade in lymph and blood vessels, they present a worm-like pattern (Ueda, 2001). Undifferentiated endometrial sarcoma, more frequently affecting older women, show heterogeneity on both T1 and T2 weighted images, multiple nodules, irregular margins, intra-myometrial worm-like extension, and heterogeneous enhancement after contrast administration (D' Angelo, 2010; Ueda, 2001)

Adenosarcomas, usually present in endometrium but in 30% of cases, are located in myometrium and in other extrauterine tissues, even in ovaries. Interestingly, the extrauterine location is commonly reported in young and adolescent women. MRI findings are: large polypoid endometrial mass, often intruding through the cervical os, with mixed cystic and heterogeneous solid components, resembling trophoblastic disease, with hyperintense lesions in the solid areas on T2 weighted images and heterogeneous enhancement after gadolinium administration (Santos, 2015).

Computed Tomography (CT)

This imaging technique has not been proven to be helpful in distinguishing fibroids from sarcomas. For example, in contrast- enhanced CT scan, endometrial stromal sarcoma can present as well-defined, low density intramural mass, which cannot be clearly differentiated from intramural myoma. Nevertheless, CT is broadly used after establishing sarcoma diagnosis, for staging, including local spread within the pelvis and metastatic disease. There is low incidence of ovarian or pelvic lymph node involvement, but peritoneal sarcomatosis, at presentation or with recurrence is a potential feature. The most frequent metastasis sites are the lungs and the liver, while brain metastasis are uncommon (Rha, 2003).

Positron Emission Tomography

In PET scanning, a radionuclide is visualised on a biologically active molecule. Fluodeoxyglucose, (FDG) is usually used for myoma imaging, but also other molecules, such as deoxyfluorothymidine

(FLT) or alphafluorobeta-estradiol (FES), have been used. Estrogen status, cellularity and the presence of malignant tissue can reflect to the uptake of FDG in a fibroid (Zhang 2011). FES's and FDG's accuracy in distinguishing leiomyosarcomas from fibroids are reported as high as 93 and 81%, respectively (Yoshida, 2011).

Biochemical Markers

A number of biochemical markers have been proposed but, none of them have been proven to be diagnostic for sarcoma, although LDH and LDH isoenzyme type 3, in combination with MRI can reach a sensitivity as high as 100% in differential diagnosis of sarcomas from benign fibroids (Goto, 2002).

Serum CA125 was found to be significantly higher in patients with leiomyosarcoma, comparing to those with uterine leiomyoma. However, there was significant overlapping of preoperative serum CA125 between leiomyoma and early-stage uterine leiomyosarcoma, which limits the clinical use (Juang, 2006).

Biopsy

Transcervical needle biopsy, as well as endometrial sampling can be used preoperatively to differentiate leiomyomas from sarcomas, with a sensitivity up to 100% and 68% respectively (Kawamura, 2002; Sagae, 2004). Even though the first one appears to have a great diagnostic value, it is not generally performed because of the need of multiple samples to increase its accuracy and to the possible risk of spread of malignant cells.

Intraoperative Assessment

Macroscopic characteristic of the tumor (yellow color, soft consistency, not precise margins of the mass) can raise suspicions of malignancy but, these findings are common in benign cases too, such as adenomyomas, so performing an unplanned hysterectomy is not justified. On the other hand, frozen sections during surgery often leads to false negative results due to limited tissue examination, thus, preoperative evaluation should be careful and thorough, focused on patients risk factors (Leibsohn, 1990; Tulandi, 2014).

Treatment of Fibroids

Treatment of fibroids should be individualized and depends on the severity of the symptoms, the wish for childbearing potential, the age of the patient, the size and the location of the mass and the coexisting risk factors.

Expectant Management

After determining risk factors and evaluating imaging and laboratory findings, annual reevaluation of patients with fibroids, is considered to be a reasonable option (Peddada, 2008; Laughin, 2011). Changes in patient's clinical presentation should be taken in account and earlier appointment should be scheduled to avoid worsening of the symptoms or identifying possible risks of malignancy. This include clinical examination and ultrasound evaluation in outpatient setting.

Medical Treatment

Nonsteroidal Anti-inflammatory Drugs (NSAID) can be used to reduce the menstrual blood loss in women with fibroids with quite good results (Milsom, 1991).

A nonhormonal antifibrinolytic agent (*Tranexamic Acid)* is also reducing menorrhagia. A notably change in blood loss was reported in women using tranexamic acid vs placebo (Lukes, 2010).

Prior to surgical removal of fibroids tranexamic acid may reduce menorrhagia depending on the size or the location of the leiomyoma. Minimal side effects were reported, but there are some concerns regarding the possibility of necrotic changes of the fibroid cells in women taking tranexamic acid (Ip, 2007) .

Estrogen- progestin contraceptive pills and progestational agents are broadly prescribed for abnormal bleeding, but there is evidence to suggest that their efficacy is limited in case of leiomyomas (Friedman, 1988).

Levonorgestrel-releasing intrauterine system is shown to be effective in reducing uterine volume and bleeding (Magalhaes, 2007; Zapata, 2010), while other progestin implants, injections and pills may reduce bleeding by causing endometrial atrophy but, also, there is a possibility to act on myometrial cells as growth factors, thus, indication for their use in case of fibroids remains controversial (Venkatachalam, 2004; Wise, 2004).

Regarding Selective Progesterone Receptor Modulators (SPRM) there are high quality data to support that they are affective, in the reduction of leiomyomas size after a three-month administration period, but they showed a moderate effect on reducing bleeding compared with placebo (Liu, 2017).

Progesterone and its receptors play a key role in uterine fibroid growth and we can modulate the progesterone pathway by use of selective progesterone receptor modulators (mifepristone, telapristone acetate, ulipristal acetate, asoprinsil) (Bestel, 2014).

Randomized trials proved the efficacy of ulipristal acetate in the management of fibroid induced symptoms (mainly menorrhagia), especially prior to surgery (Donnez, 2012).

Ulipristal acetate is approved for a three months treatment of uterine leiomyomas in Europe and Canada, whereas, in the United States its use is not approved for this indication, possibly due to rare cases of serious liver toxicity (FDA, 2018). Nevertheless, randomized trials have shown that in selected cases, both 5 and 10 mg daily where effective and well tolerated (Liu, 2018).

Novel approaches and algorithms with the use of ulipristal acetate alone or in combination with surgery, given special emphasis on infertility, have been proposed (Donnez, 2016).

GnRH agonists are considered to be the most effective medical treatment for uterine fibroids, causing hypogonadotropic hypogonadal state, similar to menopause. Thus, they reduce uterine size and bleeding but also trigger symptoms arising from estrogen drop, such as bone loss, hot flashes, sleep disorders and vaginal dryness, while their favorable effect on myomas reverts right after the discontinuation of administration (Minaguchi, 2000).

The regrowth of fibroids after GnRH agonist therapy discontinuation is a result of the increased estrogen receptor content in fibroids and possible due to lack of obvious cellular damage in fibroids that were treated with GnRH agonists (Lethaby, 2001; Theodoridis, 2005).

Uterine fibroids do not respond the same to GnRH analogue treatment. It seems that the degree of shrinkage is a function of the proportion of degenerative changes of the fibroid tissue. As fibroid cellularity increases, fibroid volume diminishes more with GnRH agonist therapy. On the contrary as the hyaline content or collagen fibers increased, the volume decreased less with application of GnRH analogues. (Kawamura, 1997).

Selective Estrogen Receptor Modulators, aromatase inhibitors, antifibrinolytic agents, androgenetic steroids have been described to be effective in reduction of bleeding and shrinkage of leiomyomas, but their exact role needs further evaluation with large randomized trials (Lingxia, 2007; Shozu, 2003; Ylikorkala, 1986).

Surgical Treatment

Hysterectomy remains the gold standard for women with leiomyomas who completed childbearing and are simultaneously diagnosed with other uterine pathology, have symptoms that do not subside, have been submitted in other therapies that failed, are at increased risk for malignancy or, have multiple myomas.

It represents the method of complete cure of symptomatic women and can be performed by the means of abdominal, vaginal or laparoscopic surgery. Subtotal hysterectomy can be offered in very carefully preoperatively evaluated cases (Erian, 2005; Erian 2008)

Myomectomy is a reasonable option for women who desire uterus preservation, either for childbearing or for personal or cultural reasons. Hysteroscopic myomectomy is nowadays the method of conservative surgical approach of submucous myomas, mainly using the slicing technique with loop monopolar or bipolar diathermy (Bettocchi, 2004; Di Spiezio, 2015).

GnRH agonists can be used prior to hysteroscopic myomectomy as they may correct associated anemia, reduce the size of the vessels surrounding the fibroid mass, and reduce the fibroid and uterine volume. Reduced operative blood loss is also notable (Theodoridis, 2005).

Laparoscopic surgery is a valid alternative to abdominal approach, for subserosal and intramural fibroids removal, as many women are against surgical treatment via laparotomy because they want to maintain cosmesis by avoiding classical surgery scars. Myoma size and location, total number of fibroids and experience in advanced laparoscopy and suturing should be criteria for choosing minimal access surgical myomectomy. Leiomyoma specimen after laparoscopic myomectomy is removed using morcellation or vaginally through cul de sac. Minilaparotomy can be also used to extract the leiomyoma and to avoid tissue spillage.

Another option for fibroid management is uterine artery embolization (UAE). Women who wish to preserve their uterus or should avoid major surgery because of other medical issues are candidates for this method. UAE is very effective in reducing symptoms, especially myoma size and heavy bleeding but there are few complications including the increased risk for surgery. Concerns arise regarding the future reproductive performance of these women (Gupta 2014).

High frequency magnetic resonance-guided focused ultrasound surgery (MRgFUS) is a non- invasive alternative, but its usefulness in daily practice of controlling fibroid symptoms is still a controversy. Limitation of outmost importance of the above technique, as with laparoscopic cryomyolysis and thermocoagulation of fibroids, is the lack of specimen for histologic evaluation (Exacoustos, 2005;Zupi 2016).

Treatment of Sarcomas

Uterine sarcomas as rare aggressive tumors with poor prognosis. Surgical staging including total hysterectomy ± bilateral salpingo-oophorectomy is the standard choice of treatment. Pelvic or paraaortic lymphadenectomy is controversial. Adjuvant chemotherapy is helpful to the control of systemic disease at advanced stages and postoperative radiotherapy could promote the control of local lesion. Uunfortunately significant or consistent improvement in the overall survival is not proven (Kyriazoglou, 2018).

In low-grade endometrial stromal sarcoma (LGESS) or in cases with positive hormone receptors (ER+/PR+) uterine leiomyosarcomas may benefit from hormonal treatment such as aromatase inhibitors (AI), GnRH-a, selective estrogen receptor modulators (SERMs) and progestins (Zang, 2019).

Novel targeted therapies including tyrosine kinase inhibitors, next generation alkylating agents, cell cycle inhibitors and epigenetic modifiers are being evaluated in clinical practice as well (Miller, 2016). Sarcomas are very rare tumors with high rates of early and recurrence. Studies regarding their optimal management are based on small number of retrospectively evaluated patients and on case reports. Hence the effect of adjuvant therapy and hormonal treatment needs further evaluation for safe conclusions.

Clinical Practice Dilemmas

Regarding the best therapeutical approach clinicians often confront a number of dilemmas:

- Is conservative therapy of fibroids dangerous for the possibility of undiagnosed malignancy?
- Is subtotal hysterectomy as safe as total, in case of an undiagnosed sarcoma?
- Furthermore, is laparoscopic myomectomy and intraperitoneal morcellation safe in any case of uterine mass?
- Is it possible that tissue fragmentation after morcellation lead to false histological evaluation of a possible malignancy?
- Should we always perform hysterectomy?

Expectant management and medical treatment are considered to be safe in case of a mass which is clinically evaluated as benign, confirmed by imaging techniques and laboratory tests. Failure to respond to medical treatment or non-excisional therapies was thought to be a malignancy indication, though there is not sufficient evidence to prove this hypothesis (Common, 2001) .

Supracervical hysterectomy is usually performed for treating myomas, but there is poor evidence whether this procedure could lead to malignant tissue spread. In a small survey, patients with uterine malignancy treated by subtotal hysterectomy where not proven to have worst prognosis that they had have, in case they had been treated by total abdominal hysterectomy (Einstein, 2008).

Regarding laparoscopic myomectomy and power morcellation, FDA released a warning reporting that, “if laparoscopic power morcellation is performed in women with uterine sarcoma, there is a risk that the procedure will spread the cancerous tissue within the abdomen and pelvis, significantly worsening the patients’ likelihood of long-term survival”. For this reason, and because there is no reliable method to predict whether a woman with fibroids has a uterine sarcoma, the FDA discourages the use of laparoscopic power morcellation during hysterectomy or myomectomy for uterine fibroids (FDA, 2014).

However, data regarding safety of morcellation in case of sarcoma are controversial, with a recent retrospective study showing no statistically significant difference in recurrence- free survival (RFS) and overall survival (OR) between patients with uterine sarcoma who underwent laparoscopy and morcellation and those who received total hysterectomy, whereas, a metanalysis of four studies support a significant correlation between uterine morcellation and increased risk of intraabdominal recurrence of patients with unexpected uterine leiomyosarcomas (Gao, 2016; Bogani, 2015). Therefore, European Society for Gynaecologic Endoscopy (ESGE) has proposed an algorithm in order to help clinicians to decide between proposing minimal invasive procedures, including morcellation, or abdominal approach. Based on ultrasonographic criteria, for treating uterine masses with necrotic appearance and

high vascularity clinicians should council against morcellation, while for those without necrosis and high vascularity they should consider patients' age: for women under forty, counselling on minimal invasive management including morcellation is rational, while in older patients, additional characteristics should be examined as well. Thus, post menopause, transvaginal ultrasound or MRI findings such as, single uterine mass or size of largest fibroid greater than 8cm, elevated LDH and abnormal uterine bleeding should be considered as factors against morcellation (Brölmann, 2015). After estimating risk factors, and evaluating imaging and laboratory findings, clinicians should always consider that the possible risk of preoperatively undiagnosed sarcoma is 0,2%, while serious complications of hysterectomy vary from 3,5 to 11% (Leung, 2009;Takamizawa, 1999).

In conclusion, hysterectomy is a rational option in patients who do not desire to keep their childbearing potential, in women who want to treat symptoms or to prevent the formation of new fibroids, in cases that conservative therapy has failed, and in all women at high risk of malignancy. However, for the vast majority of patients, all other treatment options are considered to be safe and effective.

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Chapter 21
Treatment of Uterine Pathology:
When Is Simple Hysterectomy Indicated?

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ABSTRACT

Hysterectomy is the most common gynecological operation after cesarean section. The majority of hysterectomies are performed for the treatment of benign diseases, which, although not life-threatening, may have a negative impact on the quality of patient's life. Abnormal uterine bleeding is the most common indication for hysterectomy in premenopausal women and is usually a result of myomas and adenomyosis. Another indication is chronic pelvic pain that is usually caused by endometriosis and/or adenomyosis. A simple hysterectomy can be the treatment of choice in early stages of endometrial, cervical cancer, sarcomas, or gestational trophoblastic disease. Laparoscopic hysterectomy is superior to laparotomy when a vaginal hysterectomy is contraindicated.

INTRODUCTION

Hysterectomy is the most common gynecological operation after cesarean section. (Dorsey, 1995) The majority of hysterectomies are performed for the treatment of benign diseases which, although are not life-threatening, have a negative impact in the quality of patients' life. During recent years the indications of hysterectomy tend to diminish due to more conservative approach for this kind of diseases. Abnormal uterine bleeding, the most common indication for hysterectomy, most of the times is dysfunctional and not a result of endometrial pathology. Thus, there is a decrease of the procedures of hysterectomy the past decades and a tendency to conservative approach to women with abnormal uterine bleeding.

The final decision of proposing a hysterectomy as a treatment choice, as well as the type of surgical approach should take into account several parameters as midterm and long-term benefits for the patient,

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the good quality of life and the cost-effectiveness of each approach. Subtotal hysterectomies were common during last century but now it is abandoned mainly due to the risk of cervical cancer. In addition, there is no evidence of better sexual function or reduced risk of pelvic floor prolapse as it was believed. (Lefebvre, 2018) Vaginal hysterectomy meets most of the times the described criteria, especially when is combined with laparoscopy in comparison to laparotomy. It is the least operative technique, with cost-effectiveness, with less complications and a shorter hospitalization (Kovac, 2000). Other parameters that must be taken into account are the specific indication, the size and morphology of the uterus that will be removed, the will of the patient for fertility sparing treatment, the existence of disease outside the uterus, the equipment and education of the health providers, the surgical history of the patient as well as the emergency of the operation (Wright, 2013). Laparoscopic hysterectomy is superior to laparotomy, when a vaginal hysterectomy is contraindicated. The role of robotically assisted laparoscopic hysterectomy is not evaluated and we need further experience and search in this field. Nonetheless, in clinical practice, open hysterectomy is the most common type of procedure representing 60-70% of hysterectomies for benign diseases.

Abnormal uterine bleeding is the most common indication for hysterectomy in premenopausal women and is usually a result of myomas and adenomyosis. Another indication is chronic pelvic pain that is usually caused by endometriosis and/or adenomyosis. In the USA the most common benign situations that lead to hysterectomy are myomas causing symptoms (51,4%), dysfunctional vaginal bleeding (41,7%), endometriosis (30%) and uterine prolapse (18,2%) (Backes, 2014). As far as malignancies and obstetric indications are concerned, they represent less than 10% of the cases (Lethaby, 2015).

There are several complications that can occur post-operatively in a patient that undergoes hysterectomy. All patients, regardless the indication for the surgery, should be thoroughly informed before consenting to hysterectomy. The majority of minor complications are fever, hemorrhage and infection. (Lefebvre, 2018) In addition there are lots of possible anatomical complications such as injuries to the urinary bladder, ureter, intestines, rectum, anus, and a multitude of nervous structures. Other complications are also recorded as sexual dysfunction, vaginal cuff prolapse and urinary incontinence. (Ramdhan, 2017)

BENIGN DISEASES

Myomas

Myomas are benign uterine tumors which originate from smooth muscle cells. They are the most common benign gynecological tumors. They usually occur to women of reproductive age and their prevalence is between 20-25% (Goeser, 2008). A very small percentage of myomas, between 0,1-0,4% can turn into malignancy, leiomyosarcomas. Usually, myomas are asymptomatic, so most of women can be followed-up, although their growth rate. Especially during menopause, follow up of myomas is safe, because they tend to shrink and bleeding stops. On contrary, when myomas are the cause of symptoms and complications as severe anemia, heavy vaginal bleeding, chronic pelvic pain, constipation or symptoms from the urinary tract (due to pushing effects), surgery should be considered.

FIGO introduced a classification system in 2011 considering a number of factors as the relationship of the myoma to the endometrium and the serosa This system helps clinicians to categorize the causes of bleeding, to communicate for research and to plan their treatment. (Munro, 2011b) Types 0, 1 and 2 are submucosal myomas. Type 0 are intracavitary and type 1 and 2 are intramural, <50% and >50%

respectively. Type 3 lesions are completely intramural but in contact with the endometrium. Type 4 is intramural with no communication with the endometrium or the serosa. Types 5-7 are subserosal myomas with type 5 being >50% intramural, type 6 <50% intramural and type 7 being pedunculated. Finally, type 8 myomas are characterized with no communication to the uterus, e.g. cervical, parasitic myomas. When two numbers are given, the first refers to the communication with the endometrium and the second refers to the communication with the serosa. (Munro, 2011c) The main disadvantage of this classification is that the size, number and uterine location of myomas are not taken into account. These are factors that can affect the plan of treatment. (Laughlin-Tommaso, 2017).

Current diagnosis of myomas include pelvic examination, ultrasound and a hysteroscopy and/or a MRI may be essential to determine the size and location of them. Common surgical techniques for myomectomy are hysterescopic resection (for myomas type 0-3), laparoscopic myomectomy and laparotomy. Laparoscopic myomectomy is superior to laparotomy because there are less postoperative complications reported and less time of hospitalization. (Palomba, 2007) Less complications include hemorrhage, postoperative pain and long-term less adhesions and better fertility outcome. (Herrmmann, 2014)

There is a discussion about the safety of laparoscopic myomectomy, and specially about the method of morcellation for the removal of the myoma from the abdomen. There is a very small possibility that the preoperative diagnosis is wrong and that the tumor is not a benign myoma but a leiomyosarcoma. In that case morcellation could result intra-peritoneal dissemination. The risk was mentioned from the Food and Drug Administration (FDA) since 2014. (Donnez, 2016) However, the incidence of leiomyosarcomas is very small according to lots of studies and if the preoperative diagnosis is proper, morcellation of myomas is relatively safe. (Pados, 2017) In addition, the complications of a total abdominal hysterectomy for the treatment of myomas in comparison to minimal invasive surgery with the use of power morcellation are much more. (Multinu, 2018). The technique of power morcellation in a bag is suggested to minimize this risk, but there is no evidence yet that this technique is better and needs further research. (Donnez, 2016) Preoperative differential diagnosis is crucial to avoid spreading of cancerous tissue during morcellation. There are some risk factors for uterine sarcomas such as African American race, use of tamoxifen, previous pelvic irradiation, rapid growth of the lesion in postmenopausal women, age over 50 years old. (Halaska, 2017) There are some imaging differences that can help differential diagnosis too. The shape of myomas are usually round shaped while leiomyosarcomas are ellipsoid. Leiomyosarcomas have mixed echogenicity and central necrosis while myomas have homogenous echogenicity and no necrosis is observed. In addition, leiomyosarcomas have abnormal vascularization and abnormal margins. Finally myomas are usually multiple lesions while leiomyosarcomas are presented as one lesion. (Amant, 2015) There are no reliable biomarkers that can lead to diagnosis of leiomyosarcoma pre-operatively, except of serum lactate dehydrogenase (LDH) and isozyme 3 of LDH that may be helpful. Sensitivity and positive predictive value raise when these findings are combined with MRI results for the diagnosis of these rare malignancies. (Goto, 2002)

In women of reproductive age who have not completed childbearing the surgery should be conservative, a myomectomy. If family planning is completed, hysterectomy is a definitive and radical surgical solution. The size, number and location of myomas are also factors that should be taken into account when the type of surgery is decided. In case of multiple myomas, myomectomy can be related to higher percentage of complications (Kaunitz, 2009).

Apart from surgical solutions, myomas can be treated conservatively with levonorgestrel-releasing intrauterine devices (IUD), GnRH agonists and antagonists, progestins and combined oral contraceptives. Non hormonal medication such as tranexamic acid and nonsteroidal anti-inflammatory drugs can also

help in treating abnormal bleeding. Other conservative treatment options are uterine artery embolization and MRI-guided embolization of myomas. IUDs seem to diminish uterine bleeding during menstruation up to 86% in three months and up to 97% in the first year (Soysal, 2005). They have a similar effect in the raise of hemoglobin (Leather, 1993).

GnRH agonists seem to diminish uterine volume up to 35% and uterine bleeding in 95% of patients. On the other hand, they cause lots of adverse effects as hot flashes, vaginal dryness, headache and serious reduction of bone mass. This is the reason it is better to be prescribed for short time periods in premenopausal women. GnRH antagonists are usually prescribed preoperatively, to diminish the myoma volume up to 30% in three weeks, although they can cause adverse effects from estrogen deficiency (ACOG, 2008). Progestins and combines oral contraceptives seem to diminish uterine bleeding for the time period they are used.

Another safe, minimal invasive, conservative approach to myomas is the embolization of uterine artery. This method is suggested by the American College of Obstetricians and Gynecologists to women who want to preserve their uterus but there is a question about fertility as the method seem to cause an increase in obstetric complications as abortions, premature birth, uterine atony (LeBlang, 2010).

Another innovative conservative technique for myomas is the MRI guided high intensity focused ultrasound (HIFU). This technique is proposed to women who want to preserve their fertility and its main advantage is the fast recovery and return of the patient to everyday activities (William, 2012).

In conclusion, hysterectomy is the most definitive solution in the treatment of myomas, as far as the confrontation of symptoms and the risk of recurrence are concerned. The main disadvantages is the lack of fertility sparing in premenopausal women and the possible complications of the surgery (Hoffman, 2016).

Adenomyosis

Adenomyosis is defined as the presence of ectopic nests of endometrial glands and stroma within the myometrium, surrounded by reactive smooth muscle hyperplasia. It is a common cause of dysmenorrhea, menorrhagia and chronic pelvic pain and it is often underdiagnosed (Vercellini, 2006). Adenomyosis can be presented either scattered, with lots of spots in the myometrium, or focal. Despite the evaluation of imaging methods and especially of ultrasound, adenomyosis is diagnosed most of the times from the pathology report of hysterectomy specimen (Abbott, 2017). There is prevalence of adenomyosis in hysterectomy specimens up to 20-35%. Definitive diagnosis of adenomyosis is always made with pathology. The most sensitive noninvasive method is the MRI (Ozdegirmenci, 2011). The most common imaging findings in MRI are a large, asymmetric uterus, abnormal myometrial signal intensity, small junctional zone and myometrial foci of high signal intensity. (Struble, 2015) There are lots of classification systems for adenomyosis, based on the location and configuration of the lesions, the depth of invasion in the myometrium, the histologic grade or the imaging characteristics. The most recent classification system is based on clinical and histological staging. There are four categories according to that system: diffuse adenomyosis, focal adenomyosis, polypoid adenomyomas and other forms of adenomyosis. (Grimbizis, 2014) Therapeutic approach to adenomyosis depends on the severity of symptoms and the desire of the patient for fertility sparing. The most effective medical treatment for uterine bleeding caused by adenomyosis is IUDs (Struble, 2016). Even in comparison to hysterectomy, which is the definitive treatment of adenomyosis, the results in abnormal bleeding and the improvement of everyday life is similar. Other proposed medical treatments are combined contraceptive pills, non-steroidal anti-inflammatory drugs, aromatase inhibitors and oral progestins. Medical treatment should be the first line option in all women

of reproductive age. When medical treatment fails, surgical options should be proposed as removal of adenomyomas, uterine artery embolization, MRI guided high intensity focused ultrasound (HIFU). Hysterectomy remains the definitive treatment of adenomyosis (Munro, 2011a).

Dysfunctional or Abnormal Uterine Bleeding

The term dysfunctional bleeding tends to be abolished and replaced by the term abnormal uterine bleeding. According to FIGO, abnormal bleeding is bleeding from the uterine body which is abnormal in volume, frequency and is present for at least six months (Khrouf, 2014). Dysfunctional bleeding is an indefinite term that has big heterogeneity about the causes that can lead to this pathological situation. There was a need of a more specific classification to help clinicians and researchers to plan a treatment or create guidelines of treatment. In 2011, the International Federation of Gynecology and Obstetrics (FIGO) proposed a classification system for abnormal uterine bleeding to facilitate communication, clinical care and research. PALM-COEIN (stands for: polyp; adenomyosis; leiomyoma; malignancy and hyperplasia; coagulopathy; ovulatory dysfunction; endometrial; iatrogenic; and not yet classified) system can be used to investigate the subjective disorder of uterine bleeding and propose personalized therapeutic options to the patient (Khrouf, 2014). PALM includes structural disorders that can be diagnosed with imaging and pathology while COEIN includes non structural disorders. In these cases, a further diagnostic approach is needed with laboratory tests and sometimes the contribution of other specialists as endocrinologists and hematologists.

The first diagnostic step when there is an abnormal uterine bleeding is excluding pregnancy and structural abnormalities of the uterus. Next step is the setting in the COEIN classification after taking a detailed medical history and excluding iatrogenic bleeding i.e. due to intrauterine device or drugs. A blood test for hormonal profile, coagulation factors and hemorrhophilia is necessary. The treatment should be medical at the beginning and should aim to the confrontation of the underlying disease. In cases of disorders of coagulation, there is a need for counseling from an hematologist (Cheong, 2017).

Most of times, the medical treatment proposed in abnormal bleeding is hormonal such as combined contraceptive pills, progestins, IUDs, GnRH agonists and non hormonal such as NSAIDs and/or tranexamic acid. On contrary, in cases of ovarian dysfunction only hormonal treatment is indicated.

Invasive techniques such as thermal or hysteroscopic destruction of the endometrium or hysterectomy should be proposed only in cases when medical treatment has failed and severe symptoms exist such as heavy anemia. In conclusion, abnormal uterine bleeding needs investigation and personalized treatment. Hysterectomy is the last therapeutic solution (Whitaker, 2015) (ACOG, 2015).

Endometrial Hyperplasia-EIN

There is a chronic difficulty in management of women with precancerous lesions of the endometrium. The problems occur from the difficulty in diagnosis, the unclear prediction of the natural history of each disease, different risk factors of each patient and the unclear therapeutic options in each diagnostic group. In 1994 WHO classified endometrial hyperplasia in four kinds: non-atypical hyperplasia (simple, complex) and atypical hyperplasia (simple, complex). This classification system was based on characterization of glandular architecture (simple, complex) and the presence or absence of nuclear atypia. The main disadvantages of this classification are that homogenous lesions were subdivided and as a result each group of patients do not correspond to a different therapeutic options. The main characteristic of these lesions

that would help divide patients groups is the potential of these lesions to progress to cancer. (Mutter, 2000). Although this classification was used for many years, it caused difficulties in clinical practice due to poor reproducibility of diagnosis and lack of management protocols for physicians. Estimated risk of atypical hyperplasia to progress to endometrial cancer was 8-29%. As a result there were too many hysterectomies performed for hyperplasia and there were hormonal treatment proposed for treatment of atypia. The most accurate diagnostic schema so far, proposed by WHO in 2014, is the endometrial intraepithelial neoplasia (EIN) diagnostic schema, developed by the Endometrial Collaborative Group in 2000 and accepted by the International Society of Gynecological Pathologists. It is a simple classification of hyperplasia in two kinds: endometrial hyperplasia and endometrial intraepithelial neoplasia (EIN). Endometrial hyperplasia is a benign condition and corresponds to simple hyperplasia according to the older classification, while EIN is a precancerous lesion/situation. Endometrial hyperplasia usually occurs due to anovulatory cycles or prolonged exposition to oestrogen combined with insufficient levels of progesterone. The most important risk factors for endometrial hyperplasia are obesity, tamoxifen treatment and PCOs. The recent WHO classification helps to divide patients in protocols and guidelines design as well as choosing between hormonal and surgical treatments. (Sobczuk, 2017) (Salman, 2010). A lesion with a minimum size of 1mm, with gland area that exceeds that of stroma, with cytological alterations in architecture are characterized as EIN, after excluding mimics (such as polyps etc.) and cancer. A serious disadvantage of this classification is the diagnosis of lesions that are suspicious but do not come under the diagnosis of EIN. There is a need of close contact of the clinician with the pathologist so that all factors are considered. In addition, there is low sensitivity in the methods we already use to take endometrial samplings for biopsy. We can have samplings from only 60% of total endometrium with Q &C, pipelle, even hysteroscopy (Trimble, 2012). As a result, the pathology of the specimen of hysterectomy often reveals adenocarcinoma of endometrium even if we had a diagnosis of EIN in the first biopsy. This is the reason we need to pay lots of attention in treatment of EIN. In cases of endometrial hyperplasia the treatment should be hormonal (Colombo, 2015). On the contrary, the treatment of choice for EIN lesions is total hysterectomy with or without salpingo-oophorectomy and cytology test of peritoneal washings. According to American College of Obstetricians and Gynecologists (ACOG) there is no advantage in a particular type of hysterectomy, but it is recommended to avoid subtotal hysterectomy and morcelation of the uterus in case of laparoscopic hysterectomy, to avoid spreading of possible cancer (Sobczuk, 2017). According to ACOG supracervical hysterectomy is not a surgical choice in patients with atypical endometrial hyperplasia or endometrial intraepithelial neoplasia nor are other surgical interventions as endometrial ablation. (Trimble, 2012) Fertility sparing treatment in these cases should be an option as long as the endometrial sampling is representative of the lesion and consists of oral progestins (megestrol acetate 160-320mg/day or medroxyprogesterone acetate 400-600mg/day) or IUD, follow-up every six months with endometrial samplings. If fertility sparing treatment is not successful or when family planning is completed, a total hysterectomy is indicated to complete treatment of EIN (Morantz, 2006). Other choises of hormonal treatment are oral contraceptives, danazol, GNRH analogues, aromatase inhibitors and mifepristone. (Moore, 2013)

Cervical Intraepithelial Neoplasia (CIN)

Cervical intraepithelial neoplasia is usually treated conservatively, with frequent follow-up or resection of part of the cervix, depending on the severity of neoplasia, the age of the patient, the way of life and recently on the results of biomarkers. The aim of conservative treatment is to maintain fertility while

removing the transformation zone and preventing a risk of future invasive cancer. Both excisional and ablative treatment options are used. Ablative techniques include laser, cold coagulation and cryocautery. (Mitra, 2006) The usual excisive operative techniques are LEEP (Loop Electrosurgical Excision Procedure), laser surgery and rarely knife conization when cervical cancer is suspected. About 1-2% of women will be diagnosed with CIN 2/3 annually. WHO published guidelines for management of these lesions and hysterectomy is not an option among the therapeutic options. (Santesso, 2016) In addition, American Society for Colposcopy and Cervical Pathology as well as other European guidelines have excluded hysterectomy from therapeutic options. As a result, when cancer is excluded, hysterectomy is not the treatment of choice in patients diagnosed with CIN 2/3. Sometimes hysterectomy is performed when a second conization is technically difficult after excluding any possibility of cervical cancer (Kesic, 2003) (Goldstein, 1994). Another indication for hysterectomy is the presence of a concomitant pathology or a persistent/recurrent disease of CIN 2/3. Finally, another factor that should be considered is that hysterectomy for the treatment of CIN 2/3, is a risk factor for development of Vaginal Intraepithelial Neoplasia with rates up to 6,8%. After the hysterectomy, a Papanikolaou smear should be taken 6 and 18 months postoperatively at least. (Schockaert, 2008)

Endometrial Cavity Fluid

In postmenopausal women, sometimes there is an ultrasound finding of fluid inside the endometrial cavity. This finding is often related to cervical stenosis or atrophy or obstruction due to a malignancy. According to Royal College of Obstetricians and Gynecologists, this finding is suspicious for endometrial cancer if it is combined with endometrial thickness over 3mm (Takacs, 2005). In addition, we should always get a biopsy of endometrium if fluid is echogenic and we should always consider cervical cancer with expansion to the uterine isthmus (Schmidt, 2005). In cases without symptoms, with thin endometrium a follow-up in three months should be proposed (Colombo, 2015). Only in patients when Q&C is technically impossible a diagnostic hysterectomy should be proposed.

MALIGNANCIES

Endometrial Cancer

Endometrial cancer is the most common gynecological cancer in developed countries. There are two types of endometrial cancer based on pathology. Endometrioid adenocarcinomas are type I endometrial cancers and are the most frequent (85% of patients) and all the other types (squamous and clear cell carcinomas, carcinosarcomas) are type II endometrial cancers. Type II endometrial cancer is rare but high grade carcinomas with poor prognosis. The main risk factors for type I endometrial cancer are the age of the patient (75% of patients are postmenopausal), several genetic disorders, history of breast and/or ovarian cancer, PCOs, hormonal replacement treatment, increased BMI, nulliparity and number of menstruations (Visser, 2017).

Fertility sparing treatment in women of reproductive age can be discussed only in cases with Grade I tumor and when tumor is not extended to myometrium and there is no lymphovascular invasion. Abdominal disease and/or adnexal mass should be excluded too. Treatment consists of hormonal agents for six months and follow-up with new biopsies. Hysteroscopy is the indicated method of estimation of

location and size of the lesion and of complete removement of the lesion. Patients should be informed that conservative treatment has dangers and that hysterectomy should be performed instantly after completing family planning. Treatment regimens for fertility sparing treatment are megestrol acetate 160-320mg/day or medrozyprogesterone acetate 400-600mg/day. Alternatively, an IUD with or without combination with GnRH analogues can be discussed (Rodolakis, 2015). A new sampling and a hysteroscopy should be done three months after the beginning of the treatment. According to a recent meta-analysis for patients with early endometrial cancer and atypical complex hyperplasia, hormonal treatment had good complete response. However, pregnancy outcomes were better with the use of progestins than with the use only of IUD. (Wei, 2017)

In stage I patients, according to FIGO classification, (tumor limited in the uterus), total hysterectomy with bilateral salpingoophorectomy is the indicated surgery. Cytologic test of peritoneal washings is no longer mandatory for surgical staging. Oophorectomy is performed to avoid simultaneous ovarian cancer or metastases to ovaries. In premenopausal women, younger than 45 years old, with endometrioid endometrial cancer, grade I and stage IA, with no clues of disease outside the uterus, preservation of ovaries can be discussed. In these cases, bilateral salpingectomy should be performed. Preservation of ovaries is contraindicated in women with family history of ovarian cancer or bowel camcer (BRCA mutations, Lynch syndrome). In these cases a genetic counseling is needed (Colombo, 2015).

In patients diagnosed with endometrioid endometrial cancer, grade 1-2, with <50% myometrial invasion and without LVSI (Lymphovascular Space Invasion), there is a low risk of lymph node participation. Two randomized trials indicated that in these patients there is no improvement in survival rates when there is a surgical lymph node resection. In larger stages of disease, surgical treatment should include lymph node resection (Janda, 2017).

In patients with endometrial cancer, total hysterectomy can be performed either with laparotomy, laparoscopy or with vaginal access. Laparoscopy is related to less postoperative complications and less hospitalization. Operative time is longer in laparoscopy in comparison to laparotomy (Janda, 2017). The superiority of laparoscopy is applied in women with increased BMI, if there are no contraindications regarding anesthesia and pneumoperitoneum. In a study that compared lapatotomy with laparoscopy in patients of stage I endometrial cancer, there was no significant difference in 5 year survival. Vaginal hysterectomy can be performed in patients that are contraindicated to have a laparoscopy or laparotomy.

Surgical staging of endometrial cancer is very important, because a recent meta-analysis suggested that there is an agreement in only 67% of the primary and the final diagnosis, especially for grade 2 tumors. The main cause of this differentiation is the small quantity of tissue that is examined after Q&C. Specimens examined after hysteroscopy are more sensitive up to 89% because the tissue taken is from the lesion that is visualised by the physician (Visser, 2017). Immunohistochemistry and specially p53 pathway is very promising about the future management of endometrial cancer (Chang, 2018).

Cervical Cancer

Cervical cancer is the third more frequent gynecological cancer worldwide, with significant mortality in developing countries. Rates of cervical cancer are lower in developed countries due to screening with pap test and vaccination. Vaginal and pelvic examination and cervical biopsies with or without colposcopy are crucial to the diagnosis of cervical cancer. The majority of cervical cancers are squamous-cell cancer while the second most frequent type is cervical adenocarcinoma. Similar to squamous cell carcinoma adenocarcinoma is HPV related in rates up to 88%.

For the treatment of in situ cervical adenocarcinoma, which represents about 25-30% of all cervical cancers, the indicated surgical procedures that seem to have overall similar results and prognosis are Loop Electrosurgical Excision Procedure (LEEP) and Cold Knife Conization. Hysterectomy is only indicated when there is persistent/residual disease although is a definitive solution. (Latif, 2015) This is due to the mean age of patients which is lower to 40 years and often there is a need of fertility sparing treatment. The challenge with the indicated surgical techniques is to achieve negative surgical margins because it is associated with lower rates of residual or recurrent disease. It is also important to have negative surgical margins during the first surgical procedure because a second surgical procedure regardless of surgical margins is also associated with higher rates of residual or recurrent disease. Cold Knife Conization seems to have better results as far as negative margins are concerned. (Salani, 2009)

Diagnosis of stage IA1 and IA2, according to FIGO classification, should be based in conization speciments or cervical biopsy that have been examined by an experienced pathologist. It is important that the two dimensions of the disease and LVSI are mentioned in detail in the pathology report. In women that want a fertility sparing treatment, conization with loop or laser is preferable than knife conization. Surgical margins of the cone must be free of disease and intraepithelial lesions.

Management of stage IA1 should be personalized depending on age of the patient, desire of preserving fertility and the presence or absence of LVSI. In case of positive surgical cone margins, a repetitive conization is necessary. In stage IA1 with negative LVSI there is no need of surgical staging of lymph nodes, but when LVSI is positive staging should be discussed. Conization can be the definitive treatment of cervical cancer and hysterectomy does not seem to improve the final result. In patients with stage IA2, conization or simple hysterectomy without resection of parametria are enough. Lymph node staging is necessary if LVSI is positive. Biopsy of guard lymph node, without resection of pelvic lymph nodes is an accepted alternative of lymph node staging.

Every patient that desires fertility sparing treatment and is diagnosed with invasive squamous cell cervical carcinoma, with a tumor smaller than 2cm with negative pelvic lymph nodes in imaging and negative LVSI should be given a chance. A conization or a simple trachelectomy is an adequate treatment and there is no need of hysterectomy when family planning is completed (Cibula, 2018).

Sarcomas

Uterine sarcomas are rare uterine malignant tumors, of smooth muscle cell or connective tissue origin. The diagnosis is made often postoperatively with a diagnosis of a benign disease such as myomas. For the time being, preoperative imaging cannot safely detect a sarcoma. Sarcomas represent the 3-7% of total uterine cancers and have poor prognosis in comparison to endometrioid endometrial cancer. Leiomyosarcomas are the most common uterine sarcomas, while other types are stromal sarcomas, mixed sarcomas and undifferentiated sarcomas (Benson, 2017).

The proposed treatment of early stage sarcomas is total hysterectomy with bilateral salpingoophorectomy. There is a low risk of metastases in omentum and lymph nodes. Preoperative diagnosis of a sarcoma is very important so that an inappropriate surgery (myomectomy) or a morcellation of the tumor can be avoided. According to guidelines, the primary surgical treatment should be the resection of the tumor in free surgical margins. If surgical margins are not free of disease, an hysterectomy should be performed. When there is a more extended disease in the abdomen, a cytoreductive surgery should be performed without lymph node resection, because sarcomas tend to spread through blood (Ricci, 2017).

Stromal sarcomas represent about 21% of uterine sarcomas. In early stages, the surgical treatment is total hysterectomy with bilateral salpingoophorectomy. Traditionally we remove the ovaries because these tumors have estrogen and progesterone receptors and it is believed that rates of recurrence are higher if ovaries remain. In case of recurrence, a cytoreductive surgery is required (Amant, 2014)). Management is almost the same in indifferentiated sarcomas. Adjuvant chemotherapy/radiotherapy does not seem to improve prognosis and survival rates. Postoperative pelvic radiotherapy with or without brachytherapy can be beneficial to the local control of disease but not in overall survival (Pautier, 2014).

Gestational Trophoblastic Disease

The term gestational trophoblastic disease includes gestational trophoblastic diseases that invade locally or metastasize. There are rare conditions related to pregnancy. The most common form of GTD is hydatidiform mole. Other types are invasive mole, choriocarcinoma, placental site trophoblastic tumor and epithelioid trophoblastic tumor (ETT). Patients with GTD are classified, according to WHO, in low risk and high risk. Prognostic factors that affect the risk are age of the patient, beta hcg levels, tumor size, tumor location, number of metastases and history of previous failed chemotherapy (Smith, 2005).

Treatment of hydatidiform mole is evacuation of the uterus with D%C, in all other types of GTD is chemotherapy. Follow up of the disease is made with frequent tests of beta hcg blood levels (Ngan, 2018). Surgical management with hysterectomy is made in cases with heavy vaginal bleeding but can be avoided with uterine artery embolization. In women that have completed family planning, hysterectomy can be an alternative to Q&C. Hysterectomy seems to reduce the need of postoperative chemotherapy and the risk of myometrium invasion, in cases of persistent disease (Van Trommel, 2005). In cases of placental site trophoblastic tumor and ETT, the treatment of choice in premenopausal women is total hysterectomy with ovarian preservation (Berkowitz, 1990).

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Chapter 22
vNotes (Vaginal Natural Office Transluminal Endoscopic Surgery): A New Era in Laparoscopy

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ABSTRACT

vNOTES or vaginal Natural Orifice Transluminal Endoscopic surgery is a new paradigm shift in gynaecological surgery. A first paradigm shift from conventional surgery into laparoscopic surgery was firstly observed in the 1980s and 1990s. vNOTES may represent a shift from 90° to parallel surgery. Almost all benign gynaecological operations can be performed via vNOTES. The chapter presents the technique of vNOTES along with results of various benign and mainly malignant cases. In parallel, the clinical approach of endometrial cancer is widely discussed.

INTRODUCTION

vNOTES or vaginal Natural Orifice Transluminal Endoscopic surgery is a new paradigm shift in gynaecological surgery. We saw a first paradigm shift from conventional surgery into laparoscopic surgery in the 1980's and 1990's. With vNOTES we now see a shift from 90° to parallel surgery. Almost all benign gynaecological operations can be performed via vNOTES. From our own experience, the first 1000 vNOTES cases included hysterectomies (up to 3361 grams), adnexectomies (up to 20cm), ovarian cystectomies, salpingectomies (for ectopic pregnancy and sterilization), myomectomies, appendectomies, omentectomies for borderline ovarian cancer, and endometrial cancer. In this book chapter we will mainly focus on benign hysterectomy and the potential use of vNOTES in endometrial cancer.

Hysterectomy is the surgical removal of the uterus. It is the most commonly performed major gynecologic surgical procedure in the United States of America, where more than 400,000 hysterectomies are performed annually (Corona et al., 2015). The most common benign indications for a hysterectomy are:

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fibroids 30%, dysfunctional uterine bleeding (20%), endometriosis and/or adenomyosis (20%), genital prolapse (15%), chronic pelvic pain (10%) and endometrial hyperplasia (6%) (Carlson et al., 1993).

Conrad Langenbeck performed the first reported elective hysterectomy in 1813 (Table 1) using a vaginal approach (Nieboer et al., 2006) and in 1863 the first elective abdominal (subtotal) hysterectomy was performed by Charles Clay (Nieboer et al., 2006). Harry Reich performed the first laparoscopic-assisted vaginal hysterectomy in 1989 and the first total laparoscopic hysterectomy in 1993 (Nieboer et al., 2006).

Table 2 presents the different hysterectomy techniques. Traditionally a hysterectomy could be performed via these 3 approaches: abdominal hysterectomy (AH), vaginal hysterectomy (VH) and laparoscopic hysterectomy. The laparoscopic hysterectomy can be divided into 3 categories: Laparoscopic Assisted Vaginal Hysterectomy (LAVH), Laparoscopic Hysterectomy (LH) and Total Laparoscopic Hysterectomy (TLH). With the introduction of surgical robots, hysterectomies can now also be performed robotically (RH). The technique of a RH is similar to that of a TLH, but robotic arms hold the surgical instruments and the surgeon manipulates them remotely from behind a console. Laparoscopic and robotic hysterectomies can both be performed through multiple small abdominal incisions or through one larger umbilical incision. More recently a new approach to hysterectomy via Natural Orifice Transluminal Endoscopic Surgery (NOTES) has been introduced (Table 2).

In the next section we will focus further on the different hysterectomy techniques by vNOTES, where the uterus is removed endoscopically leaving no visible scars. In section 3 we will discuss the use of vNOTES hysterectomy for benign indications. In section 5 we will look at the potential benefits of vNOTES in the treatment of endometrial cancer.

VAGINAL NATURAL ORIFICE TRANSLUMINAL ENDOSCOPIC SURGERY (vNOTES)

The advantages of laparoscopy over traditional laparotomy have been accepted worldwide for many years (Burpee et al., 2002). To further reduce surgical morbidity, the evolutionary trend has been towards even less invasive techniques, such as single-incision laparoscopic surgery (SILS) and natural orifice transluminal endoscopic surgery (NOTES). Minimally invasive surgery improves cosmetic outcome, and also reduces surgical injury, which in turn decreases the inflammatory and neuroendocrine responses, and leads to less postoperative pain and quicker recovery (Grande et al, 2002).

NOTES reaches the abdominal cavity by scar-free means. To this end, numerous surgical procedures are performed via a natural body orifice. In recent years this technique has gained popularity among general surgeons, gynecologists, urologists and gastroenterologists, and its feasibility and safety have been approved (Rattner & Kalloo, 2006).

NOTES can be performed via a variety of approaches, including the stomach, esophagus, bladder and rectum, but the majority of NOTES procedures have been performed transvaginally, as the vagina provides direct access to the peritoneal cavity (Santos & Hungness, 2011). Culdotomy has been widely used for several surgical procedures, not only by gynaecologists but also by general surgeons for extraction of large specimens, and has been approved as safe and easy to close (Tolcher et al., 2012).

In hybrid NOTES the surgical procedure is performed through a natural body orifice with transabdominal assistance. The term pure NOTES refers to procedures that involve only transluminal access.

TECHNIQUE

Two new hysterectomy techniques by pure transvaginal NOTES (vNOTES) will now be discussed:

- **VANH**: Vaginally Assisted NOTES Hysterectomy
- **TVNH:** Total Vaginal NOTES Hysterectomy

VANH

A circular incision is made around the cervix using a cold knife. The Pouch of Douglas and then the vesico-uterine peritoneum, are opened using cold scissors. Both uterosacral ligaments are transected using cold scissors and tied off using a Vicryl-1 suture. A NOTES port is inserted into the peritoneal cavity, and CO^2 used to inflate it. An optic is inserted and the peritoneal cavity is inspected. The patient is now placed in the Trendelenburg position and the small intestine lifted out of the pelvis.

The ureter is identified, but not routinely dissected. The uterine artery is coagulated using a bipolar grasper and is transected. The ovarian artery and the meso of the Fallopian tube are coagulated using a bipolar grasper and transected. In patients requiring an adnexectomy, the infundibulopelvic ligament is coagulated using a bipolar grasper and is transected. Hemostasis is checked and the peritoneal cavity is rinsed. The NOTES port and the uterus are removed transvaginally and the pneumoperitoneum is deflated.

The colpotomy is closed using a resorbable suture.

This procedure can be performed robotically as well. It is then referred to as RVANH or Robotic Vaginally Assisted NOTES Hysterectomy (Baekelandt, 2015a, 2015b).

TVNH

A vNOTES port is inserted into the vagina, and CO^2 is insufflated to create a pneumovagina. An optic is inserted into the pneumovagina. A circular incision is made around the cervix using a monopolar laparoscopic hook, and the Pouch of Douglas is opened using laparoscopic scissors. The vesico-uterine peritoneum is opened using laparoscopic scissors. Both uterosacral ligaments are coagulated using a laparoscopic bipolar grasper and transected. The patient is now placed in the Trendelenburg position and the small intestine is lifted out of the pelvis.

The ureter is identified, but not routinely dissected. It is only dissected if it cannot be identified transperitoneally. The uterine artery and the ovarian artery are coagulated using a bipolar grasper and transected. The meso of the Fallopian tube is coagulated using a bipolar grasper and is transected. In patients requiring an adnexectomy, the infundibulopelvic ligament is coagulated using a bipolar grasper and is transected. Hemostasis is checked and the peritoneal cavity is rinsed. The NOTES port and the uterus are removed trans-vaginally and the pneumoperitoneum is deflated.

The colpotomy is closed using a resorbable suture.

The major difference between TVNH and a VANH lies in the opening of the anterior and posterior peritoneum and the transection of the uterosacral ligaments. This is performed entirely endoscopically in the TVNH, whereas it is performed by classical vaginal surgery in a VANH. The TVNH technique can therefore also be used in nulliparous patients, patients without uterine prolapse, and patients with a narrow vagina where classical vaginal surgery can be more challenging (Lee et al., 2014; Agostini et al., 2003).

This procedure can be performed robotically as well. It is then referred to as RTVNH or Robotic Total Vaginal NOTES Hysterectomy (Baekelandt, in press).

TREATMENT OF ENDOMETRIAL CANCER

As vNOTES may be a less invasive approach to hysterectomy endometrial cancer patients may also benefit from this technique. Since endometrial cancer is associated with a higher BMI, a transvaginal approach may avoid operating through a thick layer of adipose tissue in the abdominal wall. Open abdominal hysterectomies in obese patients are associated with a higher risk of wound infections. The current standard for the treatment of endometrial cancer is transabdominal minimally invasive surgery performed laparoscopically or robotically. Both in the conventional laparoscopic and the robotic approach to endometrial cancer involve inserting endoscopic instruments through the abdominal wall. The thicker the layer of adipose tissue in the abdominal wall, the longer the distance the instruments have to travel before reaching the surgical site. As there is less adipose tissue in the vagina than in the abdominal wall, the distance endoscopic instruments need to travel to the surgical field when inserted transvaginally will increase less with increasing BMI than when they are inserted through the abdominal well. Therefore it would theoretically make sense to try and approach the treatment in the predominantly obese endometrial cancer population via vNOTES.

Introducing a new surgical technique for the treatment of cancer will require and even more rigorous scientific evaluation process than the introduction in benign surgery as the oncologic risks of tumor spread, recurrence rates and survival rates need to be studies. Currently there is not yet sufficient evidence supporting the safe use of vNOTES for the treatment of endometrial cancer. Further research needs to be conducted according to the principles of the IDEAL collaboration (McCulloch et al., 2009).

Protocols for the treatment of endometrial cancer vary in different countries. Generally they involve a hysterectomy with bilateral adnexectomy and depending on the protocol and the stage of the tumor a sentinel node resection or lymphadenectomy. Technically a hysterectomy with bilateral adnexectomy for early stage endometrial cancer is similar to a hysterectomy for benign indications. The use of vNOTES for the treatment of endometrial cancer is still under evaluation. Before looking at the current evidence for the treatment of endometrial cancer via vNOTES, we will give an overview of a current staging and treatment of endometrial cancer.

MINIMALLY INVASIVE SURGERY IN ENDOMETRIAL CANCER: A BELGIAN PROTOCOL

In this paragraph we will look at a Belgian protocol for the treatment of malignant tumors of the endometrium. This paper is a summary based on the oncologic treatment protocol of Vesalius Gynaecologic Oncologic Network (Vergote, 2018).

Preoperative Staging

Start by taking a thorough medical history; including personal history, family history and menopausal status. Follow with a thorough clinical and gynaecological examination, including a transvaginal ultra-

sound. Continue with routine biochemistry and CA125. We routinely perform a spiral CAT scan of the thorax, abdomen, and pelvis. Perform a preoperative ECG. Take an endometrium biopsy or differentiated curettage (preferably without hysteroscopy). Perform an examination under narcosis when there is a suspicion of cervical invasion. Perform a mammogram, if one has not been performed in the last 2 years. Perform an MRI of the uterus when the ultrasound or pathology are unclear, of when the primary therapy will only consist of radiotherapy. A PET-CT scan is scheduled when there is microscopic tumor in the pelvic or para-aortic lymph nodes. A cystoscopy, rectoscopy and bone scan are only performed on indication.

Surgical Staging – FIGO 2009

Stadium I: Tumor limited to the corpus uteri
Stadium Ia G 123: No myometrial invasion or l<1/2 of the myometrium
Stadium Ib G 123: => ½ myometrial invasion
Stadium II: Tumor infiltrating the cervical stroma

But no spread outside the uterus. Spread solely into the endocervical epithelium is classified as Stadium I.

Stadium III: Local and/or regional tumor spread
Stadium IIIa G 123: Invasion of the serosa and/or adnexae (positive peritoneal cytology is to be reported separately and is per se not sufficient to classify the tumor as Stadium III.)
Stadium IIIb G 123: Invasion of the vagina or parametria
Stadium IIIc G 123: Pelvic and/or para-aortic positive lymph node
IIIc1: Positive pelvic lymph node
iiic2: Positive para-aortic lymph node
Stadium IV: Tumor invading the bladder and/or bowel mucosa and/or distant metastasis
Stadium IVa G 123: Invasion into bladder or bowel mucosa
Stadium IVb G 123: Distant metastasis including intra-abdominal and/or inguinal lymph nodes

G 123 is the histological differentiation grade

Endometriumcarinoma Grading

WHO divides endometrium carcinoma into low grade and high grade endometrium carcinoma (Conlon et al., 2014; Roma et al., 2015).

Type1: low grade endometrioid adenocarcinoma (=grade 1 and 2)
Type2: high grde endometrioid adenocarcinoma (grade 3), serous adenocarcinoma, clear-cell adenocarcinoma, mixed adenocarcinoma (type 2 mixed with low grade endometrioid carcinoma)

Mucinous adenocarcinoma behaves like a low grade endometrioid endometrial cancer (type1)

MELF-like (Microcystic Elongated and Fragmented) invasion of the myometrium poses a higher risk of lymph node metastasis (Hertel, 2014).

Anatomical Distribution

In endometrial cancer the first lymph stations are the internal iliac and para-aortic region below as well as above the inferior mesenteric artery (contrary to ovarian cancer where the the high para-aortic lymph nodes are often affected first). In endometrial cancer the low para-aortic lymph nodes are usually only involved when there are metastases in the pelvic lymph nodes, or when there is macroscopic disease in the adnexae, or when there is tumor growing through the uterine serosa (Amant, 2007).

TREATMENT OF ENDOMETRIOID CARCINOMA AND SQUAMOUS DIFFERENTIATION

Operable Patients

See Figure 1.

Sentinel Node Procedure

A Sentinel Node procedure is performed with fluorescence after submucosal injection of 2 mg Indocyan green in the 4 quadrants of the cervix. A full lymphadenectomy is only performed after a Sentinel Node procedure in centers with insufficient experience with Sentinel Node and then for the following indications:

- Infiltration in the outer half of the myometrium
- High grade (G3) endometrioid endometriumcarcinoma
- Non-endometrioid endometriumcarcinoma (serous, clear cell and carcinosarcoma)
- Positive sentinel on frozen section

A Sentinel Node procedure is not reliable when the preoperative imaging demonstrates pathologically enlarged suspect lymph nodes

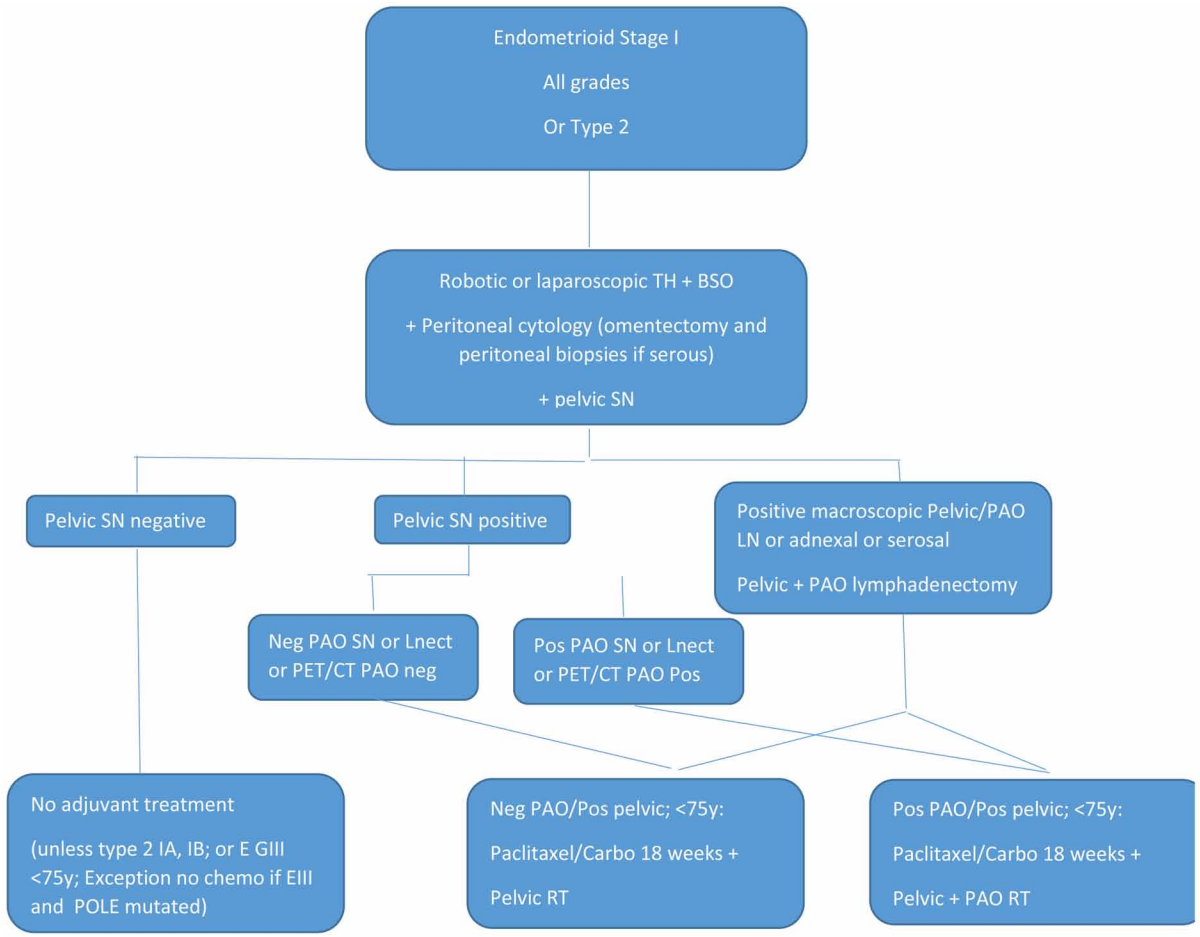
In centers with sufficient experience with a Sentinel Node procedure a positive pelvic SN is not followed by a pelvic lymphadenectomy but by a para-aortic sentinel node procedure (full para-aortic lymphadenectomy when no para-aortic sentinel node is present)

In cases where no sentinel node can be identified, a pelvic lymphadenectomy is only performed on the side where no SN can be identified for the following indications:

- High grade endometrioid (G3), or
- Serous, or
- Clear cell carcinoma, or
- Carcinosarcoma, or
- G1-G2 endometrioid with invasion into the outer half of the myometrium (=IB)

In centers with insufficient experience with sentinel nodes, a para-aortic lymphadnenectomy is only performed when macroscopic metastatic lymph nodes are identified in the pelvis during the surgery, or in case of metastases to the adnexae or transserosal tumor growth.

Figure 1.
TH: *Total Hysterectomy*
BSO: *Bilateral Salpingo-oophorectomy*
Type 2: *Serous, Clear Cell or Unidifferentiated Carcinoma or Carcinosarcoma*
G3 E: *Grade 3 endometetrioid*
SN: *Sentinel Nodes*
LN: *Lymph Nodes*
LNect: *Lymphadectomy*
RT: *Radiotherapy*
PAO: *Para-Aortic*



Stage II

In young patients in good general condition: Robotic (or Laparoscopic) Radical hysterectomy with bilateral salpingo-oophorectomy and pelvic lymphadenectomy (indications para-aortic lymphadenectomy cfr stage I) and peritoneal cytology.

In older patients: external and intracavitary radiotherapy.

Stage III

Note: Positive cytology is not stage III anymore according to FIGO 2009 classification. It is not an indication for adjuvant therapy. The meaning of positive peritoneal cytology is controversial and carries no therapeutic consequences.

IIIa preferably adjuvant therapy with paclitaxel/carboplatinum or alternatively doxorubicine/cisplatinum in women with a biological age <75years. In elderly patients or in cases of important comorbidities carboplatinum mono can be considered.

IIIb preferably radiotherapy

IIIc1 and c2 When the patient is is good general condition start chemotherapy (preferably paclitaxel/carboplatinum) first postoperatively, followed by radiotherapy. Radiotherapy is administered to the pelvic and/or para-aortic region depending on lymph node involvement. Para-aortic radiotherapy after removal of metastatic para-aortic lymph nodes is useful bases on numerous (retrospective) studies. Distant metastases need to be excluded in cases of high-paraaortic positive nodes before starting adjuvant therapy.

In cases with microscopic affected pelvic lymph nodes a PET-CT scan is performed. When the PET-CT scan shows no suspect para-aortic nodes adjuvant chemotherapy is administered followed by pelvic radiotherapy. In cases with suspect para-aortic lymph nodes a robotic (or laparoscopic) para-aortic lymphadenectomy is advised.

Stage IV

In stage IV neoadjuvant therapy is administered. In cases where there is no tumor progression after 3 cycles, and intervaldebulking is performed followed by 3 cycles of adjuvant chemotherapy.

Inoperable Patients

Patients that are inoperable due to medical reasons are treated with radiotherapy.

Follow up

Patients are followed up every 3 months during the first postoperative year, every 6 months during the next 3 years and yearly after 5 years.

Follow-up consists of a good medical history, thorough clinical examination with cytology of the vaginal vault at every check-up. There is no specific marker, but CA125 can be followed up, usually combined with liver tests and calcium. Technical examinations are only performed on indication (Corona et al., 2015).

vNOTES FOR THE TREATMENT OF ENDOMETRIAL CANCER

The research into the treatment of endometrial cancer is still in its infancy. A small number of IDEAL stage 1 studies have been published (McCulloch et al, 2009; Amant, 2007; Leblanc et al., 2016; Tantitamit & Lee, 2019). Since endometrial cancer is associated with a higher BMI, a transvaginal approach may avoid operating through a thick layer of adipose tissue in the abdominal wall. It therefore makes sense to further research into vNOTES for the surgical treatment of endometrial cancer. Current protocols for the treatment of endometrial cancer, as discussed in the previous chapter, focus fully on sentinel node resection and no longer on lymphadenectomies. The focus on research into vNOTES for the treatment of endometrial cancer should therefore lie with sentinel node resections.

Early reports focused on the traditional vNOTES approach: performing a vNOTES hysterectomy and then from the abdominal cavity open the retroperitoneum and dissect the sentinel node (Tantitamit & Lee, 2019; Leblanc et al., 2016). As it is more difficult from this approach to visualize the caudal part of the obturator fossa, this technique theoretically has a higher risk of missing the first sentinel node. A completely new technique seems to overcome this problem (Baekelandt, 2019): in this approach the sentinel node is dissected transvaginally before performing the hysterectomy. The sentinel node is access retroperitoneally via a transvaginal vNOTES access. Via an incision in the lateral fornix the most caudal part of the obturator foramen (where the obturator nerve enters the foramen) is accessed first and then dissected cranially. This access route follows the direction of the lymph vessels. The advantage of a retroperitoneal approach is that the intraperitoneal adipose tissue is not in the way and the sentinel node detection and resection can be performed without Trendelenburg position.

DISCUSSION

According to the Cochrane Database the preferred technique to perform a hysterectomy is via conventional vaginal surgery. When a vaginal hysterectomy is not possible, a laparoscopic hysterectomy may avoid the need for an abdominal hysterectomy (Nieboer et al., 2006). Vaginal hysterectomy can be safely performed for large uteri (Hwang et al., 2002) and in nulliparous women (Agostini et al., 2003). The risk of complications however is higher in nulliparous women (Agostini et al., 2003). The accessibility of the vaginal passage, disease confined to the uterus, and the surgeons experience are the major determining factors for the choice of route for hysterectomies (Chakraborty et al., 2011). In recent years, the incidence of robotic hysterectomy and laparoscopic hysterectomy has increased, whilst the incidence of vaginal and abdominal hysterectomy has decreased (Wasson & Hoffman, 2015). Conventional vaginal hysterectomy can be challenging in cases of enlarged uterus, undescensus, or because of restricted vaginal space in women who have never delivered (Lee et al., 2014). Making use of the advantages of endoscopic surgery vNOTES hysterectomy broadens the indications for vaginal hysterectomy and helps overcome its limitations, while the NOTES approach avoids abdominal wall wounds and trocar related complications.

When compared to classical vaginal hysterectomy, vNOTES hysterectomy offers good endoscopic visibility to operate, and perform haemostasis. Using the enlarged endoscopic view, the surgeon can operate accurately using endoscopic instruments, whereas in some conditions in conventional vaginal hysterectomy, certain steps can only be achieved by palpation (Lee et al., 2014). In addition, adnexal procedures in conventional vaginal surgery can be difficult due to limited accessibility in the restricted space (Lee et al., 2014). Salpingectomy, oophorectomy, ovarian cystectomy, or adhaesiolysis can be

performed via the same NOTES approach during a vNOTES Hysterectomy (Baekelandt, n.d.; Lee et al., 2012). Due to the pneumovagina, TVNH and RTVNH can be performed in nulliparous women, whereas a narrow vaginal access can make a classical vaginal hysterectomy more challenging (Lee et al., 2014; Agostini et al., 2003; Chakraborty et al., 2011)

It has been demonstrated that very large uteri can be removed via VANH, and that ligating the uterine vessels transvaginally before dissecting the rest of the uterus, results in less blood loss compared to a transabdominal laparoscopic approach, where there is more manipulation before occlusion of the feeding vessels (Lee et al., 2014; Su et al., 2012).

When compared to laparoscopic hysterectomy, vNOTES hysterectomies offer the advantage of no visible scarring. In addition, in patients with previous abdominal surgery, there is no need to perform adhaesiolysis to gain access to the pelvis in order to perform the hysterectomy via vNOTES approach, contrary to a laparoscopic approach.

vNOTES hysterectomy (TVNH and VANH) can provide surgeons with the comfort of operating under good endoscopic vision but via vaginal access without increasing the invasiveness of the procedure by making abdominal incisions. In addition, RTVNH and RVANH offer the extra advantages of robotic surgery including better ergonomics, better camera control and articulated wrist motion. However, these advantages need to be weighed against the longer operating time and higher cost. Further technical innovations in surgical robots will help overcome the problem of robotic arm collision and will therefore reduce the time of surgery.

Failure of VANH is almost always due to impedance of the transvaginal colpotomy (Lee et al., 2014). When compared to VANH, TVNH enables the surgeon to perform the colpotomy endoscopically instead of via classical vaginal surgery. This provides better visualization and, as in laparoscopic surgery, the CO2 pressure helps identify and dissect the surgical planes. This enables easy performance of the anterior and posterior colpotomy in patients who had not delivered vaginally and in patients with previous caesarean sections.

The HALON trial (Hysterectomy by transabdominal Laparoscopy of vNOTES) was the first randomized controlled trial to compare vNOTES hysterectomy with total laparoscopic hysterectomy (Zornig et al., 2009). It was a single center prospective blinded non-inferiority efficacy randomized controlled trial. The patients and outcome assessors were blinded by sham incisions in the vNOTES group. The primary outcome demonstrated that vNOTES is not inferior to TLH for the removal of an unprolapsed uterus for benign indications. The secondary outcome parameters demonstrated for vNOTES a significantly shorter operating time, significantly more patients leaving the hospital on the day of the surgery, shorter hospitalization, lower pain scores, less analgesics used and less complications. There was no difference in infection rates, in readmission rates, in total hospitalization cost, in quality of life parameters, in sexual wellbeing or dyspareunia, and in pelvic or vaginal pain.

A surgeon who wants to perform vNOTES hysterectomy should be confident in both classical vaginal hysterectomy and total laparoscopic hysterectomy (TLH). Being experienced in single incision laparoscopic surgery TLH and vNOTES for adnexal surgery certainly helps to keep the learning curve short. In addition, to perform RVANH and RTVNH, the surgeon also needs to be experienced in robotic surgery as the robotic setup for RVANH and RTVNH is complex. In our experience introduction of vNOTES into the hysterectomy armamentarium did not influence the percentage of hysterectomies performed by classical vaginal hysterectomy, but reduced the percentage of TLH in favor of the less invasive NOTES approach.

The use of vNOTES for the treatment of endometrial cancer is still in the IDEAL stage 1 (McCulloch et al., 2009). It is theoretically and based on the first feasibility trials a very promising approach but a lot of further research is needed before vNOTES can become part of the treatment protocols for endometrial cancer.

CONCLUSION

Hysterectomy has traditionally been performed by laparotomy or by conventional vaginal surgery. At the end of the 1980's and during the 1990's the first major paradigm shift occurred with the introduction of the laparoscopic hysterectomy. Hysterectomies could be performed through several small incisions, instead of through one large incision, using a camera that offered superior visualization, and long fine instruments. This less invasive approach allowed quicker recovery and a cosmetically more appealing result. After a period of skepticism, it has now become commonplace in most gynaecology departments.

According to the pioneers and early adopters, vNOTES hysterectomy is now the next paradigm shift. After a period of research, it has become a realistic alternative for an abdominal and laparoscopic hysterectomy. Besides the obvious aesthetic advantage of not creating any visible scars while maintaining superior endoscopic visualization, other potential advantages include shorter operating times, less surgical wound infection, fewer abdominal wall hernias and less abdominal wall pain, all leading to a quicker recovery and shorter hospitalization.

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APPENDIX

Table 1. History of hysterectomy techniques

Technique	Abbreviation	Year	Surgeon
Vaginal Hysterectomy	VH	1813	Conrad Langenbeck
Abdominal Hysterectomy (Subtotal)	AH	1963	Charles Clay
Laparoscopic Assisted Vaginal Hysterectomy	LAVH	1989	Harry Reich
Total Laparoscopic Hysterectomy	TLH	1993	Harry Reich
Robotic Hysterectomy	RH	2002	Concepcion Diaz-Arrastia
Vaginally Assisted NOTES Hysterectomy	VANH	2012	Chyi-Long Lee
Total Vaginal NOTES Hysterectomy	TVNH	2014	Jan Baekelandt
Robotic Vaginally Assisted NOTES Hysterectomy	RVANH	2015	Jan Baekelandt
Robotic Total Vaginal NOTES Hysterectomy	RTVNH	2015	Jan Baekelandt

Table 2. Types of hysterectomy

Abbreviation	Name	Description
TAH	Total Abdominal Hysterectomy	Total hysterectomy performed through a laparotomy under direct vision using conventional surgical instruments.
VH	Vaginal Hysterectomy	Total hysterectomy performed entirely through vaginal access under direct vision using conventional surgical instruments.
LASH	Laparoscopic Supracervical Hysterectomy	Subtotal Hysterectomy performed by transabdominal laparoscopy.
LAVH	Laparoscopic Assisted Vaginal Hysterectomy	Total hysterectomy where first the cranial part of the uterus is dissected via transabdominal laparoscopy and afterwards the caudal part of the uterus (including ligating the uterine vessels) is dissected under direct vision using conventional instruments.
LH	Laparoscopic Hysterectomy	Total hysterectomy where first the cranial part of the uterus is dissected via transabdominal laparoscopy (including ligating the uterine vessels) and afterwards part of the operation is performed vaginally under direct vision using conventional instruments.
TLH	Total Laparoscopic Hysterectomy	Total hysterectomy where the entire uterus is dissected via transabdominal laparoscopy.
RH	Robotic Hysterectomy	Total hysterectomy where the entire uterus is dissected transabdominally using a surgical robot.
VANH	Vaginally Assisted NOTES Hysterectomy	Total hysterectomy where first the caudal part of the uterus is dissected vaginally under direct vision and afterwards the rest of the hysterectomy is performed via transvaginal NOTES using an endoscopic camera and endoscopic instruments.
RVANH	Robotic Vaginally Assisted NOTES Hysterectomy	Total hysterectomy where first the caudal part of the uterus is dissected vaginally under direct vision and afterwards the rest of the hysterectomy is performed via transvaginal NOTES using a surgical robot.
TVNH	Total Vaginal NOTES Hysterectomy	Total hysterectomy where the entire uterus is dissected via transvaginal NOTES using an endoscopic camera and endoscopic instruments.
RTVNH	Robotic Total Vaginal NOTES Hysterectomy	Total hysterectomy where the entire uterus is dissected via transvaginal NOTES using a surgical robot.

Section 7
Breast Pathology

Chapter 23
Chemoprevention in Breast Cancer:
What Is the Added Value?

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ABSTRACT

Chemoprevention in breast cancer represents one of the most important therapeutic regimens in an effort to optimize survival and prevent breast cancer recurrence. The chapter aims to analyze below all potential medical regimens used in breast cancer chemoprevention, along with explaining the reasons why those are the ones selected: their characteristics, their mechanism of action, and their side effects. Among these, we may report tamoxifen, raloxifen, aromatase inhibitors, and new therapeutic regimens such as polyphenoles.

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INTRODUCTION

Below will be analyzed all of the medicine used in breast cancer chemoprevention, the reasons why those are the ones selected, their characteristics, their mechanism of action and their side effects.

SERM (Selective Estrogen Receptor Modulator)

Estrogen administration is associated with the reduction in menopausal symptoms as well as the reduction of the risk of various conditions affecting postmenopausal women. Since estrogen administration also increases the risk for breast cancer, a common dilemma faced by many women and their doctors is whether they will use estrogen replacement therapy (ERT), a selective estrogen receptor modulator (SERM) - (which competes with estrogen effects on the breast tissue but maintains some estrogenic functional properties in other organs or none)(Gabriel & Jatoi, 2012).

For women of very high risk (> 1% per year) with menopausal symptoms, alternatives should be offered and tested. Diagnosis of in situ carcinoma or invasive breast cancer within the last 2 to 5 years should be considered a relative contraindication for ERT unless the tumor was estrogen receptor negative (Fabian & Kimler, 2012).

SERMs were evaluated in phase III clinical trials in women with osteoporosis. The test compared 2 doses of lazofixin with placebo and there was a significant reduction in the incidence of breast cancer with a higher dose of lazofixin 0.5 mg but not at a dose of 0.25 mg. Although the highest dose also reduced the risk of coronary artery disease and stroke, there was an inclination towards more death in a lower dose group compared to placebo (65 deaths vs. 90 deaths, P = 0.05), decreasing overall excitement for this factor and the request for regulatory approval was withdrawn (Chlebowski, 2014).

Below are analyzed the most widely used SERMs worldwide:

TAMOXIFEN

Chemoprevention is based on the use of pharmacological or physical agents to inhibit the development of invasive cancer (Gabriel & Jatoi, 2012). Risk factors for women at least 35 years of age are necessary. Tamoxifen is the oldest and most studied drug in the prevention of breast cancer, which has been studied in many great tests, some of which (as well as their results) are reported as follows: Royal Marsden, NSABP P-1, and of IBIS I, which have been published with subsequent long-term follow-up.

A recent meta-analysis by Cuzick et al. showed an overall risk reduction of 33%. This decrease is mainly due to a large effect on invasive breast cancer, for which the rate of reduction is 44 (p = 0.0001) and a significant decrease in in situ carcinoma (DCIS) (p = 0.009).The effect largely reflects the effect on estrogen-receptor-positive breast cancers with a much lower, non-significant increase in estroge-negative breast cancer. However, according to these studies, women taking tamoxifen had a higher rate of endometrial cancer than patients receiving placebo (OR 2.18, CI 1.39-3.42, p = 0.001) and in addition, thromboembolic events (OR 1.60, CI 1.21-2.12, p = 0.001) (Sismondi et al,. 2015). and moderate cataracts (Reimers et al., 2015).. Regarding the risk for endometrial cancer, it has been shown that the increase in risk is statistically significant for women aged 50 years and above (RR, 4.01 [CI, 1.70 to 10.90]). Women aged less than 50 years who received tamoxifen in several clinical trials have not been

at increased risk. All cases of endometrial cancer in the tamoxifen group were stage 1 and no woman died of endometrial cancer. (Victor G, 2002).

The BCPT study also looked at the effect of the drug on bone fractures. BCPT showed a tendency to reduce hip and spine density (RR-Recurrence Rate, 0.81 [CI, 0.63 to 1.05] in the tamoxifen group.) In BCPT, women in the tamoxifen group are at increased risk for stroke, pulmonary embolism and deep vein thrombosis.(Victor G, 2002). However, only the difference for pulmonary embolism is statistically significant (RR, 3.01 [CI, 1.15 to 9.27]). BCPT reported increased cataract surgery risk in women who were assigned to the tamoxifen group (RR, 1.14 [CI, 1.01 to 1.29] and 1.57 [CI, 1.16 to 2.14] respectively) .The researchers also looked at the incidence of unpleasant side effects affecting quality of life. Women at BCPT reported increased rates of hot flushes (45.7% in the tamoxifen group vs. 28.7% in the placebo group). (Victor G, 2002). In another questionnaire on quality of life, the average percentage of women reported a problem within four measures of sexual function (for example, lack of sexual interest) was about 1 percentage point higher in the tamoxifen group than in the placebo group. Although these differences were statistically significant, they are probably not clinically significant (Reimers et al., 2015).

From the Breast Cancer Prevention (BCPT) P-1 conducted by the National Surgical Adjuvant Breast and Bowel Project (NSABP) with the support of the National Cancer Institute and AstraZeneca Pharmaceuticals to determine whether tamoxifen could reduce prevalence of primary breast cancer in women at increased risk, tamoxifen was found to reduce the risk of invasive breast cancer by 49%, with a cumulative effect on follow-up of 69 months by 43.4 versus 22.0 per 1000 women in its groups placebo and tamoxifen, respectively. There was a reduced risk between women ? 49 years (44% risk reduction), 50-59 years (51% risk reduction) and ? 60 years (55% reduction in risk). (Pan, Chiou, Chen & Ho, 2015).

Overall, high-risk women without menopausal symptoms are the best candidates for the only approved medicine to reduce the risk of breast cancer, tamoxifen. Although the drug is approved for women with a breast cancer risk of 5 years> = 1.7% (0.34% per year), postmenopausal women with a favorable outcome are those with an estimated Gail risk> 0.5% annually and with hysterectomy or> 1% per year if they retain their uterus. Tamoxifen reduces the recurrence of breast cancer and new cancers in the unilateral breast. Tamoxifen should not be used in women with a history of thromboembolic or precancerous endometrial conditions. Tamoxifen is commonly used in Europe in combination with transdermal ERT in women with hysterectomy without apparent loss of efficacy or increased risk of thromboembolism (Gabriel & Jatoi, 2012).

For premenopausal women at increased risk, tamoxifen, which has a relatively favorable profile in younger women, is the only available intervention to prevent breast cancer. In these, tamoxifen given for 5 years reduces the risk of estrogen-receptor-positive breast cancer (ER) for at least 10 years. Women <50 years have fewer serious side effects. Vascular and vasomotor events do not remain after treatment irrespective of age. (Mocanu et al., 2015). A greater reduction in risk is seen in women with a history of lobular carcinoma in situ (LCIS), where tamoxifen reduces the risk by 56%. Among women with atypical hyperplasia, the risk is reduced by 86%. Tamoxifen also reduces the risk of in-situ carcinoma (DCIS) by 50%. The benefit is only seen in women with positive estrogen receptors (69% risk reduction). In contrast, no benefit was seen between women with estrogen-negative receptors. Reduction of hip and spine fractures is also seen, but tamoxifen increases the risk of endometrial cancer, especially among postmenopausal women, where the relative risk is 4.01 (95% CI 1.70-10.90). Percentages of stroke, pulmonary embolism and deep vein thrombosis are also elevated, as already mentioned.

In conclusion, the 2009 recommendations of the American Society for Clinical Oncology support the use of tamoxifen (20 mg daily for 5 years) in women before and after menopause with a risk of breast

cancer for 5 years of over 1.66% or with LCIS history to reduce risk of developing breast cancer. The predicted risk of breast cancer is calculated on the basis of the Cancer Risk Assessment Tool. This tool estimates the risk of breast cancer based on age, past history of DCIS or LCIS, number of first-degree relatives who developed breast cancer and race. The benefit of risk reduction continues for at least 10 years. The impact on breast cancer mortality is unknown and has not been established in previous studies. Because of the increased risk of thromboembolic events, the agent should not be used in women with pre-existing conditions such as stroke (Chlebowski, 2014). Also, due to the increased risk of developing endometrial cancer, women taking tamoxifen need regular gynecological monitoring to assess vaginal bleeding (Reimers et al., 2015).

RALOXIFENE

Raloxifene is a second generation SERM (selective estrogen receptor modulator) with antiestrogenic effects on the bone but with less potent antiestrogenic effects on the breast than tamoxifen. Raloxifene has been approved for use in reducing the risk of osteoporosis. Whether it is as effective as tamoxifen to reduce the risk of breast cancer in postmenopausal women is the subject of ongoing trials, but its use is consistently correlated with reducing this risk (Fabian & Kimler, 2012).

In the raloxifene test compared to placebo, there was a significant reduction in the incidence of invasive breast cancer ($P < 0.0001$), reflecting a large effect on breast cancer with positive estrogen receptors and a non-statistically significant increase in breast cancer with negative estrogen receptors. Endometrial cancer did not increase in raloxifene tests (HR, 1.09 95%, CI, 0.74-1.62 $P = 0.7$) and significant fracture reduction was observed with the use of raloxifene. (Freedman et al., 2011). The use of raloxifene consistently correlates with reducing the risk of breast cancer,as already mentioned (Mocanu, Nagy & Szollosi, 2015).

Among women with high cardiovascular risk, raloxifene has a 40% reduction (RR, 0.60 [CI, 0.38-0.95]) on cardiovascular events (Victor G, 2002).. The MORE study showed a 30% to 50% reduction in vertebral fractures (RR, 0.7 [CI, 0.5 to 0.8] for 60 mg raloxifene per day and 0.5 [CI, 0.4 to 0.7] for 120 mg / kg, but there is no difference between the groups in non-vertebral fractures. In the same study, raloxifene was not associated with an excessive incidence of endometrial cancer (RR, 0.8 [CI, 0.2 to 2.7]) or thromboembolic events. The increased risk was focused on women aged 50 years or above. In the MORE study, women in the raloxifene groups had a three-fold increased risk of pulmonary embolism and deep vein thrombosis compared to those in the placebo groups (RR, 3.1 [CI, 1.5 to 6.2]) (19, 22). The study did not report the incidence of stroke. The total number of thromboembolic events in all four trials was low. MORE participants who received raloxifene also scored higher in hot flushes than those who received placebo (10.7% vs. 6.4%, $P < 0.001$) (Victor G, 2002).

Raloxifene (60 mg daily for 5 years) is now recommended as an alternative chemotherapeutic precaution in postmenopausal women at risk of developing breast cancer for 5 years of more than 1.66% or in women with existing LCIS, in order to reduce the risk of breast cancer. It is not recommended for prophylactic use in pre-menopausal women, because its effect on these women was not studied in the STAR trial. Raloxifene can also be taken for more than 5 years in women with osteoporosis, in whom reducing the risk of breast cancer is a secondary benefit (Freedman et al., 2011).

COMPARISON BETWEEN TAMOXIFEN AND RALOXIFEN

Raloxifene was initially studied in women with osteoporosis and coronary heart disease in the MORE7, CORE8 and RUTH9 studies, which showed a lower incidence of breast cancers in women receiving raloxifene than those receiving placebo. The promising results encouraged researchers to design the Study of Raloxifene and Tamoxifen (STAR or P-2 Study) 10 of NSABP. The first report, after 4 years of follow-up, showed that raloxifene was as effective as tamoxifen in preventing invasive breast cancer, with an approximately 50% reduction. Toxicity and side effects favor raloxifene with fewer cases of deep vein thrombosis and pulmonary embolism, fewer hysterectomies for benign conditions of the uterus, and a small decrease in endometrial cancer. Based on these results, the US FDA approved raloxifene for breast cancer chemoprevention in 2007 (Sismondi, D'Alonzo., Pecchio, Bounous, Robba & Biglia, 2015).

In particular, seeing the results of the MORE study, a somewhat greater effect of raloxifene on the reduction of breast cancers was observed compared to the results of the RAL study (Fabian & Kimler, 2012).

Tamoxifen had a greater effect on reducing the incidence of invasive breast cancer (HR-High Risk, 0.81, 95% CI, 0.70-0.93) in the STAR study, which directly compared tamoxifen to raloxifene with long-term follow-up) (Giammanco et al., 2015). This study showed that the prophylactic effect of raloxifene was not as long as that of tamoxifen: Raloxifene was less effective than tamoxifen to prevent invasive breast cancer in the long term, retaining only 76% of its effect compared to tamoxifen (Sismondi et al,. 2015). Raloxifene results, of course, in the overall reduction in the incidence of breast cancer, significantly reducing estrogen receptor positive cancer, but with a moderate, non-significant increase in breast cancer with negative estrogen receptors. Tamoxifen has a somewhat greater effect on reducing invasive breast cancer than raloxifene and only tamoxifen reduces ductal carcinoma in situ (DCIS). However, only raloxifene reduces fractures. Both tamoxifen and raloxifene increase thromboembolic events while only tamoxifen increases endometrial cancer and cataracts (Giammanco et al., 2015).

In postmenopausal women, raloxifene and tamoxifen reduce the risk of developing invasive breast cancer with the same efficacy, but raloxifene is associated with lower risk of thromboembolic disease, benign uterine and cataract states than tamoxifen in postmenopausal women, as already reported . There is no evidence showing whether reducing the risk of breast cancer by any of these medicines translates into a reduced mortality from breast cancer. The overall quality of life is similar with raloxifene or tamoxifen, but the incidence of dyspareunia, weight gain and musculoskeletal disorders is higher with raloxifene, whereas vasomotor symptoms, bladder incontinence, gynecological symptoms and leg cramps were higher with tamoxifen (Mocanu et al., 2015).

Despite the positive findings of breast cancer, the use of tamoxifen and raloxifene for chemoprophylaxis of breast cancer in the United States is extremely limited. According to a 2010 survey, only 21,000 women aged 35 to 79 used tamoxifen and only 97,000 women aged 50 to 79 used raloxifene for breast cancer chemoprevention. Concerns about side effects and lack of knowledge or awareness are possible explanations. To direct appropriate use, Freedman et al.21 has developed a benefit-criterion marker to quantify the benefits of chemoprevention using tamoxifen or raloxifene. The results of tamoxifen and raloxifene were subsequently evaluated in the NSABP P-116, 17 and other breast cancer prevention trials. For women aged 50 years and older without hysterectomy, raloxifene had a more favorable benefit index than tamoxifen, but in most cases only moderate risk-benefit was observed. For women who had had a hysterectomy, the risk-benefit profile for raloxifene and tamoxifen was similar and, while more women would be candidates for chemoprevention, strong evidence of the benefit that compensates for

the dangers was seen mainly in younger postmenopausal women and in women with significant breast cancer risk over 5 years (Chlebowski, 2014).

AROMATASE INHIBITORS

Another family of chemoprevention drugs are aromatase inhibitors (AIs). Two large clinical trials have compared aromatase inhibitors with placebo in the primary prevention of breast cancer (Holmberg, 2015).

1. MAP.3 was a randomized, placebo-controlled, double-blind trial of 25 mg of exemestane administered to women with a high risk of breast cancer after menopause. The study showed a relative reduction of 65% of the annual incidence of breast cancer (0.35 HR, 95% CI 0.18 -0.70, p = 0.002) (Sismondi et al,. 2015). Exemestane is an aromatase inhibitor that prevents peripheral conversion of androgens to estrogen. In the MAP.3 study, of the 4560 postmenopausal women with an increased risk of breast cancer based on the Gail risk score and participating in the study (with mean follow-up of 35 months), there was a statistically significant reduction in the incidence of invasive breast cancer in the exemestane group (HR: 0.35; 95% CI: 0.18-10.70). The incidence of breast cancer was 0.19% in the exemestane group versus 0.55% in the placebo group. Concerning the risk of other cancers, the incidence of vomit was 1.9% compared to 1.7% in the placebo group (p = 0.58), while the negative cardiovascular events were 4.7% compared with 4.9% (p = 0.78) in the control group. The adverse reactions that occurred at a statistically significant higher rate in the exemestane group compared to placebo were hot flashes (40 vs. 32%, p <0.001), fatigue (23 vs. 21%, p = 0.03), insomnia compared to 8%, p = 0.04), diarrhea (5 vs 3%, p = 0.002), nausea (7 vs 5%, p = 0.04) and arthritis (Chlebowski, 2014).

Also, it is worth mentioning the aromatase inhibitor letrozole, which in a previous NCIC study was shown to play a role in reducing the risk of primary breast cancer in women who had received 5 years of tamoxifen treatment (Micallef S., Micallef D., Schembri-Wismayer, Brincat & Calleja-Agius, 2015).

2. The International Breast Cancer-II Intervention Study (IBIS-II) 13, in which 1,920 women were randomly assigned to take anastrozole 1 mg daily and in 1944 placebo. At the end of the trial, there were significantly fewer breast cancers in the anastrozole group (including in situ carcinoma) compared to the placebo group (32 vs. 64 cases; HR, 0.50, 95% CI, 0, 32-0.76, P = 0.001), and few estrogen receptor positive cancers (HR, 0.42, 95% CI, 0.25-0.71, P = 0.30, 95% 0.74, P = 0.009). Again, the side effects profile was as expected for an estrogen-lowering aromatase inhibitor. While the musculoskeletal side effects were common in the anastrazole group, it was predominantly of moderate severity. Vascular symptoms were commonly observed in both groups, but the incidence was higher in women who were taking anastrozole. There were no increases in fractures, myocardial infarction or heart failure among the groups. It is worth noting that there were significantly fewer known cancers in the anastrozole group, including cancers of the skin and colon. Thus, the side effect profile of aromatase inhibitors is quite favorable for use in the prevention of breast cancer (Chlebowski, 2014)..

However, according to this study, fewer negative estrogen receptors (HR, 0.78, 95% CI 0.35-1.72) were not observed. Estrogen negative tumors, which represent about 30%, remain to be further analyzed for chemoprevention (Fabian & Kimler, 2012). Current approaches to cancer prevention focus mainly on estrogen receptors. Several classes of drugs have been shown to block estrogen-negative breast cancer in animal models, including fenretinide, cox inhibitors and tyrosine kinase inhibitors such as lapatinib and gerphinib (Sismondi et al,. 2015).

COMPARISON OF SERMs AND AROMATASE INHIBITORS

Patients at increased risk due to increased estrogen exposure are more likely to benefit from endocrine therapy treatments, namely selective estrogen receptor modulators (SERMs) and aromatase inhibitors (AIs) (Sismondi et al,. 2015).

Currently, as no test has directly compared aromatase inhibitors with SERM, in the prevention of breast cancer, the comparisons are based on conclusions from all the tests performed. Compared to placebo, the aromatase inhibitors appear to reduce the incidence of breast cancer to a greater extent than tamoxifen or raloxifene. In addition, in aromatase inhibitor trials, there was no additional increase in breast cancer with negative estrogen receptors. An aromatase inhibitor should generally be favored for chemoprophylaxis in postmenopausal women due to a better side effect profile. Also, aromatase inhibitors reduce the recurrence of breast cancer and new breast cancers in the other breast. Unlike tamoxifen and raloxifene, exemestane and anastrozole do not appear to increase the risk of blood clots (Pan et al., 2015). However, they can cause menopausal symptoms, loss of bone density and other side effects. The American Society of Clinical Oncology (ASCO) and the NCCN (National Comprehensive Cancer Network) list excipients and anastrozole as drug options to reduce the risk in postmenopausal women with a higher risk of breast cancer. However, these drugs are not FDA approved for use in risk reduction regulation.

Thus, despite the great complexity of the mechanisms that lead to the development of breast cancer, it is remarkable that a single intervention, such as a decrease in estrogen levels with the aromatase inhibitors, can reduce the incidence of breast cancer by 50% to 65% (Micallef S., Micallef D., Schembri-Wismayer, Brincat & Calleja-Agius, 2015).

NEW PROPOSALS

Polyphenoles - Vitamin D

Extensive research over the past decade has implicated hormonal response, tumor microenvironment, and breast cancer cells (BCSCs) in the development of breast cancer, its therapeutic sensitivity and relapse. Indeed, the occurrence of a malignant phenotype is dependent on the endocrine, autocrine and paracrine networks of the major oncogenic mediators such as NRS receptors, tyrosine kinase receptors, proteolytic enzymes, inflammatory cytokines and chemokines, Notch, β-catenin, nicotinic acetylcholine receptors (nAChRs), ATP transporters etc. Equally important today's studies have found that various selective epigenetic mechanisms can mutually interact with hormone signaling (eg, estrogen receptor (ER)) to regulate gene expression and cause genetic alterations. Therefore, the deregulation of epigenetic events

can contribute to the initiation and promotion of carcinogenicity and malignant phenotype, and indeed it is involved in tumor hormone processes (Pan et al., 2015).

Recently, several clinical studies support the belief that dietary polyphenols can reverse gene expression and modify processes such as DNA methylation, histone modification and RNA coding (miRNA) (Mocanu et al., 2015). Phenolic compounds can be classified into two groups: flavonoids and non-flavonoids, which are large and ubiquitous groups of phytochemicals naturally occurring in a wide variety of fruits and vegetables. For preclinical application, healthy dietary modification with the consumption of foods rich in biologically active ingredients (i.e., fiber, fruit, vegetables and whole grains) is currently supported as a potentially beneficial way for significant chemoprevention in breast cancer (Pan et al., 2015).

Chemoprevention is defined as the use of agents of natural or synthetic origin in order to try and reduce the likelihood of disease progression and to prevent or stop the risk of developing cancer or relapse. At present, breast cancer chemoprophylaxis through endocrine therapy using selective estrogen receptor modulators (SERMs) and aromatase inhibitors (AIs), already mentioned above, is promising. However, studies have found that many dietary phenolic compounds can provide better preventative options and potential therapeutic efficacy, while generally exerting low toxicity compared to conventional drugs. Recent literature and reviews have shown that natural phenolic compounds can prevent breast tumor genesis, improve phytochemical bioavailability and increase drug sensitivity. At present, phenolic compounds such as EGCG and resveratrol are believed to have high potency as anticancer compounds, as they have been reported to exert prophylactic action on cancer by regulating disease-specific molecular paths in dozens of studies, including clinical trials (Pan et al., 2015).

It has been found that endocrine signaling can affect the development and progress of breast cancer. Endocrine signaling may be activated by nuclear receptors (NRs), including steroid hormone receptors, estrogen receptor (ER), progesterone receptor (PR), androgen receptor (AR), glucocorticoid receptor (GR), and non-steroidal thyroid hormone (TR) hormones, vitamin D receptor (VDR), retinoids (α, β, β) and PPAR (Gabriel & Jatoi, 2012). Apigenin, luteolin, tangerhetin, chrysine, cresetin, cambopherol, genistein, calicosin and resveratrol exhibit estrogenic / anti-estrogenic and androgenic / anti-androgenic effects as well as GR and PR antagonist activities with subsequent antioxidant, anti-toxic, antiproliferative and pro-apoptotic actions. Studies have shown that genistein, apigenin and luteolin have estrogen agonist and progesterone antagonist activity by binding to ER and PR ligands, respectively (Pan et al., 2015).

Also, luteolin, ekeretin, narinin, theaflavin (TF-1), theavalinine 3,3'-biphthalate (TF-3) and genistein inhibit aromatase enzyme activity, AP-1 by binding protein thus suppressing cell proliferation. However, genistein may also reactivate ERAR expression by reshaping the chromatin structure in the ERa promoter and preventing tumor genesis in ERa-negative breast cancer that is clinically aggressive and does not respond to conventional estrogen target therapies (Chlebowski, 2014).

Regulation of the estrogen pathway may also be the result of epigenetic changes from post-translational modifications and methylation of DNA. A variety of enzymes and miRNAs involved in epigenetic signaling can be used for early detection and prevention of breast cancer. Recent studies have reported that formonectin and calcikosin can enhance antiproliferative capacity and cause apoptosis by inhibiting miR-375 expression, increasing ERB levels and altering signaling pathways (Pan et al., 2015).

Luteolin also tends to induce gene transcription in MCF-7 breast cancer cells through an epigenetic mechanism involving histone H4 acetylation in kinase 1 (PLK-1) promoter, thereby inhibiting mitotic progression. These findings suggest that phenolic compounds can exert profound effects on breast cancer chemoprophylaxis and chemotherapy through endocrine signaling (Pan et al., 2015).

Analytical results have shown that chrysine, genistein and curcumin can regulate the expression of basic oncogenes associated with HDAC8 inhibition, HMT induction, and demethylation of CpG, which effectively reduces cellular proliferation and causes differentiation and apoptosis of cells (Mocanu et al., 2015).

During breast carcinogenesis, resveratrol demonstrated protective effects by activating Nrf2-mediated pathways and downstream expression of the target gene (NQO1, SOD3, OGG1, AOX1 and FMO1), which were partially regulated by modifying the methylation of Nrf2 that targets the expression of the miR-93 gene. Therefore, oxidative stress targeting can be a useful strategy to prevent further damage in the development of breast cancer (Pan et al., 2015).

Recently, several studies have shown that IGF-1R can increase cell proliferation and enhance metastasis by interacting with circulating estrogen levels. Luteolin and two isoflavones (calicosine and formonodein) effectively inactivate the IGF / PI3K / Akt and p38 pathways in in vitro and in vivo studies, possibly due to an increase in apoptosis sensitivity (Mocanu et al., 2015).

In addition, the exposure of breast cancer cells to apigenin, luteolin and garsinol indicate significant stimulation of apoptosis by inhibiting FK3K / Akt binding proteins, p90 ribosomal S6 kinase (RSK) / Y-box (YB-1), Notch- Wnt / B-catenin, GSK3β and NF-?B signaling pathways (Mocanu et al., 2015). Specifically, in vitro studies demonstrate that cummustrol and curcumin can cause cellular aging and DNA damage, suppress precarcinogenic potential in MCF-7 breast cancer cells and may also activate CAF-associated fibroblasts. Cumsulin and curcumin induce cell aging by increasing gene expression of 16, p21 and p53 and inactivating CKII and Janus kinases (JAK) 2 mutations and they also activate STAT3 signaling pathways. Data from a breast cancer promoting model induced by bisphenol A (BPA) showed that curcumin inhibited the oncogenic expression of miR-19a and miR-19b and reversed unregulated miR-19 proteins, including PTEN, p-AKT, p -MDM2, p53, and proliferation of nuclear antigenic cells (pCNA), leading to suppression of cellular proliferation. Polyphenol curcumin has additionally been found to inhibit the expression of pro-inflammatory cytokines CXCL1 and -2, leading to reduced formation of breast cancer metastases. Using miRNA expression assays, it is observed that curcumin regulates the expression of a series of miRNAs, including miR181b, in breast cancer metastatic cells. MiR181b also mediates the effects of curcumin on inhibiting proliferation as well as inducing apoptosis. Cumsrol also acts as an ER antagonist competing with 17-β-estradiol and other estrogen compounds (Kronski, 2014).

Terpenoids are a group of substances found in almost all natural foods. This class has been shown to be beneficial for maintaining and improving health and includes various subcategories such as mono-terpenes (limonene, carbonate and carveol), diterpenes (retinoids), triterpenes (oleic acid and uricolic acid) and tetraperphenes (α- and β- carotene, lutein, lycopene, zeaxanthin and cryptoxanthin) (Rabi & Bishayee, 2009).. These subclasses have been shown to have a number of mechanisms of action that affect (among others) oxidative stress, carcinogenicity and cardiovascular disease. Below are the main ones:

Monterpenes

They are widely known as secondary plant metabolites and components of essential oils and aromatic plants. The chemoprotective effects of monoterpenes during the onset of breast carcinogenesis are due to the induction of carcinogenic phase II metabolism enzymes, resulting in detoxification of carcinogen by blocking the active mechanism. The chemopreventive and chemotherapeutic effects of mononucleotides in the post-onset phase may be due to induction of tumor cell apoptosis, tumor redifferentiation and / or inhibition of post-translational isoprenylation of cell growth-regulating proteins (Rabi & Bishayee, 2009)..

Sesqueterpenes

Sesquippenic phlorosol found in lemon, chamomile and lavender shows that it is a stronger compound than d-limonene or perglycolic alcohol in vivo and is in progress to prevent breast cancer. Farnesol has been selected for clinical development through the Rapid Access to Preventive Intervention (RAPID) program of the National Cancer Institute (RAPID) and has been found to induce a decrease in ER levels and increase progesterone receptor expression. Parathenolide (PTL) is a sesquiterpene lactone that is the main active ingredient in Feverfew (Tanacetum parthenium), a herbal medicine that has been used to treat migraine and rheumatoid arthritis for centuries. PTL has been found to have anti-cancer activity and inhibits DNA synthesis and cell proliferation in different cell lines (Rabi & Bishayee, 2009).

Table 1. Breast Cancer: Advantages and disadvantages of the use of polyphenols

Advantages	Disadvantages
Antioxidant activity promotes the protection of DNA against carcinogenesis	Heterogeneity in: applied doses, the duration of administration, cells and animal models that are used in the studies.
Reduced glucose uptake into cancer cells	Reduced bioavailability and stability
Cessation of the cell cycle, induction of pre-apoptotic proteins and inhibition of anti-apoptotic proteins	The chemopreventative and therapeutic role of polyphenols as individual agents or in combination with each other, are being studied in ongoing tests currently, without any final conclusions.
Decreased expression of plasma membrane – receptors, that are normally overexpressed in breast cancer.	In most in vitro studies, large concentrations have been used, that are unlikely to be achieved in vivo
Reduced intracellular protein phosphorylation	
There has been notified a significant reduction of the risk of breast cancer in Chinese and Japanese women. This reduction is also associated with high soy intake during adolescence.	
Reduced risk of breast cancer recurrence (after consistent intake of nadizine)	

Finally, experimental observations suggest that the chemoprotective effects of vitamin D appear to be mainly due to its activity in important biological functions such as cell proliferation, cell differentiation, growth factor expression, apoptosis (Pan et al., 2015).. In addition, vitamin D has been shown to inhibit the progression of the breast cancer cell cycle (and that of prostate cancer) by inhibiting cells in the G1 / S cell phase transition (Istfan et al., 2007, Jensen et al., 2001). This phenomenon appears to be due to the conversion of the Rb gene, a direct target of cyclin-CDK complexes, into its active hypophosphorylated form (Jensen et al., 2001).

Also, vitamin D has been shown to promote apoptosis in breast cancer. Recent in vitro studies by Sergeev (2012) suggest that, in breast cancer cells, vitamin D may act as an apoptotic primate that directly intakes Ca (2+). Finally, Tse et al. (2010) reported that vitamin D3 inhibits NF-kB activity in human breast cancer cells (Reimers et al., 2015).

METFORMIN

Metformin is a safe drug that is widely used by millions of people, in order to treat non-insulin dependent diabetes. The logic behind the use of metformin in the prevention of breast cancer arose at first due to obesity, which is an independent risk factor for breast cancer in post-menopausal women. Many studies have shown that long-term use of metformin can have a beneficial effect on the risk of breast cancer. Small biomarker studies have been performed in women with breast cancer with placebo and are showing beneficial results. (Harrisson, 2017).

There are multiple ways in which metformin might be leading to favorable outcomes as far as the risk of breast cancer is concerned.

1. NFκB pathways are essential for transformation and cancer stem cell formation. Metformin prevents the nuclear translocation of NFκB and phosphorylation of STAT3 in cancer stem cells compared with non-stem cancer cells in the same population, therefore suppressing the early stages of the inflammatory pathway that is associated with cancer. (Hirsch, Iliopoulos & Struhl, 2013)
2. The use of metformin can lead to the suppression of both proliferation and migration of breast cancer cells. This occurs due to the dysregulation of the matrix metalloproteinases MMP-2 and MMP-9, in addition to downregulation of oncogenic microRNAs miR-21 and miR-155 by this agent. (Sharma & Kumar, 2018)
3. Lastly, metformin administration inhibits protein synthesis and gluconeogenesis, by indirectly activating AMPK. This results in reduced availability of nutritional substrates that are mandatory for cancer cell proliferation . AMPK further inhibits mTOR which is a downstream activator of growth factors in malignant cells and has also been engaged in multiple drug resistance (MDR) in various forms of cancer (Jalving et al., 2010). More specifically, in in vivo and in vitro animal studies, metformin has been proven to reduce the expression of several proteins that cause MDR. Moreover, it has actually been suggested that metformin may not only prevent MDR, but may even re-sensitise cancer cells to standard chemotherapy agents to which they were once sensitive (Davies et al., 2017).

The dose of metformin required to achieve a favorable effect is unidentified. Several doses have been used in studies with varying clinical effects. According to Schexnayder et al. (2018), metformin administered at pharmacologically achievable concentrations inhibits inflammatory signalling and metastatic progression of the disease through reduced ICAM1, COX2, PGE2 and ROS levels, but it does not have a significant effect on the viability of breast cancer cells. However, decreased cell viability was reported at higher concentrations of administered metformin.

The ALTTO trial on metformin use in $HER2^+$ breast cancer showed that metformin may improve the worse prognosis that is associated with diabetes and insulin treatment in patients with $HER2^+$ and hormone receptor positive breast cancer (Sonnenblick et al., 2017).

The potential for chemopreventative benefits of metformin in patients at risk for breast cancer is rapidly becoming an area of interest in both clinical oncology and endocrinology (Dowling et al., 2015). However, more long-term double blinded-randomised trials are needed to explore the precise role that metformin can play. Most current studies have reported a mixed picture on metformin's efficacy, which could be due to the different doses of metformin as well as varying periods of follow-up used in these studies. It is clear that metformin holds considerable promise with regard to a potential anti-tumour role.

BISPHOSPHONATES

Bisphosphonates were originally developed to treat osteoporosis and are commonly used to regulate breast cancer, control the loss of bone mass which is caused by chemotherapy and prevent metastasis. Several studies have shown that bisphosphonates lead to reduction of breast cancer risk in postmenopausal women by about 30%. Of course, more studies are needed in order to fully explore the risk versus benefit analogy of these factors in breast cancer prevention. It has also not been made clear whether they are suitable for premenopausal women.

Chlebowski et al. (2010), showed the results of the Women's Health Initiative (WHI) regarding the risk of breast cancer in women who used bisphosphonates. In this observational study of 154,768 patients, 2816 of whom used oral bisphosphonates (90% alendronate and 10% etidronate), it was found that the incidence of invasive breast cancer was lower in patients who used bisphosphonates ([HR]= 0.68, 95%CI, 0.52-0.88; $p < 0.01$), after 7.8 years of follow-up. Further analysis showed that the favorable outcome was identified both in patients with ER- positive breast cancer, where a reduction of the incidence reached a HR of 0.70 (95%CI, 0.52-0.94; $p < 0.02$), and in ER- negative patients, although the results in the last group were not statistically significant, probably due to the low number of women in this group (HR, 0.66, 95%CI, 0.31-1.39; $p < 0.27$). In an interesting study by Rennert, Pinchev & Rennert (2010), it was found that bisphosphonates administration for at least 1 year before the diagnosis of breast cancer, was associated with a significant reduction in the risk of breast cancer ([OR] 0.61; 95%CI, 0.50-0.76).

Moreover, biphosphonates are valuable in adjuvant therapy of breast cancer. They have been found to induce cell apoptosis and proliferation, reduction of angiogenesis, inhibition of tumor-cell invasion, activation of the immune system against cancer cells, synergy with anti-cancer agents, osteoclast inhibiting activity and prevention of tumor growth factors release. In their study Powles, Paterson, McCloskey, Schein, Scheffler & Tidy (2006), have observed that the administration of oral clodronate reduces bone relapse and improves overall survival in breast cancer patients.

They randomized 1,079 patients with early stage breast cancer to standard adjuvant therapy and placebo or clodronate (1,600 mg/day) for 2 years and reported a decrease in the incidence of bone metastases during the initial 2 years ($p = 0.01$) and increased survival in the clodronate arm after a median follow-up of 5.6 years versus placebo ($HR = 0.77$, $p = 0.048$). These studies arouse scientific interest and thus adjuvant trials involving zoledronic acid (ZOL) were initiated that target not only bone mineral density (BMD) maintenance but also breast cancer recurrence and overall survival (Bedard, Body& Piccart-Gebhart, 2010).

However, whether they are used for breast cancer chemoprevention or treatment, it should be noted that bisphosphonates are not free of risk, with the potential for renal toxicity, osteonecrosis of the jaw and, rarely,atypical femoral fractures. Oral bisphosphonates are especially associated with gastrointestinal problems.

NON – STEROIDAL ANTI – INFLAMMATORY DRUGS

Long-term follow-up studies, through randomized trials, of people using aspirin to prevent vascular disease has shown that daily use has reduced the incidence of several types of cancers. In addition, data from cohort studies show a reduced risk of breast cancer by about 10% for aspirin and possibly a little more for ibuprofen. Similar results have been found with other non-steroidal anti-inflammatory drugs.

Although the effect of NSAIDs on reducing breast cancer risk is too small to reach a definitive decision on their use and approval, these drugs may be part of an expanded approach to treating breast cancer long term.

Studies that support the previous data will be presented below:

1. Clarke et al. (2017), observed 20% reduction in risk of developing HR-positive/HER2-negative breast cancer in women who were using low-dose aspirin at least three times per week. No such association was observed for use of regular-dose aspirin (325 mg) or other NSAIDs though.
2. In another study, NSAID consumption resulted in a 24% reduction of risk in developing breast cancer ([OR] : 0.76; 95% [CI]: 0.64–0.89). These results were not observed while admininstering aspirin though, but for acetic acid derivatives, propionic acid derivatives and COXIBs. Similar results were found in postmenopausal and premenopausal women. Moreover, the use of NSAIDs was found to protect against HER2-positive cancers, but not against triple negative breast cancer. Agents associated with the COX-2 factor seem to have a favorable association with breast cancer outcome (i.e. OR < 1), except in advanced clinical stage and triple negative cancers (Dierssen-Sotos et al., 2016).
3. In the recent study conducted by Kehm et al., (2019), regular aspirin use was associated with a 39% and 37% reduced risk of breast cancer in the prospective (HR = 0.61; 95% CI = 0.33–1.14) and combined cohorts (HR = 0.63; 95% CI = 0.57–0.71) respectively. Regular use of COX-2 inhibitors was associated with a 61% and 71% reduced risk of breast cancer (prospective HR = 0.39; 95% CI = 0.15–0.97; combined HR = 0.29; 95% CI = 0.23–0.38).

CONCLUSION

As far as chemoprevention is concerned, selective estrogen receptor modulators (SERMs) - tamoxifen and raloxifene, reduce the incidence of breast cancer. In a direct comparison, tamoxifen resulted in a greater reduction in breast cancer than raloxifene, but with a higher risk for endometrial cancer. Aromatase inhibitors, exemestane and anastrozole, also reduce the risk of breast cancer. In hormone therapy, in postmenopausal women without previous hysterectomy, estrogen along with progestin increased the incidence and death from breast cancer, whereas estrogen alone in women with previous hysterectomy led to a reduced incidence of breast cancer and decreased deaths from breast cancer. For premenopausal women with an increased risk of breast cancer, tamoxifen is a good choice with a favorable toxicity profile. For postmenopausal women, while there is no direct comparison of SERMs and aromatase inhibitors for chemoprevention, comparisons in crossover studies indicate greater efficacy and a more favorable side effect profile for the use of aromatase inhibitors, especially for older women (Vogel, 2011).

In particular, many large randomized clinical trials (NASBP P-1, IBIS I, STAR, and NCIC CTG MAP.3) have shown that tamoxifen, raloxifene and exemestane (aromatase inhibitor) may reduce the risk of invasive breast cancer in women who are at increased risk. The randomized clinical trial NSABP P-1 showed that tamoxifen (20 mg daily for 5 years) reduced the incidence of estrogen receptor positive breast cancer in both premenopausal and postmenopausal women at increased risk. The side effects of tamoxifen include an increased risk of developing endometrial cancer and thromboembolic events. The randomized NSABP P-2 STAR clinical trial showed that compared to tamoxifen, the selective estrogen receptor modulator raloxifene (60 mg daily for 5 years) also reduced the incidence of breast cancer in

postmenopausal women. Adverse reactions include a small risk for thromboembolic events, but there was no increased risk of endometrial cancer, as was found with tamoxifen. Extemestane, an aromatase inhibitor (25 mg daily), has been shown to be effective in the NCTC CTC MAP.3 trial to reduce the risk of breast cancer in postmenopausal women at high risk. It was not associated with an increased risk of developing endometrial cancer or thromboembolic events, but it is associated with an increased risk of hot flashes and arthritis (Chlebowski, 2014).

Also, it can be assumed that any agent that can reduce the recurrence of breast cancer and reduce the contralateral breast cancers in adjuvant trials will also be an effective chemoprevention agent if combined with a favorable side effect profile. Factors that could benefit in this concept are metformin, biphosphonates and NSAIDs, as some researchers support (Giammanco et al., 2015).

Finally, all women, regardless of the risk of breast cancer, are advised to take various steps to reduce the risk, including normal body weight, exercise, adequate calcium and vitamin D intake, and abstain from smoking and alcohol . Preventive choices are best weighed during a personalized consultation where symptoms of woman's menopause, the risk of breast cancer and other illnesses can be considered, and options for improving postmenopausal health can be discussed (Reimers et al., 2015).

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Section 8
Miscellaneous

Chapter 24
Surgery, Chemotherapy, and Radiotherapy for Gynaecological Cancer:
What Are the Main Complications to Overcome?

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ABSTRACT

Gynaecological oncology treatment yields no fewer complications and side effects than those met in any other oncology field. Patients and clinicians are highly alerted by the ominous diagnosis and sometimes seek for high risk, experimental, or even unproven therapies and are consequently prepared to accept high complication rates that would otherwise be unacceptable. Still, risk reduction remains a high priority. This is achieved by appropriate risk assessment, risk-to-benefit ratio balancing, treatment individualisation, close follow up through all treatment stages, and prompt patient informing and participation in decision making. The chapter aims to summarize the main complications of surgery, chemotherapy, and radiotherapy as well as the main ways to overcome them.

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INTRODUCTION

Gynaecological oncology treatment yields no less complications and side effects than those met in any other oncology field. Patients and clinicians are highly alerted by the ominous diagnosis and sometimes seek for high risk, experimental or even unproven therapies and are consequently prepared to accept high complication rates that would otherwise be unacceptable. Still, risk reduction remains high priority. This is achieved by appropriate risk assessment, risk to benefit ratio balancing, treatment individualisation, close follow up through all treatment stages and prompt patient informing and participation in decision making.

Cardiovascular and Thrombosis

Malignant disease is known to increase risk of thrombosis and oncology treatment is a standalone additional risk factor for thrombosis (Horsted). Women who undergo surgery for gynaecological cancer face 25% increased risk for thrombosis (Nicolaides). This risk increase may be associated with complicated and time lengthy surgical procedures and is observed in both open and laparoscopic operations. A successful risk reduction strategy includes mechanical alongside with pharmaceutical thromboprophylaxis. The use of intermittent compression devices in operating theatre, graded compression stockings post-operatively, leg elevation and early mobilisation may be beneficial (Clarke-Pearson). Administration of heparin or low molecular weight heparin should commence 2 hours pre- operatively or 8 hours post-operatively. The combination of mechanical and pharmaceutical thromboprophylaxis appears to be superior to one or the other and should be used concomitantly (Zheng). The duration of thromboprophylaxis should well exceed that of hospitalisation, as it has been shown that most thrombosis incidents occur later than the 21st post operative day in oncology patients (Agnelli G).

Several classical chemotherapy medications, as well as newer ones that target angiogenetic agents, which are associated with tumur metastases, may exhibit angiotoxicity, which, in turn increases risk of hypertension, thrombosis, heart failure, myocardiopathy and arrythmias (Cameron 2016). The prevalence of cardiovascular disease that is potentially attributable to chemotherapy is expected to rise in the future due to the increase in life expectancy of oncology patients, as well as the general population. Angiotoxicity effects are short and long term; management of these includes early recognition with prompt cardiology review and monitoring of appropriate indices that may include blood pressure, electrrocardiogramme, ultrasound and flow studies and renal function tests. Women must be informed when an increased long term or even life long cardiovasular disease risk is anticipated, so as, they seek for continuing care after oncology follow up may be completed.

The effect of radiotherapy on the cardiovascular system has not been extensively researched. In vitro studies have shown that irradiation activates the vascular endothelium via an inflammatory reaction, also interferes with vitamin C and exhibits a thrombogenic capacity in total (Halle). Notably irradiation has been used for palliative coagulative treatment. Limited clinical data indicate that patients who received radiotherapy have an increased risk of thrombosis and cerebrovascular bleeding (Guy). Based on these data, those who undergo chemotherapy may also receive individualised thromboprophylaxis.

Sepsis and Infection

Sepsis is a major morbidity and mortality contributor in debilitated and immunosupressed oncology patients. Wound infection after major abdominal surgery for gynaecological malignancies has been reported from 3 to 36% (Mahdi, Saeed). A comprehensive strategy including skin dissinfection that comenses 24 hours pre-operatively, bowel preparation with enema and antibiotics, targeted intra-operative antibiotic administration, sterile wound closure and meticulous bandaging and postoperative euglycaemia may dramatically decrease the risk of postoperative wound infection (Lippitt).

Most chemotherapy medications cause immunosupression and this is one of the commonest and most threatening complications of oncological treatment. Neutropenia is not rare although it is usually mild with newer chemotherapy agents. Systemic fungal infection is a major risk in immunosupressed patients. Prevention of sepsis starts from nutrition improvement, a healthy life style and monitoring of inflammation indices. Any infection should be treated promptly and targeted and best practice standards should be observed in order to avoid development of pathogens resistance to antibiotics. It is imperative that unnecessary hospital admissions are avoided. The risk of infection should be re-accessed at every stage of treatment and special tools may be used for this purpose e.g. the Multinational Association of Supportive Care of Cancer (MASCC) risk-index score (Gunderson).

Those who receive radiotherapy may develop systemic immunosupression or local infection associated with herpes simplex viruses. On the other hand active herpes infection may cause resistance to radiotherapy thus necessitating dose increase. When infection with herpes simplex viruses is disseminated to the viscera it can be lethal. Sometimes a herpetic skin lesion may be taken for such that is associated with radiotherapy dermatitis; high vigilance for these lesions is mandatory, as well as early initiation of treatment (Ramirez-Fort).

Metabolic Disorders and Renal Function

Chemotherapy has been associated with reduced bone density in women of both reproductive and menopausal age although these data are not unanimous (Handforth, Christensen, Axelsen). In any case women who receive treatment for gynaecological malignancies should be screened for osteoporosis and treated carefully, also taking their renal function into account. Treatment with monoclonal antibodies has been associated with rear incidence of newly diagnosed type 1 diabetes mellitus and treatment with ifosfamide has been associated with a 10-15% risk of encephalitis and also risk of nephrogenic diabetes insipidus (Chae, Tsukamoto). Cisplatin causes dose related nephrotoxicity and so does radiotherapy. There is some data that concomitant administration of magnesium or a prazole is somewhat protective (Saito, Ikemura).

Haematological Disorders

Thrombosis and neutropenia, which are referred to above, are not the only haematological disorders of gynaecological oncology treatment. Chemotherapy on its own or combined with radiotherapy has been associated with leukaemia and myelodysplastic syndrome (Shimada). Such data are more available for alkylating agents, topoisomerase inhibitors and platins, while for newer medications there is not enough data. Haematological malignancies after oncology treatment should not be considered as mestatic disease and should be treated with appropriate combined chemotherapy and bone marrow transplantation if

required. Prognosis of such cases is equivalent to primary leukemia if the disease responds to combined chemotherapy, however recurrence risk is higher.

Older and newer chemotherapy agents may cause myelotoxicity, including e.g Poly (ADP-ribose) polymerase inhibitors, which have been reported to cause acute myelosuppression with neutropenia, thrombocytopenia and anaemia.

Gastrointestinal Disorders

Surgery for gynaecological malignancies may involve several viscera either due to extension of the disease or surgical technique. Although preoperative imaging and staging can usually predict the surgical plane, bowel manipulation or injury is not rare. Enterotomy, enterectomy and colostomy may be required. For this reason women who undergo gynaecological oncology surgery should have bowel preparation and dissinfection similar to that for bowel surgery. Also, a gynaecological oncology surgeon should be trained in bowel surgery and possibly a colorectal surgeon should be available upon request to join in surgical theatre. When advanced bowel surgery is performed, women run the risk of relevant complications which include malnourishment or malabsorption and chronic abdominal pain, which hinders recuperation and further treatment; also, in case of a colostomy, women face problems with self care and changes in their self image. A multidisciplinary health professional team is required for these patients and this should be offered by the health service provider.

Many chemotherapy agents exhibit hepatotoxicity although this is rare and is usually attributed to idiosyncratic reaction (type B adverse reaction). Hepatotoxicity must be distinguished from hepatitis flare up, mainly HBV associated, and also from liver metastatic disease. A comprehensive pre-treatment liver function check, along side with routine follow up during and after treatment, can uncover those cases with true hepatotoxicity and will allow for prompt discontinuation of medication.

Most chemotherapy medications exhibit generalised toxicity on mucosae. Gastrointestinal lesions are very common, as the epithelium resembles malignant tumours in that it has a high cell proliferation rate. The endothelium of the visceral blood vessels is also affected and contributes to the most ominus side effects like the ischaemic intestinal necrosis (Li). Neurotoxicity on the visceral innervation is currently researched and may cary the potential to be used in the therapeutics (Escallante).

Prevention of gastrointestinal adverse effects includes selection of safest medications and there is a lot to be anticipated from newly developed drugs in the future. Close monitoring during treatment is necessary in order to timely readjust dosage and prevent necrosis and perforation. Limitation to diagnosis of gastrointestinal chemotherapy related lesions is, unfortunately, caused be the fact that endoscopy, especially of the large bowel, runs increased risk of perforation in these patients due to the exact nature of the toxicity and should be limited to selected patients (Boussios).

Radiotherapy also, is known to exhibit toxicity on mucosae. Radiation enteritis presenting with diarrhea and abdominal pain is present in at least 50% of patients who receive pelvic or abdominal radiotherapy. Symptoms usually start on the third week of radiotherapy and are treated with antidiarrheals, somatostatin and strong pain relief (Shafi). Sometimes symptoms extend to the anus and rectum within 6 weeks and apart from diarrhea they may include fecal urgency, tenesmus and anal bleeding. This early onset proctitis responds well to symptomatic relief and resolves within 6 months from radiotherapy. Late onset chronic proctitis, however, which can occur up to 12 months post radiotherapy, is more bothersome and can cause anorectal strictures or persistent bleeding that may be challenging to

treat. Treatment includes hyperbaric oxygen sessions, short chain fatty acids enemata and endoscopical cauterisation or excision (Mayer, al-Sabbagh).

Post radiotherapy lesions of the intestines may lead to fistulae to the urogenital system or the skin.

Urinary Tract

Surgical treatment of gynaecological oncology patients often inevitably involves the urinary tract viscera. Tumour expansion, anatomical variations and close adjacency make the urinary tract vulnerable to intended and unintended surgical trauma. Preoperative imaging may allow for improved risk management and appropriate measures e.g. prophylactic ureteral stenting, while intra-operative availability of lower urinary tract endoscopy equipment may also be of benefit. All intra-operative injuries must be recognised and treated, in order to minimise risk of strictures and fistulae.

Both the ureters and the bladder may be put at harm by chemotherapy as well as radiotherapy. A typical complication is post radiation cystitis. It is presented with urinary frequency with small voided volume, urgency, painful bladder, dysuria and haematuria. It is believed that the pathophysiology includes vascular damage leading to ischaemia, fibrosis and bladder wall shrinkage. Although symptoms subside within 12 months, often the woman is left with persisting overactive bladder syndrome of some degree, which is associated with reduced bladder capacity and is refractory to conservative treatment. Haemorrhagic cystitis may require laser ablation under cystoscopy (Zhu). Overactive bladder that is refractory to conservative treatment may require intravesical hyluronic acid instillation, intramural botulinum toxin injections or hydrodistension. Future therapies may include intravesical instillation of relaxin-2, tacrolimus and vascular endothelial growth factor or other rejuvenating agents (Ikeda, Rajaganapathy, Soler).

Psychological Burden

Women who receive treatment for gynaecological cancer face significant psychological challenges. Additional to fear of death and incapacitation, which are common amonsgts all oncology patients, women with gynaecological cancer also face sexual self image challenges and even family planning complications. Sexual self image is at the core of human personality and any violent alteration may result in serious psychological disturbances. Notably the diagnosis of a malignancy is associated with increased risk of major depression and a double risk of suicide within the first 12 months (Saad).

Gynaecological oncology treatment must incorporate comprehensive patient information and patient participation in decision making. Ever possible attempt must be made for cosmetic restoration e.g after a mastectomy and functional restoration e.g. after vulvectomy or colpectomy. All treatment planning must take into account the women's family life and promote family bonds and marital relationships, considering that all these enhance the patients' psychological endurance and survival drive. Providers that offer gynaecological oncology services should have in place referral patterns to psychological support and psychiatric review.

Fertility

Women who receive treatment for gynaecological cancer have been considered in the past to permanently lose their fetility potential and this remains a public belief up to date. However, newer less invassive approaches to surgery for gynaecological cancer, as well as cryopreservation techniques for ovarian tissue,

ova, and embryos have opened a whole new world for pregnancy after gynaecological cancer. Women of reproductive age who are diagnosed with gynaecological cancer should be counselled regarding their fertility threats and solutions at an early stage by appropriately trained clinicians.

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Chapter 25
Medical and Nursing Civil Liability and Ethics in the Provision of Health Services:
Forensic Pathologists as Experts

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ABSTRACT

After 2000, specific legislation on civil liability and ethics of nurses and doctors was introduced, as well as specific acts. For nurses and the nursing profession, since 2001, the Code of Nursing Ethics (NCSD, Presidential Decree 216/2001) has been in force. In 2005, the current Code of Medical Ethics (KID, Law 3418/2005) was passed. Special Law 3305/2005 on the application of assisted reproduction methods was introduced to specify how the methods introduced in the Civil Code were applied as methods of generating kinship among persons under Law 2089/2002 (MAP). The chapter summarizes the main points regarding civil liability of medical and nursing activity with a special focus on oncological patients.

INTRODUCTION

The Law 1565/1939 was the first Greek law on the fields of the medical legislation and concerned the conditions for practicing the medical profession. Later at 1955, the Royal decree on the medical ethics concerned mainly rules about the way of practicing medicine in a relationship doctor's-patient.

The first rule to the patient-doctor relationship concerning the obligation to inform the patient, as we mean it today, which however involved hospitalized patients, existed in the law for the National Health System (NHS) in 1998.

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In 1997, a European Convention on Human Rights and Biomedicine was signed in Oviedo, Spain, at the initiative of the European Council. The first chapter is devoted to the obligation of States to provide health services based on human interest and on a professional level. The second chapter defines the basic requirement of providing any medical intervention to inform the person concerned and his / her consent. This Convention was ratified in Greece by Law 2619/1998.

After 2000, specific legislation on civil liability and ethics of nurses and doctors was introduced, as well as specific acts. For nurses and the nursing profession, since 2001, the Code of Nursing Ethics (Code of Nursing Ethics, 2001) has been in force. In 2005, the current Code of Medical Ethics (Code of Medical Ethics, 2005) was passed. Special Law 3305/2005 on the application of assisted reproduction methods was introduced to specify how the methods introduced in the Civil Code were applied as methods of producing parentage among persons under. The law L.2737/1999 concerning the organs transplantations replaced the previous one and itself has already been replaced by L.3984/2001on the scope of its harmonization of national legislation with the European one.

MEDICAL LIABILITY

Liability Concept

Liability in law is divided into civil, criminal and disciplinary. Individuals (doctors, nursing staff) and legal entities of public law (as the public hospitals) or private law (as the private clinics) and the State are responsible. This responsibility concerns the real facts of their employers or members of their managing boards.

The civil liability creates a claim either for performance or for compensation. The one or the other case depends by the real facts. The legal responsibility concerns to individuals for their own liabilities, as doctors, nursing staff etc., or for liabilities concerning actions of other persons depending of them or third parties in his service or authority, who serves to perform their duties. Legal responsibility may also have the State (art. 104, 105 LIntrAK) also the public legal persons, as the public hospitals, for the acts of the members of their managing boards. The private legal persons are also responsible for the acts of their bodies during the execution of their duties (art. 71 AK), also for the real facts of their employers.

The criminal liability entails the conviction of the person to a custodial sentence or financial consequence.

The disciplinary liability draws mainly administrative penalties.

The doctor-patient relationship and the quality of the services provided, and the responsibility of the doctors are based on the general provisions of the Code of Medical Ethics (L. 3418/2005). The Code of Nursing Ethics (presidential degree No 216/2006) precise the nurse's duties, responsibility and relationships to the patients. Specific Rules of Ethics are also introduced by L. 3305/2005 on the application of medically assisted reproduction methods.

MEDICAL ACTS AND PERSONS CONCERNED

Medical Acts

Medical acts falling under the concept of law are described in detail in the provision of Article 2 of the Code.

The concept of medical acts includes any procedures that aims human's health as the prevention, the diagnosing, the treating and the restoring health by any scientific method. Medical acts are also those of a research nature, as they are intended to more accurately diagnose, restore or improve the health of the person or to promote science. Otherwise as medical act is considered the prescribing, the order for each paraclinical examination, the issuance of medical certificates and confirmations, and the general counseling of the patient.

Liability arises from the damage caused by a breach of these acts and is determined by the provisions of this law, in conjunction with the general provisions on liability.

Regardless of these, the Act also includes the acts provided for in L. 2089/2002 concerning the assisted reproduction, and its application which are regulated in L. 3305/2005. The latter also provides for liability in their execution and penalties for infringements.

Persons Concerned

The article 1 of the Code of Medical Ethics (Code of Medical Ethics, 2005) describes the persons to whom the responsibility of doctors relates or may be involve. In the next article 2 of the Code of Medical Ethics describes the profile of a doctor.

Doctor is the person who performs the function of providing health services with the desired result of the patient's treatment, in accordance with the generally accepted and applicable rules of medical science (Code of Medical Ethics, 2005, article 2§3). It is the doctor's responsibility to maintain, improve and restore a person's physical, spiritual and mental health, as well as to relieve pain.

Patient is the person who needs health services (Code of Medical Ethics, 2005, article 1§2), regardless o f his health condition.

"**Familiar**" is a person specifically mentioned in the law, because he or she is in some way involved in the health care service's process. The concept of "familiar member" includes relatives by blood and by marriage in direct line, adoptive parents and children, spouses, permanent companions, brothers/sisters, spouses and the permanent companions of the brothers/sisters, and the curators or custodians of the patient or persons in judicial assistance.

To these people should be added the "***friend***" or a person very close to the patient recently before the illness. Nowadays, many people do not live with their family. Common is living singly or more with friends or third parties with which there is no legal or traditional kinship bond or judicial intervention.

In case of illness or inability to communicate with the persons of the "relatives", as provided by law, it makes this view necessary. The purpose is to communicate with the patient's perspective that is not conscious, in aim to be informed and give consent for a medical procedure that must take place. But even after the medical procedure, these should be information about the patient's progress and the treatment that should be followed. The expensive interpretation of the concept of "familiar" facilitates the communication of physicians and individuals who provide services to persons who may not legally represent the adult patient.

DOCTOR / PATIENT RELATIONSHIP

The doctor performs his function in accordance with the generally accepted and applicable rules of medical science (Code of Medical Ethics, 2005, article 2§3)).

The duty of the physician is to maintain, improve and restoration of physical, mental and spiritual health of man and the relief of pain (Code of Medical Ethics, 2005, article 2§1).

The behavior of the physician to the patient should be as fair and appropriate in the science and sending his position (Article 8 §1, RLS). The physician in the exercise of his function may discriminate among patients for any reason, where they relate to illness or social status of the patient. Those who provide medical services should promote equal access to health services and equal distribution of resources (Code of Medical Ethics, 2005, article 4 §1).

These provisions shall apply to the provision of health services at any level of public health care in the public or private sector regardless of the manner, individually or in groups, or the form of exercise of the medical profession, in a company or as a free profession (Code of Medical Ethics, 2005, article 1§5) and arise from the principles of the Oviedo Convention (Roscam, 1998) The right of the patient to quality of medical practice and the position of migrant doctors within the EU is deined at European Journal of Health Law, 5/1998, 377.

INFORMATION AND CONSENT AS BASIC PRINCIPLES OF HEALTH AND MEDICAL EDUCATION

Information

Information is a basic duty of the doctor towards the patient for any medical treatment. The physician must inform the patient (Code of Medical Ethics, 2005, article 11§1) in full and comprehensive manner about the true state of his/her health, the content and the results of the proposed medical act. Also, the physician must inform the patient about the consequences and possible risks or complications of its implementation, the alternative proposals, as well as the possible time of rehabilitation, so that the patient can give a full picture of the medical, social and economic factors and consequences of his/her condition and proceed accordingly to decision-making.

According to the law's definition (Code of Medical Ethics, 2005, article 11§1), the information of the patient is the duty to the true of the physicians. Nevertheless, the patient may choose not to be informed (Code of Medical Ethics, 2005, article 11 §2). The duty of the physician is not cancelled or depreciated. The patient has the rights to designate another, or more than one person, they will be informed on their behalf. In some cases, such as infectious diseases, the patient, adult or minor, have the obligation to inform both his health situation and the way of precautions, especially because the latter concerns the interest of the public health. The information should be fellfield that relate not only to the state of health, but also the content or by-effects of the proposed medical acts, or the consequences and risks of its execution, and their degree of probability.

The person, competent to provide information, is the doctor who will perform the medical procedure. If doctors of different specialties are involved in the medical procedure, each of them must inform the interested persons of the medical procedure that he will perform. In some special cases, the information requires more attention on the part of the physician and perhaps the assistance of a psychologist. The

law designates the interventions of organs or tissues transplantations, the methods of medically assisted procreation, the sex change or rehabilitation, the aesthetic or cosmetic surgery (Code of Medical Ethics, 2005, article 11 §3). The indicative enumeration allows adding other cases, such as transmissible diseases. (Fountedaki, 2003; Fountedaki, 2007)

The information is addressed to an adult person and capable of legal action. In any case the physician should inform even persons, not capable to consent to a medical intervention, as much as possible.

The information in favor of a minor or incompetent person should be to his legal representative, parent, tutor or legal assistant. The teenager minor should be also personally informed, especially in severe cases, such as infectious diseases.

The information concerns the person himself and not third parties, even family members or his sexual partner. The legal representative of the minor or incompetent person is not a third parties, because acting on the interest of the represented.

Consent in Medical Practice

The consent of the person is a condition for any medical service (Code of Medical Ethics, 2005, article 12 §1). Consent also involves research. In principal, no one may be forced to undergo an intervention without his or her consent.

Consent is a declaration of will of a legally capable person. Consent is valid when informed in a full, clear and comprehensible manner to the patient and he has the capacity to consent (Code of Medical Ethics, 2005, article 12 §2). The patient should have the autonomy to express freely their consent to accept or refuse health care.

For the persons who are incapables to consent, such as minors and incompetent persons, the consent is given by the person who represents them.

Consent doesn't need any form. In special cases, such as the medical assisted procreation or organ transplantation, a written form is required.

Consent is freely revocable in any time and involves also the research.

MEDICAL CONFIDENTIALITY

Medical confidentiality governs the information that comes to the doctor and concerns the patient. Medical confidentiality concerns both the doctor and the nurses, every person who meets the information, even the administrators who post the data or the cleaning staff, if information has come to their notice, and even the spouses of these persons.

The Code of Medical Ethics codified a law known at the time of its drafting.

NURSING RESPONSIBILITY

Nursing Concept

A nurse or nurse is a healthcare practitioner who, along with other health professionals, doctors, physiotherapists, speech therapists, takes care of the health of the person, patient or other healthcare provider.

Nurses are guardians of the health of the people, whom the state entrusts them and are required to declare, as the law requires, to the competent authorities any breach of a law concerning public health and order.

According to Article 1 of the Code of Nursing Ethics (Code of Nursing Ethics, 2001), the nurse must be a model of an honest and exemplary person in all occasions of his life, protecting the dignity of the nursing profession and doing his duty in accordance with modern scientific data, moral and ethical principles, the provisions of the Code of Ethics and the provisions relating to the exercise of the nursing profession.

Nurses help provide care, which has been decided by the doctor.

Capacities, Characteristics

A special duty of the nurse (Code of Nursing Ethics, 2001, article 3) is any kind of health care, physical, mental, spiritual, such as the creation of an appropriate therapeutic environment, for the enjoyment of the best possible health, physical, mental, spiritual, also satisfying the patient's needs according to his/hers ideological, religious and other attitudes.

It is the nurse's duty to respect the personality and value of the patient's life (Code of Nursing Ethics, 2001, article 5) as well as respect for the value of human life (Code of Nursing Ethics, 2001, article 7). The nurse must take all measures to rescue or preserve the life of the recipient of his services and refrain from any action likely to lead to the recipient's life being at risk.

SERVICES PROVISION

Nature of Service

The provision of services must be de lege artis (Code of Nursing Ethics, 2001, article 8 §1) and without discrimination between patients.

The Code of Nursing Ethics contains principles from which it is judged to be in accordance with the principles of the science and art of nurses performing their services, but also the limits whose overrun renders the services unlawful. Nurses can also participate in research and / or in special cases, such as assistance to dying patients, participation in assisted reproduction, hospitalization in pediatric or psychiatric clinics. Nurses can also participate in public health services.

Patient Update

There is a duty of information for the nurse before any nursing or medical practice relating to the diagnosis, prognosis, treatment, potential risks or benefits, in conjunction with the instructions of the attending physician who has the responsibility and duty of information (Code of Nursing Ethics, 2001, article 10). The information does not concern the medical act itself, but the hospitalization related to it. Information about the medical act concerns only the physician. (Gogos, 2009)

Patient Consensus

Consent is necessary for the lawful conduct of any health-related act of diagnostics, therapy, or research (laboratory or pharmaceutical). Consent means the voluntary participation, partnership and cooperation of the patient, particularly those who understand the condition of his/her health, the content of the medical act, the risks, consequences and effects of the act.

Consent, as a declaration of will, requires full legal capacity. Consent of those who are incapable, minors or adults, is provided by their legal representatives. In cases of emergency, nursing is provided without consent to adults or minors. (Gogos, 2009)

CONFIDENTIALITY

Nurses have a duty of confidentiality for the hospitalization they provide, but also the patient's private will in general. Confidentiality concerns doctors but also extends to nurses, as persons who have access to medical information. (Code of Nursing Ethics, 2001)

COOPERATION WITH OTHER STAFF

Nurses have a duty to cooperate well with other staff and physicians on a personal and scientific level. This obligation is not related to the nursing process, but rather to the general behavior of the nurse as an assistant staff member, whose position is not the leading position of a doctor. (Code of Nursing Ethics, 2001)

LIABILITY OF NURSE

The provision of nursing services must be comprehensive and ethically correct. Services must be governed by respect for the patient and his or her interest. Also, discrimination against patients is forbidden, for any reason. The ban also follows from the Oviedo Convention, which requires Member States to provide professional and non-discriminatory health services (Code of Nursing Ethics, 2001, article 3)

Violations of these principles in the provision of services creates liability for the nurse.

FORENSIC PATHOLOGIST AS EXPERT

The Forensic Pathologist as Experts (Articles 183-203 Code of Civil Procedure)

The forensic pathologist is the person possessing special knowledge of science or art and decides on facts related to a certain crime, for which the judge's legal or general knowledge is not enough.

The assistance and consultation of some specialists, who may be forensic pathologists, psychiatrists, graphologists, etc., are being asked for assistance. The forensic pathologists as experts are selected from

the list of experts and the prosecutor may limit the number to three. If he does not accept the order, he is punished for disregard for the provisions of the penal code.

Experts may be excluded for the reasons mentioned in Article 15 (suspicion of bias - kinship), which apply accordingly. The prosecutor and the parties have the right to apply for an exception, and they can do so until the experts begin their work. (Code of Civil Procedure, 1995)

THE FORENSIC PATHOLOGIST AS TECHNICAL ADVISOR (ARTICLES 204-208 CODE OF CIVIL PROCEDURE)

The forensic pathologists, as technical advisor of the parties who may be present during the expert's report, may ask experts questions, get acquainted with what documents they and the experts know, and ask for information on what they and the experts ask. The institution of technical advisers established the system of audited expertise as they present and control the work of the experts by safeguarding and safeguarding the rights and interests of the parties who have appointed them. The number of technical consultants: each party may appoint a technical adviser. If the accused, civilly or civilly liable are more than one and have opposing interests, any group of common interest may appoint up to two technical advisers. If there is no conflict of interest, up to two technical advisers are appointed for all. The technical advisers shall provide, to the Prosecutor or the Interrogator written observations on their expert's report, no later than three days before the hearing.

Experts - technical advisers (2 or more) who are appointed, following the necessary instructions from the main investigative or investigating authorities, are legally entitled to attend the forensic procedure. (Code of Civil Procedure, 1995)

LIABILITY AND ERROR

Complication

Complication is the pathological condition that occurs either during or because of another disease, which often worsens, either during or as a result of a therapeutic intervention (e.g., surgery).

The complication should be avoided or well-known and waiting for it.

Undesirable Effect

An undesirable effect or side effect is the secondary unwanted effect of a drug or treatment on the patient. All medical interventions, even the simplest ones, involve complications or undesirable effects with greater or lesser probability of risk. The specialist physician must be familiar with existing therapies, pharmaceutical or surgical, as well as the expected benefits and potential risks, to choose the one in which the benefit outweighs the risk, always with the correct information and consent of the patient. (Papazisi, 2003; Fountedaki, 2007).

Medically Liability

Nowadays, the surgeon's surgery or *the lege artis* treatment, which has a legitimate outcome, is not considered a physical injury because the ultimate purpose is the patient's health towards which the treatment is intended to be a socially appropriate act. (Kremlalis, 1987; Papazisi, 2003)The physician has the duty to illuminate the patient for the parameters related to the treatment. The criminal responsibility of a doctor exists when he / she violates the commonly recognized rules of science, for which no doubt may arise.

Medical Error

Medical error is the violation by the medical practitioner of the rules of medical science and experience or lack of due diligence in general caused by the average wise representative of the circle to which the physician belongs, who by action or omission caused injury to the patient resulting in bodily harm to the patient or even death.(Papazisi, 2003).

EPILOGUE

The responsibility of doctors and nurses is based on the principles of service provision according to the rules of their art and science Failure to comply with these rules may result in civil law consequences, such as liability for compensation where the services are provided privately. In the case of hospital doctors or nurses civil liability lies in principle with the state, and the individual responsibility is shared.

On the other hand, for a criminal offense doctors or nurses have a personal responsibility. Actions related to the service relationship of doctors or nurses involve disciplinary liability.

The responsibilities of laboratories dealing with assisted reproduction services are specifically provided for in L. 3305/2005. Liability is linked to violations of the provisions of the law on the lawful way of providing health services in medical assisted reproduction.

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