Shalini Rajaram
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Editors

Uterine Cancer

Diagnosis and Treatment

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Foreword

Uterine cancer is the commonest genital tract cancer diagnosed in women in the developed world and is increasingly being diagnosed in less developed countries where cancer of the cervix is the dominant genital tract malignancy in women. In 2012 it was estimated that there were 319,605 new cases of endometrial cancer diagnosed and 76,155 deaths were recorded (Globocan 2012) with a 5-year prevalence of 121,504 cases. It was the seventh most common cancer among women with breast being the most common. There have been interesting new developments in the classification of uterine cancers particularly related to genetic profiles. The Cancer Genome Atlas Research Network studied using endometrial carcinosarcomas array and sequencing- based techniques and indicated that endometrial cancers can be classified into at least four subtypes on the basis of molecular characteristics. These and other data are discussed in this comprehensive text book, *Uterine Cancer: Diagnosis and Treatment*.

The textbook will be ideal for those specializing both as generalists and as subspecialists in gynecological oncology. The contents are organized into eight sections beginning with epidemiology, molecular biology, familial endometrial cancer, screening, diagnosis, and staging. Controversies are addressed and the arguments set out in a clear and understandable manner. This is followed by an excellent and detailed section on the pathology of uterine cancers, including uterine sarcomas and prognostic and predictive factors for endometrial cancers. The chapter on surgical anatomy is a comprehensive overview and will be of huge value in understanding the lymphatic drainage of the uterus, including the rationale behind and value of sentinel node mapping. The surgical management of endometrial cancer is addressed, including the controversies around lymphadenectomy, use of laparoscopic and robotic surgery, and the role of adjuvant therapies, such as radiation and chemotherapy. The fourth section deals with advanced stage disease as well as therapeutic strategies in recurrent and metastatic disease. There is an entirely separate section on uterine sarcomas, which is appropriate since FIGO now has a separate classification for sarcomas. An interesting section is on "special cases" which evaluates situations such as fertility sparing surgery, use of hormone replacement therapy in women who have endometrial cancer, and women who receive an incidental diagnosis of endometrial cancer (among others). Finally there is a comprehensive chapter on palliative care.

The great value of this textbook is that it covers all aspects of the diagnosis, treatment, and palliation of women with endometrial cancer, and it takes

a holistic approach while acknowledging the controversies and unresolved issues in the management of endometrial cancer. The authors are to be congratulated on a highly scholarly yet practical textbook.

Cape Town, South Africa

Lynette Denny, MBChB,
MMED (O&G), FCOG (SA), PhD

Preface

The incidence of endometrial cancer is rising worldwide but at the same time a better understanding of the disease especially at the molecular level has ensued. In addition, landmark published trials in the past decade have led to a paradigm shift in the management of uterine cancers focusing on an integrated multidisciplinary approach. We felt that a comprehensive and dedicated book on uterine cancers that covers all aspects in a well presented, graphically illustrated, easy to understand format was needed. This genre of book will be useful to all pursuing the field of gynecologic oncology, namely gynecologic oncologists, fellows in gynecologic oncology, practitioners of gynecology, and postgraduates in Obstetrics and Gynecology. Fellows and practitioners of medical and radiation oncology will also find valuable, the well-researched and well- written chapters in their disciplines.

The first two sections cover topics fundamental to the understanding of uterine cancer, its diagnosis, clinical evaluation, staging, imaging modalities, and pathology of both endometrial cancers and sarcomas. Section III addresses and describes comprehensively all surgical techniques required for management of endometrial cancer. Sentinel node evaluation, role of lymphadenectomy, and pelvic and para-aortic lymphadenectomy are described at length. There are two excellent robotic surgical videos with chapters contributed by surgeons from two far ends of the globe! Laparoscopic retroperitoneal para-aortic lymphadenectomy is a skill to be learned and mastered; readers will benefit from an excellent chapter on this technique. Management of Stage II endometrial cancer falls into a "gray" zone, and this chapter is extensive and supported by current literature. Advances in radiation, chemotherapy, therapeutic options for high-risk cancers, and follow-up complete this section. Part IV explores management choices in advanced cancers. Parts V, VI, and VII are unique and one-off, covering chapters not usually discussed at length in any book of oncology. We felt our book on uterine cancer will be incomplete without these valuable chapters.

Finally, we hope that this book is widely read and finds itself on bookshelves and electronic media of all those who care for women with gynecologic cancers.

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Part I

Epidemiology, Molecular Biology, Familial Endometrial Cancer, Screening, Diagnosis and Staging

Epidemiology of Endometrial Cancers and Uterine Sarcomas

1

Gauravi Mishra, Sharmila Pimple, and Surendra Shastri

Introduction

Majority of the cancers that affect the body of the uterus originate in the endometrial lining and are endometrial carcinomas while uterine sarcomas arise in the muscle layer or supporting connective tissue of the uterus.

Globally, cancer of the body of the uterus, also known as corpus uteri cancer, is the sixth most common cancer among women. It has been estimated that in the year 2012, cancers of the corpus uteri accounted for 319,605 new cases. This accounted for 4.8 % of the total cancers among women with an age-standardized rate (ASR) of 8.3 per 100,000 women. There were an estimated 76,160 deaths due to endometrial cancers among women globally during 2012. The ASR for mortality due to endometrial cancer was 1.8 per 100,000 women accounting for 2.1 % of the total cancer deaths among women [1]. An estimated 49,560 new cases and 8,190 deaths due to cancer of the corpus uteri were expected to be diagnosed in the United States in 2013 [2].

In India, it is estimated that there were 12,325 new corpus uteri cancer cases in the year 2012. It ranked as the tenth most common cancer accounting for 2.3 % of all cancers among women with an ASR of 2.3 per 100,000 women and was responsible for an estimated 4,773 cancer deaths (1.5 % of total cancer deaths among women) [1].

Endometrial cancers are commonly diagnosed among postmenopausal women in their 60s. Several risk factors, mentioned below, have been implicated and studied in populations across the globe.

Age

The risk of endometrial cancer increases as a woman gets older. Most cases of endometrial cancers are found in women over 55 years of age. A few cases may occur before age 45 [3].

Risk Factors Related to Reproduction

Menstrual Factors

Early menarche is associated with 1.5–4-fold increased risk of endometrial cancer [4, 5]. Early menarche was identified as a risk factor for endometrial cancer among Turkish women [6] and late menarche as a protective factor in the European Prospective Investigation into Cancer and Nutrition (EPIC) [7]. Also, a reduction in endometrial cancer risk was observed in women with early menopause

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in the EPIC study [7]. Menstrual span of more than 39 years was associated with 4.2 times higher risk than one with less than 25 years [8].

Parity

Lower parity has been identified as a risk factor for endometrial cancer [6] and high parity as a protective factor [7]. Parity, age at first birth, age at last birth and time since last birth are highly correlated. It is difficult to separate their independent effects, although some studies have shown that late age at last childbirth reduces the risk of endometrial cancer [9, 10]. A study from Norway shows that the risk of endometrial carcinoma decreased significantly with increasing parity as well as with increasing age at first and last birth [11].

Pregnancy

Pregnancy acts as a protective factor [2]. Decreased risk of endometrial cancer was associated with cumulative duration of full-term pregnancy (FTP) [7].

Studies done so far report contradictory findings regarding the association between spontaneous and induced abortion with risk of endometrial cancer. In comparison with women reporting no induced abortion, the odds ratio (OR) of endometrial cancer was 0.6 in women reporting one and 0.4 in those reporting two or more induced abortion [10]. Certain conditions like Stein–Leventhal syndrome characterized by accumulation of incompletely developed follicles in the ovaries have been linked to endometrial cancer [12].

Oral Contraceptive Pills (OCPs)

Oral contraceptive use lowers the risk of endometrial cancer [7] with the lowest risk observed in women taking pills for a long time [2]. Combined oral contraception has shown to have a protective effect ranging from less than 5 years to greater than 15 years after cessation of the pills [13].

A nationwide, population-based case–control study among postmenopausal women aged 50–74 years in Sweden shows that oral contraceptives decrease the risk for endometrial cancer by 30 %, while progestin-only pills reduced the risk more markedly. Reduction in the risk was noticeable following 3 or more years of use for combined oral contraceptives and increased with duration of intake, reaching 80 % lower risk after 10 years of use. The protection remained for at least 20 years after cessation of use [14].

Intrauterine Devices

Theoretically, IUD use may decrease endometrial cancer risk through at least two mechanisms: Intrauterine devices act as protective factor through either one of the following mechanisms. IUDs may exert an intense inflammatory response leading to other lysosomal and inflammatory actions including recruitment of cells responsible for early elimination of abnormal, precancerous, hyperplastic endometrial epithelial cells. IUDs may induce changes in endometrial environment and endometrial response to hormones leading to more complete shedding of the endometrium, thereby decreasing chances of endometrial hyperplasia which is a known risk factor for endometrial carcinoma [15]. The meta-analysis by Beining RM found a protective association among women who reported ever use of an intrauterine device and risk of endometrial cancer [16].

Oestrogen-Related Risk Factors

Polycystic Ovarian Syndrome

Women with polycystic ovarian syndrome (PCOS) have a 2.7-fold increased risk for developing endometrial cancer, most of which are well-differentiated tumours with good prognosis. The link between PCOS and endometrial cancer involves prolonged endometrial exposure to unopposed oestrogen due to anovulation and endometrial progesterone resistance. This is accompanied by several gene abnormalities controlling progesterone action and cell proliferation [17].

Use of Unopposed Oestrogen Replacement Therapy

There is strong evidence suggesting oestrogen therapy unopposed by progesterone therapy is a major risk factor for endometrial cancer in women with an intact uterus, with the risk substantially increasing with current, long-duration use [18].

Many studies show that women taking combination of oestrogen–progesterone therapy exhibit a similar risk to women who do not take postmenopausal hormone therapy. However, a meta-analysis including ten case–control studies and one cohort study calculated a significant reduction of risk, with a relative risk (RR) of 0.44, 0.33 and 0.28 after 4, 8 and 12 years of combined oral contraceptive (COC) use, respectively. This was based on 33 time-dependent estimates of RR, adjusted for age, adiposity, parity and use of oestrogen replacement therapy [19].

It is now considered that risk varies with specific categories of oestrogen plus progestin usage, like the use of long duration of sequential progestins increases the risk, whereas decreased risk is observed for users of short-duration continuous progestins. Higher risk noted among thin to normal-weight women could indicate that there is an endogenous oestrogen threshold beyond which exogenous oestrogen exposures fail to increase the risk [18].

Hormone Replacement Therapy (HRT)

HRT use was identified as a risk factor for endometrial cancer among Turkish women [6]. Oestrogen-only HRT substantially increases the risk of endometrial cancer in women with a uterus [20].

Tamoxifen Therapy

Tamoxifen is one of the selective oestrogen receptor modulators (SERMs) and has primarily antioestrogenic properties in the breast tissue. However, it also has modest estrogenic activity and hence is found to be associated with endometrial carcinoma. There is an increasing risk of endometrial cancer associated with longer tamoxifen treatment, extending well beyond 5 years which does not diminish in follow-up to at least 5 years after the end of the last treatment [21].

In the Israel national breast cancer cohort, tamoxifen use was associated with elevated risks of uterine cancer incidence and mortality [22].

Endometrial Hyperplasia

A population-based study of women with endometrial hyperplasia, who remained at risk for at least 1 year, indicates that the overall progression risk for endometrial hyperplasia is three times higher than the average population risk of endometrial carcinoma. Fewer than 5 % of women with non-atypical or simple endometrial hyperplasia will experience progression to carcinoma, but 28 % of women with atypical hyperplasia will progress to carcinoma during 20 years [23].

Breast or Ovarian Cancer

Women diagnosed with breast cancer have a higher incidence of second primary cancers, particularly of endometrial cancer in women over 50 at diagnosis [24]. The granulosa–theca cell tumour of the ovary secretes oestrogen, which is uncontrolled, and this can sometimes lead to high oestrogen levels, leading to stimulation of the endometrium and resulting in endometrial cancer [2].

Hereditary Nonpolyposis Colorectal Cancer (HNPCC) Syndrome or Lynch Syndrome

This disorder is commonly caused by a defect in either the gene *MLH1* or the gene *MSH2*. Defects in other genes can also cause HNPCC, namely, *MLH3*, *MSH6*, *TGBR2*, *PMS1* and *PMS2*, and increase the risk of endometrial cancer [2].

Lifestyle Factors and Other Non-communicable Diseases

Obesity

The risk of endometrial cancers has been recorded as high among obese women [18]. Endometrial cancer is twice as common in overweight women and more than three times as common in obese women.

Endometrial cancer is inversely related to the age at menarche and directly related to the age at menopause. Women with higher BMI tend to be younger at menarche than the ones with lower BMI, and conversely, women with higher BMI tend to be older at menopause than women with lower BMI [25]. Some studies suggest that the association between high BMI and endometrial cancer is stronger in postmenopausal women than in premenopausal women [26]. This indicates that obesity may have a continuous and cumulative effect on the development of endometrial cancer [27].

McCullough et al. in their prospective cohort found adult body mass index (BMI) as a strong predictor of risk. The use of oestrogen plus progestin postmenopausal hormone therapy modified the association. Among never users, risk was significantly linear across the entire range of BMI examined, but among ever oestrogen plus progestin users, the association was not significant. No difference in risk was observed according to the tendency for central versus peripheral fat deposition [28]. Weight gain and lack of weight stability are associated with risk of endometrial cancer [29].

Adiposity causes an increase in the frequency of anovulatory and irregular menstrual cycles, resulting in the reduction of luteal phase progesterone levels and ultimately increased exposure to unopposed oestrogen, thus explaining the increased risk of endometrial cancer in younger women [30, 31]. Obesity in postmenopausal women is associated with excess aromatization of androgen into oestrogen in the adipose tissue and lowered circulating sex hormone-binding globulin [32].

Sedentary Behaviour

Excessive sitting time is associated with an increased endometrial cancer risk, independent of the level of moderate–vigorous physical activity. Physical activity was clearly associated with reduced risk of endometrial cancer, with active women having an approximately 30–33 % lower risk than inactive women [33]. In addition, consistent overweight or obesity during adulthood was associated with greater risk of endometrial cancer than being overweight or obese only in later adult life.

High-Fat Diet

Percent energy from fat was associated with an increased risk of endometrial cancer, with saturated and monounsaturated fats being the main contributors of risk. A number of studies have concluded that diets rich in fat and poor in complex carbohydrates and fibre are associated with increased risk of endometrial cancer, while some studies have shown independent association between the two after adjusting for BMI and total energy intake [34, 35]. There was a stronger association between dietary fat and endometrial cancer among groups with higher circulating oestrogen levels [36].

Metabolic Factors

Hypertension

Hypertension was identified as a risk factor for endometrial cancer in studies conducted in women in Finland as well as in Turkey [37, 6].

Diabetes

The risk of endometrial cancer is high among women with diabetes. High glucose levels increases the risk by providing energy for proliferation of cells, generating free radicals causing damage to DNA and DNA repair enzymes [38, 39].

A meta-analysis of cohort studies suggests significant association between diabetes mellitus and increased risk of incidence of endometrial cancer but no increased risk of mortality due to endometrial cancers [40]. Another meta-analysis involving both case–control and cohort studies found diabetes to be statistically significantly associated with an increased risk of endometrial cancer with the risk estimates being somewhat stronger for case–control studies [41]. Diabetes was identified as a strong risk factor for endometrial cancer in a nationwide record-linkage study in Finland [37] and among Turkish women [6]. Diabetes was associated with a two-fold increased risk, and combination of diabetes with obesity and low physical activity was associated with a further increased risk for endometrial cancer [42].

Uterine Sarcomas

Uterine sarcomas are rare tumours that affect relatively younger women and account for less than 5 % of uterine malignancies [3, 43].

Uterine sarcomas fall under the broad category of soft tissue sarcomas and are extremely rare. They are generally considered as aggressive tumours with poor prognosis. They have further pathological subgroups with around 50 % being carcinosarcomas, arising in the endometrium [also known as malignant mixed Müllerian tumour (MMMT)]; followed by leiomyosarcoma (30 %), arising from the myometrial muscle; and the remaining comprising of endometrial stromal sarcoma (ESS) (10 %), arising in the endometrial stroma. Each group is known to harbour its own risk factors and clinical manifestations including response to treatment and prognosis [44]. Carcinosarcomas have the same risk factors as endometrial carcinomas [45].

The aetiology of uterine sarcomas has been investigated in only a few case–control studies due to the very low incidence of this disease. Overall, obesity, menopausal use of oestrogen plus progestin, oral contraceptives and tamoxifen use are associated with increased risks of uterine sarcoma, whereas cigarette smoking and parity were associated with a reduced risk [46].

Few factors that are known to change the risk of developing uterine sarcomas are as follows:

Race

The risk of uterine sarcomas is low among white or Asian women and about twice as common in African-American women. The reason for this increased risk is unknown [3].

Menarche and Menopause

Older age at menarche is inversely associated with uterine sarcoma risk (≥15 years vs. <11 years) [43]. Most of the uterine sarcomas occur after menopause [47].

Obesity

Obesity and increased body mass index (BMI) significantly increase the risk of uterine sarcomas [46].

Diabetes

History of diabetes increases the risk of uterine sarcomas [46].

Pelvic Radiation Therapy

Prior pelvic radiation therapy has been documented as an aetiologic factor in 10–25 % of uterine sarcomas. High-energy ionizing radiation used to treat some cancers can damage the cell DNA, thus increasing the risk of developing a second type of cancer. Uterine sarcomas are diagnosed from 5 to 25 years after exposure to the radiation [47].

Hormone Therapy

Estrogen–progestin therapy (EPT) was associated with an increased risk for uterine sarcomas in the nationwide cohort study on Finnish women more than 50 years of age [48]. Uterine sarcomas appear to be overrepresented among women in Israel who use tamoxifen [22]. An increased incidence of uterine sarcoma has been associated with the use of tamoxifen given either in treatment of breast cancer or to prevent breast cancer in women at increased risk [47–51]. Hence, patients on tamoxifen should have follow-up pelvic examinations and should undergo endometrial biopsy if there is any abnormal uterine bleeding [49–51].

Retinoblastoma Gene Changes

An increased risk of uterine leiomyosarcomas is noted among women born with an abnormal copy of the retinoblastoma gene [3].

In general, the endometrial stromal sarcoma and leiomyosarcoma had similar risk factor associations to those observed for all uterine sarcomas combined which are suggestive of an overlap in the biological mechanisms associated with the development of these tumours [46]. Overall, uterine sarcomas are considered a rare yet fatal uterine cancer subtype and tend to behave more aggressively having a poorer prognosis than endometrial carcinoma [43].

Conclusions

A major aetiologic pathway for endometrial cancers is exposure to oestrogen without cyclic exposure to progesterone. Most of the established risk factors for endometrial cancer appear to affect risk at least in part through this pathway. Increasing age, early menarche, larger menstrual span, lower parity, PCOS, unopposed oestrogen replacement therapy, use of tamoxifen, endometrial hyperplasia, women with breast or ovarian cancer and women with HNPCC or Lynch syndrome are at greater risk. The risk is also more among women with hypertension and diabetes. Pregnancy, use of combined oral contraceptive pills and intrauterine device act as protective factors. Physical activity is clearly associated with reduced risk of endometrial cancer. Consistent overweight or obesity during adulthood is found to harbour greater risk of endometrial cancer than being overweight or obese only in later adult life though the relation of body mass at different time periods in life and weight change over time to endometrial cancer risk are less well understood.

Key Points

1. Majority of the cancers that affect the body of the uterus initiate in the endometrial lining of the uterus and are called endometrial carcinomas.
2. Cancer of the muscle and supporting tissues of the uterus, known as uterine sarcomas, comprises less than 1 % of gynaecological malignancies and 2–5 % of all uterine malignancies.
3. The commonly identified risk factors of endometrial carcinomas are higher age, early age at menarche, late age at menopause, lower parity, polycystic ovarian syndrome, use of unopposed oestrogen replacement therapy, use of hormone replacement therapy, tamoxifen therapy, atypical endometrial hyperplasia, breast or ovarian cancer, hereditary nonpolyposis colorectal cancer (HNPCC) syndrome or Lynch syndrome, obesity, sedentary behaviours, high-fat diet and hypertension.
4. The protective factors for endometrial carcinomas are late menarche, early menopause, increased parity (Decreased risk of endometrial cancer was associated with cumulative duration of full-term pregnancy), use of oral contraceptive pills and use of intrauterine device.

5. The risk factors for uterine sarcomas are race (African-American), older age at menarche, postmenopausal status, obesity and increased BMI, prior pelvic radiation therapy, oestrogen–progestin therapy (EPT), tamoxifen therapy and women with retinoblastoma gene changes.
6. The aetiology of uterine sarcomas has been investigated in only a few case–control studies due to the very low incidence of this disease. Overall, obesity, menopausal use of oestrogen plus progestin, oral contraceptives and tamoxifen use are associated with increased risks of uterine sarcoma, whereas cigarette smoking and parity were associated with a reduced risk.

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2 Molecular Pathology and Cytogenetics of Endometrial Carcinoma, Carcinosarcoma, and Uterine Sarcomas

Anupama Rajanbabu

Introduction

Uterine neoplasms include epithelial cancers (endometrial carcinomas and carcinosarcomas) and mesenchymal neoplasms (leiomyosarcomas and endometrial stromal sarcomas). The epithelial cancers occur much more frequently than uterine mesenchymal tumors, and hence more information is available on their molecular pathology. Carcinosarcoma of the uterus previously considered as mixed neoplasms with stromal and epithelial elements is now classified as high-grade endometrial carcinoma on the basis of genetic and molecular characteristics. This chapter will describe the molecular and cytogenetic features of uterine cancers.

Molecular Pathology and Cytogenetics of Endometrial Carcinoma

In 1983 Bokhman proposed that there are two different pathogenetic types of endometrial carcinoma that require different approaches to detection and treatment [1]. Type I tumors, which account for 70–80 % of endometrial cancers, follow the estrogen-related pathway. They arise in a background of unopposed estrogen stimulation, coexist with complex and atypical hyperplasia, and express estrogen (ER) and progesterone receptors (PR) [2]. These tumors occur in premenopausal and perimenopausal women and histologically show low-grade endometrioid differentiation. Mucinous adenocarcinomas are also included under type I as they are of low grade and express ER and PR receptors.

Type II tumors in contrast are more aggressive and mostly include the high-grade serous and clear cell subtypes. These tumors arise in a background of atrophic endometrium unrelated to estrogen stimulation [3]. ER and PR receptor expression is negative or sometimes weakly positive in these tumors. Type II tumors occur at an older age, roughly 5–10 years later than type I tumors [2]. It has now been proved that both these types of tumors are caused by different molecular alterations [4, 5]. Main molecular alterations seen in type I endometrial cancers are MSI (microsatellite instability) and mutations affecting the PTEN, KRAS, PIK3CA, and CTNNB1 genes. Type II cancers on the other hand commonly exhibit P53 alterations, LOH (loss of heterozygosity) on several chromosomes, and molecular alterations affecting p16, STK15, E-cadherin, and c-erb-B2 [6].

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The integrated proteomic, transcriptomic, and genomic analysis of endometrial cancers by The Cancer Genome Atlas (TCGA) Research Network has shown that endometrial cancers can be subdivided into four different clusters based on these characteristics [7]. Progression-free survival analysis has shown significant survival differences between the groups with cluster 1 having the best and cluster 4 having the worst outcome. This genomic-based classification may lead to changes in the management of endometrial cancers as we need to consider whether endometrioid tumors belonging to cluster 4 may have improved survival with addition of chemotherapy or patients belonging to cluster 1 can be left alone without any adjuvant treatment [7].

Microsatellite Instability (MSI)

The genes responsible for microsatellite instability (MSI) encode proteins involved in DNA mismatch repair (MMR). The ability of cells to repair defects produced during DNA replication is affected when a mutation affects these genes. Hence, cells with defective MMR genes replicate DNA mistakes more frequently than others [8]. These faulty mutations can accumulate in the coding and noncoding DNA sequences, including microsatellites, which are short tandem repeats. Some mononucleotide repeats are located within the coding sequences of important genes (BAX, IGFIIR, hMSH3, hMSH6, MBD4, CHK-1, Caspase-5, ATR, ATM, BML, RAD-50, BCL-10, and Apaf-1) [6].

Seventy five percent of endometrial cancers associated with Lynch syndrome and 25–30 % of sporadic endometrial cancers demonstrate MSI [8]. In sporadic endometrial cancers, MSI is due to MLH-1 promoter hypermethylation and is associated with type I endometrioid cancers rather than type II. The presence of MSI is associated with a higher histological grade [6]. In Lynch syndrome, MSI arises due to mutations arising in MSH2, MH6, MLH1, or PMS2.

Phosphatase and Tensin Homolog (PTEN)

PTEN is a tumor suppressor gene, which has important functions in the regulation of cell cycle and apoptosis [9, 10]. This gene is located on chromosome 10q23 and encodes for a protein – phosphatase and tensin homolog (PTEN) – with tyrosine kinase function. The PTEN gene product regulates many key processes in cell such as proliferation, adhesion, migration, and apoptosis and is also a suppressor of tumor growth [11]. PTEN also exerts its effect on cell survival and proliferation through the phosphatidylinositol 3-kinase (PI3K)/Akt pathway [12]. It inhibits PI3K-Akt pathway inducing apoptosis and/or cell cycle arrest [12]. Hence, loss of PTEN function causes aberrant cell proliferation and escape from apoptosis.

The expression of PTEN in the endometrium is controlled by estrogen and progesterone and is expressed more in the proliferative phase than in the secretory [12]. PTEN gene inactivation can occur by point mutation, promoter hypermethylation, or deletion (loss of heterozygosity (LOH)) at 10q23 [6]. PTEN inactivation is seen in 60–80 % of endometrioid cancers and in only less than 10 % of non-endometrioid endometrial cancers [12–15]. The authors have shown loss of PTEN expression in endometrial hyperplasia with and without atypia, and hence, it is thought to play an important role in endometrial cancer tumorigenesis [16]. Altered PTEN expression has been reported in up to 55 % of precancerous lesions of the endometrium, and this is thought to be initiated in response to known hormonal risk factors. Progesterone has shown to promote involution of PTEN-mutated tumor cells [13]. PTEN mutations can coexist with MSI with 60–86 % of MSI-positive endometrial cancers showing PTEN mutations [6]. Data regarding the prognostic significance of PTEN mutations are controversial [17], but Salveston et al. showed correlation between PTEN mutations, low FIGO stages, and favorable prognosis [18]. In this study patients with PTEN mutations had better 5-year survival compared with those with no mutations.

PTEN-deficient cells are sensitive to mammalian target of rapamycin (mTOR) inhibitors in vitro since loss of PTEN leads to activation of Akt which upregulates mTOR activity [19]. mTOR inhibitor temsirolimus showed a response rate of 26 % in endometrial cancer patients [20].

RAS-RAF-MEK-ERK Signaling Pathway

This pathway plays an important role in tumorigenesis. Mutations in KRAS proto-oncogene is not present in the normal endometrium but is seen in 6–16 % of atypical hyperplasia and 10–30 % of endometrial carcinomas [13, 21]. It has been shown that as the endometrium changes from normal to varying degrees of hyperplasia, there is an increase in KRAS point mutations [22]. Increased frequency of KRAS mutations is reported in endometrial cancers associated with MSI [23]. BRAF, another member of the RAS-RAF-MEK-ERK pathway, is mutated very infrequently in endometrial cancer [24]. Activated RAS is associated with enhanced cell proliferation, transformation, and cell survival. RAS effectors like RASSF1A (RAS association domain family member 1) are thought to have an inhibitory signal, which needs to be inactivated during tumorigenesis [6]. The increased activity of the RAS-RAF-MEK-ERK pathway can also be due to RASSF1A inactivation by promoter hypermethylation [25].

PIK3CA

PI3K (phosphatidylinositol 3-kinase) is a heterodimeric enzyme with a catalytic (p110) and regulatory (p85) subunit. The PIK3CA gene codes the p110α catalytic subunit of this enzyme, which is located on chromosome 3q26.32 [6]. Mutations affecting this subunit have been implicated in many malignancies and may contribute to the alteration of PI3K/AKT signaling pathway in endometrial cancer [13]. Mutations affecting the PIK3CA gene are located mainly in the helical (exon 9) and kinase (exon 20) domains, but mutations can also occur in exons1–7 [6]. In 24–39 % of endometrial cancers, PIK3CA mutations occur, and they coexist frequently with PTEN mutations [26]. PIK3CA mutations affecting exon 20 have been associated with high histological grade and myometrial invasion. Though initially described in endometrioid carcinomas, PIK3CA mutations can also occur in non-endometrioid endometrial carcinomas and mixed tumors. Mutation affecting the p85a inhibitory subunit of PI3K has also been detected in 43 % of endometrioid carcinomas and 12 % of non-endometrioid cancers [6].

β-Catenin

Studies have shown elevation of beta-catenin in several cancers including endometrial carcinoma and atypical endometrial hyperplasia [27, 28]. The increased beta-catenin levels occur due to mutation of the beta-catenin gene (CTNNB1) located in chromosome 3p21. Beta-catenin is a part of the E-cadherin-catenin complex, which has a role in cell differentiation and maintenance of normal tissue architecture. When mutation occurs in the exon gene of CTNNB1, there is stabilization of beta-catenin protein leading to its cytoplasmic and nuclear accumulation. It also forms complexes with the DNA-binding proteins and participates in the signal transduction [6]. These mutations are seen in 14–44 % of endometrial cancer and are independent of the presence of MSI, PTEN, or KRAS mutation. Beta-catenin mutations are distributed homogenously in different areas of the tumors suggesting that they play a role in the early steps of endometrial tumorigenesis [13]. There are controversial data regarding the prognostic significance of beta-catenin, but they probably occur in tumors with good prognosis [6].

Fibroblast Growth Factor Signaling Pathway

Studies have indicated that fibroblast growth factor (FGF) signaling pathway is important in

endometrial cancer. FGF receptor (FGFR) is downregulated by a protein SPRY-2 that is found inactivated in endometrial cancer [6]. Inactivation of SPRY-2 causes increased cell proliferation. Almost 20 % of endometrial cancers have reduced SPRY-2 immunoexpression. In 6–12 % of endometrial carcinomas, especially in endometrioid types, somatic mutations affecting the receptor tyrosine kinase FGFR2 have been detected [29]. It is of interest to note that FGFR mutations and PTEN mutations often coexist, whereas FGFR mutations and KRAS mutations are mutually exclusive [6]. FGRF2 receptor antibodies are currently considered as targeted therapy agents in endometrial carcinoma.

TP53

TP53 mutations are mainly seen in non-endometrioid endometrial cancers (90 %). 10–20 % of endometrioid cancers (mainly grade 3) also exhibit these mutations [3, 30]. TP53 is a tumor suppressor gene located in chromosome 17 (locus 17p13.1). This gene encodes a phosphoprotein called TP53, which participates in cell cycle regulation, DNA repair systems, and apoptosis [11]. Loss of its normal activity prevents apoptosis and promotes tumor progression [31]. An increase in P53 expression from the normal endometrium to hyperplasia through to endometrial carcinoma has been demonstrated by Horee et al., suggesting a possible role in disease progression [32]. Overexpression of TP53 was found to be correlated with advanced stage, lymph node metastases, and high-grade endometrial cancers [33].

HER2/neu

HER2/neu receptor is a membrane-bound tyrosine kinase receptor, which belongs to the epidermal growth factor receptor family. It plays a role in regulating cell growth and differentiation. HER2/neu gene amplification results in overexpression of the receptors resulting in increasing cell proliferation. The amplification of HER2/neu is seen in a wide variety of malignancies including breast, ovarian, and endometrial [34–36]. In endometrial cancers HER2/neu overexpression is associated with reduced disease-free and overall survival [37]. Increased expression of HER2/neu is found in about 30 % of uterine serous cancers and 10–20 % of high-grade endometrioid cancers. Well-differentiated endometrioid cancers rarely exhibit HER2/neu positivity [12, 38]. Trastuzumab is a monoclonal antibody, which has targeted action against the HER2/neu protein and is being used widely in breast cancer patients who are HER2/neu positive. But trials using trastuzumab in advanced or recurrent HER2-positive endometrial cancers have failed to show benefit [39].

E-cadherin

E-cadherin is a transmembrane glycoprotein of the cadherin family, which promotes and maintains cell adhesion. Cadherins are tissue specific and are required for the assembly of cells into solid tissues [12]. Epithelial cells express E-cadherin and its levels are reduced in many carcinomas including breast, lung, prostate, and also endometrial [12, 40]. Reduced E-cadherin expression was more seen in type 2 endometrial cancers and also in those carcinomas with advanced stage [41]. Fifty seven percent of type 2 endometrial cancers demonstrated loss of heterozygosity of E-cadherin gene at 16q22.1 compared to 22 % of type 1 carcinomas [6].

P16

P16 tumor suppressor gene is located on chromosome 9p21 and this encodes for a cell cycle regulatory protein. Inactivation of p16 leads to uncontrolled cell growth. P16 inactivation was seen in 45 % of serous carcinomas and some clear cell cancers [42].

EGFR

EGFR is a transmembrane tyrosine kinase receptor, whose mutation has been identified in many

malignancies. EGFR overexpression has also been identified in uterine serous carcinomas [43]. Overexpression of EGFR is associated with advanced stage and poor prognosis [44]. EGFR antagonists include tyrosine kinase inhibitors like gefitinib, erlotinib, and lapatinib and anti-EGFR monoclonal antibody cetuximab[42].

Other Molecular Alterations in Non-endometrioid Malignancies

The molecular feature that has been described as most typical of non-endometrioid cancer is the widespread chromosome gains and losses, which reflect aneuploidy [45]. The mitotic spindle checkpoint genes STK15, BUB1, and CCNB2 are upregulated in non-endometrioid endometrial cancers [6]. STK 15 is the gene essential for chromosome segregation and centrosome functions and it is frequently amplified in non-endometrioid endometrial cancers. Serous carcinoma has other documented potential biomarkers like epithelial cell adhesion molecule (EpCAM), claudin-3 and claudin-4 receptors, serum amyloid A, folate-binding protein, mesothelin, and insulin-like growth factor II mRNA-binding protein 2 (IMP2) [6].

Clear cell carcinomas of the endometrium appear to arise from a different pathogenetic pathway. There are morphological similarities between the ovarian and endometrial clear cell carcinomas and both exhibit PIK3CA and PTEN mutations. The ARID1A gene mutation and loss of corresponding protein BAF250a that is seen in clear cell and endometrioid carcinomas of the ovary are also seen in 26 % of clear cell endometrial cancers [6].

Non-endometrioid endometrial carcinomas differ from endometrioid carcinomas in expression profiling as shown by cDNA array studies [46]. In endometrioid carcinomas TFF3, FOXA2, and MSX2 genes are upregulated, whereas in serous carcinomas IGF2, PTGS1, FOLR, and p16 are increased. When the expression profiles of similar histological types of ovarian and endometrial carcinomas were compared, it was found that there were striking differences in the endometrioid and serous carcinomas, whereas clear cell carcinomas, regardless of the organ of origin, had a similar profile [6].

MicroRNAs (miRNAs) are 20–25 nucleotide noncoding RNAs regulating the expression of target genes. Aberrant expression of miRNA is associated with malignant behavior and specific miRNAs are associated with each cancer types. MiRNA profiling has been shown to differentiate tumors better than traditional gene expression analysis [6]. In endometrial cancer miR-185, miR106a, miR-210, miR-423, miR-103, miR-107, miR-Let7c, miR-205, miR-200c, miR-449, miR-429, miR-650, miR-183, miR-572, miR-200a, miR-182, miR-622, miR-34a, and miR-205 were shown to be upregulated, and miR-Let7e, miR-221, miR-30c, miR-152, miR-193, miR-204, miR-99b, miR-193b, miR-204, miR-99b, miR-193b, miR-411, miR-133, miR-203, miR-10a, miR-31, miR-141, miR-155, miR-200b, and miR-487b were downregulated [6]. The miRNA signatures of serous carcinomas differed from that of endometrioid endometrial carcinoma.

Integrated Genomic Characterization by the TCGA Network

The Cancer Genome Atlas (TCGA) network did molecular analysis of 373 patients with endometrial cancer (307 endometrioid and 66 serous) and found MSI in 40 % endometrioid and 2 % serous tumors. They subclassified endometrial carcinomas into four clusters based on (i) MSI status, (ii) copy number clusters, and (iii) nucleotide substitution frequencies and patterns [7]. Cluster 1 was the ultra-mutated group with very high mutation rates, and this group had mutations in the exonuclease domain of POLE (catalytic subunit of DNA polymerase epsilon involved in DNA replication and repair). Cluster 2 had hypermutated tumors showing increased MSI and most of them with promotor 1 hypermethylation. Cluster 3 was microsatellite stable (MSS) and had a lower mutation frequency and most of the tumors were endometrioid. Cluster 4 had a low

mutation frequency but a high rate of somatic copy number alterations (SCNAs), and the group contained most of the serous and mixed histology tumors with frequent TP53 mutations. When the progression-free survival was analyzed after a median follow-up of 32 months, it was found that cluster 1 had a significantly better progression-free survival (PFS) compared to other clusters with cluster 2 having better PFS than cluster 3 and cluster 4 having significantly worse PFS than others [7].

Thus, the integrated molecular analysis of endometrial carcinomas by TCGA led to the identification of four different groups of endometrial carcinomas as opposed to the traditional classification of type I and type II tumors. The new POLE subtype (cluster 1) comprised about 10 % of the endometrioid tumors. This group is characterized by hotspot mutations in the exonuclease domain of POLE, ultrahigh somatic mutation frequency, and MSS. The survival analysis showed a significantly high progression-free survival for this group. The analysis of SCNAs also added new information about endometrial cancers showing that the extent of SCNAs correlated with the progression-free survival [7]. Twenty-five percent of high-grade endometrioid carcinomas had extensive SCNAs and increased TP53 similar to that of uterine serous carcinomas.

Therapeutic Implications

The improved knowledge about the molecular characteristics of endometrial carcinoma should ideally translate into targeted therapy offering better survival with less treatment-related toxicity to the patient. Gynecologic Oncology Group (GOG) had conducted phase II trials for trastuzumab, bevacizumab, lapatinib, and gefitinib in the treatment of endometrial cancers.

Trastuzumab is a monoclonal antibody directed against HER2 receptor and has proven survival advantage in HER2-positive women affected with breast cancer. GOG 181-B looked into treating patients with advanced or recurrent HER2-positive endometrial carcinoma with trastuzumab [39]. Trastuzumab did not show any activity against HER2-positive endometrial cancer in this phase II trial. Serous tumors have high frequency of HER2 amplification, and trials have shown that uterine serous carcinoma may respond to HER2 inhibition [47]. Further research is warranted in this area.

Bevacizumab is a recombinant humanized monoclonal antibody against vascular endothelial growth factor A (VEGF-A). It is used in the treatment of many malignancies including ovarian and cervical malignancies. The GOG 229-E phase II trial assessed the activity of bevacizumab in recurrent or persistent endometrial cancer and found that 40 % of patients survived progression free for 6 months and 13.5 % of patients had objective clinical response [48]. The results were similar across all histologies. The results of GOG 086-P, a randomized phase II trial combining bevacizumab with chemotherapy, is awaited.

Lapatinib is a member of the 4-anilinoquinazoline class of kinase inhibitors and acts as a dual inhibitor of both EGFR and HER2 tyrosine kinase activity [49]. GOG 229-D assessed the efficacy of lapatinib in endometrial cancer and found that it had insufficient activity to warrant its use as a single agent in endometrial cancer [50]. The GOG 229-C trial involving gefitinib, yet another tyrosine kinase inhibitor, did not show improved response rates for patients with persistent or recurrent endometrial cancer [51].

Konency et al. assessed the activity of fibroblast growth factor receptor (FGFR) inhibitors Dovitinib and NVP-BGJ398 in human endometrial cancer cells and found that both molecules had significant antitumor activity in FGFR2-mutated endometrial cancer xenograft models [52]. The antiproliferative effect of metformin in obese endometrioid endometrial cancer patients was analyzed by Schuler et al. who found that 65 % of patients responded to metformin and it reduced proliferation by 11.75 % supporting further therapeutic clinical trials using metformin [53].

Molecular Pathology of Carcinosarcoma

Carcinosarcoma comprises of 2–5 % of all endometrial cancers. Morphologically these tumors contain admixed carcinomatous and sarcomatous components. But the epithelial and stromal components of carcinosarcomas show identical patterns of X chromosome inactivation, indicating their origin from a single stem cell clone [54]. Studies have shown that both the epithelial and mesenchymal elements show immunohistochemical expression of p53, MSH2, and MSH6 confirming the monoclonal origin [13]. In carcinosarcomas the malignant epithelial cells which express E-cadherin transdifferentiate into malignant mesenchymal cells that express N-cadherin and cadherin-11. This epithelial mesenchymal transition (EMT) promotes the tumor cell interaction with the stroma, promoting invasion and metastasis [55]. On the basis of mutations, carcinosarcomas have been subclassified into endometrioid type with mutations involving PTEN and ARID1A and serous type with TP53 and PPP2R1A mutations [56]. Another important feature noted is the downregulation of miR-200 family of miRNAs and overexpression of miR-214 in the mesenchymal component of carcinosarcoma [57].

Molecular Pathology and Cytogenetics of Leiomyosarcomas

Leiomyosarcomas (LMS) comprise approximately 1–3 % of all uterine malignancies and about 40–50 % of all uterine sarcomas [58]. They are clinically aggressive and have an overall poor prognosis [59]. Majority of them arise de novo, while a small subset is associated with benign leiomyoma. Studies have shown that loss of heterozygosity, overexpression, amplification, and mutations can contribute to the development of LMS [60]. In LMS, LOH at chromosome 10 was more frequently seen when compared to leiomyoma and may contribute to sarcomagenesis [60]. Mittal et al. [61] showed that chromosomal gains and losses in the benign leiomyomatous areas were retained in the sarcomatous areas with additional gains and losses occurring in the sarcomatous areas.

LMS show differential expression of many genes involved in cell proliferation and cell cycle regulation unlike benign leiomyomas. CDKIN2A that codes for p16 is upregulated enabling the immunohistochemical detection of p16 in LMS [62].

Mutation in p53 was noted in 24 % of LMS [60]. In LMS the expression of Ki-67, p53, and p16 was substantially higher, and the expression of tumor suppressor genes PTEN, RASSF1A, and DAP (death-associated protein) was downregulated compared to benign leiomyoma. The downregulation is caused by promotor hypermethylation of the genes [60]. Increased expression of twist homolog 1 (TWIST 1) and fascin homolog 1(FSCN 1) is associated with tumor progression and metastases. Other poor prognostic factors are strong expression of Ki-67, p53, p16, ESR 1(estrogen receptor 1), PGR (progesterone receptor), cyclin D1, and phospholipase D1 as well as low expression of BCL-2 [60]. Loss of BRCA 1 is also said to be involved in the progression of LMS.

Mutations in MED12 gene (mediator complex subunit 12) were identified in 50–80 % of conventional leiomyomas. These mutations are specific to uterine smooth muscle tumors but are less common in leiomyosarcomas [60–65]. Gene products which regulate mitotic centrosome and spindle functions like UBE2C, Aurora A and B kinases, TPX2, and Polo-like kinase 1 are overexpressed in LMSs. Targeting Aurora A has been shown to induce apoptosis and decrease proliferation in uterine LMSs [57]. Increased tyrosine kinase receptor activity and enhanced mTOR signaling have also been demonstrated in uterine LMSs [59].

MiRNAs are important in smooth muscle cell differentiation of uterine LMSs. The miRNA signature of LMS is more similar to bone marrow-derived human mesenchymal cells, whereas the miRNAs of benign leiomyomas are

linked with more mature smooth muscle cells and myometrium [66]. But it is unclear as to whether the LMS cells are derived from the differentiation blockade of smooth muscle progenitor cells or de-differentiation of mature smooth muscle cells [66].

Molecular Pathology and Cytogenetics of Endometrial Stromal Tumors

Endometrial stromal tumors (EST) are rare uterine neoplasms comprising about 1 % of all uterine malignancies [67]. According to the World Health Organization, these tumors are classified into three categories: endometrial stromal nodule (ESN), low-grade endometrial stromal sarcoma (ESS), and undifferentiated endometrial sarcoma (UES) [68]. Low-grade ESS is a tumor with low malignant potential and a favorable prognosis, whereas UES is relatively uncommon and has got a poor prognosis.

ESTs are genetically heterogeneous group of tumors and have distinct cytogenetic abnormalities [69]. It was in 1988 that Dal Cin et al. published the first cytogenetic change in ESS, the insertion of chromosome 19 into chromosome 10 [70]. Three years later, the now hallmark mutation of ESTs, t(7;17)(p21;q12), was reported by Sreekantiah et al. [71]. Since the publication of these results, there have been numerous reports of chromosomal translocations in ESTs, but they are all primarily on low-grade ESS.

The most common and extensively studied translocation in ESTs is that of JAZF1-SUZ12 gene fusion. In this the first three exons of JAZF1 on chromosome 7p15 join the last 15 exons of SUZ12 on chromosome 17q21 [59]. This translocation is very specific to ESTs and has not been noticed in other uterine mesenchymal neoplasms. The JAZF1-SUZ12 gene fusion has been demonstrated in 65 % of ESNs, 48 % of ESSs, and 12 % of UESs [59, 69]. The presence of these mutations in ESNs and ESSs suggests that the chromosomal translocation and gene rearrangement is an early event in the pathogenesis of ESS. It is postulated that ESNs develop from normal endometrial stroma by acquiring the t(7;17) translocation and later transform into ESS by genetic or epigenetic silencing of the unrearranged JAZF1 allele [72]. The small percentage of UESs showing this translocation suggests that they may be developing from ESSs or ESNs via dedifferentiation [73]. But majority of the UESs seem to develop by genetic pathways, which are different from that of ESNs and ESSs [69].

Other less commonly seen gene fusions in ESTs are PHF1-JAZF1, EPC1-PHF1, and MEAF6-PHF1 [59]. MiRNAs also seem to contribute to the pathogenesis of ESTs. Studies have shown similar miRNA profiles in ESSs with or without gene rearrangements. Also several miRNAs altered in ESSs and UESs are involved in Wnt, VEGF, and EGFR signaling pathways suggesting a common pathogenesis [74].

Conclusions

Endometrial carcinomas were traditionally classified as the histologically low-grade type I tumors and type II tumors with high-grade histologies including papillary serous and clear cell types. Mutations differ between these two types with type I tumors showing more PTEN, PIK3CA, β-catenin, RAS-RAF-MEK-ERK pathway mutations, and MSI. Type II tumors have overexpression of P53, HER2/neu, and EGFR and inactivation of E-cadherin and P16. The recent work by TCGA research network has subclassified endometrial cancers into four different types based on proteomic, transcriptomic, and genomic analysis. Survival analysis also showed distinctive progression-free survival curves for these groups. This classification may lead to changes in the management of endometrial cancers in the future.

Molecular studies of carcinosarcomas have confirmed their monoclonal origin, there is transdifferentiation of the malignant epithelial cells into malignant mesenchymal cells, and this epithelial mesenchymal transition promotes invasion and metastases. Loss of heterozygosity, gene amplification, and mutations contribute to the development of leiomyosarcomas. Endometrial stromal sarcomas have characteristic translocations, the most common one being JAZF1-SUZ12 gene fusion.

Key Points

1. Endometrial carcinomas are broadly divided into type I and type II which are caused by different molecular alterations.
2. Main molecular alterations seen in type I endometrial cancers are MSI (microsatellite instability) and mutations affecting the PTEN, KRAS, PIK3CA, and CTNNB1 genes.
3. Type II cancers commonly exhibit P53 alterations, LOH (loss of heterozygosity) on several chromosomes, as well as molecular alterations affecting p16, STK15, E-cadherin, and c-erb-B2.
4. TCGA has reclassified endometrial carcinoma into four groups based on molecular characteristics, with the POLE-mutated group having very good survival rates.
5. Both the epithelial and mesenchymal elements of carcinosarcoma show immunohistochemical expression of p53, MSH2, and MSH6 confirming the monoclonal origin.
6. On the basis of mutations, carcinosarcomas have been subclassified into endometrioid type with mutations involving PTEN and ARID1A and serous type with TP53 and PPP2R1A mutations.
7. LOH at chromosome 10 was more frequently seen in LMS when compared to leiomyoma and may contribute to sarcomagenesis.
8. In LMS the expression of Ki-67, p53, and p16 was substantially higher, and the expression of tumor suppressor genes PTEN, RASSF1A, and DAP (death-associated protein) was downregulated compared to benign leiomyoma.
9. t(7;17)(p21;q12) is the hallmark mutation of endometrial stromal tumors.
10. JAZF1-SUZ12 gene fusion is very specific to endometrial stromal tumors.

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3 Hereditary Cancers of the Endometrium: HNPCC Syndrome and Beyond

Anupama Rajanbabu and Walter H. Gotlieb

Introduction

The incidence of endometrial cancer is increasing worldwide [1]. Identifying women who are at increased risk of endometrial cancer can help in the early diagnosis and prevention of the disease. Obesity, early menarche and late menopause, tamoxifen use, hereditary factors like hereditary nonpolyposis colorectal carcinoma (HNPCC) syndrome, diabetes mellitus, systemic hypertension, etc. are some of the high-risk factors associated with carcinoma of the endometrium. The lifetime risk for endometrial cancer increases from 2.6 % to about 60 % in HNPCC syndrome [2].

What Is HNPCC Syndrome?

Hereditary nonpolyposis colorectal carcinoma syndrome or Lynch syndrome (named after American oncologist Henry T. Lynch) is an autosomal dominant syndrome resulting from germline mutations in one of four DNA mismatch repair (MMR) genes, MLH1, MSH2, MSH6, or PMS2. In addition to the increased risk of endometrial carcinoma, women affected with Lynch syndrome have a 25–50 % lifetime risk of colorectal cancer; 10 % lifetime risk of pelvic epithelial (previously referred to as ovarian), ureter, renal pelvis, and stomach cancer; and also increased risk of small bowel cancer, skin cancer, glioblastomas, and biliary and pancreatic tumors [3]. Studies about Lynch syndrome have mainly centered on colorectal carcinomas and preventive strategies were developed for colorectal cancer prevention. But it has been noted that women affected with Lynch syndrome have an equal or increased risk of developing gynecological malignancies when compared to colonic cancer [4]. In fact more than half of the affected patients present with gynecologic cancer, mostly endometrial carcinoma as "sentinel cancer" [5].

Defining Criteria

Clinical and familial criteria have been used to identify patients with HNPCC. The Amsterdam criteria [6] and Bethesda [7] guidelines (Tables 3.1 and 3.2) focus mainly on patients with colorectal carcinomas. The Bethesda guidelines have better sensitivity than Amsterdam criteria with respect to identifying MMR gene mutation [8]. The Society of Gynecologic Oncology (SGO) guidelines focus on patients with gynecologic cancers

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Table 3.1 Amsterdam criteria for Lynch syndrome screening [6]

Amsterdam criteria I
Three or more family members with a confirmed diagnosis of colorectal cancer, one of whom is a first-degree (parent, child, sibling) relative of the other two
Two successive affected generations
One or more colon cancers diagnosed under age 50 years
Familial adenomatous polyposis (FAP) has been excluded
Amsterdam criteria II
Three or more family members with HNPCC-related cancers, one of whom is a first-degree relative of the other two
Two successive affected generations
One or more of the HNPCC-related cancers diagnosed under age 50 years
Familial adenomatous polyposis (FAP) has been excluded

Table 3.2 Revised Bethesda guidelines [7]

Diagnosed with colorectal cancer before the age of 50 years
Synchronous or metachronous colorectal or other LS/HNPCC-related tumors (which include stomach, bladder, ureter, renal pelvis, biliary tract, brain (glioblastoma), skin (sebaceous gland adenomas, keratoacanthomas), and small bowel (carcinoma)), regardless of age
Colorectal cancer with a high-microsatellite instability morphology that was diagnosed before the age of 60 years
Colorectal cancer with one or more first-degree relatives with colorectal cancer or other LS/HNPCC-related tumors. One of the cancers must have been diagnosed before the age of 50 years (this includes adenoma, which must have been diagnosed before the age of 40 years)
Colorectal cancer with two or more relatives with colorectal cancer or other LS/HNPCC-related tumors, regardless of age

along with colorectal cancers and identify patients in whom genetic risk assessment may be helpful [9] (Table 3.3). Yet 75 % of the patients affected with Lynch syndrome do not have a suggestive family or personal history and also do not fit into the Amsterdam or Bethesda criteria [10, 11]. A comparison of the various screening methods has shown that only 36 % of endometrial cancer

Table 3.3 Society of Gynecologic Oncology (SGO) guidelines [9]

SGO guidelines: patients with a >20–25 % chance of having an inherited predisposition to endometrial, colorectal, and related cancers for whom genetic risk assessment may be helpful
Patients with endometrial or colorectal cancer who meet the revised Amsterdam criteria
Patients with synchronous or metachronous endometrial and colorectal cancer with the first cancer diagnosed prior to age 50 years
Patients with synchronous or metachronous ovarian and colorectal cancer with the first cancer diagnosed prior to age 50 years
Patients with colorectal or endometrial cancer with evidence of mismatch repair defect (i.e., microsatellite instability or immunohistochemical loss of expression of MLH1, MSH2, MSH6, or PMS2)
Patients with first- or second-degree relative with a known mismatch repair gene mutation
SGO guidelines: patients with a >5–10 % chance of having an inherited predisposition to endometrial, colorectal, and related cancers for whom genetic risk assessment may be helpful
Patients with endometrial or colorectal cancer diagnosed prior to age 50 years
Patients with endometrial or ovarian cancer with a synchronous or metachronous colon or other LS/HNPCC-associated tumor at any age
Patients with endometrial or colorectal cancer and a first-degree relative with LS/HNPCC-associated tumor diagnosed prior to age 50 years
Patients with colorectal or endometrial carcinoma diagnosed at any age with two or more first- or second-degree relatives with LS/HNPCC-associated tumors, regardless of age

patients with Lynch syndrome met the revised Bethesda criteria while 58 % met the Amsterdam II criteria. The SGO guidelines gave better results by identifying 71 % of patients with the 20–25 % screening criteria and 93 % identified through the 5–10 % criteria [12].

Clinical Presentation

Patients affected with Lynch syndrome develop colorectal cancer before the age of 50 years, and in around one-third of the patients, another HNPCC-related malignancy occurs within 10 years [13]. Individuals affected with Lynch

syndrome have a 25–70 % lifetime risk of developing endometrial carcinoma [3]. Now, it is known that more than 50 % of the affected patients present with endometrial cancer as their sentinel cancer [5].

These patients usually do not have features of estrogen excess like obesity, diabetes mellitus, estrogen, tamoxifen use, or polycystic ovarian syndrome [14]. An association with low body mass index (BMI) has been suggested [15]. They can present with irregular menstrual bleeding but are less likely to be associated with endometrial hyperplasia. A clinical suspicion of Lynch syndrome should arise when a patient is presenting with endometrial cancer without the usual risk factors. A patient has 25 % chance of developing a second cancer in 10 years and 50 % chance at 15 years following the diagnosis of a Lynch syndrome-related endometrial carcinoma [14]. Therefore, a clinical suspicion and diagnosis will help in screening for other cancers and will also be beneficial for the patient and her family members.

Genetic Basis

Lynch syndrome is caused by germline mutations in the MMR genes MLH1, MSH 2, MSH 6, and PMS 2. Rarely patients can have deletions of the EPCAM gene upstream to the MSH2 gene causing Lynch syndrome [8]. The MMR genes provide stability to the DNA by correcting the mismatches that are produced during DNA replication. Any mutation in the MMR gene causes loss of function and microsatellite instability (MSI) leading to the formation of cancer [16]. MSI can also be caused by an epigenetic mechanism – hypermethylation of MLH1 promoter gene leading to gene silencing and MSI. This is seen in 20–25 % of patients with sporadic endometrial cancer [17]. Carcinogenesis in the presence of MSI appeared to be due to frame-shift mutations of microsatellite repeats within the coding regions of the genes. PTEN seems to be the candidate gene in endometrial carcinoma [18].

Frequency of mutations of MMR genes in Lynch syndrome-related endometrial carcinomas is 50–66 % for MSH2, 24–40 % for MLH1, 10–13 % for MSH 6, and less than 5 % for PMS2 [19, 20]. Even though MSH6 mutations are less frequent, they have an increased risk of endometrial cancer compared to individuals with MSH2 or MLH1 mutations [3].

Pathology

It has been noted that endometrial cancers due to Lynch syndrome arise predominantly in the lower uterine segment. Overall 10–15 % of the lower uterine segment tumors are associated with Lynch syndrome [11, 21]. Both endometrioid and non-endometrioid tumors occur in Lynch syndrome. The non-endometrioid varieties include clear cell carcinoma, serous carcinoma of the endometrium, carcinosarcoma, and also undifferentiated tumors of the endometrium [22, 23]. In a study by Honoré et al. [24], it was found that MSI correlates with high tumor grades in endometrioid adenocarcinoma. The MSI-related beta-catenin mutations cause the upregulation of Cmyc which in turn stimulates CDK4, leading to the inactivation of the retinoblastoma suppressor gene, thus activating the CDK4/cyclin complex and sequestering the cell cycle inhibitors like p16, p21, and p27. This is the probable mechanism behind the high tumor grade in MSI [24]. Honoré et al. also state that the MSI-related endometrioid adenocarcinoma arises in a background of atrophic endometrium and is associated with more myometrial invasion, lymphovascular space invasion, and nodal metastases, which are adverse prognostic factors in carcinoma of the endometrium.

There are several histological features that are linked to MSI and MMR protein deficiency in endometrioid adenocarcinomas. Most prominent among them are the undifferentiated and de-differentiated tumor patterns [3]. Other features that are thought to be suggestive of MSI are prominent peritumoral lymphocytes, dense tumor infiltrating lymphocytes (TIL), and tumor heterogeneity [3]. The undifferentiated tumor pattern was initially described by Altrabulsi et al. [25] as solid sheets of medium-sized,

monotonous epithelial cells with complete absence of glandular proliferation. The term dedifferentiated carcinoma is used when an undifferentiated tumor pattern is associated with a focus of well to moderately differentiated endometrioid adenocarcinoma [26]. Tumor-infiltrating lymphocytes are considered as a marker of MMR protein deficiency and are seen in both genetic and sporadic conditions. More than 42 TIL per 10 high power fields has been proposed as more suggestive of Lynch syndrome [27]. Peritumoral lymphocytes are defined as readily appreciable aggregates of lymphocytes around the tumor at scanning magnification [28]. Tumor heterogeneity is defined as a tumor having two or more morphologically separate patterns, each constituting at least 10 % of the tumor with each component being juxtaposed and not intimately admixed [28].

Pelvic epithelial tumors, previously referred to as "ovarian tumors" found in association with Lynch syndrome, are well to moderately differentiated endometrioid carcinomas and clear cell carcinomas. Pelvic epithelial clear cell ovarian carcinoma in a younger patient has a strong association with Lynch syndrome [15, 29]. There are reports of synchronous endometrioid carcinomas of uterus and pelvic clear cell carcinoma ovary in women with MMR protein defects [15, 29].

Which Patients with Endometrial Carcinomas Are to Be Tested for Lynch Syndrome?

In unselected endometrial cancer patients, 1.8–2.1 % MMR gene mutation rates have been found [10, 30]. These rates are similar to the MMR mutation rates found in colorectal carcinoma [31]. In patients below the age of 50 years affected by endometrial cancer, the rates of MMR gene mutations have been found to be as high as 9 % [32]. The identification of patients affected with these mutations is important as they have increased risk for synchronous and metachronous cancers. They themselves and their family members would benefit from surveillance methods to detect other related cancers and genetic counseling. Also there could be prognostic and therapeutic implications for the affected patients [27]. The Amsterdam criteria [6] and Bethesda guidelines [7] focus mainly on colorectal cancers. The SGO guidelines [9] focus on gynecologic cancers and give better screening results [12] but still underestimate these cancers.

Screening for Lynch syndrome in all patients of endometrial cancer has been advocated and also implemented by some centers [14]. But it is not practical to screen all patients with endometrial cancers for Lynch syndrome. Many criteria have been proposed based on the age, family history, and pathological factors for screening Lynch syndrome. Using 50 years as a cutoff age will cause underdetection, as many women (especially patients with MSH6 mutations) above the age of 50 years present with MMR protein-deficient endometrial cancer [33]. Using the tumor morphology – lower segment tumors, presence of TIL, peritumoral lymphocytes, and undifferentiated and dedifferentiated tumor patterns – has been suggested to increase the detection rates of endometrial cancer patients at risk of HNPCC [27].

Use of immunohistochemistry (IHC) to detect the four main MMR proteins is an easy procedure and can detect most mutations, at significant direct cost but potential high returns and value over the long run for both the patient and her family [34]. Kwon et al. compared various criteria for Lynch syndrome testing for women with endometrial cancer and found that IHC triage of women having endometrial cancer at any age having at least one first-degree relative with Lynch associated cancer is a cost-effective strategy for Lynch syndrome detection [34].

Detecting Lynch Syndrome

The definitive way to detect Lynch syndrome is mutational analysis of the MMR gene DNA. In view of the cost, it is suggested that mutational analysis be used only as a confirmatory test after screening with IHC, MSI analysis, and MLH1 methylation studies [3].

Modica et al. have reported a sensitivity of 91 % and a specificity of 83 % for IHC in detecting MSI phenotype in endometrial carcinoma when antibodies against all four MMR proteins were used [35]. As MLH1 dimerizes with PMS 2 and MSH2 dimerizes with MSH 6 in their functional state, mutations of MLH1 and MSH2 will lead to loss of PMS2 and MSH 6, respectively. Using antibodies only against MLH1 and MSH2 only provides 69 % sensitivity and 100 % specificity and can be used as an economical alternative to the four-antibody test [35]. IHC has the advantage being a simple and less expensive test and can direct the gene sequencing to one or more specific genes.

MSI analysis is by polymerase chain reaction (PCR) amplification of the National Cancer Institute reference loci (BAT25, BAT26, D2S123, D5S346, and D17S250) on tumor and normal tissue for each patient [36]. Tumor with no instability detected is termed as MSI stable, instability at one focus is termed MSI low, and instability at two loci is termed MSI high. MSH6 mutations may be MSI stable or MSI low, and if MSI is used as a screening test, some mutation carriers may not be detected [3].

All tumors showing inactivation of MLH1 by IHC or MSI analysis should be subjected MLH1 promoter methylation assay. This is because MLH1 inactivation can occur also due to an acquired mechanism – MLH1 promoter methylation resulting in loss of protein. Tumors showing MLH1 promoter methylation are likely to be associated with Lynch syndrome [3].

DNA MMR mutation test is the confirmatory test to establish the diagnosis of Lynch syndrome. This is usually performed when the abovementioned screening tests show a strong possibility of Lynch syndrome [3].

Surveillance and Risk Reduction for Endometrial Carcinomas

There is limited data on the efficacy of endometrial cancer screening in women with Lynch syndrome. Vasen et al. have recommended annual physical examination and transvaginal sonography along with endometrial biopsy from the age of 30 to 35 years [37]. NCCN still states that there is no clear evidence to support screening for endometrial cancer in Lynch syndrome [38]. This may stem from the fact that screening for endometrial cancer had not produced improved outcomes, as well as reports of interval carcinomas not detected by screening [39]. But Renkonen-Sinisalo et al. showed that screening with endometrial biopsies in women affected with Lynch syndrome detected endometrial cancers at an early stage and there were more frequent detection of premalignant lesions which enabled prophylactic hysterectomy in the screened group. Compared with the unscreened group presenting with mutation-positive endometrial cancer, the surveillance group presented with a more favorable stage distribution and there were no deaths due to endometrial cancer [40].

The study by Lécuru et al. showed that ultrasonography showed 100 % sensitivity and 100 % NPV when used to screen patients with HNPCC/Lynch syndrome for atypical hyperplasia and endometrial cancer. But in this study endometrial cancers were diagnosed in women who presented with abnormal vaginal bleeding [41]. NCCN also stresses the fact that all women with Lynch syndrome must be made aware that abnormal uterine bleeding needs evaluation [38].

Little is known about the role of oral contraceptives in preventing endometrial carcinomas in women affected with Lynch syndrome. Prophylactic hysterectomy and bilateral salpingo-oophorectomy once childbearing is complete [38] or after the age of 35 years [42] can prevent the development of endometrial cancer in women with Lynch syndrome. Compared to gynecological surveillance, risk-reducing surgery is a comparatively less expensive option [43]. But the disadvantages of surgical menopause (if ovaries are also removed) and surgical complications must be explained. There is a chance of occult malignancy in the endometrium/ovary; hence, patients must consent for staging should there be intraoperative evidence of malignancy [3].

Other Hereditary Syndromes Associated with Endometrial Carcinomas

Endometrial carcinomas are also associated with breast-ovarian cancer syndrome and rarely with Cowden syndrome (PTEN hamartoma tumor syndrome).

Some isolated studies from Israel have associated uterine papillary cancers with BRCA germline mutations [44, 45]. These findings in the Ashkenazi Jewish population, in whom BRCA mutations are high, remain to be confirmed. Kwon et al. reported prolonged survival in advanced-stage endometrial carcinomas associated with BRCA mutations. The improved prognosis may be due to a difference in the tumor biology making these tumors more susceptible to radiation and chemotherapy [46]. This association of uterine serous cancers to the BRCA-related tumors has implications in the management of unaffected BRCA1 and 2 mutation carriers. Whether a hysterectomy is to be recommended as well in addition to a risk-reducing bilateral salpingo-oophorectomy will need to be further investigated [44].

PTEN hamartoma syndrome is an autosomal dominant syndrome characterized by the development of multiple gastrointestinal hamartomas, mucocutaneous lesions, and increased risk of certain malignancies. A number of disorders including Cowden syndrome, Bannayan-Riley-Ruvalcaba syndrome, and Proteus syndrome come under this [47]. NCCN recommends patient education and prompt response to symptoms in an affected patient for endometrial cancer screening, and risk-reducing hysterectomy must be discussed with the patient [38].

Conclusion

HNPCC syndrome is the most common hereditary syndrome associated with endometrial cancer which is caused by germline mutations in the MMR genes MLH1, MSH 2, MSH 6, and PMS 2 leading to microsatellite instability and development of cancer. Women affected with HNPCC syndrome have 60 % lifetime risk of endometrial cancer, and more than half of the affected patients present with gynecologic cancer, mostly endometrial carcinoma as their "sentinel cancer." SGO guidelines for screening HNPCC syndrome can identify 93 % of affected women. Currently NCCN does not recommend screening for endometrial cancer in affected women, but studies have shown that screened cohort had detection of more premalignant lesions at early stage of diagnosis. Other syndromes associated with endometrial cancer are BRCA mutations and PTEN hamartoma syndrome. Women affected with hereditary syndromes should be educated to seek prompt evaluation in case of abnormal uterine bleeding and advised that prophylactic hysterectomy after completion of childbearing/after 35 years can prevent endometrial cancer.

Key Points

1. HNPCC syndrome or Lynch syndrome is the most common cause of hereditary cancer of the endometrium providing a 40-fold increased chance of endometrial cancer in affected when compared to general population.
2. Other hereditary syndromes associated with endometrial cancer are breast-ovarian cancer syndrome and Cowden syndrome.
3. SGO guidelines can identify 93 % of patients affected with Lynch syndrome.
4. In diagnosed Lynch syndrome patients without endometrial cancer, annual screening with sonography and endometrial biopsy and prophylactic hysterectomy after completion of childbearing can reduce the risk of endometrial cancer.
5. A clinical suspicion of Lynch syndrome should arise when a patient is presenting with endometrial cancer without the usual risk factors or endometrial hyperplasia.

6. Pathological factors like lower segment tumors, presence of TIL, peritumoral lymphocytes, undifferentiated and dedifferentiated tumor patterns, increase detection of Lynch syndrome.
7. In suspected women IHC testing, MSI analysis, and MLH1 methylation studies should be done followed by the definitive test "mutational analysis of the MMR gene DNA" to confirm Lynch syndrome.

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Screening and Prevention of Carcinoma Endometrium

4

T.J. Simi Raj and K. Chitrathara

Introduction

Carcinoma endometrium is the most common malignancy of the female genital tract in the developed world and the fourth most common cancer in women after breast, lung, and colorectum. The estimated new cases from endometrial cancer in the United States are 52,630 and deaths are 8,590 [1]. It is the second most common malignancy of the female genital tract in the developing world. The incidence in developing countries and Japan are four to five times lower than the developed world. In India, the rates are as low as 4.3 per 100,000 [2]. In recent years incidence in India is increasing – double the incidence as per recent cancer registry data. Due to increasing magnitude of the problem, screening and steps of prevention are of great importance.

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Screening of Carcinoma Endometrium

Whom to Screen?

The American Cancer Society recommends that at the time of menopause, all women should be told about the risks and symptoms of endometrial cancer. Women should report any unexpected vaginal bleeding, discharge, or spotting.

Women at Low Risk for Endometrial Cancer

At this time, there are no acceptable, reliable, and valid screening tests or examinations to identify endometrial cancer early in women who are at average endometrial cancer risk and have no symptoms.

Women should have regular pelvic exams. A pelvic exam can find some cancers, including some advanced uterine cancers, but it is less effective in finding early endometrial cancers.

The Pap test (or Pap smear), which screens for cervical cancer, can occasionally find some early endometrial cancers, but it is too insensitive and nonspecific for screening for endometrial cancer [3]. In Papanicolaou smears, benign appearing endometrial cells bear no significance in predicting uterine endometrial adenocarcinomas [4].

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Measuring endometrial thickness (ET) with transvaginal ultrasound (TVU) and endometrial sampling with cytological examination have been proposed as possible screening modalities for endometrial cancer. But, there is no evidence that screening by ultrasonography (e.g., endovaginal ultrasound or transvaginal ultrasound) or endometrial sampling (i.e., biopsy) reduces mortality from endometrial cancer. Most cases of endometrial cancer (85 %) are diagnosed in early stage because of symptoms, and survival rates are high. Based on evidence, screening asymptomatic women by measuring endometrial thickness will result in unnecessary additional biopsies because of false-positive test results.

Routine screening of asymptomatic women for endometrial cancer has not been evaluated for its impact on endometrial cancer mortality. Although high-risk groups can be identified, the benefit of screening in reducing endometrial cancer mortality in these high-risk groups has not been evaluated. Using the same cutoffs to define an abnormal ET in asymptomatic women as used in symptomatic women [5, 6] would result in large numbers of false-positive test results and larger numbers of unnecessary referrals for cytological evaluations. Published recommendations for screening certain groups of women at high risk for endometrial carcinoma are based on opinion regarding presumptive benefit [7].

Women at Increased Endometrial Cancer Risk

The American Cancer Society recommends that most women at increased risk should be informed of their risk and be advised to see their doctor whenever there is any abnormal vaginal bleeding. However, there are no guidelines on screening asymptomatic high-risk women and the choice is left to gynecologists. Women at increased risk for carcinoma endometrium include [8] estrogen therapy unopposed by progesterone therapy in a postmenopausal woman with intact uterus, tamoxifen, anovulatory cycles including polycystic ovary syndrome, obesity, high fat diet, diabetes mellitus, hypertension, nulliparity, early menarche, late menopause, hereditary nonpolyposis colorectal cancer (HNPCC) syndrome, atypical endometrial hyperplasia, and pelvic radiation therapy.

Women who have (or may have) hereditary nonpolyposis colon cancer (HNPCC, Lynch syndrome) have a very high risk of endometrial cancer. If colon or endometrial cancer has occurred in several family members, genetic counseling should be offered. The reader is referred to Chap. 3 for complete information on hereditary cancers. Apart from family history other features direct genetic testing and mutational analysis.

The American Cancer Society recommends that women who have (or may have) HNPCC be offered yearly testing for endometrial cancer with endometrial biopsy beginning at age 35. This applies to women known to carry HNPCC-linked gene mutations, women who are likely to carry such a mutation (those with a mutation known to be present in the family), and women from families with colon cancer where genetic testing has not been done.

Modalities of Endometrial Cancer Screening

The methods of screening available are:

1. Measurement of endometrial thickness by ultrasonography
2. Endometrial aspiration biopsy
3. Endometrial curettage

Measurement of Endometrial Thickness and Endometrial Biopsy in Women Without Vaginal Bleeding

Transvaginal sonography (TVS) is a relatively less invasive investigation and is freely available. There is interest in trying to reduce the morbidity from endometrial cancer through early detection, and endovaginal ultrasound as a method to screen women to detect endometrial cancer is a promising option. It measures endometrial thickness that may help determine which women should undergo endometrial biopsy.

Fleischer et al. screened 1,926 asymptomatic postmenopausal women using TVS for endome-

trial disease as part of osteoporosis prevention trial, and 93 of them had endometrial thickness greater than 6 mm. Out of the 1,750 women who underwent biopsy, there were five cases of endometrial abnormality (adenocarcinoma [$n=1$] and atypical hyperplasia [$n=4$]). The negative predictive value was >99 %. One case of adenocarcinoma was detected in the 42 women who had endometrial thickness >6 mm and underwent biopsy. Among this population of asymptomatic postmenopausal women, the estimated sensitivity for TVS with a threshold value of 6 mm was 17 %. The study reveals that despite a high negative predictive value, TVS may not be an effective screening procedure for detection of endometrial abnormality in untreated postmenopausal women who are asymptomatic [9].

Saatli et al. did a retrospective analysis of 530 asymptomatic postmenopausal women who underwent ultrasonographic evaluation with subsequent endometrial sampling if endometrial thickness was above 5 mm. The mean endometrial stripe thickness was 8.7 mm (range: 6–26), and five cases of adenocarcinoma (0.9 %) and 65 (12.2 %) cases of simple/complex atypical hyperplasia were diagnosed [10]. Although TVS can be used to evaluate asymptomatic and occult endometrial pathology, the technique has not been evaluated as a screening method for reducing mortality in asymptomatic women.

Screening endometrial biopsy has also been considered as a way to detect neoplasia early. However, Archer et al. concluded that the yield for neoplasia is so low that screening endometrial biopsy is not justified in asymptomatic perimenopausal and postmenopausal women [11].

Measurement of Endometrial Thickness and Endometrial Biopsy in Women with Vaginal Bleeding

In a study on postmenopausal women with bleeding per vaginum, using a 5-mm threshold to define abnormal endometrial thickening, 96 % of women with cancer had an abnormal TVS result, whereas 92 % of women with endometrial disease (cancer, polyp, or atypical hyperplasia) had an abnormal result. This did not vary by hormone replacement use. However, the number of women with normal histology who had an abnormal TVS result did vary by hormone replacement use. The specificity varied by whether women used hormone therapy or not. Among nonusers, the specificity was 92 % [6].

In another study, women with postmenopausal bleeding underwent transvaginal sonographic measurement of endometrial thickness and curettage and were followed for > or = 10 years. Of the 339 participants, 39 (11.5 %) were diagnosed with endometrial cancer (four had an ET of 5–7 mm and 35 had an ET>8 mm) based on histopathology from curettage. No cancers were detected in women with an ET of less than 4 mm. Using a cutoff point of 4 mm, TVS has 100 % sensitivity and 60 % specificity. Postmenopausal bleeding confers a 64-fold increase risk in endometrial cancer. There was no increased risk of endometrial cancer or atypia in women who did not have recurrent bleeding, whereas women with recurrent bleeding were found to be a high-risk group. No endometrial cancer was missed when endometrial thickness measurement (cutoff value, < or = 4 mm) was used, even if the women were followed up for < or = 10 years concluding that transvaginal sonography is an excellent tool for determining whether further investigation with curettage or endometrial biopsy is necessary in symptomatic women [12]. In this population, 46 % ($N=156$) of the women had an ET greater than 4 mm.

Ultrasonography in Women Using Tamoxifen

Tamoxifen is widely used as part of adjuvant therapy for breast cancer and as chemoprevention for women at increased risk of breast cancer. In addition to the protective effects for breast cancer, the biological and endocrine effects of tamoxifen increase a woman's risk of developing endometrial pathology, including endometrial polyps, endometrial hyperplasia, and endometrial carcinoma.

In a prospective, observational study of 304 women using tamoxifen over 6 years, women underwent annual endovaginal ultrasound screening; women with abnormal ultrasound findings and women who were symptomatic with bleeding

all underwent endometrial biopsy. Thirty-two percent of the ultrasound examinations had associated significant uterine abnormalities identified that required further medical or surgical investigation and treatment. However, most abnormalities (80 %) represented benign polyps for which no treatment was needed. Six cases of primary endometrial cancer were detected, and all cases presented with irregular bleeding. The sensitivity of ultrasound was only 63.3 %, with a specificity of 60.4 %, and had a low positive predictive value for cancer of only 1 % [13].

Routine ultrasound surveillance in asymptomatic women using tamoxifen is not useful because of its low specificity and low positive predictive value. Evaluation of the endometrium in women taking tamoxifen should be limited to women symptomatic with vaginal bleeding.

ACOG Committee Opinion (June 2014) [14] recommends that women taking tamoxifen should be informed about the risks of endometrial proliferation, endometrial hyperplasia, endometrial cancer, and uterine sarcomas. They should be encouraged to promptly report any abnormal vaginal symptoms, including bloody discharge, spotting, staining, or vaginal discharge. Any abnormal vaginal bleeding, bloody vaginal discharge, staining, or spotting should be investigated.

Premenopausal women treated with tamoxifen have no known increased risk of uterine cancer and as such require no additional monitoring beyond routine gynecologic care. Postmenopausal women taking tamoxifen should be closely monitored for symptoms of endometrial hyperplasia or cancer [15, 16].

Correlation is poor between ultrasonographic measurements of endometrial thickness and abnormal pathology in asymptomatic tamoxifen users because of tamoxifen-induced subepithelial stromal hypertrophy [17]. In asymptomatic women using tamoxifen, screening for endometrial cancer with routine transvaginal ultrasonography, endometrial biopsy, or both has not been shown to be effective [13, 18, 19].

Although asymptomatic postmenopausal tamoxifen-treated women should not have routine testing to diagnose endometrial pathology, sonohysterography has improved the accuracy of ultrasonography in excluding or detecting anatomic changes, when necessary [20].

Unless the patient has been identified to be at high risk of endometrial cancer, routine endometrial surveillance has not proved to be effective in increasing the early detection of endometrial cancer in women using tamoxifen. Such surveillance may lead to more invasive and costly diagnostic procedures and, therefore, is not recommended.

There is evidence that suggest the presence of high-risk and low-risk groups for the development of atypical hyperplasias with tamoxifen treatment in postmenopausal women based on the presence or absence of benign endometrial polyps before therapy. Thus, there may be a role for pretreatment screening of postmenopausal women with transvaginal ultrasonography, and sonohysterography when needed, or office hysteroscopy before initiation of tamoxifen therapy [21–24].

Endometrial cancers that occur in tamoxifen-treated women are very similar to those cancers occurring in the general population, with respect to stage, grade, and histology [15, 25, 26]. Prognosis is good and not affected by early detection [27]. To date, there have been no published studies evaluating the effect of endometrial cancer-screening modalities on mortality among women taking tamoxifen for breast cancer treatment or prevention.

Sonohysterography

Sonohysterography is a diagnostic test done in asymptomatic women and distinguishes space occupying endometrial lesions from a thickened endometrium. There are no studies to show that routine screening sonohysterography will confer clinical benefit. Transtubal spill does occur during sonohysterography, but the probability of cancer cell dissemination is low [28].

Endometrial Sampling in Women with Uterine Bleeding

In the setting of abnormal uterine bleeding, endometrial biopsy has gained favor largely as an

alternative to more invasive procedures such as fractional curettage. Several methods of biopsy exist (e.g., Pipelle, Tao Brush, and Uterine Explora Curette) to identify endometrial pathology. Although endometrial biopsy has largely replaced D&C as the first choice in the evaluation of women with bleeding, issues of access to the endometrial cavity and sampling error limit the clinical significance of a negative result. In the Arimidex, Tamoxifen, Alone, or in Combination trial, 36 % of biopsies had insufficient tissue for diagnosis [29].

No studies have evaluated the use of endometrial sampling as routine screening in reducing endometrial cancer mortality.

Hysteroscopy

Hysteroscopy is used in the office setting to directly visualize the uterine cavity. A group of researchers noted that hysteroscopy is not as useful in detecting endometrial cancer as biopsy or D&C [30]. It has not been evaluated as a screening tool [31]. Theoretical risk of tumor spill into the abdominal cavity via the fallopian tube exists in hysteroscopy in cases of endometrial cancer. A study done in Beijing showed that hysteroscopy did not increase the positive peritoneal cytology rate or affect the prognosis of patients with carcinoma endometrium [32].

Although it no role in screening, hysteroscopy may be done in women who have a negative biopsy but continue to bleed or when ultrasonography shows a polyp.

Screening Women on Hormone Replacement Therapy

There is no evidence to suggest that screening women prior to or during estrogen–progestin therapy, also known as hormone therapy, would decrease endometrial cancer mortality [33, 34].

Thus, women on hormone therapy should have a prompt diagnostic work-up for abnormal bleeding. Although women using certain hormone regimens have an increased risk of endometrial cancer, most women who develop cancer will have vaginal bleeding. There is no evidence that screening these women will decrease mortality from endometrial cancer.

Hereditary Nonpolyposis Colorectal Cancer

The lifetime risk of endometrial cancer for women with hereditary nonpolyposis colorectal cancer (HNPCC) and for women who are at high risk for HNPCC is as high as 60 %. These cases are often diagnosed in the fifth decade, 10–20 years earlier than sporadic cases [35–39].

Based on limited evidence, it appears that 5-year survival among HNPCC women diagnosed with endometrial cancer is similar to that of non-hereditary cases in the general population [40]. Because the risk of endometrial cancer is so high among these women, international guidelines suggest gynecologic surveillance including annual transvaginal ultrasound with endometrial biopsy beginning in women aged 25–35 years [7, 41].

The most recent American Cancer Society Cancer Detection Guidelines (updated January 2005) recommend annual screening with endometrial biopsy beginning at age 35 years [42]. Helder-Woolderink et al. screened 75 women above 30 years of age with Lynch Syndrome (LS) or first-degree relatives at 50 % risk of Lynch syndrome annually and concluded that adding standard endometrial sampling to annual TVS has no additional value in the early detection of (pre) malignant endometrial lesions in women with Lynch syndrome [43].

Problems with Screening

Screening of low-risk population leads to huge economic burden. Abnormal ultrasound will warrant further investigation including endometrial biopsy (sampling). Endometrial sampling may result in discomfort, bleeding, infection, and rarely uterine perforation. A study designed to evaluate performance, patient acceptance, and cost-effectiveness of blind biopsy, hysteroscopy with biopsy,

and ultrasound, in 683 women with vaginal bleeding, reported that minor events, including discomfort and distress, occurred in 16 % of women who had hysteroscopy with biopsy and in 10 % of women who had a blind biopsy [44]. Risks associated with false-positive test results include anxiety and additional diagnostic testing and surgery. Endometrial cancers may be missed on endometrial sampling and ultrasound.

Prevention of Carcinoma Endometrium

Most cases of endometrial cancer cannot be prevented, but there are some interventions that may lower the risk of developing this disease. One way to lower endometrial cancer risk is to change modifiable risk factors whenever possible.

Interventions to Reduce the Risk of Carcinoma Endometrium

Oral Contraceptives

Oral contraceptive pills lower the risk of carcinoma endometrium. The relative risk of carcinoma endometrium in ever users of oral contraceptives in comparison with never users is 0.1 (95 % confidence interval 0.0–0.7). The reduction in risk was proportionate to the duration of use [45]. However, compared with never users of oral contraceptives, the relative risks of cervical cancer increased with increasing duration of use [46].

In a meta-analysis of 11 studies, 10 studies found that 4 years of combined oral contraceptive (COC) use was associated with a risk reduction of approximately 56 %; with 8 years use, 67 % reduction in risk; and with 12 years use, 72 % risk reduction. Even though the single-prospective study did not show a duration response, the risk was reduced by 80 % after 9 years of follow-up [44]. A case–control study among postmenopausal women aged 50–74 years in Sweden, which included 709 subjects with incident, histopathologically verified endometrial cancer, and 3,368 controls with an intact uterus confirmed the protective effect of COC. Women who used any type of oral contraceptive had a 30 % risk reduction (odds ratio [OR] = 0.7; 95 % CI, 0.5–0.9) and women who used progestin-only pills had a 60 % risk reduction (OR = 0.4; 95 % CI, 0.2–1.4). Women who used COCs for at least 3 years had a 50 % risk reduction (OR = 0.5; 95 % CI, 0.3–0.7), and those who used COCs for at least 10 years had an 80 % risk reduction (OR = 0.2; 95 % CI, 0.1–0.4). Overall, risk decreased by 10 % per year of COC use and was observed for atypical hyperplasias as well as all grades of invasive endometrial cancer. The protective effect remained for at least 20 years after cessation of use. Subsequent use of hormone replacement did not modify these protective effects [47].

Prevention of Obesity and Increased Physical Activity

Obesity is one of the risk factors for carcinoma endometrium. In obese women serum estrone level is increased due aromatization of androstenedione in adipose tissue into estrogen [48]. There is also a reduction in sex hormone-binding globulin levels in obesity, thus increasing the bioavailable estrogen [49]. Obesity has been associated with several factors known to increase the risk of endometrial cancer, including upper-body or central adiposity, polycystic ovary syndrome, physical inactivity, and a diet high in saturated fat [50]. Hence, steps to reduce obesity will help in primary prevention of carcinoma endometrium. However, the Iowa Women's Health Study found no association between endometrial cancer incidence and intentional weight loss of at least 20 lbs (RR = 0.93; 95 % CI, 0.60–1.44) [51].

Data analyzed from Nurses' Health Study revealed that greater recent physical activity of moderate duration and intensity, such as walking, may reduce endometrial adenocarcinoma risk. This correlation is largely mediated or confounded by body mass index [52].

A recent meta-analysis showed a linear relationship between increase in leisure-time physical activity and decrease in risk of endometrial cancer, within the range of 0–50 h MET (metabolic equivalent of task)/week or 0–15 h/week [53].

In the Netherlands cohort study on diet and cancer, 62,573 postmenopausal women were followed up for 9 years and 226 endometrial cancer case patients were identified. A 46 % reduction

(RR = 0.54; 95 % CI, 0.34–0.85; $P = 0.002$) in risk of endometrial cancer was reported in those women who were physically active 90 min or more per day compared with less than 30 min each day [54]. One case–control study of 822 endometrial cancer cases and 1,111 population controls showed that regular exercise was associated with a 38 % decrease in risk (OR = 0.62; 95 % CI, 0.51–0.76) without a trend for increasing duration or intensity of physical activity [55]. The Breast Cancer Detection Project Follow-up Study used a prospective cohort to assess past-year physical activity of all types and found that recent physical activity is not strongly related to the risk of endometrial cancer and that prolonged exposure and longer follow-up may be necessary [56]. A meta-analysis of five cohort studies, which together comprise 2,663 cases, revealed that excessive sitting time seems to contribute to endometrial cancer risk independently of moderate-to-vigorous-intensity physical activity.

Physical activity is hypothesized to decrease endometrial cancer risk because it reduces serum levels of estradiol and increases levels of sex hormone-binding globulin (SHBG), the binding protein for estradiol [57]. These effects of physical activity may be mediated through prevention of weight gain. In postmenopausal women, adipose tissue is the primary source of estrogen where the aromatization of androgen precursors occurs within this tissue [58]. Consequently, women who maintain a healthy body weight tend to have lower circulating estrogen levels [59].

Encouraging Pregnancy and Breast Feeding

Increasing parity and lactation reduces the risk of breast, endometrial, and ovarian cancers. This is probably due to inhibition of ovulation. The higher the number of full-term pregnancies, the greater the protection. The risk of endometrial cancer is reduced by 30 % for a woman's first birth and by 25 % for each successive birth, and later maternal age at last birth has also been shown to reduce the risk [60]. A case–control study comparing 85 women with carcinoma endometrium and 668 healthy women showed a 58–72 % reduction in risk of endometrial cancer associated with increasing duration of lactation [61]. Hence, encouraging pregnancy and lactation will reduce the risk of endometrial cancer.

Progestins for the Prevention of Prolonged Anovulatory Cycles

Progesterone has been described as the ultimate endometrial cancer suppressor. Estrogen drives endometrial epithelial proliferation. Progesterone inhibits growth and causes cell differentiation. The importance of progesterone as a key inhibitor of carcinogenesis is reflected by the observation that women who ovulate and produce progesterone almost never get endometrial cancer. Cyclical progestins reduce the risk of hyperplasia in women with anovulation [62].

Treatment of Endometrial Hyperplasia

Endometrial hyperplasia can progress to endometrial cancer. A nested case–control study of progression of endometrial hyperplasia (EH) to carcinoma was done with 138 cases, who were diagnosed with EH and then with carcinoma at least 1 year later, and 241 controls. With disordered proliferative endometrium (DPEM) as the referent, atypical hyperplasia significantly increased carcinoma risk with a relative risk of 14 (RR = 14, 95 % CI, 5–38). Progression risks for simple hyperplasia (RR = 2.0, 95 % CI, 0.9–4.5) and complex hyperplasia (RR = 2.8, 95 % CI, 1.0–7.9) were substantially lower and only slightly higher than the progression risk for DPEM [63].

Progestin therapy is very effective in reversing endometrial hyperplasia but is less effective with atypia. For women with atypical complex hyperplasia who no longer desire fertility, hysterectomy is recommended [64].

Avoid Unopposed Exogenous Estrogen

Cochrane database systematic review showed that unopposed estrogen is associated with increased risk of endometrial hyperplasia at all doses and durations of therapy between 1 and 3 years. For women with a uterus, the risk of endometrial hyperplasia with hormone therapy comprising

low-dose estrogen continuously combined with a minimum of 1 mg norethisterone acetate (NETA) or 1.5 mg medroxyprogesterone acetate (MPA) is not significantly different from placebo at 2 years (1 mg NETA: OR 0.04; 95 % confidence interval (CI) 0–2.8; 1.5 mg MPA, no hyperplasia events). The review concluded that hormone therapy for postmenopausal women with an intact uterus should comprise both estrogen and progestogen to reduce the risk of endometrial hyperplasia [65]. Another meta-analysis showed that in women using HRT, those who used progestins continuously (>25 days/months) are at reduced risk relative to nonusers (meta-analysis relative risk, RR, based on observational studies = 0.78, 95 confidence intervals, CI, 0.72–0.86). The reduction in risk is greatest among heavy women. However, women who have ever used progestins sequentially for <10 days each month are at increased risk [meta-analysis results showing on overall RR of 1.76 (1.51–2.05)], while progestins given for 10–24 days/month appear unrelated to risk (RR = 1.07, 0.92–1.24) [66].

Interventions of Unproven or Disproven Effects on Risk

Fruits, Vegetables, and Vitamins

There are case-control studies evaluating the association between dietary factors, particularly fruit and vegetable intake, and endometrial cancer. A systematic review was done which failed to establish an association between fruit intake and endometrial cancer [67, 68].

There is case-control evidence suggesting that regular consumption of soy products reduces the risk of endometrial cancer [69, 70].

A consortium of seven prospective cohort studies examined the association between serum vitamin D levels and the development of endometrial cancer. After controlling for BMI, there was no evidence of an association between circulating vitamin D and risk of endometrial cancer [71]. Multivitamin use has little or no influence on the risk of common cancers, including endometrial cancer, or on total mortality in postmenopausal women [72].

American Cancer Society Recommendations for Prevention of Cancers [73]

Maintain a Healthy Weight Throughout Life

- Avoid excess weight gain at all ages. If currently overweight or obese, losing even a small amount of weight has health benefits and is a good place to start.

Adopt a Physically Active Lifestyle

- Adults: Engage in at least 150 min of moderate intensity activity or 75 min of vigorous-intensity activity each week, preferably spread throughout the week.
- Children and adolescents: Engage in at least 1 h of moderate- or vigorous-intensity activity each day, with vigorous-intensity activity at least 3 days each week.

Consume a Healthy Diet, with an Emphasis on Plant Sources

- Choose foods and beverages in amounts that help maintain a healthy weight.
- Limit consumption of processed meat and red meat.
- Eat at least 2.5 cups of vegetables and fruits each day.
- Choose whole grains in preference to refined grain products.
- If you drink alcoholic beverages, limit consumption.
- Drink no more than one drink per day for women or two per day for men.

Public, Private, and Community Organizations Should Work Collaboratively at National, State, and Local Levels to Implement Policy and Environmental Changes That:

- Increase access to affordable, healthy foods in communities, worksites, and schools, and decrease access to and marketing of foods and beverages of low nutritional value, particularly to youth.

- Provide safe, enjoyable, and accessible environments for physical activity in schools and worksites and for transportation and recreation in communities.

Conclusion

There are no acceptable, reliable, and valid screening tests or examination to diagnose endometrial cancer in asymptomatic women. Universal screening of women using TVS or endometrial sampling is not recommended. Combined oral contraceptive pills, progestins, avoiding unopposed estrogen therapy and lifestyle changes can be used to prevent carcinoma endometrium.

Key Points

1. All women should be told about the risks and symptoms of endometrial cancer at the time of menopause. Menopausal women should be asked to report in case of any unexpected vaginal bleeding, discharge, or spotting.
2. At this time, there are no acceptable, reliable and valid screening tests or exams to identify endometrial cancer early in women who are at average risk for endometrial cancer and have no symptoms.
3. There is no evidence that screening by ultrasonography or endometrial sampling reduces mortality from endometrial cancer as most cases of endometrial cancer (85 %) are diagnosed in early stage because of symptoms, and survival rates are high.
4. Women who have (or may have) hereditary nonpolyposis colon cancer (HNPCC, Lynch syndrome) have a very high risk of endometrial cancer and American Cancer Society recommends that women who have (or may have) HNPCC be offered yearly testing for endometrial cancer with endometrial biopsy beginning at age 35.
5. Routine ultrasound surveillance in asymptomatic women using tamoxifen is not useful because of its low specificity and low positive predictive value. Evaluation of the endometrium in women taking tamoxifen should be limited to women symptomatic with vaginal bleeding.
6. There is no evidence to suggest that screening women prior to or during estrogen-progestin therapy would decrease endometrial cancer mortality.
7. Interventions to reduce the risk of carcinoma endometrium are oral contraceptives, prevention of obesity and increased physical activity, progestins for prevention of prolonged anovulatory cycles, treatment of endometrial hyperplasia and avoiding unopposed exogenous estrogen.

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Clinical Evaluation of Abnormal Uterine Bleeding

5

Shalini Rajaram and Garima Yadav

Introduction

Abnormal uterine bleeding is one of the most common problems a woman faces in her reproductive life span, and it accounts for 20 % of visits to the gynecologic clinic. Abnormal uterine bleeding (AUB) is defined as "bleeding from the uterine corpus that is abnormal in regularity, volume, frequency or duration" and accounts for 25 % of all gynecologic procedures [1]. All clinicians dealing with a case of abnormal uterine bleeding face the basic challenge of excluding genital tract malignancy by formulating a well-organized and logical approach for evaluation of the symptom. Abnormal uterine bleeding is caused by the disruption of normal physiology, anatomical changes in the endometrium, or endometrial malignancy; therefore, the role of detailed history and clinical examination of the pelvis, besides endometrial sampling and imaging studies, forms the backbone of evaluating this condition.

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The International Federation of Gynecology and Obstetrics Working Group on Menstrual Disorders has recently developed a classification system (PALM-COEIN) for causes of AUB in non-gravid women of reproductive age. There are nine main categories, which are arranged according to the acronym PALM-COEIN: polyp, adenomyosis, leiomyoma, malignancy and hyperplasia, coagulopathy, ovulatory dysfunction, endometrial, iatrogenic, and not yet classified [2]. According to the proposed classification system, nonspecific terms like dysfunctional uterine bleeding should be abandoned to favor a more specific etiology like ovulatory dysfunction.

In order to identify the underlying etiology, evaluation of the women presenting with AUB must be undertaken in a comprehensive manner which not only justifies the suspected clinical situation but also suits available resources of a given setup. The clinician must always be suspicious of endometrial cancer and hyperplasia especially in perimenopausal and postmenopausal age group and must establish the diagnosis based on visual and histopathologic assessment of the endometrium. The various diagnostic techniques advocated are transvaginal ultrasound (TVS), saline infusion sonohysterography (SIS), hysteroscopy, MRI, and endometrial sampling. Finally, the management should be devised for each patient regardless of age, incorporating all risk factors for malignant disease [3].

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Evaluation of Abnormal Uterine Bleeding

There can be multiple identifiable factors that can contribute to abnormal uterine bleeding in a woman. Besides systemic, iatrogenic, and hormonal age-related causes, endometrial pathologies (endometrial polyps, submucous myomas, endometrial hyperplasia, and endometrial carcinomas) should always be suspected and thoroughly investigated. Up to 8 years before menopause, women may have intermittent anovulation resulting in recurrent irregular cycles, and the presence of recurrent anovulation causes increased risk of endometrial cancer [4]. About 14 % of premenopausal women with recurrent anovulatory cycles develop endometrial carcinoma or its precursor, hyperplasia with atypia [5]. About 10–20 % of endometrial cancers are diagnosed in premenopausal women, and women at highest risk of cancer have advanced age, obesity, nulliparity, infertility, diabetes mellitus, family history of colon cancer, long-term use of unopposed estrogen therapy, or a history of tamoxifen use [6]. There is a need for a protocol of diagnostic modalities which give us high sensitivity and specificity as well as high negative predictive value for evaluation of women with AUB.

Guidelines and Rationale for Investigation

General Assessment

The role of detailed history taking and a thorough general and pelvic examination cannot be overemphasized. A clinician must always rule out pregnancy in any women of reproductive age group before proceeding further. History should elicit the duration and severity of symptoms, any associated vaginal discharge, and postcoital bleeding. History of any chronic medical condition like hypertension or diabetes should be taken along with history of any drug intake (e.g., tamoxifen in breast cancer patients, hormone therapy in postmenopausal females). Family history of cancer such as in cases of hereditary non-polyposis colorectal cancer should be sought as such women are at risk of developing endometrial cancer (lifetime risk being 60 %). Initial basic investigation must include a complete blood count to assess degree of anemia, and after confirming that bleeding is from uterus, one must proceed in a systematic fashion to ascertain the exact cause of abnormal uterine bleeding.

Anovulatory bleeding is characterized by abnormal duration, frequency, or volume of bleeding over baseline occurring at irregular intervals and often interspersed with periods of amenorrhea. All reproductive age and perimenopausal females with suspected recurrent anovulatory cycles must undergo evaluation for anovulation which includes endometrial sampling.

Endometrial Sampling

Histopathologic evaluation of the endometrium can efficiently exclude endometrial hyperplasia or malignancy but is not required for all patients of AUB. The treating clinician must select women based on a combination of factors which when present increase the risk of endometrial hyperplasia or endometrial carcinoma. Several reports and guidelines use age, personal, and genetic risk factors along with TVS screening for endometrial echo complex thickness to determine which patients should undergo endometrial sampling [5, 7, 8]. Although age over 35 years is nowadays considered as the lower limit for biopsy in women with abnormal bleeding but regardless of age, persistent AUB that is unexplained or not adequately treated requires endometrial sampling, if possible, in association with hysteroscopic evaluation of the endometrial cavity [2, 3]. Several techniques can be used to perform endometrial sampling, but most importantly, one must ensure to obtain an adequate sample before declaring that a woman is at low risk of malignant neoplasm [9].

Office endometrial aspiration is a relatively inexpensive, convenient, and safe procedure which is now preferred over a blind endometrial curettage. It is performed using a small flexible suction cannula (Pipelle device) which suctions the shedded endometrial cells especially the malignant ones which are relatively more fragile, and hence, even a focal malignant lesion is likely to be picked up. In premenopausal women, endometrial biopsy (EB) using Pipelle is 82.3 % sensitive for detecting

endometrial hyperplasia with atypia and 91 % sensitive for detecting endometrial carcinoma, while the specificity is 98 % for both. In postmenopausal women the sensitivity is as high as 99.6 %, thus making it the best device for endometrial sampling, and inadequate sampling has been reported only in 10–12 % of cases [10]. Inadequate samples must be re-evaluated with TVS and hysteroscopy to avoid missing an endometrial cancer and must not be construed as negative for malignancy.

ACOG recommends that women with postmenopausal bleeding must be assessed to exclude malignancy with either endometrial biopsy or TVS; the initial assessment does not require performance of both the tests. If on TVS, endometrial thickness (ET) is ≤4 mm, EB is not required, but endometrial thickness of >4 mm or inability to adequately visualize the endometrium must trigger alternative evaluation including office hysteroscopy or EB [11].

Imaging Studies

Transvaginal Ultrasonography (TVS)

To evaluate the structural abnormalities of the uterine cavity, TVS has been utilized as the first-line screening tool in evaluating AUB. The benefits of TVS lie in its effectiveness in assessing the complete pelvis, its ease of application, patient acceptability, and immediate results. On TVS, endometrial thickness is measured as the maximum anteroposterior thickness of the endometrial echo on a long axis view of the uterus. If TVS shows ET of less than 5 mm, the probability of the woman having endometrial cancer is 1.7 % and it is 0.8 % when the cut-off is taken as 4 mm. In perimenopausal and postmenopausal women with AUB, endometrial sampling is generally considered unnecessary when the endometrial thickness is less than 4 mm since the risk of endometrial hyperplasia or cancer is extremely low. Endometrial biopsy is indicated when the clinical history is suggestive of long-term estrogen exposure even when the ET is normal on ultrasound (5–12 mm), and biopsy must be considered when ET is greater than 12 mm even when the clinical suspicion of disease is low [12]. Transvaginal ultrasound detects intracavitary abnormalities like uterine tumors, polyps, and endometrial and myometrial abnormalities with a sensitivity of 60–92 % and a specificity of 62–93 % in perimenopausal women [13, 14]. Since TVS is not 100 % sensitive for diagnosing endometrial polyps and other small lesions, examination with other imaging techniques like saline infusion sonohysterography (SIS) or hysteroscopy should be considered [15]. Another limitation of ultrasound is that it cannot always reliably distinguish between benign proliferation, hyperplasia, polyps, and cancer, and in 5–10 % of women with postmenopausal bleeding, the endometrium cannot be identified on USG, these women need further evaluation with more sensitive techniques [16].

Doppler Studies

It is usually considered that benign lesions have high resistance vessels (mostly single feeding artery) and malignant lesions have low resistance vessels (mostly multiple feeding vessels with broad base); based on this principle, Doppler studies may be considered useful in differentiating between the two, but studies have shown that Doppler does not improve the detection of premalignant and malignant lesions of the endometrium [17].

Saline Infusion Sonohysterography

Saline infusion sonohysterography (SIS) or sonohysteroscopy is the technique of contrast enhancement of transvaginal scan which further increases the sensitivity and negative predictive value of sonographic evaluation. The procedure involves instillation of 5–10 ml of saline in the uterine cavity using 5–8 F Foley's catheter followed by TVS. Once the cavity is distended by anechoic saline, lesions like endometrial polyps, submucous fibroid, and lesions distorting endometrial contour are better identified. In a study by Mathew et al., SIS has been shown to have a better sensitivity in evaluating endometrial cavity as compared to TVS alone (91.4 % vs. 72.4 %). Negative predictive value of SIS was found to be 94.1 % as compared to 74 % for TVS [18]. The combination of sonohysterography and endometrial biopsy offers a high sensitivity and negative predictive value for detection of endometrial and uterine pathologies,

especially in women with focal endometrial lesions [19]. Although it is feasible to conclude that SIS can be used as an effective screening tool prior to hysteroscopy in evaluating women with abnormal uterine bleeding, increased cost and limited availability as compared to TVS must also be considered. Further studies have also compared the role of 3-D sonohysterography and hysteroscopy in detecting intrauterine lesions and concluded that 3-D sonohysterography is comparable to hysteroscopy for investigating intrauterine lesions in perimenopausal and postmenopausal females with AUB [20].

Magnetic Resonance Imaging

MRI has no established role in the initial evaluation of women with AUB but may be useful in evaluating females with difficult vaginal access where TVS, SIS, and hysteroscopy are not the feasible options. MRI can reliably distinguish between adenomyosis and leiomyomata and can also demonstrate the proximity of these lesions to the uterine cavity, but cost-effectiveness for this purpose needs to be justified. In case of diagnosed endometrial cancer, MRI helps in identifying the site and size of endometrial tumor along with the degree of myometrial invasion and lymph node metastasis and is described in detail in Chap. 8.

Hysteroscopy

Hysteroscopy helps in direct visualization of the endometrial cavity and, hence, is now considered to be the gold standard for diagnosis and treatment of intrauterine pathologies. It helps in assessing the endometrium and taking directed biopsy from the suspected lesion in the same sitting. Earlier, the major concern with hysteroscopy used to be the need for general anesthesia, which increased the applied cost and also delayed the diagnosis of endometrial cancer in women with hypertension and diabetes. The advent of modern hysteroscopes with an outer diameter of 2–3 mm now permits diagnostic and minor operative procedures in office setting with minimal anesthesia. Hysteroscopy being an invasive procedure may be associated with complications like uterine perforation, infection, and excessive bleeding, but adequate training minimizes the incidence of such complications. Hysteroscopy is more expensive than TVS and it does not evaluate the myometrium or ovaries but the sensitivity and specificity is better for diagnosing intracavitary abnormalities, i.e., 94 % and 99 %, respectively, with an overall success rate of 96.9 % [21].

For better diagnostic accuracy, ideally, hysteroscopy should be scheduled in the follicular phase after the cessation of menstruation. Irregular proliferative or luteal phase endometrium may have irregular topography and can be falsely interpreted as endometrial polyps. Lasmar et al. studied the importance of hysteroscopic view in provisionally diagnosing endometrial hyperplasia and cancer in patients with AUB. They found that in 97 out of 103 (94.2 %), hysteroscopic evaluation with suspected cancer findings had histological diagnosis of cancer or hyperplasia, and hence, they concluded that there is good validity of hysteroscopic diagnosis for endometrial hyperplasia and cancer but histological study is mandatory in patients with AUB [22]. Hysteroscopy-guided biopsy is now considered gold standard procedure for evaluating women with postmenopausal bleeding and in whom ET is >4 mm. Women with ET <4 mm and persistent postmenopausal bleeding should also undergo hysteroscopic evaluation of the endometrium and directed biopsy. Blind biopsy with curettage may not be reliable for evaluation of endometrial pathology especially in women with thin endometrium and focal endometrial lesions; in these women too hysteroscopic evaluation of the endometrial cavity becomes necessary for diagnosis. Theoretical risk of spill of cancer cells into peritoneal cavity exists but studies have shown no impact on prognosis.

Women on Tamoxifen Therapy

Tamoxifen is a nonsteroidal selective estrogen receptor modulator (SERM) used in breast cancer patients for its anti-estrogenic effects, but it also has some estrogenic effects on the endometrium. It is associated with endometrial proliferation, hyperplasia, and polyps and is known to increase the relative risk of endometrial cancer by two to three times than the age-matched controls [23]. This risk further increases with advanc-

ing age of the patient and duration of use, leading to poorer prognosis due to less favorable histology and higher stage; hence, we need follow a strict protocol for evaluating these women when they present with AUB [24]. The following are the ACOG recommendations for evaluating patients on tamoxifen [25]:

(a) Postmenopausal women taking tamoxifen should be monitored closely for symptoms of endometrial hyperplasia and cancer.
(b) Premenopausal women taking tamoxifen have no increased risk for uterine cancer and as such require no additional monitoring beyond routine gynecologic care.
(c) Women should be informed the risk and should be asked to promptly report any abnormal discharge or bleeding.
(d) Any abnormal bleeding, discharge, or spotting should be investigated.
(e) Emerging evidence indicates the presence of low- and high-risk groups for development of atypical hyperplasia with tamoxifen in postmenopausal women based on the presence of benign endometrial polyps. Hence, there may be a role of pretreatment screening with TVS, SIS, or office hysteroscopy before initiating therapy.
(f) Routine surveillance, except in high-risk groups, does not increase the chances of early detection of endometrial cancer in women using tamoxifen.

Conclusions

Abnormal uterine bleeding is one of the leading gynecologic complaints in women of perimenopausal and postmenopausal age group. Until recently, there has been confusion in not only the nomenclature of abnormal bleeding patterns but also in investigation protocols of women with AUB. FIGO has now proposed a new classification for AUB named PALM-COEIN which mainly highlights the various and most common etiologies causing abnormal uterine bleeding [2]. The new classification helps in standardizing the investigation algorithm for AUB and helps in adapting a more comprehensive and practical approach for such patients universally.

Women presenting with abnormal uterine bleeding irrespective of age should be diligently investigated, keeping in mind the high-risk factors for endometrial hyperplasia and cancer. Previously, blind endometrial curettage was used to evaluate the endometrium, but current practice recommends endometrial aspiration biopsy and, preferably, hysteroscopy-guided biopsy wherever indicated and feasible. Imaging studies like TVS are commonly used as a first-line investigation as it is readily available, noninvasive, and easily acceptable with added advantage of evaluating the myometrium and adnexa, over hysteroscopy. SIS has its role in evaluating endometrial polyps and submucous fibroids with better detection rate over TVS.

MRI has a role in preoperative evaluation of patients with endometrial cancer, for planning appropriate surgery. Hysteroscopy and directed biopsy is the "gold standard" approach for most accurate evaluation of the endometrium and diagnosing endometrial cancer. It is a one-step approach, especially in high-risk women (obesity, diabetes, family history of endometrial, ovarian, or breast cancer) as well as in women with endometrial hyperplasia (>4 mm in postmenopausal bleeding and >12 mm in premenopausal AUB) as it combines diagnosis of the endometrial lesion, directed biopsy, and treatment, all with minimal anesthesia and least complications.

Key Points

1. Abnormal uterine bleeding accounts for 20 % of patients seeking gynecologic referral and 25 % of all gynecologic procedures.
2. Any perimenopausal woman with AUB who is >35 years old, postmenopausal women with bleeding, or younger women with high-risk factors should be thoroughly investigated for endometrial hyperplasia/cancer.
3. TVS is accepted as the first screening test to look for endometrial, myometrial, or adnexal pathologies of AUB. Further

evaluation is required in case of normal ultrasound findings, inconclusive results, thickened endometrium, or ET >4 mm in case of postmenopausal females.
4. SIS has a better sensitivity and negative predictive value for imaging small endometrial polyps and submucosal fibroids.
5. An endometrial aspiration biopsy is to be done for histopathologic evaluation wherever indicated.
6. Hysteroscopy-directed biopsy is the gold standard technique for diagnosing endometrial pathologies like endometrial hyperplasia, cancer, and focal lesion.
7. Hysteroscopy being a single-step approach for diagnosis and treatment of endometrial pathologies might be preferred in cases of postmenopausal bleeding where detecting endometrial cancer as soon as possible is crucial.
8. Routine surveillance, except in high-risk group, does not increase the chances of early detection of endometrial cancer in women on tamoxifen.

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Risk Factors, Diagnosis, and Staging of Endometrial Cancer

6

Anupama Rajanbabu

Introduction

Endometrial cancer is the seventh most common cancer in women worldwide and the fourth common cancer in women in developed countries [1]. The incidence of uterine cancer based on the US national database Surveillance, Epidemiology and End Results was 24.6/100,000 women [2]. The incidence of endometrial cancer though low in India as compared to developed countries is rising steadily possibly due to changes in lifestyle and urbanization [3, 4]. The age-adjusted rates (AARs) for uterine cancer is high in urban areas with Bangalore topping the list with 6.2/100,000 women. Thiruvananthapuram has an AAR of 5.7/100,000 followed by Delhi, Chennai, and Mumbai with AARs ranging from 4.1 to 4.4/100,000 women. The lowest incidences were noted from northeastern states and also from rural Ahmedabad and Maharashtra—AARs <1/100,000 [5].

The median age at diagnosis of endometrial cancer is 62 years in the USA, whereas in India the median age reported was 54 years [2, 6]. The age distribution of endometrial cancer in the USA from 2005 to 2011 is shown in Table 6.1 [2]. Endometrial carcinomas are divided into two different clinicopathological types: type I tumors with favorable prognosis accounting for 80 % of endometrial carcinomas and type II tumors with a poor prognosis accounting for about 20 % of cancers. This chapter will be describing the risk factors for endometrial carcinomas and also the diagnosis and staging of endometrial cancer.

Risk Factors for Endometrial Carcinoma

As mentioned, majority of the endometrial cancers are type I tumors with endometrioid histology. The main risk factor for an endometrioid endometrial carcinoma is long-term exposure to excess estrogen, either endogenous or exogenous. Other risk factors include nulliparity and infertility, obesity, hypertension, diabetes, polycystic ovarian syndrome, early menarche, late menopause (after 55

Table 6.1 Age distribution of endometrial cancer [2]

Age groups (years)	Percentage of new cases (%)
<20	0
20–34	1.6
35–44	5.6
45–54	18.4
55–64	33.9
65–74	23.4
75–84	12.6
>84	4.6

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years), and hereditary syndromes like Lynch syndrome, BRCA mutations, etc. [7].

Excess Estrogen Exposure

Excess estrogen exposure can be exogenous or endogenous. The exogenous exposure includes postmenopausal estrogen therapy and tamoxifen use. In a woman with intact uterus, unopposed estrogen therapy causes two to tenfold increases in the risk of endometrial cancer. The risk increases with the increased duration of use [7]. Using combined estrogen–progestin preparation in a woman with intact uterus can reduce the risk. Tamoxifen is a selective estrogen receptor modulator with agonistic action on the endometrium and antagonistic action on the breast. Prospective trials including over 20,000 women have shown that tamoxifen use increased the risk of endometrial cancer [8]. Phytoestrogens that are present in many plants and vegetables like soy have both estrogenic and antiestrogenic properties. Prospective studies have shown significantly higher rate of endometrial hyperplasia in women taking soy isoflavone supplements [9].

Obesity, chronic anovulation, early menarche, late menopause, and rarely estrogen-secreting tumors are causes for excessive endogenous estrogen. In anovulatory women, there is chronic estrogen production unopposed by progesterone allowing continued proliferation of the endometrium leading to endometrial hyperplasia and carcinoma. Polycystic ovary syndrome is the most common endocrine cause of anovulation followed by thyroid dysfunction and hyperprolactinemia. In obese women there is increased conversion of androstenedione to estrone and also increased conversion of androgens to estradiol occurring in the peripheral adipose tissue leading to increased endogenous estrogen. The risk of endometrial carcinoma significantly increased with each increase in body mass index (BMI) of 5 kg/m^2 [10]. Obesity is also associated with endometrial carcinoma occurring at a younger age (<45 years) [11]. Early menarche and late menopause result in prolonged estrogen stimulation leading to increased risk of endometrial cancer. Granulosa cell tumors of the ovary secrete excess estrogen and are seen associated with endometrial hyperplasia in 25–50 % and endometrial malignancy in 5–10 % of affected women [12, 13].

Other Risk Factors

Nulliparity and infertility are not independent risk factors for the development of endometrial carcinoma. The risk of developing endometrial carcinoma is inversely related to parity. The risk associated with infertility is related to the increased number of anovulatory cycles in infertile women. Studies have not yet shown an association of infertility treatment and endometrial cancer [14, 15]. The increased endometrial cancer risk seen in diabetes mellitus or hypertension is partly due to the existence of comorbid conditions, mainly obesity [16]. The presence of hyperinsulinemia, insulin resistance, and increased levels of insulin-like growth factors in diabetics may cause endometrial proliferation and lead to the development of endometrial carcinoma [17, 18]. The increased risk of endometrial carcinoma associated with hereditary syndromes is discussed in detail in Chap. 3.

Type II endometrial tumors are typically described as estrogen-independent tumors, but pooled analysis has shown that estrogen-driven proliferation is also important in type II cancers and both type I and type II cancers share common etiologic pathways [19]. Studies have shown the association for BMI with type II tumors though the strength of association is less strong than for type I [19–21]. The relative risk for various risk factors in causing endometrial cancer is summarized in Table 6.2.

Table 6.2 Relative risk of various risk factors in causing endometrial cancer [7]

Risk factor	Relative risk (RR)
Unopposed estrogen therapy	2–10
Tamoxifen	2
Late menopause	2
Nulliparity	2
Polycystic ovarian syndrome	3
Obesity	2–4
Diabetes mellitus	2

Clinical Presentation

More than 90 % of endometrial cancers occur in women above 45 years with the majority diagnosed between the ages of 55 and 64 [2]. Abnormal uterine bleeding including postmenopausal bleeding, heavy menstrual bleeding, or intermenstrual bleeding is the most common presenting symptoms with about 75–90 % of women with endometrial cancer presenting similarly [22]. Rarely, women affected with endometrial cancer can present with atypical glandular cells on regular screening cervical cytology. Any bleeding occurring in postmenopausal women including mild spotting should be evaluated as about 3–20 % of women presenting with postmenopausal bleeding are found to have endometrial carcinoma [23]. Abnormal uterine bleeding occurring in women who are above the age of 45 should be evaluated with an endometrial biopsy to rule out carcinoma. In women who are younger than 45 years, abnormal uterine bleeding which occurs in a background of unopposed estrogen as in obesity or polycystic ovarian disease or in patients with a family history of Lynch syndrome or BRCA mutation must be evaluated immediately. Also, persistent abnormal uterine bleeding not responding to medical management in women younger than 45 years should be viewed with suspicion as about 7 % of endometrial carcinomas occur in this age group. A thickened endometrial lining seen on pelvic imaging for other causes also warrants evaluation to rule out endometrial carcinoma. At the time of diagnosis, two-thirds of patients with endometrial cancer have disease confined to the uterus [2].

Evaluation of a Patient with Suspected Endometrial Carcinoma

A patient with suspected endometrial carcinoma should be subjected to a thorough physical and pelvic examination. The size and mobility of the uterus and the presence or absence of gross cervical involvement, extrauterine mass, or ascites should all be assessed. The supraclavicular area must be examined to rule out enlarged nodes. Pelvic sonography, especially transvaginal ultrasound (TVS), is often the first line of investigation used in a woman with abnormal uterine bleeding. Hysterosonography, where sterile saline is placed within the endometrial cavity and uterus imaged using TVS, can help distinguish diffuse or focal thickening of endometrium and endometrial polyps. In a postmenopausal woman endometrial thickness more than 4 mm warrants a biopsy to rule out malignancy.

Endometrial biopsy is the gold standard test, which can help to confirm the presence of endometrial carcinoma. It can be done as an outpatient/office procedure without anesthesia or under local anesthesia, by using Pipelle sampling device. This is the least invasive technique for obtaining an endometrial biopsy and has a sensitivity of 73 % and specificity of 100 % for detecting endometrial disease [24]. A dilatation and curettage (D&C) needs to be performed only if the office endometrial biopsy shows insufficient endometrial cells for evaluation. Hysteroscopy can assist to identify focal lesions in the endometrium and ensure biopsy of them and thus can be helpful when ultrasound results are inconclusive. There have been concerns about the possibility of spill of malignant cells into the peritoneal cavity by the high pressure induced in the uterine cavity during the procedure and thereby worsening the prognosis [25, 26]. But the published data presently available in the literature seems to indicate that hysteroscopy is not statistically associated with worse outcome, and based on this most authors conclude that hysteroscopy can be used in patients with endometrial cancer without adversely affecting the prognosis [27–29]. Endocervical curettage at the time of endometrial biopsy can help to rule out cervical involvement in endometrial cancer. Cervical cytology used to be recommended in the initial evaluation of a patient with endometrial cancer but was removed in the revised National Comprehensive Cancer Network (NCCN) guideline [30].

Preoperative Evaluation

Women with endometrial cancer are likely to have medical comorbidities like diabetes mellitus, hypertension, or coronary artery disease that will need optimization prior to surgery. Preoperative

elevated CA125 levels have been shown to be an important factor predictive of extrauterine disease in women with endometrial cancer [31, 32]. Preoperative pelvic and abdominal imaging is helpful to rule out cervical involvement and extrauterine disease. Although of value in selected cases, routine preoperative imaging is of arguable cost-effectiveness, as most patients will undergo surgery and endocervical curettage at the time of endometrial biopsy, and intraoperative findings will guide therapeutic decisions in the majority of cases without the need for imaging.

Ultrasonography is the most inexpensive imaging modality available, and TVS can predict myometrial or cervical invasion better than a computerized tomography (CT) scan. But it is not as sensitive as CT scan or magnetic resonance imaging (MRI) in detecting the abdominopelvic lymph nodes or omental/peritoneal metastases and results are operator dependent. CT scan and MRI are more accurate in the radiological staging of endometrial cancer. MRI has a very good soft-tissue contrast resolution and can predict the cervical involvement and myometrial invasion better than a CT scan or ultrasound [33]. MRI/CT can be done to look for the presence of ascites or omental/peritoneal/nodal/ovarian disease [34]. A prospective multicenter study evaluating the diagnostic performance of PET/CT and MRI found that both modalities have equal sensitivities in predicting myometrial invasion, cervical involvement, and lymph node metastases in endometrial cancer [35]. Initial evaluation also should include an imaging of the chest. NCCN recommends genetic counseling and testing for all patients with endometrial cancer below the age of 50 years and also in patients with a significant family history of endometrial or colorectal cancer [30].

Staging

FIGO staging for endometrial carcinoma was adopted initially in 1950 to include just two criteria—tumors clinically confined to the uterine corpus and extending outside. Both the categories were subdivided into medically operable or not. This was modified in 1961 to include cervical involvement (stage II), disease confined to the pelvis (stage III), and disease extending beyond the pelvis or involving the bladder and rectum (stage IV). In 1971 the staging was changed to incorporate the depth of the uterine cavity (as it was ascertained that the virulence of the tumor increased with the increasing size of the uterus) as well as the grade of the tumor. After the surgicopathological staging trial of the Gynecologic Oncology Group (GOG) [36], the primary treatment for endometrial carcinoma is surgical and the staging was changed to a surgicopathological one in 1988 which divided uterine-confined cancers into three substages [37].

Presently endometrial carcinoma is surgically staged according to the joint 2010 International Federation of Gynecology and Obstetrics (FIGO)/TNM classification system [38, 39]. They are represented in Table 6.3. The revised staging eliminated the cervical glandular involvement and ascitic fluid cytology from the staging, grouped together both IA and IB of the previous staging as IA, and substratified stage IIIC. This staging system for endometrial cancers has been found to be highly prognostic in the case of endometrioid tumors [40]. But the size of the tumor and lymphovascular space invasion (LVSI), which are also considered as prognostic factors, are not included in the current staging.

Complete surgical staging for endometrial carcinoma includes total hysterectomy, bilateral salpingo-oophorectomy, and bilateral pelvic and para-aortic lymphadenectomy. If there is cervical involvement, radical hysterectomy is recommended and serous or clear cell cancers are staged like ovarian cancer including omentectomy and peritoneal biopsies [30]. Thorough visual evaluation of the peritoneal and bowel surfaces with biopsy of any suspicious lesions is important to exclude extrauterine disease [41]. In the case of ascites, peritoneal or ovarian disease, omental thickening, or obvious nodal involvement, complete surgical debulking is recommended. If there is initially unresectable disease involving the vagina or parametrium, or infiltrating the bladder, bowel, or rectum, radiation or chemotherapy is preferred over surgery [30].

Table 6.3 TNM and FIGO staging for endometrial cancer 2010 [38, 39]

Primary tumor (T) (surgicopathologic findings)		
TNM categories	FIGO stages	Definition
TX		Primary tumor cannot be assessed
T0		No evidence of primary tumor
Tis		Carcinoma in situ (preinvasive carcinoma)
T1	I	Tumor confined to corpus uteri
T1a	IA	Tumor limited to endometrium or invades less than one-half of the myometrium
T1b	IB	Tumor invades one-half or more of the myometrium
T2	II	Tumor invades stromal connective tissue of the cervix but does not extend beyond uterus
T3a	IIIA	Tumor involves serosa and/or adnexa (direct extension or metastasis)
T3b	IIIB	Vaginal involvement (direct extension or metastasis) or parametrial involvement
T4	IVA	Tumor invades bladder mucosa and/or bowel mucosa
Regional lymph nodes (N)		
NX		Regional lymph nodes cannot be assessed
N0		No regional lymph node metastasis
N1	IIIC1	Regional lymph node metastasis to pelvic lymph nodes
N2	IIIC2	Regional lymph node metastasis to para-aortic lymph nodes, with or without positive pelvic lymph nodes
Distant metastasis (M)		
M0		No distant metastasis
M1	IVB	Distant metastasis (includes metastasis to inguinal lymph nodes, intraperitoneal disease, or the lung, liver, or bone. It excludes metastasis to para-aortic lymph nodes, vagina, pelvic serosa, or adnexa)
Anatomic stage/prognostic groups		
Stage I	T1 N0M0	
Stage IA	T1a N0M0	
Stage IB	T1b N0M0	
Stage II	T2 N0M0	
Stage III	T3 N0M0	
Stage IIIA	T3a N0M0	
Stage IIIB	T3bN0M0	
Stage IIIC1	T1-T3N1M0	
Stage IIIC2	T1-T3N2M0	
Stage IVA	T4 any N M0	
Stage IVB	Any T any N M1	

Pelvic lymphadenectomy involves the removal of the nodal tissue over the distal half of common iliac arteries, around the external iliac vessels unto the circumflex iliac veins, and removal of the nodal tissue around the internal iliac vessels and also obturator pad of fat above the obturator nerve. Ten percent of women with endometrial cancer apparently confined to the uterus have lymph node metastases [42]. Para-aortic lymph node involvement occurs in 50 % of women with positive pelvic nodes, but isolated para-aortic involvement can occur (up to 6 %). Higher histologic grade, deep myometrial invasion, cervical involvement, and lymphovascular space involvement are the other factors that can predict a para-aortic nodal involvement [42]. Para-aortic node dissection involves the removal of the nodal tissue over the inferior vena cava and aorta from the level of renal veins unto the level of mid-common iliac arteries. Many surgeons limit the para-aortic nodal dissection up to

the level of inferior mesenteric artery (IMA). But about 77 % of patients with para-aortic nodal involvement are found to have positive nodes above the level of IMA [42]. Patients with serous or clear cell cancers are staged as with ovarian cancer including omentectomy and peritoneal biopsies. Though peritoneal cytology does not affect staging, FIGO and AJCC continue to recommend that it may be obtained and reported.

Traditionally the staging for endometrial carcinoma has been done through a large incision, but the advancement in minimally invasive surgery has made laparoscopic staging possible. Since Childers et al. first described the use of laparoscopy for staging endometrial cancer in 1993, many studies have been published describing the use of laparoscopic or a combined laparoscopic and vaginal approach to completely stage endometrial cancer [43–45]. Laparoscopically assisted vaginal hysterectomy (LAVH) was found to have fewer complications and decreased hospital stay [46]. Kohler et al. and Eltabbakh et al. have demonstrated the adequacy of lymphadenectomy with the laparoscopic approach [45, 47]. Recurrence rates and 5-year survival rates were also found to be similar to that achieved by laparotomy [48, 49]. The randomized LAP-2 trial involving 2,616 patients was conducted by the GOG to compare laparoscopic and open approaches in surgical staging of uterine cancers. The laparoscopic group had fewer adverse events, shorter hospital stay, and an improved quality of life [50, 51]. The recurrence rates and 5-year survival rates were similar in both arms [52].

The last decade saw the emergence of robotic-assisted surgery in oncology. The use of a robotic platform reduced surgical morbidity and hospital stay and also reduced conversions to laparotomy [53]. Leitao et al. reported that among patients undergoing robotic surgery, there were a higher proportion of obese patients, but overall the robotic surgery group had a shorter hospital stay and similar pelvic nodal counts when compared to laparoscopy [54]. For further details on the role of minimally invasive surgery in the treatment of endometrial cancer, please refer to Chaps. 20 and 21.

The topic of lymphadenectomy in endometrial cancer remains a much-debated one. Lymph nodal involvement remains one of the most important prognostic factors affecting endometrial cancer, but the therapeutic benefit of lymphadenectomy is doubted. The risk of having an affected lymph node increases with grade of the tumor and depth of MI (Table 6.4). It ranges from 3 % in well-differentiated superficially invasive tumors to up to 30 % in poorly differentiated and deeply invasive malignancies [36]. Tumors more than 2 cm size and high-grade histologies like serous and clear cell types have more chance of having nodal involvement.

In lymphadenectomy an important factor that needs to be considered is the optimal extent of node dissection. A universally accepted cutoff is yet to be defined as to the number of nodes that need to be removed to represent adequate surgery. Chan et al. showed that removal of 21–25 nodes had an 80 % probability of detecting at least a single positive node [55]. Authors from Mayo Clinic have reported that the removal of a minimum of 22 pelvic nodes and 10 para-aortic lymph nodes is adequate [56]. Cragun et al. showed that the removal of more than 11 pelvic nodes improved overall and progression-free survival in early poorly differentiated endometrial

Table 6.4 Incidence of pelvic and para-aortic lymph node metastases in clinical stage I endometrial carcinoma [36]

Percentage of lymph nodes involved	Histologic grade	*n*	Depth of myometrial invasion			
			None	Inner	Middle	Outer
Pelvic	1	180	0	3	0	11
	2	288	3	5	9	19
	3	153	0	9	4	34
Para aortic	1	180	0	1	5	6
	2	288	3	4	0	14
	3	153	0	4	0	24

cancers [57]. A cutoff of 12 pelvic lymph node removal for high-risk patients was proposed by Lutman et al. [58]. Nodal count depends upon the surgical expertise, anatomical variations, and also thoroughness of the pathologist [41]. Cormier et al. have shown that lymph nodal counts vary between pathologists and have advised exercise of caution when drawing conclusions from the published nodal counts in endometrial cancer [59]. Considering all this, surgeon is the best judge of whether the nodal dissection performed was optimal or not [60].

The therapeutic benefit of lymphadenectomy in early stage endometrial cancer has been reported by retrospective studies [57, 61]. But two randomized studies questioned the benefit of lymphadenectomy in endometrial cancer [62, 63]. Panici et al. analyzed over 500 patients with early stage endometrial cancer and found no difference in the disease-free and overall survival between the lymphadenectomy and no lymphadenectomy group [62]. A Study in the Treatment of Endometrial Cancer (ASTEC) trial included 1,400 patients who were randomized into lymphadenectomy and no lymphadenectomy group. This trial did not show any benefit in terms of overall or recurrence-free survival for lymphadenectomy group, and hence, the authors concluded that pelvic lymphadenectomy cannot be recommended as a routine procedure in endometrial cancer [63]. ASTEC trial received widespread criticism on several accounts, prominent among them being ignoring the nodal status of the patients in deciding adjuvant treatment resulting in undertreatment for many node-positive patients. Also the study involved low-risk patients and the results may not be applicable for the high-risk endometrial subgroups. The Panici trial was also criticized for the over usage of adjuvant therapy in the no lymphadenectomy group and also for doing lymphadenectomy for 16 % of patients randomized into the no lymphadenectomy group [64]. The Survival Effect of Para-aortic Lymphadenectomy in Endometrial Cancer (SEPAL) study showed that combined pelvic and para-aortic lymphadenectomy was superior to pelvic lymphadenectomy alone in intermediate-risk and high-risk patients as overall, disease-specific, and recurrence-free survival was superior in them [65]. A prospective trial to evaluate the therapeutic benefit of lymphadenectomy in high-risk subtypes has been proposed by GOG.

Until these controversies regarding lymphadenectomy are resolved, a strategy to identify high-risk features will be useful so that lymphadenectomy is not omitted in the high-risk group. Non-endometrioid histology or higher tumor grade in the preoperative endometrial biopsy and the presence of deep myometrial invasion or enlarged lymph nodes on preoperative imaging are features which indicate increased nodal spread and mandate lymphadenectomy. The use of intraoperative frozen section (IFS) can identify high-risk features like deep myometrial invasion, high-grade histological subtypes, and tumor grade. A meta-analysis involving 2,567 patients showed that IFS has a sensitivity of 75 % and a specificity of 92 % in assessing myometrial invasion [66]. Studies using IFS to identify the grade of the disease show discordance ranging from 1.3 % to 15 % when compared with the final pathology [67, 68]. Mayo Clinic omits lymphadenectomy if all of the following features are present on IFS—maximal tumor diameter less than or equal to 2 cm, MI nil or 1–49 %, endometrioid subtype, and tumor grades 1–2 with no evidence of disease outside the corpus. This group of patients had a 99 % 5-year survival rate and none of them had a nodal recurrence at the median follow-up of 5 years [67]. But the caveat is that these results were obtained in high volume center with a dedicated gynecologic oncopathologist.

During the recent years the technique of sentinel lymph node (SLN) mapping in endometrial cancer has been gaining in popularity. This technique can provide an accurate assessment of the lymph nodes while reducing the morbidity associated with a complete lymphadenectomy [64]. After the pilot study by Burke et al. showing a 67 % sentinel node detection rate, many studies have come up with cervical, subserosal, or hysteroscopic injections with sensitivities ranging from 45 % to 100 % [64, 69]. The multicenter prospective Senti-Endo study involved 133 patients and had an overall detection rate of 89 % [70]. The prospective study by How et al.

evaluated intraoperative cervical injection of blue dye and technetium colloid in 100 patients. They showed a detection rate of 93.5 % for endometrioid types and 88.5 % for non-endometrioid subtypes with 99 % negative predictive value [71]. The retrospective multicenter study by Raimond et al. showed that SLN procedure detected more metastatic lymph nodes than lymphadenectomy which helped modify the adjuvant therapy for half the patients, but SLN biopsies had no impact on recurrence-free survival [72]. For further details on the role of sentinel lymph node dissection in the treatment of endometrial cancer (see Chap. 15).

Staging in Inoperable Patients

In women unfit for surgery due to medical conditions, endocervical curettage at the time of endometrial biopsy, along with imaging, can help in clinical decisions.

Conclusions

Endometrial cancer is surgically staged according to the joint 2010 International Federation of Gynecology and Obstetrics (FIGO)/TNM classification system. Complete surgical staging involves total hysterectomy, bilateral salpingo-oophorectomy, and pelvic and para-aortic lymphadenectomy. If there is cervical involvement, radical hysterectomy is recommended and serous or clear cell cancers are staged like ovarian cancer including omentectomy and peritoneal biopsies. If there is initially unresectable disease involving the vagina or parametrium or infiltrating the bladder, bowel, or rectum, radiation or chemotherapy is preferred over surgery. Laparotomy or minimally invasive surgery can be used to stage endometrial cancers. Lymphadenectomy in endometrial cancer remains much debated even though lymph nodal involvement is considered as one of the most important prognostic factors. Sentinel lymph node mapping can provide an accurate assessment of the lymph nodes while reducing the morbidity associated with a complete lymphadenectomy.

Key Points

1. The main risk factor for developing endometrial carcinoma is long-term exposure to excess estrogen, either exogenous or endogenous.
2. 75–90 % of women with endometrial cancer present with abnormal uterine bleeding.
3. The gold standard test, which can confirm the presence of endometrial carcinoma, is endometrial biopsy.
4. Endometrial carcinoma is surgically staged according to the joint 2010 International Federation of Gynecology and Obstetrics (FIGO)/TNM classification system
5. Complete surgical staging includes total hysterectomy, bilateral salpingo-oophorectomy, and bilateral pelvic and para-aortic lymphadenectomy.
6. If there is cervical involvement, radical hysterectomy is recommended and serous or clear-cell cancers are staged like ovarian cancer including omentectomy and peritoneal biopsies.
7. Minimally invasive surgery can also be used to stage endometrial carcinoma with similar recurrence and survival rates.
8. Lymphadenectomy in endometrial cancer remains much debated even though lymph nodal involvement is considered as one of the most important prognostic factors.
9. A universally accepted cutoff is yet to be defined as to the number of nodes that need to be removed to represent adequate surgery.
10. A combination of preoperative and intraoperative parameters along with intraoperative frozen section can identify high-risk subtypes in whom lymphadenectomy should not be omitted.
11. Technique of sentinel lymph node mapping can provide an accurate assessment of the lymph nodes while reducing the morbidity associated with a complete lymphadenectomy.

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Imaging in Uterine Malignancy: Role of Ultrasonography, CT, and PET-CT

7

Thara Pratap

Introduction

Imaging modalities for evaluation of uterine malignancy include ultrasonography, sonohysterography, computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET-CT). The role of color Doppler with spectral tracing is limited. 3D ultrasonography, contrast ultrasonography, and ultrasound elastography are new techniques which may be useful for better evaluation in certain situations.

Imaging modalities are important in diagnosis, treatment planning, monitoring response to therapy, and detecting recurrence. The improved survival of women with endometrial cancer is due to better pretreatment imaging and choice of optimal primary surgery. For overall pretreatment staging, MRI performs better. Recently PET-CT has been incorporated as an adjuvant in preoperative planning, as it may detect unsuspected distant metastasis in the mediastinum or supraclavicular region which upgrades tumor staging [1]. MRI in the management of endometrial cancer is covered in the next chapter.

In low resource countries where advanced imaging modalities are not available, clinical examination and ultrasound still play an important part in tumor evaluation. No sophisticated imaging is required in a patient with low-grade tumor and a normal-sized uterus at physical examination [2]. All women with high-grade tumor and indeterminate findings on clinical examination require imaging.

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Role of Ultrasonography

Transabdominal assessment of endometrial thickness is not always accurate. Sonography with transvaginal probe is the initial modality of choice in women with abnormal uterine bleeding in pre- and postmenopausal age groups. A thorough evaluation is vital, and it depends on many factors like the probe resolution, body habitus of woman, patient compliance, and technique used. Transrectal ultrasound is helpful in evaluating the uterus in nulliparous women.

Normal Sonographic Appearance of Endometrium in Premenopausal Women

The sonographic appearance of the endometrium varies during menstrual cycle. During the proliferative phase, the endometrium has a three-layered appearance, thickness reaching 4–8 mm. The deep layer of the endometrium (stratum basale) is echogenic, and the superficial

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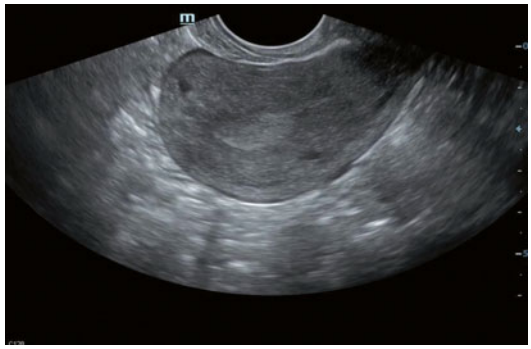

Fig. 7.1 TVS showing uniformly echogenic endometrium in the secretory phase

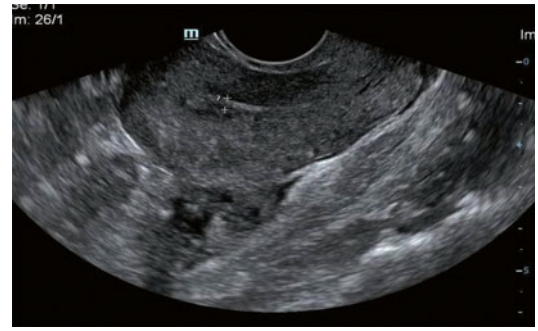

Fig. 7.2 TVS showing postmenopausal thin endometrium

layer of the endometrium (stratum functionale) is relatively hypoechoic. The central opposing surface appears as thin echogenic reflective stripe termed "endometrial stripe." During the secretory phase, the echogenicity of functional layer increases; the endometrium becomes uniformly echogenic and measures between 7 and 14 mm (Fig. 7.1).

Normal Sonographic Appearance of Endometrium in Postmenopausal Women

Postmenopausal endometrium is thin, homogenous, and echogenic (Fig. 7.2). In 2001, the Society of Radiologists in an ultrasound consensus panel recommended a cutoff value of 5 mm endometrial thickness in postmenopausal women with bleeding for intervention which conferred 96 % sensitivity for the detection of endometrial cancer [3]. ACOG guidelines recommend that an endometrial thickness up to 4 mm reliably excludes endometrial cancer [4].

Endometrial Measurement on Transvaginal Sonography

The endometrium is best measured in midline sagittal scan of the uterus at the thickest point and includes both layers of echogenic endometrium (Fig. 7.3). Small amount of fluid within the endometrial cavity may be a normal finding. This fluid

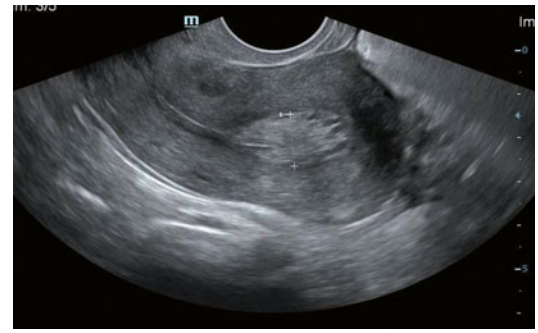

Fig. 7.3 TVS showing an endometrial thickening of 1.1 cm (note the correct placement of calipers)

should be excluded while measuring the endometrium (Fig. 7.4).

Transvaginal Sonography in Premenopausal Bleeding

Ten to twenty percent of endometrial cancers are diagnosed in premenopausal women with abnormal uterine bleeding [5].

Transvaginal ultrasonography is the initial screening modality in premenopausal bleeding to assess the endometrial thickness and to rule out structural abnormalities like endometrial polyps, submucosal fibroids, polycystic ovaries, or other hormone-producing tumors of the ovary.

Sonosalpingography and other invasive tests like hysteroscopy and endometrial biopsy are important in this age group to rule out endometrial malignancy if bleeding persists despite medical management.

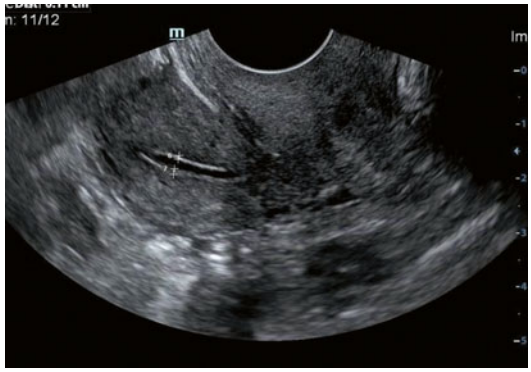

Fig. 7.4 TVS showing accurate placement of calipers to measure endometrial thickness, if there is fluid within the endometrium

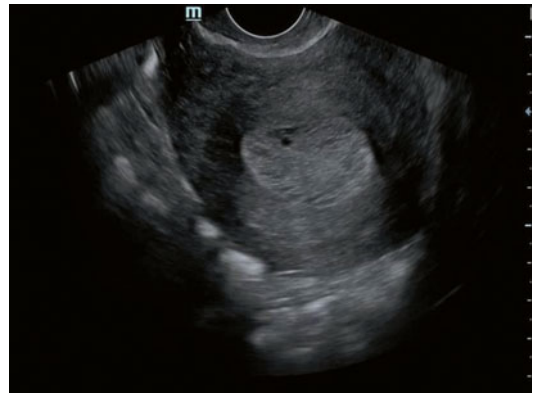

Fig. 7.5 TVS showing 20 mm thickened endometrium with cystic areas

Transvaginal Sonography in Postmenopausal Bleeding

Ten percent of cases with postmenopausal bleeding have endometrial cancer [3]. Any vaginal bleeding in a postmenopausal woman should be investigated to exclude malignancy, the other causes being polyps, endometrial atrophy, atrophic vaginitis, endometrial hyperplasia, hormone therapy, medications, and other cancers.

The ultrasound appearances in endometrial malignancy in a postmenopausal woman with bleeding are as given below (Figs. 7.5, 7.6, and 7.7):

1. Uniformly thickened echogenic endometrium. Cystic changes within the thickened endometrium may be seen in 5–15 % case of endometrial cancer.
2. Focal endometrial thickening due to polypoidal lesions.
3. Heterogenous mass replacing the endometrium.
4. Diffuse uterine enlargement due to large tumors infiltrating the myometrium.
5. Tumors in the lower endometrium may obstruct the endometrial cavity, resulting in hematometra.

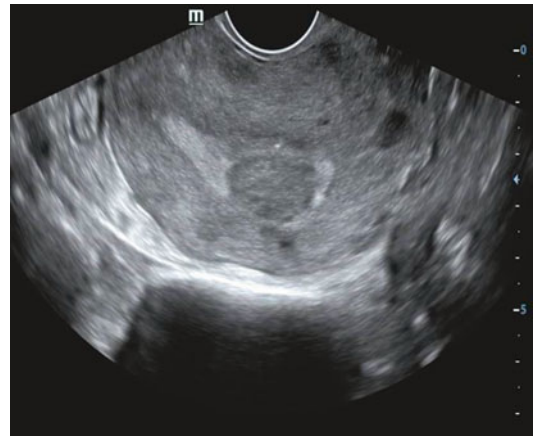

Fig. 7.6 TVS showing hypoechoic polypoidal mass within the endometrium

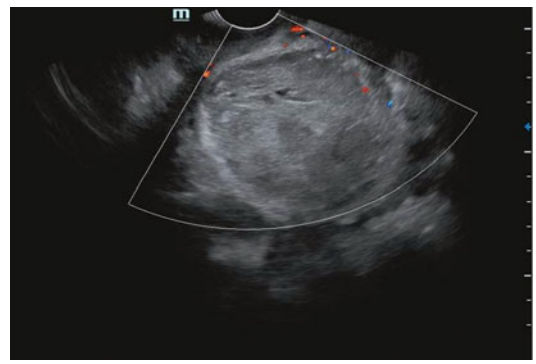

Fig. 7.7 TVS with Doppler showing diffuse infiltrating endometrial cancer with uterine enlargement

Role of Transvaginal Sonography in Staging of Endometrial Cancers

Once the diagnosis is established by biopsy, transvaginal ultrasound can help in staging the tumor to a certain extent, by determining the involvement of the myometrium and depth of myometrial invasion. Myometrial invasion is seen as irregularity of the endometrial–myometrial border with

disruption of subendometrial echo. The tumor–myometrial interface would be preserved in early lesions and poorly defined with irregular margins in advanced disease. However, this differentiation is often difficult. It is stated that ultrasound has accuracies ranging from 73 % to 84 % in assessing myometrial invasion [6]. 3D ultrasonography with virtual navigation software may help in better identifying myometrial invasion in the future [7].

The Endometrium and Hormone Therapy

For women receiving hormone therapy, endometrial thickening varies with the regimen used—continuous or cyclical.

Women taking sequential continuous estrogen–progestin replacement regimen in perimenopausal age group have endometrial thickening, almost 15 mm during estrogen phase and then decreasing after progesterone is added. The endometrial thickness in such cases should be measured immediately after the progesterone phase when it is the thinnest. The cutoff threshold is 5 mm.

Approximately 50 % of postmenopausal women taking unopposed continuous estrogen alone may have an endometrium exceeding 8 mm in diameter (range 6–10 mm). A thickness of 8 mm is considered the upper limit of normal if the patient is asymptomatic. However, if the woman reports postmenopausal bleeding, a thickness cutoff of 5 mm is used for deciding upon further investigations as in the other postmenopausal women [8].

The Endometrium and Tamoxifen

The use of tamoxifen as an adjunctive treatment for breast cancer has resulted in an increased prevalence of endometrial hyperplasia with or without cystic changes. Subendometrial cystic atrophy is a benign process that can occur as part of tamoxifen-associated endometrial changes.

Most women with thickened endometrium are asymptomatic. Some investigators have proposed a cutoff of 5–8 mm for diagnosing endometrial abnormalities in asymptomatic postmenopausal women receiving tamoxifen [8].

Transvaginal sonography has a sensitivity of 63.3 % and specificity of only 60.4 % for the detection of endometrial malignancy in patients on tamoxifen even when the cutoff is 9 mm.[9]. Hence, routine ultrasound surveillance in asymptomatic women using tamoxifen is of limited use.

Advantages of Ultrasonography

1. Transvaginal sonography in a postmenopausal woman with bleeding has a high negative predictive value and hence is a good screening modality.
2. Transvaginal sonography avoids endometrial biopsy in majority of postmenopausal bleeding with normal/atrophic endometrium [10].
3. Transvaginal sonography (TVS) identifies appropriate cases with endometrial thickening in women with abnormal uterine bleeding for further investigations.
4. TVS can classify endometrial lesions as focal (polyps, submucosal fibroids) and diffuse (endometrial hyperplasia). Diffuse lesions may require biopsy for further delineation, whereas focal lesions may require more invasive work-up with hysteroscopy and targeted biopsy [8] or removal.

Pitfalls in Diagnosis and Staging Using TVS

1. It is not possible to get a reliable measurement of endometrial thickness by TVS in all cases. Preexisting conditions like fibroid, adenomyosis, and previous uterine surgery make the accurate assessment of endometrial thickening and myometrial invasion difficult. In such cases, alternative assessment should be suggested.
2. If there is uterine enlargement, the entire endometrium up to the fundal region may not

be optimally visualized by TVS probe. Maneuvers like anterior and extreme probe angulation and abdominal compression may bring the uterus to the focal zone of the transducer.

3. In some cases, the sonographic appearance of a diffusely thick endometrium may be due to focal isoechoic endometrial polyps.
4. Bulky endocavitary polypoid tumor that produces myometrial thinning may be confused with advanced and invasive tumors on staging.
5. It is difficult to delineate cervical and parametrial infiltration even with high-resolution vaginal probe.

Role of Doppler

The role of Doppler is limited as there is significant overlap in Doppler indices in benign and malignant conditions. Color and power Doppler reveals diffuse or focal increased vascularity in endometrial carcinoma, and spectral Doppler may show low-resistance flow pattern. Color and power Doppler may help in ensuring that biopsies are targeted from areas of increased blood flow (Fig. 7.8).

Role of Saline Infusion Sonohysterography (Sonosalpingography)

Hysterosonography, i.e., transvaginal US evaluation of the uterus after intracavitary saline infusion, has been used for evaluating myometrial invasion, with accuracies ranging from 84 % to 89 % [10]. It may help to reach a conclusive diagnosis in difficult situations (Figs. 7.9 and 7.10).

Advantages of Sonosalpingography over TVS

- When fluid outlines the endometrium, the endometrium can be better assessed for irregularities and polypoid masses that are missed at conventional transvaginal US. It can thus differentiate focal from diffuse endometrial thickening better than TVS.
- It helps to differentiate between polyps and submucosal fibroids. A polyp is seen arising from the endometrium, while normal endometrium is seen overlying submucous fibroid.
- Sonohysterography plays an important role as an adjuvant to endovaginal sonography in

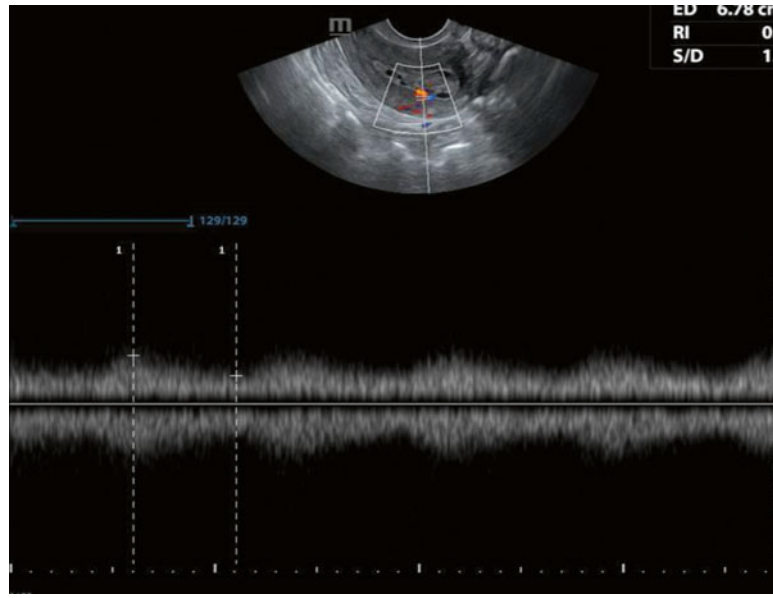

Fig. 7.8 TVS with Doppler showing low-resistance flow pattern in endometrial malignancy

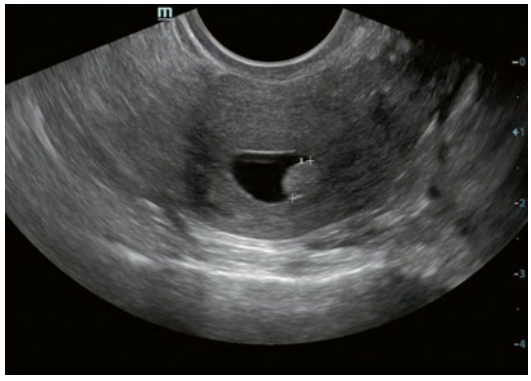

Fig. 7.9 Sonosalpingography showing small uniformly hyperechoic endometrial polyp

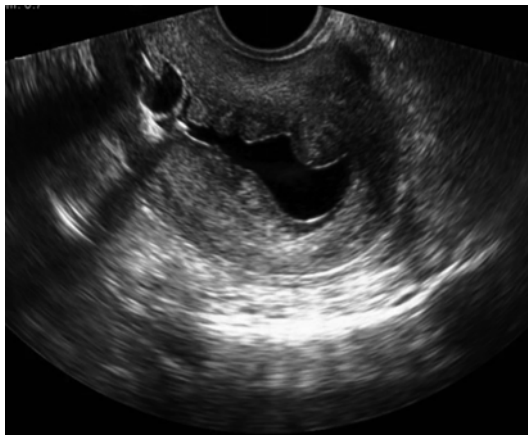

Fig. 7.10 Sonosalpingography showing polypoidal endometrial thickening

patients on tamoxifen by delineating endometrial and subendometrial disorders and selecting patients requiring hysteroscopy versus sampling in symptomatic women with vaginal bleeding.

The role of sonosalpingography is controversial in endometrial malignancy as this procedure may disseminate malignant cells into the peritoneal cavity [10].

Sonosalpingography Versus Hysteroscopy

- Sonohysterography is less invasive, less expensive, well tolerated, and without major complications compared to hysteroscopy.
- Sonohysterography and hysteroscopy show similar performance characteristics with regard to sensitivity (95–96 %) and specificity (88–90 %) for detecting and characterizing focal endometrial abnormalities [8]. However, hysteroscopy enables sampling and helps in tissue diagnosis.

Role of CT Scan

CT remains the imaging modality used most frequently in clinical practice for preoperative evaluation as it is widely available. In advanced disease where surgery is not a treatment option, CT can be used for preoperative staging and follow-up.

Endometrial cancer is isodense to myometrium in plain CT scan and shows relatively low attenuation compared with myometrium after intravenous contrast. The sensitivity, specificity, and accuracy of 16-slice multidetector CT scan in evaluating myometrial invasion were 100 %, 80 %, and 95 %, respectively, and for assessing cervical infiltration were 78 %, 83 %, and 81 %, respectively [11]. The performance of higher slice CT may be marginally better.

CT scan cannot differentiate between stage 1a, b, and II disease and also cannot detect early cervical, vaginal, and parametrial involvement. However, CT can demonstrate obvious parametrial involvement, infiltration of the bladder and rectum, pelvic and para-aortic nodal involvement, and peritoneal metastasis in advanced disease. Peritoneal metastasis on CT appears as peritoneal thickening with soft tissue deposits and ascites.

CT and MRI are comparable in the overall detection of tumor spread outside the uterus (Figs. 7.11a, b and 7.12a, b).

Lymph Node Metastasis on CT

Diagnosis of lymph node metastasis is based on size criteria (short axis diameter 8–10 mm). It is not always possible to differentiate metastatic from reactive node. A cutoff of 1 cm in short axis

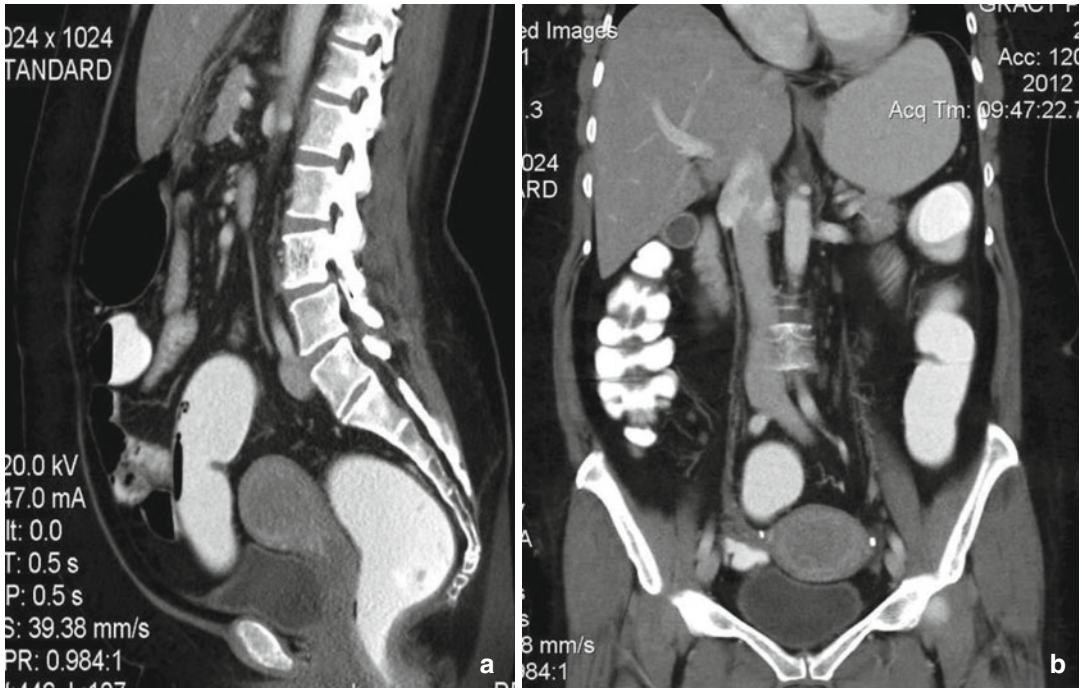

Fig. 7.11 (**a**, **b**) Contrast-enhanced sagittal and coronal CT images showing hypodense central endometrial mass confined to the uterus with thinned out myometrium in the periphery (proven stage 1 endometrial carcinoma)

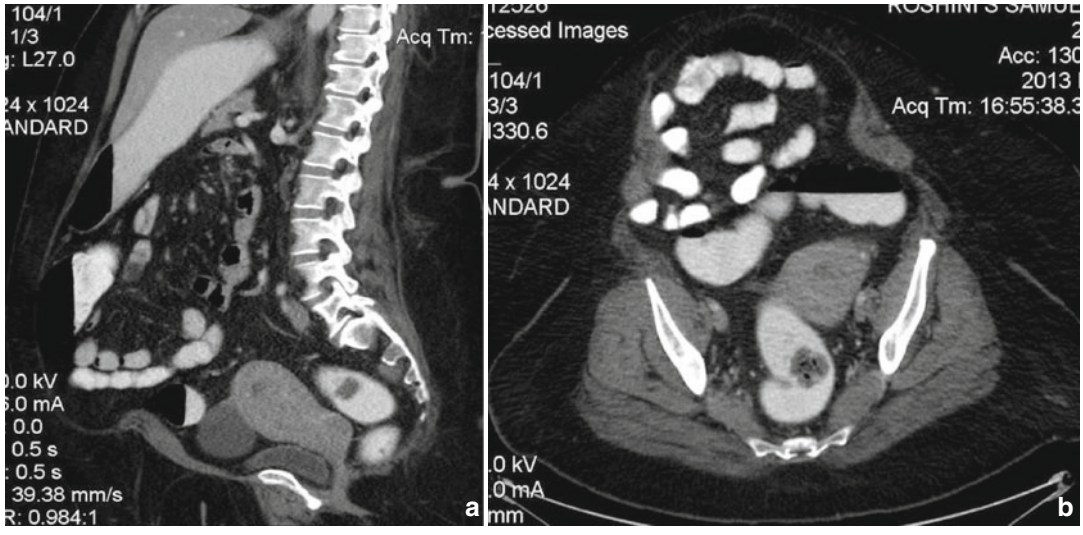

Fig. 7.12 (**a**, **b**) Contrast-enhanced sagittal and axial CT images showing central heterogeneous mass (proven FIGO stage 2 endometrioid adenocarcinoma). It is difficult to delineate cervical infiltration on CT scan

diameter gives a sensitivity of 50 % and specificity of 95 % in uterine cancers [1]. Contrast enhancement may show heterogeneity and necrosis of involved nodes in some cases.

Tumors from the middle and inferior uterus drain to the parametrial and obturator nodes, whereas those from the proximal body and fundus drain to the common iliac and para-aortic nodes.

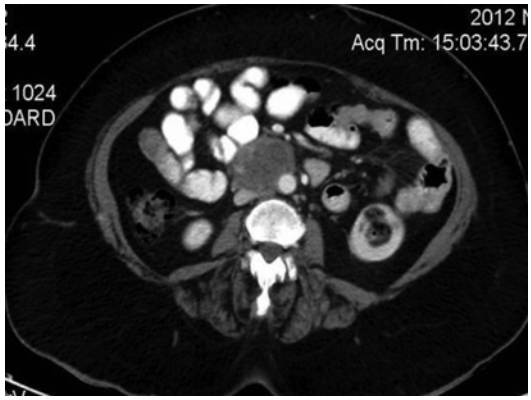

Fig. 7.13 Contrast-enhanced axial CT showing heterogeneous soft tissue retroperitoneal lymph nodal mass in a case of endometrial carcinoma

Tumor can spread via the round ligament to inguinal nodes. Sometimes endometrial carcinoma can involve para-aortic nodes without pelvic node involvement, in a fundal growth (Fig. 7.13).

Pitfalls in Diagnosis with CT Scan

1. Central low attenuation within the uterus after IV contrast in CT scan can also occur due to physiological endometrial thickening and hence detection of tumor becomes difficult.
2. On CT scan, margin of endometrium is not visualized distinctly from the myometrium even after contrast and hence is not accurate for measuring the endometrial thickness.
3. Even multislice CT cannot reliably show the extent of cervical infiltration because of its inferior soft tissue resolution in the pelvis due to beam hardening artifacts.

Role of Chest Radiograph Versus CT Scan of Thorax for Metastatic Work-Up

Chest radiograph is mandatory in advanced cases of endometrial cancer to detect lung parenchymal metastasis. Performing chest CT as an alternative to radiography for the initial diagnostic work-up is controversial [1]. However, CT scan is the best modality available to detect lung metastasis.

Role of Imaging in Other Uterine Malignancies

Other uterine malignancies include carcinosarcomas, sarcomas, and rare tumors like lymphomas, metastatic tumors, and choriocarcinoma:

1. *Carcinosarcoma* appears as intracavitary mass on endovaginal sonography with expansion of endometrial cavity and has a predilection for the uterine fundus [12]. The tumor is echogenic/heterogeneous on sonography with heterogeneous hypodense appearance on contrast-enhanced CT scan (Fig. 7.14). Myometrial invasion is common. This tumor, now regarded as carcinoma more than sarcoma, should be staged like endometrial carcinoma.
2. *Sarcomas* usually present as lobulated hypoechoic lesions on ultrasound and as hypodense uterine mass on CT scan with irregular margins and heterogeneity due to necrosis and hemorrhage. Tumors show increased vascularity on Doppler with variable enhancement on CT scan. Calcification in tumors is better detected on CT scan. Deep myometrial invasion and peritoneal seeding are usually seen at presentation [13].
   (a) *Leiomyosarcoma* is the most common uterine sarcoma. It mostly occurs de novo or rarely from preexisting leiomyomas

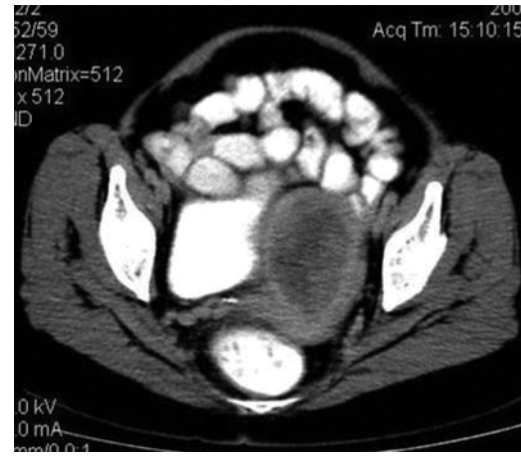

Fig. 7.14 Contrast-enhanced axial CT sections showing heterogeneous hypodense uterine mass (proven carcinosarcoma)

(0.1–0.8 %) [1]. The radiological appearance is similar to that of leiomyomas. Large tumors have irregular central area of low attenuation on CT due to necrosis or hemorrhage (Fig. 7.15). Other leiomyosarcoma mimics are benign metastasizing leiomyomas, diffuse peritoneal leiomyomatosis, and intravenous leiomyomatosis.

(b) *Endometrial stromal sarcoma* is the second common sarcoma and can present as *low-* or *high-grade* type. Low-grade type occurs in younger age group and high-grade aggressive type is seen in older age group. Low-grade endometrial stromal sarcomas are usually well-circumscribed lesions. CT features of stromal sarcomas are variable, from a polypoid endometrial mass to a myometrial mass mimicking intramural myoma. Low-grade endometrial sarcomas can invade adjacent structures even with scanty cytological atypia [13].

High-grade endometrial stromal tumors have a more aggressive course, infiltrating myometrium with vascular and lymphatic involvement. Hemorrhage and necrosis are frequently present in the aggressive type [13].

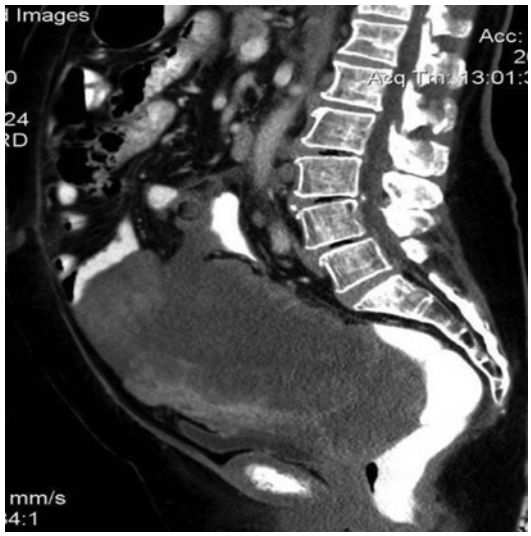

Fig. 7.15 Contrast-enhanced sagittal CT showing large lobulated heterogeneous hypodense mass replacing the uterus with loss of cleavage plane with rectum (proven leiomyosarcoma)

(c) *Adenosarcoma* appears as a well-demarcated polypoid mass that arises in the endometrium and protrudes through the cervical os [14]. Adenosarcomas are staged like endometrial stromal sarcoma.

(d) *Embryonal rhabdomyosarcoma* usually occurs in children less than 5 years and young women. The tumor originates in or involves the uterus, vagina, vulva, bladder, and pelvic floor. Tumor appears as large lobulated soft tissue mass in the pelvis with heterogeneous appearance at times inseparable from the uterus with enhancing components (Fig. 7.16a, b). Lymph nodal involvement and lung metastasis may be seen at presentation.

3. *Lymphomas and metastasis* are very uncommon in the uterus; their appearance is nonspecific on imaging. Progressive uterine enlargement due to myometrial tumor infiltration can occur in metastatic breast cancer.
4. *Choriocarcinoma*

Choriocarcinoma associated with the spectrum of gestational trophoblastic disease arises from complete or partial mole in half the number of cases, 30 % occur after an abortion, and 20 % occur after apparently normal pregnancy. Choriocarcinoma can also occur after ectopic gestation. In case of intraplacental choriocarcinoma, the mother may present with multiple metastases during the course of pregnancy.

Ultrasonography shows diffuse enlargement of the uterus with heterogeneous central masses due to tumor necrosis and hemorrhage with poorly defined margins. Color and power Doppler shows peripheral vascularity. CT scan shows central hypodense mass with peripheral enhancing areas due to tumor vascularity (Fig. 7.17a, b) [1]. Hypervascular and hemorrhagic metastasis occur in the lung, liver, and brain.

Role of Positron Emission Tomography (PET) with ^{18}F-FDG

18F (fluorine), the radiotracer used in positron emission tomography (PET) scanner, is labeled with fluorodeoxyglucose, abbreviated as FDG. FDG

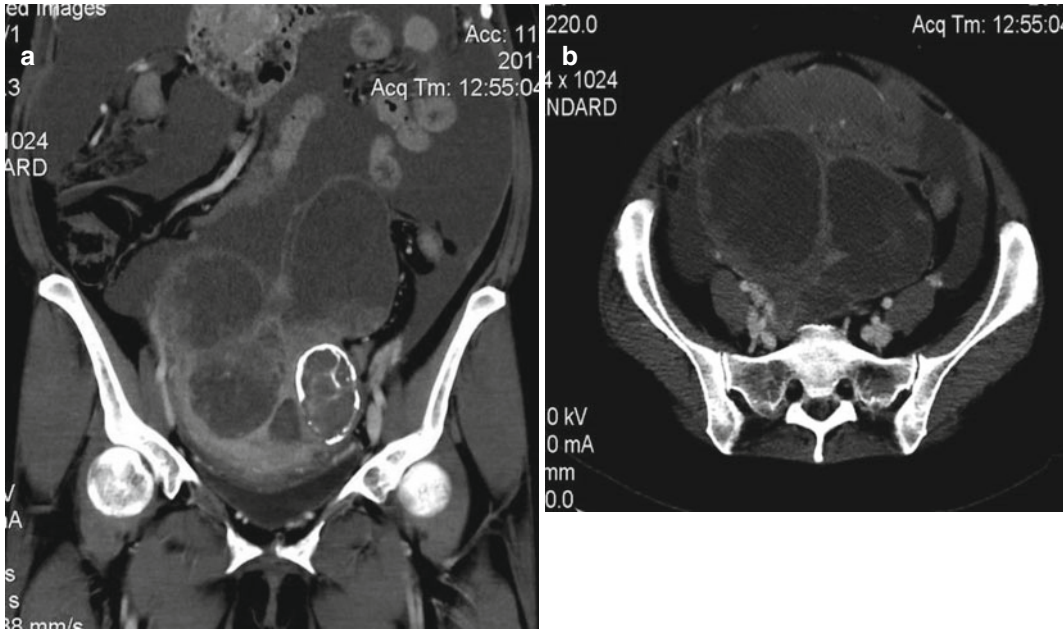

Fig. 7.16 (**a**, **b**) Contrast-enhanced axial and coronal CT showing uterine enlargement with lobulated contour with enhancing solid areas and low-density necrotic masses; one of the lesions shows peripheral wall calcification (proven rhabdomyosarcoma)

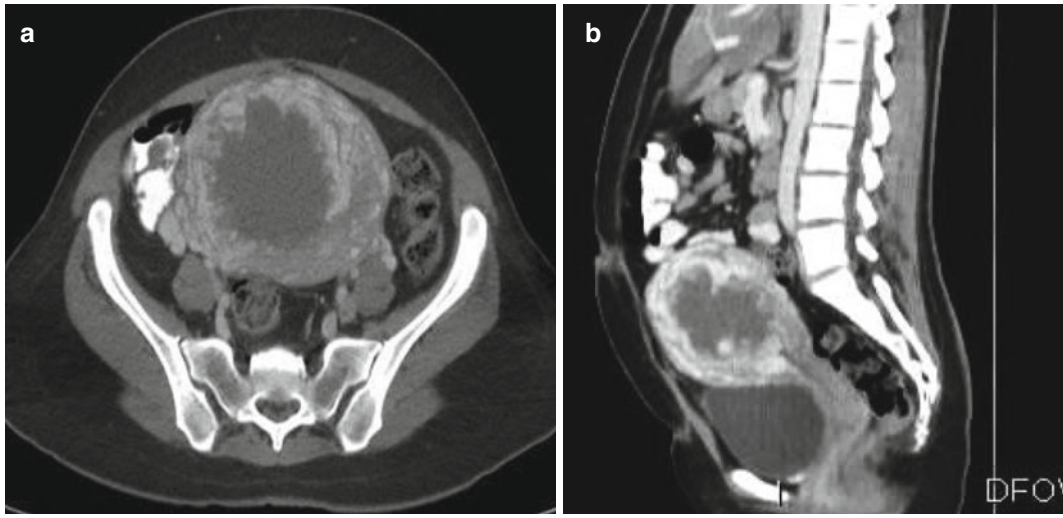

Fig. 7.17 (**a**, **b**) Contrast-enhanced axial and sagittal contrast-enhanced CT scan showing central hypodense mass with peripheral enhancing areas in an enlarged uterus (proven choriocarcinoma)

is a glucose analogue, taken up by high glucose-using cells, phosphorylated by hexokinase (which is elevated in rapidly growing malignant tumors), and is retained by tissues with high metabolic activity, such as most types of malignant tumors.

18F-FDG uptake is quantified in terms of standardized uptake value (SUV). SUV is automatically obtained in the patients' final report, and it is calculated as ratio of activity per cubic cm of tissue to activity in injected

dose of 18F-FDG per kilogram of patient body weight [15].

18F-FDG uptake in the endometrium can be physiological or due to benign and malignant causes. In premenopausal woman normal endometrial uptake of FDG changes cyclically, increasing during ovulatory and menstrual phase. In majority of postmenopausal women, some FDG uptake was noted within the endometrium for few years after cessation of menstrual cycle. Hormonal therapy in postmenopausal women is not associated with significant alteration in endometrial FDG uptake. Lerman et al. reported that the mean endometrial standardized uptake values (SUVs) in premenopausal women were 5 ± 3.2 (SD) and 3.7 ± 0.9 during the menstruating and ovulating phases and 2.6 ± 1.1 and 2.5 ± 1.1 during the proliferative and secretory phases, respectively. They also reported that the mean endometrial SUV of postmenopausal women was 1.7 ± 0.7 [16].

For primary work-up, FDG PET has a limited role in local staging as the uptake depends on many factors as described above and on the grade and size of tumor. High-grade endometrial tumors show intense FDG uptake, while tumors with low cellularity and small malignant tumors may not show uptake [16]. Uterine sarcomas and metastatic tumors show increased FDG uptake.

FDG PET is the most accurate method of detecting adenopathy in pretreatment staging. It can detect metastasis in normal-sized nodes, which is not possible by CT or MRI.

The role of FDG PET in endometrial malignancy as of now is mainly for follow-up of treated cases to detect recurrence in the pelvis or at distant sites. FDG PET has a sensitivity of 96–100 % and specificity of 78–88 %, compared to MRI or CT alone [17]. FDG PET in conjunction with anatomic imaging (CT/MR imaging) has been reported to be more sensitive, specific, and accurate than CT or MR imaging alone (Fig. 7.18a, b, c) [17].

PET-MRI is under evaluation and may have an edge over PET-CT in the future.

Pitfalls in diagnosis with PET:

1. Although FDG generally accumulates in malignant lesion because of high glucose metabolism, FDG can also accumulate in normal tissue like bowel, blood vessels, bone marrow, skeletal muscle, and urinary system and in benign lesions like fibroid/adenomyoma and tissues affected by inflammatory processes.

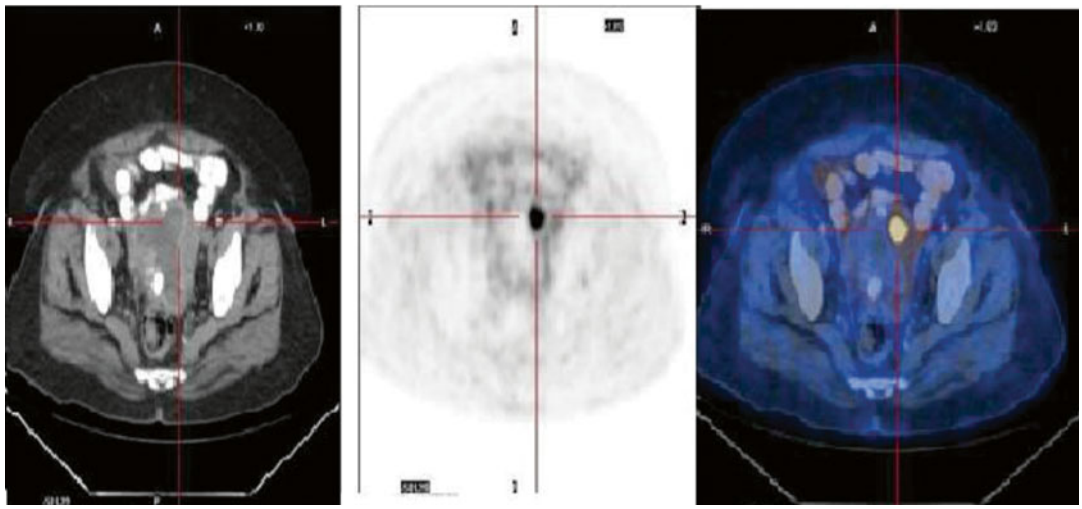

Fig. 7.18 (**a**) Axial CT sections showing thickened heterogeneous endometrium with soft tissue area at the marked site. (**b**) Axial PET images showing FDG-avid endometrial malignancy. (**c**) Co-registered PET-CT image showing hypermetabolic area (*bright yellow* mass)

2. Physiological endometrial uptake is seen around the first 3 days of menstruation and during ovulatory phase. Ovaries also show cyclical uptake of FDG PET.
3. PET cannot be used to differentiate endometrial cancer from hyperplasia as hyperplasia also shows minimal FDG uptake.
4. Forty five percent of endometrial cancers are grade I and hence not FDG avid [18].
5. Inflammatory changes from recent surgery and radiation therapy have also demonstrated increased PET uptake.
6. High endometrial SUV was also associated with uterine fluid collection which may be secondary to cervical stenosis.
7. Identifying micrometastasis in lymph nodes which is under a PET machine sensitivity remains a problem even for PET, though this is the most sensitive imaging modality.
8. Leiomyosarcoma show variable uptake, and hence, PET cannot be used to differentiate leiomyoma from leiomyosarcoma. Leiomyomas may show mild or intense uptake depending on several factors like tumor cellularity and vascularity. Also leiomyoma in premenstrual women shows high uptake during luteal phase than during other phases [16].

Comparison Between Ultrasound, CT, MRI, and PET

In studies comparing CT with US and MRI, the accuracy of CT for myometrial invasion is reported to be from 58 % to 61 % versus 73 % to 84 % for transvaginal ultrasound and 88 % to 89 % for MRI [18]. The depth of myometrial invasion is the most important prognostic factor for endometrial malignancy [19].

For assessing cervical involvement, MRI is the best tool. Cervical extension can be diagnosed reliably with accuracy ranging from 86 % to 95 % [19].

For assessing lymph nodes, CT and MRI perform almost equally—83–90 % for CT and 86–90 % for MRI [19]. The new MRI lymph node-specific contrast agents marginally improve identification of involved nodes. MRI is superior to CT in detecting early parametrial invasion, though CT is better in detecting and distinguishing omental and mesenteric metastasis from bowel.

In high-grade FDG-avid tumors, PET-CT is better than MRI to detect involved nodes (<1 cm).

In patients who require multifactorial assessment, contrast-enhanced MR imaging is the only modality that can be used to accurately evaluate myometrial, cervical, and nodal involvement [19].

Recurrence in Endometrial Carcinoma and Role of Imaging

Endometrial carcinoma tends to recur mostly in the pelvis, especially vaginal vault. Other sites for metastasis are the pelvic and para-aortic nodes, peritoneum, liver, lung, and bone. Sometimes hydronephrosis due to ureteral obstruction by pelvic recurrence or lymph node is the first sign of recurrence.

Ultrasound scan and chest radiograph is used for routine surveillance after surgery. Chest CT could be obtained as a part of post-therapy surveillance in patients with higher FIGO stage or tumor grade.

If there is widespread disease on USS, CT/PET-CT scan is done to confirm and localize recurrent disease, and tissue diagnosis is made from the most appropriate site for second-line treatment (Figs. 7.19, 7.20, 7.21, and 7.22). FDG PET is the best modality to detect recurrence.

If the recurrence is confined to the pelvis, MRI is done for better assessment of the local extent of tumor, to identify patients who may benefit from second surgery like local resection or pelvic exenteration.

In patients who had radiation therapy, serial imaging, PET scan, or biopsy helps in distinguishing recurrent disease from post-irradiation changes.

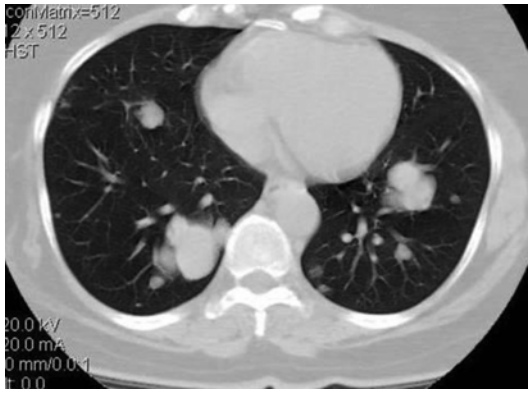

Fig. 7.19 Contrast-enhanced axial CT scan showing multiple lobulated masses in both lung fields suggestive of lung metastasis

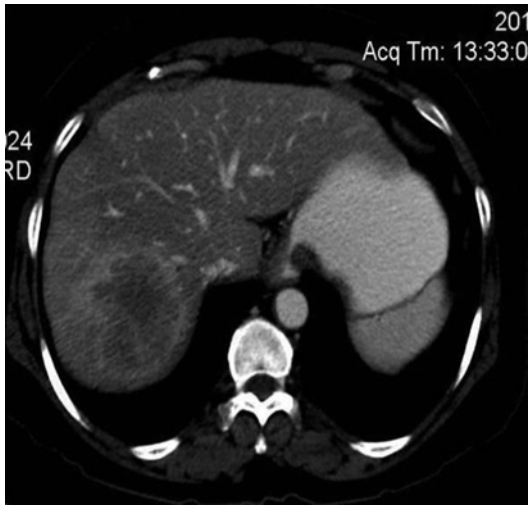

Fig. 7.20 Contrast-enhanced CT showing moderate-sized solitary hepatic deposit with enhancing periphery and necrotic center in an operated case of uterine carcinoma

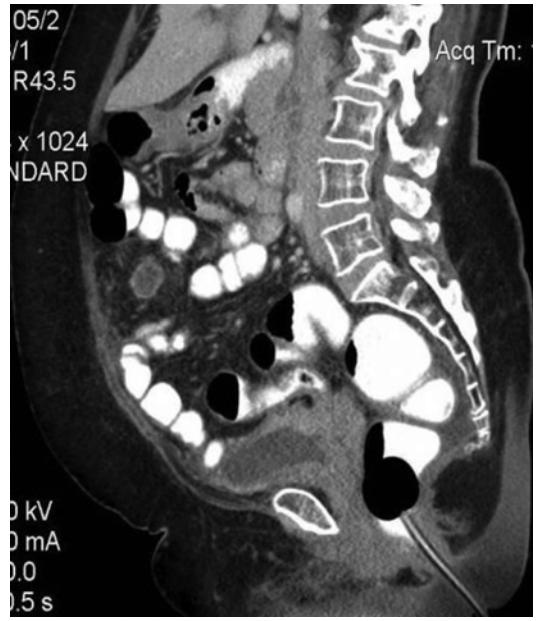

Fig. 7.21 Contrast-enhanced CT showing soft tissue mass in the pelvis in an operated case of clear cell endometrial carcinoma

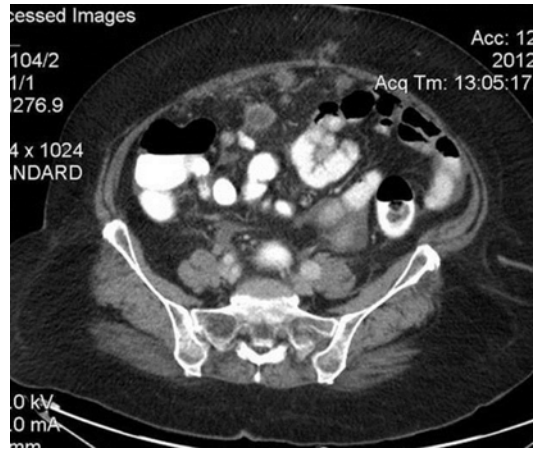

Fig. 7.22 Contrast-enhanced axial CT showing soft tissue deposits with necrotic areas in the omentum suggestive of omental deposits

Conclusion

Imaging is an important adjunct to clinical evaluation of women with endometrial carcinoma. The pitfalls and limitation of imaging should always be considered while evaluating patients. The high sensitivity of transvaginal scan makes it an excellent noninvasive test for screening and diagnostic triage. With the development of technology in ultrasound, multislice CT, development of new radiotracers, and evolution of PET-MR may provide even greater sensitivity and specificity for imaging endometrial cancer in the future. FDG PET is the best modality to detect recurrence.

Key Points

1. All postmenopausal women with vaginal bleeding should be investigated.
2. Transvaginal sonography is the most cost-effective screening tool; however, if accurate assessment of endometrium is not possible, other modalities should be suggested.
3. Thickened heterogeneous endometrium, irregular endo-myometrial interface, and abnormal vascularity on Doppler raise suspicion of endometrial malignancy.
4. An endometrial thickness of less than 4 mm in postmenopausal woman without focal thickening is consistent with atrophy, and endometrial sampling is not indicated.
5. A negative endometrial sampling despite thickened endometrium on TVS warrants further evaluation.
6. All women on tamoxifen with abnormal vaginal bleeding should be investigated.
7. Premenopausal women with thickened endometrium and abnormal uterine bleeding require investigation in the appropriate clinical setting.
8. None of the imaging modalities can differentiate leiomyoma from leiomyosarcoma. An irregular margin of leiomyoma and relatively rapid growth may indicate malignant transformation.
9. Low-grade endometrial stromal sarcoma mimics leiomyoma on imaging.
10. The significance of an endometrial thickness of more than 4 mm in an asymptomatic postmenopausal woman has not yet been established.

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Magnetic Resonance Imaging in Endometrial Cancer

8

Rekha S. Cherian

Introduction

Magnetic resonance imaging (MRI) has been widely accepted as the most reliable and accurate modality for diagnosis, staging, treatment planning, and follow-up of endometrial carcinoma. MRI is the best modality to assess the uterus given its excellent soft tissue resolution and direct multiplanar capabilities. It is the only modality that demonstrates the zonal anatomy of the uterus and therefore is essential for the preoperative staging of endometrial carcinoma. The depth of myometrial invasion is the most important morphologic prognostic factor and can only be accurately assessed with MRI [1].

Diffusion-weighted MRI and dynamic contrast-enhanced MRI are also useful adjuncts for evaluation of the uterus and pelvis in endometrial cancer.

Technique

Optimal MRI of the female pelvis should be performed on a high-field strength MRI system (1.5 T or 3 T systems) using local phased array coils. These surface coils provide increased signal to noise ratio which allows a small field of view image with high spatial resolution. An endoluminal coil (such as endo-vaginal/endorectal coil) has less patient acceptance and additionally causes local artifact; this is hence not used.

Imaging Protocols

It is recommended that prior to the MRI scan, the patient fasts for about 4 h to reduce artifact from bowel motion. Alternatively, an antiperistaltic agent such as hyoscine butyl bromide/glucagon can be administered. Vaginal gel, such as ultrasound gel, is inserted to distend the vagina.

Imaging is performed in sagittal, coronal, and axial planes and most importantly in an axial oblique plane perpendicular to the endometrial cavity. These high-resolution images obtained perpendicular to the uterus are important when assessing for myometrial invasion.

Diffusion-weighted images are obtained. Dynamic contrast images may also be obtained using a three-dimensional GRE T1-weighted LAVA acquisition after administration of gadolinium (at the rate of around 2 ml/s). Post-contrast images are obtained at around 25 s, 1 min, and 2 min and after 4 min [1]. This is done as the different zones of the uterus enhance at different

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times, and this is helpful to assess for the depth of myometrial invasion in endometrial carcinoma.

(Note: Gadolinium is generally avoided in women with renal impairment.)

Normal Uterine Anatomy

On T1-weighted images, the uterus is similar in signal intensity to the muscle, and the zonal anatomy is not displayed.

On T2-weighted images, however, zonal anatomy is excellently demonstrated [2] with the uterus showing three distinct zones (Figs. 8.1 and 8.2) as follows:

1. The central high-signal intensity endometrium
2. The middle low-signal junctional zone, i.e., the inner myometrium
3. The intermediate-signal outer myometrium

The central endometrium has a high T2 signal due to the endometrium and secretions. The endometrium varies in thickness with the menstrual cycle and menopausal status. It can measure up to 14 mm in the secretory phase but is thinned in the follicular phase. Postmenopausal women should have a homogenous endometrium with a width less than 5 mm [3].

The myometrium is separated into (1) the inner myometrium, also known as the junctional zone which appears like a low-signal band on T2-weighted images, and (2) the outer myometrium which has an intermediate T2 signal.

When using oral contraceptives, the endometrium becomes thinned and the junctional zone less prominent.

After menopause, the junctional zone is thinned and not visualized consistently.

Post-contrast, the junctional zone shows the earliest enhancement, the outer myometrium enhances slightly later, and the endometrium enhances last.

The cervix shows four distinct zones on T2-weighted images:

1. Central hyperintense-signal mucus.
2. High-signal endocervical mucosa and glands.
3. Hypointense fibrous stroma; this is continuous with the junctional zone of the uterus.
4. Outer intermediate-signal loose stroma.

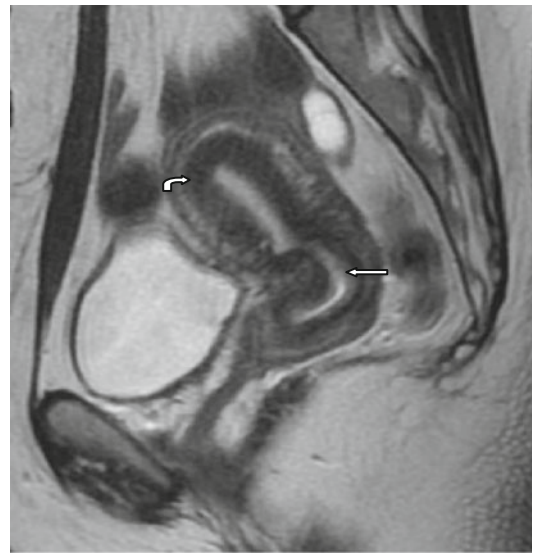

Fig. 8.1 Normal uterus; sagittal T2-weighted MRI clearly depicting the zonal anatomy of the uterus with the three zones displayed: intermediate signal of the endometrial lining (*straight arrow*), low signal of the junctional zone, i.e., the inner myometrium (*curved arrow*), and intermediate signal of the outer myometrium

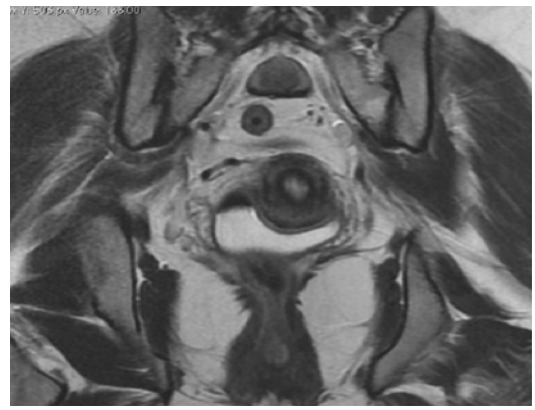

Fig. 8.2 Axial T2-weighted MRI showing three distinct zones of the uterus

MRI in Endometrial Carcinoma

MRI is essential for preoperative staging because it demonstrates the depth of myometrial invasion which is the most important morphologic prognostic factor. The depth of myometrial invasion and histological grade correlate strongly with the presence of lymph node metastases and patient survival. Lymph node metastases prevalence increases from 3 % with superficial myometrial invasion to 46 % with deep myometrial invasion [4, 5].

Evaluation of the extent of myometrial invasion by gross inspection at surgery or at frozen section remains inaccurate in a significant number of patients [6]. Though the majority of patients present with Stage 1A where the standard treatment is total abdominal hysterectomy with bilateral salpingo-oophorectomy, the challenge is to identify patients at risk for recurrence who would require more radical surgery or adjuvant therapy and avoid overtreating low-risk patients [6]. Preoperative MRI hence helps in this decision making between lymph node sampling for Stage 1A disease and radical lymph node resection for Stage 1B disease.

MRI also assesses more advanced disease such as cervical stromal involvement. Gross cervical invasion could require preoperative radiation therapy or a different surgical approach such as a radical hysterectomy rather than a total abdominal hysterectomy. Adnexal involvement, uterine tumor size/volume, and the presence of ascites or nodal disease can also be assessed. These can help determine the surgical approach such as transabdominal, transvaginal, or laparoscopic.

Full assessment of the abdomen can be done to assess for lymph nodal involvement/ hepatic or peritoneal disease. In high-risk patients for surgery due to comorbidities, MRI is helpful in planning alternative therapy such as radiation or hormonal therapy for Stage 1 disease. *Depth of myometrial invasion which is the most important morphologic prognostic factor can only be evaluated with MRI, as MRI is the only modality which demonstrates the zonal anatomy of the uterus.*

The FIGO staging system was updated in 2009 with three important changes which are relevant to MRI.

Tumors confined to the endometrium (previous Stage 1A) and those involving the inner half of the myometrium (previous Stage 1B) are now combined together in *Stage 1A*. This actually improves the accuracy of MRI, as with the old system distinguishing between the two was difficult in some patients due to thinning/loss of the junctional zone or poor tumor to myometrium contrast.

One of the important changes in the FIGO staging system (2009) is the clubbing together of tumors confined to the endometrium (previous Stage 1A) and those involving the inner half of the myometrium (previous Stage 1B); both come under Stage 1A. This improves the accuracy of MRI (Figs. 8.3 and 8.4).

The other change is in **Stage II**. IIA tumors were those with endocervical glandular invasion, and IIB tumors were those with cervical stromal invasion. In the new system, endocervical glandular invasion is included in Stage 1 disease and those with cervical stromal invasion, **Stage II** disease.

Stage IIIA disease invades the serosa or adnexa (Figs. 8.5 and 8.6).

Stage IIIB disease involves the vagina or parametrium. Vaginal invasion is shown as segmental loss of the low-signal line of the vaginal wall. Parametrial involvement appears as disruption of the serosa with direct extension into the surrounding parametrium.

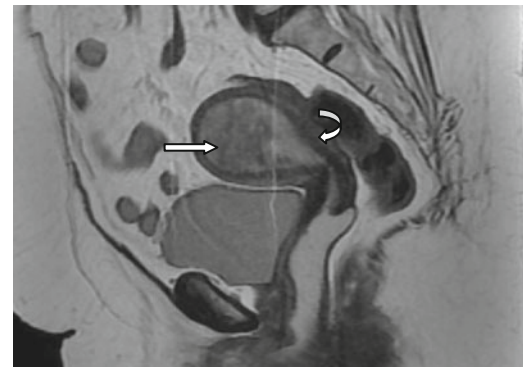

Fig. 8.3 81-year-old lady with postmenopausal bleed. Sagittal T2-weighted MRI showing a large mass filling the endometrial cavity (*straight arrow*). Intact junctional zone clearly demonstrated (*curved arrow*) with no extension of mass into the myometrium. No extension to the vagina

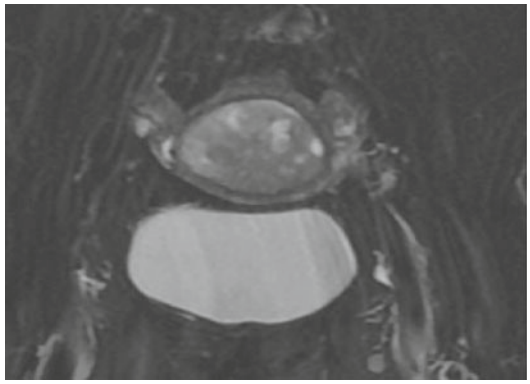

Fig. 8.4 Axial T2-weighted MRI showing the large mass filling the endometrial cavity. Intact junctional zone clearly demonstrated with no extension of mass into the myometrium

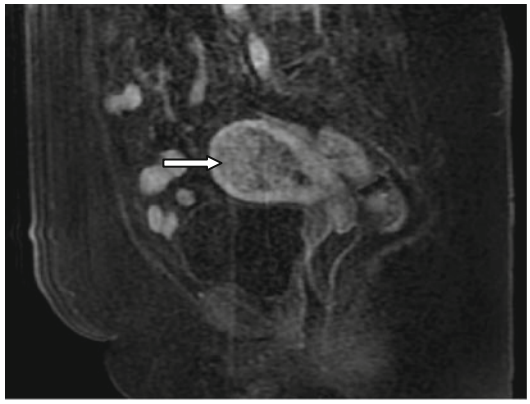

Fig. 8.5 Post-contrast sagittal T1 fat-suppressed image showing the mass in the endometrial cavity (*straight arrow*), enhancing less than the adjacent myometrium

MRI Appearances

Endometrial carcinoma shows heterogeneous intermediate-signal intensity on T2-weighted images when compared to the normal hyperintense endometrium.

It is mildly hyperintense on T2-weighted images when compared to the myometrium. The depth of myometrial penetration with extension beyond/breach of the junctional zone is well seen on the high-resolution T2 images in the sagittal plane and axial oblique plane obtained perpendicular to the endometrial cavity except where there is thinning of the junctional zone or poor tumor to myometrium contrast.

In a postmenopausal woman, in addition, there is often an overall thinning of the myometrium due to uterine involution which can render accurate assessment of myometrial invasion difficult.

Other pitfalls which make accurate assessment difficult include extension into the cornua, compression of the myometrium by a large polypoid tumor/tumor filling the endometrial cavity with compression of the overlying myometrium, and presence of leiomyomas or adenomyosis.

In these cases, additional imaging such as dynamic contrast or diffusion-weighted imaging is of help. The depth of myometrial penetration with extension beyond/breach of the junctional zone is well seen on the high-resolution T2

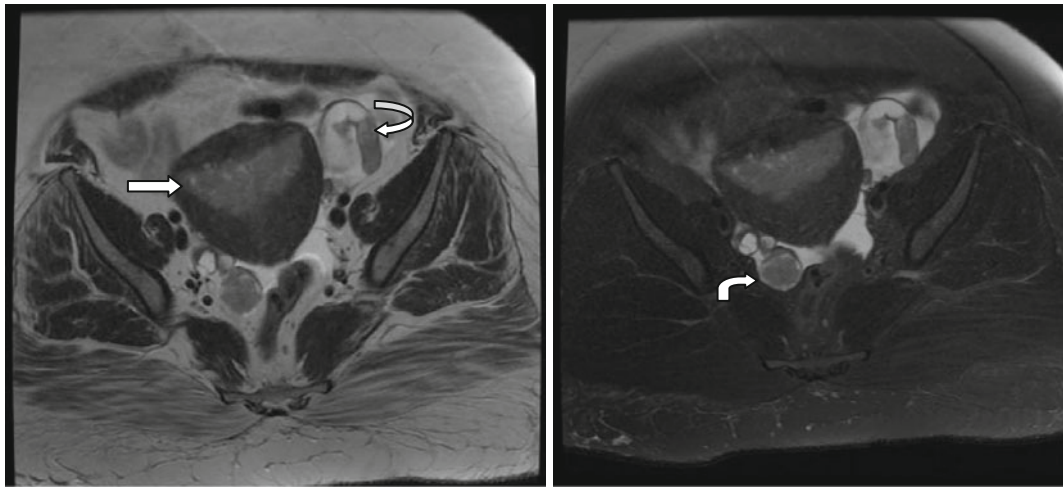

Fig. 8.6 39-year-old lady with biopsy-proven endometrial carcinoma, axial T2 and T2 fat-suppressed images showing mass in the endometrial cavity (*straight arrows*) and extension to the bilateral fallopian tubes (*curved arrows*) – Stage IIIA disease

images in the sagittal plane and most importantly in the axial oblique plane which is obtained perpendicular to the endometrial cavity.

Dynamic Contrast-Enhanced MRI

This has been shown to improve the diagnostic accuracy of MRI from 55 % to 77 % for routine non-contrast MRI to 85–91 % for dynamic contrast-enhanced images [6].

Differential enhancement of the tumor allows the tumor to be distinguished from non-enhancing blood products/debris.

In general, endometrial tumors enhance earlier than the normal endometrium and later than the adjacent myometrium. This helps in defining small tumors confined to the endometrium and also myometrial infiltration.

The early enhancement phase (0–1 min) allows identification of the junctional zone which enhances earlier than the rest of the myometrium. This is useful in detecting early myometrial invasion especially in postmenopausal women who have thinned junctional zones which make identification of this difficult on routine T2-weighted images. An intact junctional zone as indicated by a band of sub-myometrial enhancement excludes deep myometrial invasion.

The equilibrium phase (2–3 min after injection) allows better evaluation of deep myometrial invasion (maximum contrast between the myometrium and the endometrium is between 50 and 120 s).

Differential enhancement of the tumor allows the tumor to be distinguished from non-enhancing blood products/debris. Different zones of the uterus enhance at different times, and this is helpful to assess for the depth of myometrial invasion in endometrial carcinoma.

The delayed phase (3–4 min) helps in the evaluation of cervical stromal involvement.

Diffusion-Weighted Imaging

Diffusion-weighted imaging has recently proved to be able to distinguish between normal and endometrial disease. As endometrial tumors have high cellularity, they appear bright on diffusion-weighted images. T2 images and contrast-enhanced images have traditionally been used to determine the depth of myometrial invasion. Dynamic contrast images are helpful to detect depth of myometrial penetration as most of the tumors are hypovascular relative to the vascular myometrium and hence stand out well. However, a significant number of tumors are iso- or hypervascular relative to the myometrium, and hence, these tumors are not well delineated on contrast-enhanced imaging. Diffusion is however independent of differences in vascularity and hence can be very useful for detecting myometrial invasion [7]. It has been found to depict tumor foci that are not appreciated on T2 or contrast images in the uterus or even peritoneal spread. It is also very useful when contrast administration is not possible such as in renal failure. As endometrial tumors have high cellularity, they appear bright on diffusion-weighted images, and this can be a useful adjunct to determine the depth of myometrial invasion (Figs. 8.7–8.15).

The only drawback of diffusion-weighted images is reduced anatomic detail and decreased signal intensity. To overcome the morphologic deterioration of diffusion-weighted images, fusion of the T2-weighted images with diffusion-weighted images has been performed to assess for myometrial invasion [8].

Diffusion-Weighted Imaging of Nodal Disease

Both benign and malignant nodes appear bright on diffusion with low ADC values. Necrotic areas in nodes can be misleading. Comparison of the signal intensity of the primary tumor with the nodes can be helpful. Diffusion-weighted imaging can be used for node mapping, especially in patients with ascites or paucity of intra-abdominal fat.

Lymph Node Disease

MRI and CT both rely on size criteria, both having a comparable accuracy in detecting lymph nodal metastases, 83–90 % for CT and 86–90 % for MRI [6]. Relying on size criteria results in a low sensitivity (43–73 % for MRI) as metastasis in normal-sized nodes is not detected.

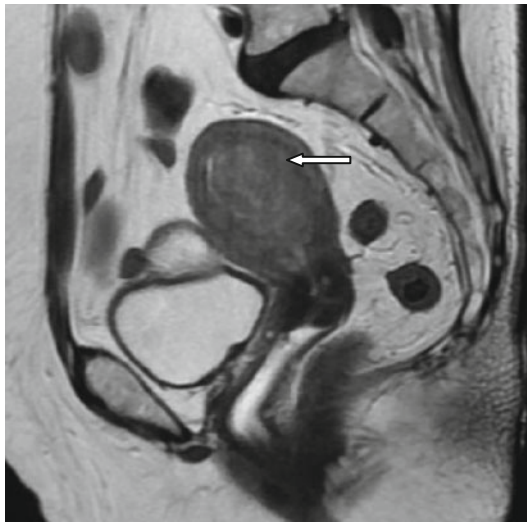

Fig. 8.7 83-year-old lady with history of postmenopausal bleed; T2 sagittal MRI showing mass filling the endometrial cavity (*straight arrow*). Poor tumor to myometrial differentiation is noted, making accurate assessment of myometrial infiltration difficult

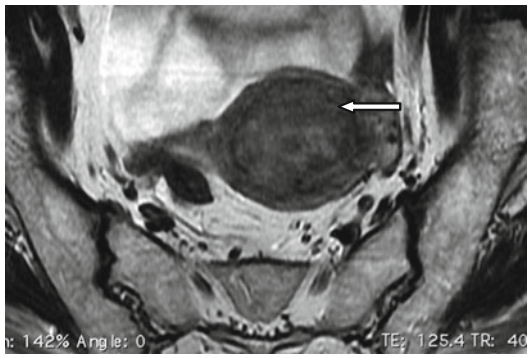

Fig. 8.8 Axial T2 weighted image with history of postmenopausal bleed; T2 axial MRI showing mass filling the endometrial cavity (*straight arrow*). Poor tumor to myometrial differentiation is noted, making accurate assessment of myometrial infiltration difficult

The use of lymph node-specific MRI contrast agents such as ultrasmall super-paramagnetic iron oxide (USPIO) particles has been shown to improve the sensitivity and specificity of detection [9]. Rockall et al. [9] showed an increase in sensitivity from 29 % to 93 % when using USPIO on a node to node basis and an increase from 27 % to 100 % on a patient to patient basis.

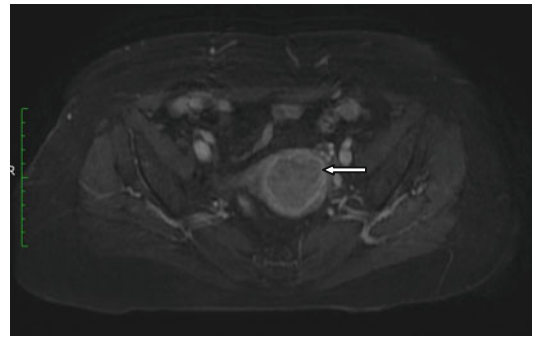

Fig. 8.9 Post-contrast axial T1-weighted fat-suppressed image showing mass in the endometrial cavity surrounded by intact early and brightly enhancing junctional zone (*straight arrow)*; early contrast phase allowing easy distinction of the endometrial mass from the junctional zone

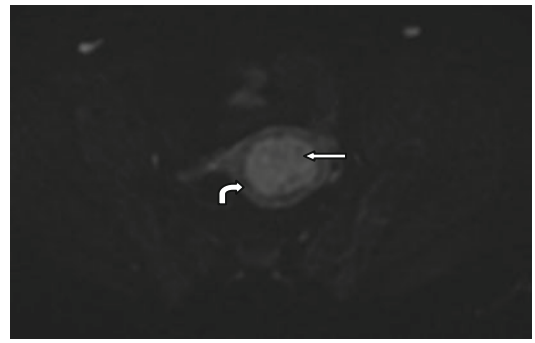

Fig. 8.10 Diffusion-weighted image showing restricted diffusion (bright signal) in the endometrial mass confined to the endometrial cavity (*straight arrow)*. Low-signal intact junctional zone (*curved arrow*) clearly depicted surrounding the mass with no extension of mass into the myometrium

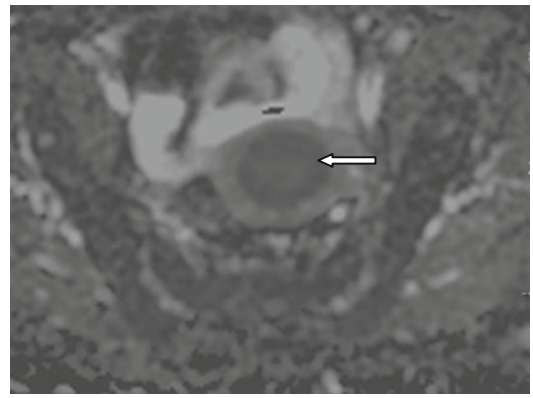

Fig. 8.11 ADC map at the same level showing low signal in the corresponding region (*straight arrow*), confirming restricted diffusion

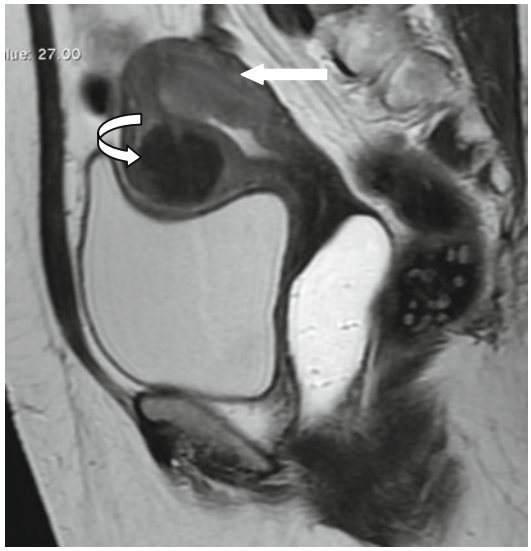

Fig. 8.12 63-year-old lady with postmenopausal bleed, T2 sagittal and axial MRI showing mass in the endometrial cavity infiltrating the myometrium (*straight arrow*). An anterior wall fibroid is also noted (*curved arrow*)

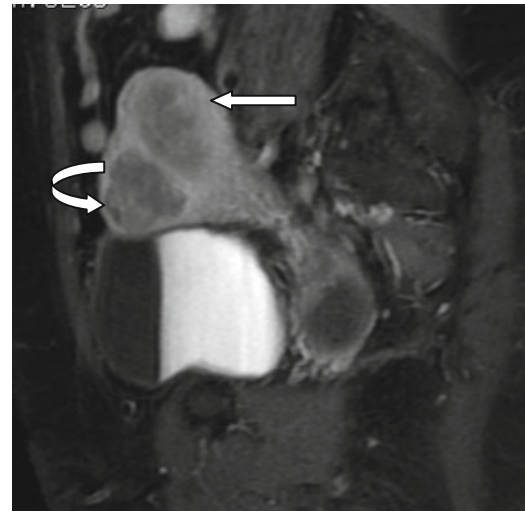

Fig. 8.14 63-year-old lady with postmenopausal bleed, T1 sagittal and axial MRI showing mass in the endometrial cavity infiltrating the myometrium, more than 50 % thickness (*straight arrow*). An anterior wall fibroid (*curved arrow*) is also noted

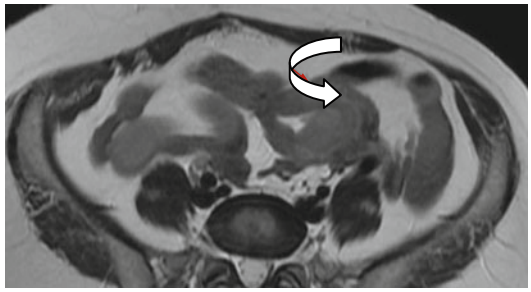

Fig. 8.13 63-year-old lady with postmenopausal bleed, T2 sagittal and axial MRI showing mass in the endometrial cavity infiltrating the myometrium (*curved arrow*)

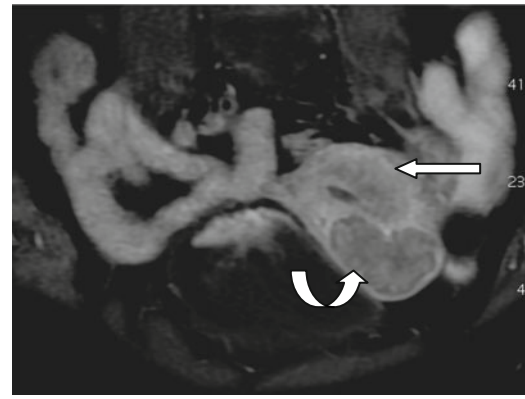

Fig. 8.15 63-year-old lady with postmenopausal bleed, T1 sagittal and axial MRI showing mass in the endometrial cavity infiltrating the myometrium, more than 50 % thickness (*straight arrow*). An anterior wall fibroid (*curved arrow*) is also noted

Recurrent Disease

Most recurrence occurs within 2 years of therapy, and the most common sites include the vaginal vault. Other sites include the perirectal fascia, pelvic and retroperitoneal lymph node, and the pelvic side wall. Distant metastases such as liver, bone, and peritoneal metastases are also seen.

Vaginal vault recurrence after surgery is indicated by the loss of the low-signal intensity linear configuration and replacement by a high-signal intensity soft tissue mass, similar in signal to the initial primary tumor. When a patient has had radiation, distinguishing between recurrent disease and postradiation changes is critical. Recurrent disease appears as a heterogeneous soft tissue mass of similar signal to the initial tumor, while fibrosis has a low T2 signal [6].

Note is made, soon after radiation, due to inflammation and edema in the adjacent soft tissues; parametrial invasion can be overestimated due to edema showing high T2 signal similar to the primary tumor [2].

Delayed enhancement is not specific and can be seen in recurrent tumors/postradiation fibrosis/inflammation/radiation necrosis.

On dynamic contrast scans, however, recurrent mass shows earlier enhancement than fibrosis (maximum enhancement at around 45–90 s). Contrast scans are also helpful in assessing parametrial and side wall recurrence.

When not clear, serial imaging, imaging-guided biopsy, or PET may be required for clarification.

Sarcomas of the Uterus

These are rare and account for 3–5 % of all uterine cancers. MRI can provide information about their size and extent preoperatively. Uterine sarcomas are broadly divided into three groups: smooth muscle tumors, endometrial stromal tumors, and tumors with both smooth and epithelial components. The primary modality for imaging the uterus is MRI in view of its ability to demonstrate local spread well. CT is however commonly used for staging, assessment of metastases, and follow-up.

1. Carcinosarcomas are the most common uterine sarcomas. They generally appear as large broad-based bulky masses replacing the endometrial cavity and can prolapse through the endocervical canal. They may have a stalk-based attachment or multifocality. Hemorrhage and necrosis are prominent features. Though they can spread hematogenously, local lymphatic spread and intraperitoneal seedling are more common. These tumors are staged using the same FIGO staging as for endometrial carcinoma.
2. Leiomyosarcomas may arise de novo from the uterine musculature or connective tissue of a blood vessel or in a previously existing leiomyoma. They usually present as massive uterine enlargement with extensive necrosis and hemorrhage. Spread occurs to the myometrium, lymph nodes, and contiguous pelvic structures and distantly to the lungs. An irregular margin has been suggested as a finding to suggest sarcomatous transformation of a leiomyoma, but the specificity of this finding has not been proven yet [10].
3. Low-grade endometrial stromal sarcomas tend to invade the myometrium and adjacent structures. They can have a variable appearance appearing as a polypoid endometrial mass to a myometrial mass mimicking a leiomyoma with cystic degeneration. A high-grade endometrial sarcoma has a more aggressive appearance with infiltration of the myometrium in a destructive manner and areas of hemorrhage and necrosis. On MRI, they often appear as a large polypoid markedly heterogeneous mass showing contiguous extension into adjacent structures because of marked vascular and lymphatic involvement of the tumor [10].

Conclusion

MRI is superior to CT in the staging of uterine malignancies, in particular with regard to endometrial carcinoma. In addition, it may aid in differentiating radiation fibrosis from recurrent tumor. MRI has been shown to be a "one-stop shop" minimizing the costs in some clinical settings and obviating the need for more expensive invasive diagnostic tests or surgical procedures.

Key Points

1. Depth of myometrial invasion is the most important morphologic prognostic factor that can only be evaluated with MRI. MRI is the only modality which demonstrates the zonal anatomy of the uterus.

2. One of the important changes in the FIGO staging system (2009) is the clubbing of tumors confined to the endometrium (previous Stage 1A) and those involving the inner half of the myometrium (previous Stage 1B); both now come under Stage 1A. This improves the accuracy of MRI.
3. The depth of myometrial penetration with extension beyond/breach of the junctional zone is well seen on the high-resolution T2 images in the sagittal plane and most importantly in the axial oblique plane which is obtained perpendicular to the endometrial cavity.
4. Differential enhancement of the tumor allows the tumor to be distinguished from non-enhancing blood products/debris. Different zones of the uterus enhance at different times, and this is helpful to assess for depth of myometrial invasion in endometrial carcinoma.
5. As endometrial tumors have high cellularity, they appear bright on diffusion-weighted images, and this can be a useful adjunct to determine depth of myometrial invasion.

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Part II

Pathology of Uterine Cancers

Steroid Receptors in Normal Endometrium and in Endometrial Cancer

9

Neelam Wadhwa

Introduction

The endometrium, composed of endometrial glands and stroma with its subjacent myometrium, constitutes a dynamic functional unit. From monthly preparation in anticipation of implantation to pregnancy, sex steroid hormones, especially estrogen and progesterone, have an integral role in endometrial physiology. Endogenous estrogenic hormones include estrone (E1), estradiol (E2), and estriol (E3). E2 is the most potent estrogen in premenopausal women, ovaries being the main site of production. In postmenopausal state, E1 derived from adipocytic conversion of adrenal dehydroepiandrosterone predominates [1]. Hence, study of estrogen receptor (ER) and progesterone receptor (PR) is essential for appreciating their role in healthy endometrial biology and its carcinogenesis. Recent discovery of new ER types and PR isoforms is expected to add to our current understanding of their role in endometrial function and carcinoma.

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Role of Estrogen in Endometrial Carcinogenesis

Endometrial carcinoma is the most common malignancy of the female genital tract in developed countries [2]. Even in developing nations including India, its incidence is said to be increasing [3]. Traditional risk factors of endometrial carcinoma include those associated with chronic hyperestrogenic states, anovulation, and obesity. Early menarche, late menopause, nulliparity, and low parity prolong estrogen exposure duration [2, 4]. Chronic hyperestrogenism coupled with lack of progesterone as occurs in chronic anovulatory states like polycystic ovarian syndrome (PCOS) and estrogen-only hormone replacement therapy (without progestational agents, as was common earlier) also predisposes to endometrial carcinoma [5, 6]. In a longitudinal study of Swedish women, the odds ratio of developing endometrial cancer after 5 or more years of estradiol or conjugated estrogens was found to be 6.2 and 6.6, respectively, as against 1.6 of using estrogen-progestin combination [5]. Patients of PCOS are three times more likely to develop endometrial carcinoma compared with women without the condition [6]. Excess body weight (body mass index >25 kg/m^2) with or without association with PCOS too increases the relative risk of endometrial cancer by at least 1.6 times, primarily by increased adipocytic conversion of circulating androgens to estrogens [2–4, 7].

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Types of Sex Steroid Receptors

Nuclear Sex Steroid Receptors

The conventional ER and PR are members of nuclear receptor family, others being receptors for androgen, glucocorticoid, vitamin D, thyroxine, etc. [8, 9]. In general, the unbound receptor monomer resides in the cell cytoplasm; upon ligand binding, it dimerizes and translocates to the nucleus. The ligand-receptor dimer complex attaches to specific sequences of DNA (hormone response element), in association with transcriptional cofactors (activators or repressors) in the promoter region upstream of target genes. The eventual outcome is modulation of gene expression. The target genes of ER include proto-oncogenes like c-myc, n-myc, c-jun, etc. Most literature on ER expression in human tissues including the endometrium is on this type of ER [10–12]. In 1996, another ER type was isolated from rat prostatic epithelium [13]. It was found to be encoded by ESR2 gene on chromosome 14q23-24.1, unlike the earlier known receptor whose gene, ESR1, was known to be located on chromosome 6q25.1. The new ER was called ER beta (β), and the earlier known ER was redesignated as ER alpha (α). Not only is the systemic distribution of ERβ distinct from ERα, their cellular localization in a given tissue and biologic effects are also at variance from each other [14, 15]. Gene expression profiling studies following activation of ER have identified a vast number of target molecules like growth factors, cell adhesion molecules, and cell cycle regulators, some with differential results between ERα and ERβ [16, 17]. Both types of ER have several functional domains (named A to F). While their structural homology at the DNA binding site (C domain) is more than 90 %, they share only 55 % and 20 % of their structure at the ligand binding domain (E domain) and domains A and B, site for other protein interactions, respectively. Although both ER types bind to E2 and antiestrogens like tamoxifen with comparable affinity, they have differential role in endometrial function. The differences in their functional outcomes could be attributed to significant differences between their amino acid sequences at domains A, B, and F where protein-protein interactions take place, variable posttranslational modifications, and variable dimer formation (α-α, β-β homodimer or α-β heterodimer). The detailed downstream effects of ERβ are still undetermined [16, 17]. PR too occurs in two isoforms, PRA and PRB. Both isoforms are products of PR gene located on chromosome 11, unlike ER types which are products of different genes. They differ in their polypeptide length owing to differential promoter sites, PRB having a 165-amino acid longer domain A and being heavier by 30 kDa than PRA [18–20]. Both isoforms of PR are expressed in the human endometrium. While PRB isoform has stronger transcriptional activity than PRA, the latter exerts direct dominant negative effect on ER function [13, 14]. Most published work on PR is actually on PRA isoform as early antibodies did not recognize PRB.

Sex Steroid Receptors Outside the Nucleus

The concept of sex steroid receptors having exclusively nuclear transcriptional modulatory action, as mentioned above, has been challenged for long [21]. Experimental work has shown estrogen to be capable of mediating cellular responses like vasodilation and regulate blood pressure and insulin signaling in periods as short as few minutes. These rapid cellular events involve activation of intracellular kinases and second messengers like Ca+ [2] ions and cAMP within seconds or minutes of estrogen exposure [22]. Modulating gene transcription requires a minimum of few hours and effects may last for up to a few days. This implies nongenomic (pregenomic) estrogen action mechanisms. Moreover, these outcomes have been shown to be unaffected by transcriptional inhibitors. While the genomic mechanism of action of sex steroid receptors is most widely studied, nongenomic mechanisms are the current area of research.

At least two types of non-nuclear ER are known. A new type of ER has been localized to cytosolic fraction, in the endoplasmic reticulum and to some extent on the plasma membrane, in association with organelle membrane G protein.

It is said to be structurally different from the mERα and named as G protein-coupled ER (GPER) [23–25]. Nuclear ERα and GPER have differing binding affinities toward various estrogenic substances. Its affinity for estrogen is said to be ten times that of nuclear ER [26]. Its expression is regulated by progesterone. Among its major actions, GPER controls epidermal growth factor receptor activation and Ras protein phosphorylation [23–25]. By cell fractional techniques, classic ERα, similar to nuclear ERα, has been isolated from the cell membrane fraction as well. Subsequent to membrane receptor internalization, dimerization occurs akin to nuclear ERα. The mERα forms a complex with various cell signaling proteins leading to the formation of signalosome, leading to immediate cellular events independent of nuclear transcription. Further details of mERα are still unresolved [27]. Other recently discovered new types of membrane ER include ERα-36, a truncated form of ERα, and ER-X [28, 29]. Functional cross talk between GPER, nuclear ER, and mERs is expected although the details are not known yet [23].

Sex Steroid Receptor Expression in Healthy Endometrium

All sex steroid receptors show rhythmic changes in their expression status during a healthy menstrual cycle.

ERα

In the proliferative phase of the menstrual cycle, ERα is expressed on both endometrial glands and stroma of the stratum functionalis. The expression of ERα (as measured by staining intensity, percentage of cells, or a combinational score) is higher in glandular cells than stromal cells. ERα expression increases steadily reaching its peak in preovulatory period, wherein almost all endometrial cells show strong nuclear reactivity. This increase occurs in response to ovarian estrogen production. After ovulation, both glandular and stromal cells show downregulated ERα expression, but the fall is discordant. The decline in ERα expression is gradual in glandular cells, but rather abrupt in stromal cells. The declining trend continues unabated in the glandular compartment to negligible expression in the late secretory phase, which is even lower than the expression during menstruation. On the other hand, stromal cells after their nadir in the early secretory phase show a gradual increment in ERα expression in mid- to late secretory phase. Pre-decidualized stromal cells are known to express ERα in small amounts, albeit at lower levels than those during active bleeding [11, 12, 30–37].

ERα expression in the stratum basalis is as high as the stratum functionalis of the proliferative phase and remains unaltered throughout the menstrual cycle [11]. The sub-endometrial myometrium too expresses ERα; the expression and trends parallel those of the functional endometrium. The bulk of myometrium shows high ERα expression through all phases of the menstrual cycle, without any cyclic change [12]. Postmenopausal women with atrophic endometrium continue to express ERα, levels of which are comparable to those in the late proliferative phase of young women [11]. This implies that ERα expression in the endometrium and to some extent in the myometrium is constitutive; the decline as observed in postovulatory state is induced by rising levels of progesterone secreted by the corpus luteum. This simplistic view is however put to test by results of an interesting study on postmenopausal women on hormone replacement therapy [38]. The authors failed to find a decline in ERα expression in women with breakthrough bleeding. They suggested that the mechanisms underlying bleeding in these patients were different from the physiologic ones operative in the reproductive period.

ERβ

ERβ, the recently discovered another ER, has differential endometrial expression than ERα [14, 36, 37]. Its absolute quantity is also much lower than ERα. Its expression is more intense in the proliferative than secretory phase. However, its peak occurs in the peri-ovulatory period, i.e., days 14–15 lasting for a very short while. Thus, there is

a brief period just prior to the ovulation, when both endometrial glandular ERα and ERβ expressions are at their peak. Besides the minimal temporal lag between ERα and ERβ, spatial expression of ERβ also differs from ERα. While ERα glandular expression is independent of topology, ERβ shows gradual decrease in staining intensity from epithelial cells near the lumen to near total absence in deeper glands. The endometrial stromal cell ERβ expression peaks in the late secretory phase, between days 25 and 27 of the menstrual cycle. The increase is more prominent in stromal cells in perivascular location. Thus, in the late secretory phase, glandular cells of the stratum functionalis have hardly any expression of ERβ, while the expression in stromal cells is maximum. The variance between endometrial stromal ERα and ERβ expression especially in the secretory phase suggests ERβ as probably having a role antagonistic to ERα or modulating the expression of the latter. One significant observation is the presence of ERβ in endothelial cells of endometrial blood vessels, including spiral arterioles [36, 37]. The receptor has also been found in smooth muscle fibers of spiral arterioles. Experimental work on endometrial endothelial cells has confirmed the role of ERβ in vascular biology [39]. This observation has clinical relevance. It is possible that endometrial vascular ERβ expression underlies the beneficial effect of some estrogenic compounds in cases of abnormal uterine bleeding. ERβ is also expressed in the stratum basalis; its expression does not differ between pre- and postovulatory phases.

GPER

Being a relatively new receptor, literature of endometrial GPER expression is limited. A cyclic change in GPER mRNA expression has been reported by few authors [40, 41]. Maximum gene expression was detected in the proliferative phase with a decline in the secretory phase. This pattern is similar to that of ERα expression but different from ERβ. In the proliferative phase, the glandular cells have both apical and basal staining, which became limited to basal regions in the secretory phase. The stromal GPER expression was diffuse and did not differ significantly between the proliferative and secretory phase. The GPER receptor was not detected in blood vessels or myometrium [40].

PR and Its Isoforms

PR exists in two isoforms, PRA and PRB, which are products of the variable promoter region of the same gene. These isoforms differ in their structure, transcriptional efficiency, and potential for modulation of ER-mediated cellular events. Relative levels of both determine nature and magnitude of cellular response to progesterone [19, 20]. Earlier studies on endometrial PR expression used antibodies with higher affinity toward PRA isoform [11, 12, 35]. As a whole, PR levels continue to rise in endometrial glandular cells from day 1 of the menstrual cycle. The peak expression is reached in the early secretory phase, following which there is a sudden fall in the mid-secretory phase and negligible receptor amount in the premenstrual period. Both PRA and PRB isoforms are expressed simultaneously and in comparable amounts in the proliferative phase. By the mid-secretory phase, only PRB persists in the glandular cells [18, 42]. By confocal microscopy, the nuclear distribution of PR has been shown to change with progression of the menstrual cycle from even to focal, the change being related to rising progesterone levels [43]. In contrast to the dramatic fold changes in PR glandular expression, changes in stromal PR levels in the menstrual cycle are insignificant [11, 12, 35]. PRA is the predominant stromal receptor isoform [18, 42]. These observations suggest that there is biologic segregation of PRB and PRA functions in endometrial glands and stroma, respectively. PR expression is also documented in endothelial cells and vessel wall smooth muscle fibers [36, 44]. PR expression in the stratum basalis shows similar trends as the functional layer, albeit with smaller range of change. Atrophic endometrial PR expression is pronounced similar to ER expression [11, 12]. Presence of PR on endometrial stem cell has been confirmed by clonal culture techniques [45].

Other Steroid Receptors: Androgen Receptor (AR), Glucocorticoid Receptor (GR)

Endometrial expression of receptors for androgens and glucocorticoids has also been studied. The hormone interconversion, especially between estrogens and androgenic hormones, suggests a possible role of AR in the cyclic changes of healthy endometrium. Endometrial AR expression changes are cyclical, similar to ER [46–49]. In the proliferative phase of the menstrual cycle, AR is expressed predominantly in the stromal cells; epithelial receptor expression is minimal. This fact is corroborated by upregulation of stromal AR following exogenous estrogen exposure [50]. Androgens acting via AR have been shown to induce prolactin, a marker for endometrial differentiation [51]. The receptor levels decline with progression of the menstrual cycle; in the late secretory phase, the receptor is no longer detected in both cell types. Administration of antiprogestational drugs results in expression and enhancement of AR in endometrial glandular and stromal components, respectively [47]. Endometrial GR expression differs strikingly from other steroid receptors. It is completely absent from glandular epithelial cells. Stromal GR expression is strong throughout the menstrual cycle, with only slight decrease in the secretory phase. Endothelial cells too express GR [52]. Despite these results, the exact role of AR and GR remains incompletely understood in endometrial physiology.

Sex Steroid Receptors in Endometrial Carcinoma: Expression Status and Clinical Implications

Endometrial carcinogenesis is considered dualistic [53]. Type 1 carcinomas outnumber type 2. The former (endometrioid type) arise often in premenopausal, obese women with evidences of hyperestrogenism. These patients typically have preceding endometrial hyperplasia progressing to atypia. The tumors are likely to be low grade and low stage with preserved hormonal responsiveness. Type 2 carcinomas occur in postmenopausal ladies without hyperestrogenic association. The lesions are aggressive, have high-grade morphology, and present at advanced stage.

Receptor Levels in Type 1 and Type 2 Endometrial Carcinomas

Type 1 endometrial carcinomas due to their preceding estrogenic stimulatory conditions are significantly (and expectedly) more likely to express both ER and PR (average 70 %) than type 2 carcinomas (average 20 %) [54]. Carcangiu et al. too noted declining expression levels from endometrioid type to clear cell type through adenosquamous and serous type [55]. The expression of sex steroid receptors as detailed below refers to type 1 endometrial carcinomas, unless specified otherwise.

Receptor Levels in Type 1 Endometrial Carcinoma Compared to Healthy Endometrium

The expression of ER in endometrial glands shows progressive decrease from proliferative endometrium to invasive carcinoma; endometrial hyperplasia shows intermediate levels. While the declining trend is noted universally, only few authors have found the difference between groups to be significant [30, 31, 33]. Another observation is loss of ER staining with appearance of nuclear atypia in the setting of endometrial hyperplasia [31].

Similar to ER total, ERα shows decreasing expression trend from proliferative endometrium to hyperplasia without atypia, atypical hyperplasia, and invasive carcinoma. The reduction in ERα level in carcinoma compared to proliferative endometrium has been found to be consistently significant by several authors [34, 35]. Bircan et al. noted almost all cells (96 %) in proliferative endometrium to be positive for ERα; in endometrial carcinoma, only 31.6 % of cells expressed the protein [34]. However, intra-spectrum comparative studies between proliferative endometrium and hyperplasia without atypia, simple and complex hyperplasia

without atypia and atypical hyperplasia, and atypical hyperplasia and invasive carcinoma have shown variable results, few reporting significant differences and others showing a trend toward reduced protein levels with advancing lesion, but insufficient to achieve statistical significance [34, 56, 57]. It may hence be concluded that loss of ERα is associated with progressive malignant potential of the lesion. Grade II tumors have lower protein content compared to grade I cancers [35].

With increasing severity of lesions from proliferative endometrium to invasive carcinoma, there is significant loss of ERβ expression [35, 56, 57]. While most authors have recorded this trend across groups, Cai et al. demonstrated the reduction in ERβ content in atypical hyperplasia and carcinoma compared to adjacent uninvolved endometrial areas [56]. It is noteworthy that although both ERα and ERβ types are reduced in endometrial carcinoma compared to proliferative endometrium, the decline is more marked for ERα. This results in reversal of ERα/ERβ ratio from >1 in proliferative endometrium to <1 in endometrial carcinoma [35, 57, 58]. In fact, several authors have suggested that it is the reversal of ERα/ERβ ratio which determines the neoplastic progression rather than absolute values themselves. It should also be highlighted that ERβ-expressing tumors almost invariably express ERα, but the reverse is less likely to be true [59].

Total PR expression and its isoforms PRA and PRB expression, all are reduced in endometrial carcinomas compared to healthy endometrium [35, 60]. Arnett-Mansfield et al. demonstrated the difference between PRA and PRB between invasive carcinoma, normal endometrium, and areas of complex hyperplasia within same patient samples to be significant [60]. Mylonas et al. however did not find PR difference between healthy endometrium and endometrial carcinoma to be significant [35]. Unlike healthy endometrium, in which PRA and PRB isoforms are co-expressed and often co-localize within the same cell, endometrial carcinomas often express only one receptor isoform. The intranuclear pattern of reactivity too differs between healthy endometrium and endometrial carcinomas [43]. GPER is expressed in endometrial carcinoma but in reduced amounts compared to healthy endometrium; up to sixfold reduction has been described [61]. Up to 40 % of endometrial carcinomas express AR [49]. Staining is observed in malignant epithelial cells; this is unlike the healthy endometrium wherein glandular AR expression is minimal. The exact significance of this observation is not known, but is likely to be low as androgens do not play a central role in endometrial functioning.

Receptor Expression in Type 1 Endometrial Carcinoma: Correlation with Clinicopathological Factors

High/positive ER expression in invasive endometrial carcinoma correlates with the degree of tumor differentiation [54, 55, 62–64]. Carcangiu et al. demonstrated significant correlation between ER-positive status and low FIGO grade and low nuclear grade ($p<0.001$ and 0.0001, respectively) [55]. ER-positive tumors are more likely to be well differentiated than poorly differentiated. Conversely, poorly differentiated tumors are unlikely to express ER. Kounelis et al. found all endometrioid carcinomas to be ER (and PR) positive [54]. McCarty et al. found 85 % of well-differentiated tumors to be ER positive, while only 13 % of poorly differentiated tumors had detectable protein level [64].

ER expression in endometrial carcinoma also shows significant positive correlation with low tumor stage ($p \leq 0.026$–0.001) [54, 55, 62, 65, 66]. Chambers et al. found that early stage tumors were more likely to be ER positive. They pointed out that tumor grade was a co-variable in their study, the effect of which could not be excluded [62]. Deeply invasive cancers are less likely to be ER positive [65]. ER expression correlation with other evidences of tumors' aggressive nature has been variable. Geisinger et al. reported inverse correlation between ER positivity and lymphovascular invasion. More than 80 % of their tumors lacking lymphovascular invasion were ER expressing, while majority of tumors with such invasion were receptor negative [67]. However, Iwai et al. found no correlation between ER expression and lymph node metastases [68].

Expression of ERα and ERβ in endometrial carcinoma has been correlated with tumor grade and stage by various authors [34, 35, 56–59, 69, 70]. Jongen et al. found significant correlation between preserved ERα expression and early tumor stage ($p<0.02$) [70]. High-stage cancers have significantly lower ERα content than early stage tumors ($p<0.002$) [56]. Significant correlation between ERα expression and histologic grade too has been described in several publications. ERα-expressing tumors are significantly more likely to be of low grade [69, 70]. However, Bircan et al. did not find significant correlation between ERα expression status and any clinicopathological feature [34]. Mylonas said that loss of ERβ was associated with myometrial invasion; however, results of Jongen et al. did not find such correlation [35, 70]. Hu et al. too did not find any prognostic implication of either ERα or ERβ expression [57].

PR immunostaining like ER expression has been found to correlate significantly with well-differentiated tumor histology ($p=0.026$–0.003) [54, 62, 63, 66, 71]. With tumor dedifferentiation, there is loss of PR. Positive association between PR and early tumor stage is also widely reported [59, 65, 66]. Deeply invasive tumors (> half of the myometrium) are likely to have undetectable PR levels ($p=0.006$). However, Chambers et al. did not find correlation between PR status and disease stage to be significant [62]. PR negativity has been found to be significantly associated with lymphovascular invasion and lymph node metastases [55, 67, 68]. Upon multivariate analysis, Iwai et al. found negative PR to be a significant prognostic variable for lymph node metastases, independent of other clinicopathological parameters [68]. Most endometrial carcinomas express predominantly only one PR isoform; however, dual expression is described in low-grade tumors. With increasing tumor grade, there is loss of either isoform. Arnett-Mansfield et al. found no difference between PRA and PRB frequency within the carcinoma group (30 % versus 28 %) [60]. In vivo GPER expression in endometrial carcinoma has been studied only recently. GPER expression has been reported to occur more frequently in high-grade, aggressive histologic type, advanced-stage, and PR-negative endometrial cancers [72].

Receptor Expression in Type 1 Endometrial Carcinoma as a Prognostic Factor

Many authors have found significant correlation between ER expression and final patient outcome [62, 66, 73–76]. Pertschuk et al. concluded that their ER-negative endometrial carcinoma patients were almost four times more likely to die of the disease than those who expressed the receptor [74]. In several studies, ER-positive cases have had significantly longer disease-free survival than ER-negative patients [62, 73, 74, 76]. However, others found the difference between the groups to be insignificant [66, 77].

ER is considered to be a favorable feature by almost all researchers, although literature on its role as an independent prognostic factor in endometrial carcinoma is still not clear. Using multivariate and multi-regression analysis, many authors have suggested it to be so [73, 76]. However, others did not conclude the same [62, 66]. Tornos et al. compared ER and PR expression status between two sets of patients with stage I and grade I endometrial carcinoma – those who died within 4 years and those who survived beyond 10 years. ER expression did not differ significantly between groups [77]. Fanning et al. found tumor stage and grade but not ER expression as a predictor of recurrence in high-risk endometrial carcinoma [78]. Loss of ERα in endometrial carcinoma has been reported to be associated with poor survival [69]. Absence of ERα was found to be an independent factor associated with death due to disease (odds ratio = 7.28) by Jongen et al., but not by Shabani et al. [69, 70]. Loss of ERβ has not been found to have any effect on survival figures [69].

Positive PR status is also known to be a significant prognostic factor for disease-free survival (DFS) ($p=0.0025$–0.001) [66, 76, 77]. Its performance as a predictor of DFS ($p<0.001$) is independent of other clinicopathological factors and exceeds that of ER-positive status ($p<0.01$) [76]. Tornos et al. found the absence of PR to be one of the four statistically significant adverse prognostic factors in stage I grade I adenocarcinoma, others being myometrial invasion, vascular invasion, and high mitoses. Patients who died within 4 years

of diagnosis were significantly more likely to have absent PR than those who survived >10 years [77]. PR-positive status confers better chances of overall survival too. These patients live significantly longer than PR-negative patients [62, 67]. Positive PR status identifies advanced carcinoma patients for progestin therapy. Reported response rates in PR-positive cases (82–91 %) are significantly better than those of PR-negative patients (11 %) [79, 80]. Ehrlich et al. have reported 94 % of their nonresponders to be PR poor [71]. However, in high-risk endometrial carcinoma (those with high stage and poor differentiation), PR positivity may not protect against tumor recurrence [78]. PRA loss has been found to be an independent prognostic factor for disease relapse [70]. Although loss of both PRA and PRB has been associated with poor survival, loss of PRB isoform only achieved independent adverse prognostic factor status for cause-specific survival [70]. It has also been suggested that negative PRB immunostaining result may help in identifying potentially worse-outcome patients for more aggressive adjuvant therapy.

Significantly poor survival has been reported in GPER-expressing cancers by Smith et al. [72]. In endometrial cell lines with downregulated GPER levels, exposure to exogenous estrogen has been found to induce GPER expression [41, 81]. Significantly upon progesterone transfection of the same cell line, the increment failed to occur [41]. This may probably explain the mechanism of action of non-ovarian-origin circulating estrogens on endometrial cancers including ER-negative ones in postmenopausal women and beneficial effects of progestins in endometrial cancers. Skrzypczak et al. found G-1, a compound, to have significant downregulatory effect on GPER expression in endometrial cancer cell lines, implying a potential therapeutic target [61].

Conclusions

The dynamic interplay of sex steroid hormones is evident in healthy endometrial biology. The discovery of novel sex steroid receptor types including those at extranuclear sites has renewed interest in endometrial physiology and carcinogenesis. Recently described ERs include ERβ, G protein-coupled ER, and cell membrane ERα. PRB is a relatively recently discovered isoform of PR. ERβ differs from ERα in its cyclic variation during menstrual cycle, lower quantum of expression, topologic distribution, and downstream cellular events. GPER and mERα are implicated in mediating rapid effects of estrogen, which cannot be explained by the conventional roles of nuclear ER as a nuclear transcription factor.

Endometrial cancers express lower levels of sex steroid hormones than proliferative endometrium. The decline in ERβ exceeds ERα leading to reversal of ERα/ERβ ratio. All receptor expressions show positive association with early stage, low-histologic grade, type 1 cancers and better patient outcome in terms of disease-free survival, overall survival, and response to hormone therapy.

Key Points

1. Estrogen is implicated in both endometrial physiology and carcinogenesis.
2. ERβ is a novel nuclear receptor for estrogen. It differs from ERα (the classical ER) in its cyclic variation during menstrual cycle, lower quantum of expression, topologic distribution, and downstream cellular events. Unlike ERα, it is expressed in endothelial cells.
3. Both ERα and ERβ show their peak tissue expression in the late proliferative phase; in healthy endometrium, ERα/ERβ ratio remains >1 throughout the menstrual cycle.
4. Progestational agents induce secretory activity. Healthy endometrium co-expresses PRA and PRB, the two isoforms of progesterone receptor. Maximum tissue expression is seen in the early secretory phase.
5. Type I endometrial carcinomas very often express ERα, ERβ, and PRs, respective expression levels being significantly lower than proliferative

endometrium. Selective ERα loss results in reversal of ERα/ERβ ratio in endometrial cancers. Of PR isoforms, only one type predominates.

6. Tissue expression of these receptors correlates with well-differentiated phenotype, early tumor stage, low proliferation, disease-free survival, and overall survival.
7. ERα and PRB have been reported to be independent predictors of disease-free and overall survival, respectively. Absent PR expression is likely to identify worse-outcome patients for aggressive adjuvant therapy.
8. Recently new ER types (G protein-coupled ER, mERα, and ER-X) on cell and organelle membranes have been discovered. Their role in mediating typical transcriptional effects and rapid cellular events is a current area of research.

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Pathology of Endometrial Hyperplasia and Carcinoma

10

Bharat Rekhi, Kedar K. Deodhar, and Santosh Menon

Introduction

Endometrial cancer forms the fifth most commonly diagnosed cancer in women worldwide and the fourth most commonly diagnosed cancer in the United States [1, 2]. On an average, 154 cases are annually received at Tata Memorial Hospital (TMH), as per TMH Based Cancer Registry (2002–2005) [3]. These tumors occur mostly in postmenopausal women.

Endometrial carcinomas are adenocarcinomas that arise from the lining epithelium of the endometrial cavity. It is vital to understand the various types of hyperplasias before we embark upon detailed histopathology of endometrial cancers.

Endometrial Hyperplasia

According to the International Federation of Gynecology and Obstetrics (FIGO) and World Health Organization (WHO) systems, endometrial hyperplasias are subclassified as (i) simple and (ii) complex types. Both these types are subdivided as typical and atypical [4]. Thus, the four types of endometrial hyperplasias are simple hyperplasia without atypia, complex hyperplasia without atypia, atypical simple hyperplasia, and complex atypical hyperplasia (Table 10.1).

Simple Hyperplasia

Histopathological appearance of simple hyperplasia includes uniformly rounded glands with marked variation in shape, including several cystically dilated forms. The lining epithelium of the glands reveals pseudostratification or multilayering, but lacks nuclear atypia. This may be associated with tubal metaplasia. The stroma is compact (Fig. 10.1). The differential diagnoses include atrophy, wherein glands are lined by flattened epithelium and benign endometrial polyp, in which the glands are covered by a similar benign-appearing hyperplastic epithelium on three surfaces with hyperplastic glands within the stroma that also contains blood vessels (Fig. 10.2). Simple cystic hyperplasia also should be differentiated from proliferative and disordered endometrium, especially the latter wherein endometrial glands are hyperplastic, but without an increase in volume [5]. Chronic endometritis can lead to an overdiagnosis of atypical hyperplasia, especially when inflammatory cells lead to reactive nuclear atypia noted within the glands. The presence of neutrophils on surface and plasma cells within stroma is indicative of chronic endometritis.

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Table 10.1 Histopathological classification of epithelial tumors and related lesions of the uterine corpus

Endometrial hyperplasia
Non-atypical hyperplasia
Simple
Complex
Atypical hyperplasia
Simple
Complex
Papillary hyperplasia
Simple
Complex
Endometrial polyp
Tamoxifen-related lesions
Endometrial carcinoma
(i) Endometrioid adenocarcinoma
Variant with squamous differentiation
Villoglandular variant
Secretory variant
Ciliated variant
(ii) Mucinous adenocarcinoma
(iii) Serous adenocarcinoma
(iv) Clear cell adenocarcinoma
(v) Mixed cell adenocarcinoma
(vi) Squamous cell carcinoma
(vii) Malignant mixed müllerian (mesodermal) tumor (MMMT) (carcinosarcoma)
(viii) Transitional cell carcinoma
(ix) Small cell carcinoma
(x) Undifferentiated carcinoma
(xi) Others

One needs to be careful in such cases, especially while dealing with a biopsy. Clinically, patient history related to intake of hormonal medications and an appraisal of thickness of the endometrium, on imaging, are useful in reinforcing a correct diagnosis in some cases with equivocal histopathological features.

Complex Hyperplasia (Typical and Atypical)

This reveals increase in endometrial glands leading to their fusion and causing a common arch bars between the glands. While lack of atypia is noted in simple and complex hyperplasias without atypia, atypical hyperplasias reveal nuclear and cytoplasmic abnormality in the form of lack of polarity, irregular multilayering, and anisocytosis, accompanied by nuclear enlargement, hyperchromasia, chromatin clumping, and prominent nucleoli [5, 6]. Invariably, atypical hyperplasias are complex, wherein cribriform appearance of glands is noticeable, and in certain such cases, differentiation from grade I endometrioid adenocarcinoma becomes challenging (Fig. 10.3).

Papillary Hyperplasia

These are rather uncommon lesions. Papillary proliferations of the endometrium were initially reported by Lehman and Hart [7], who described nine cases mostly in postmenopausal women,

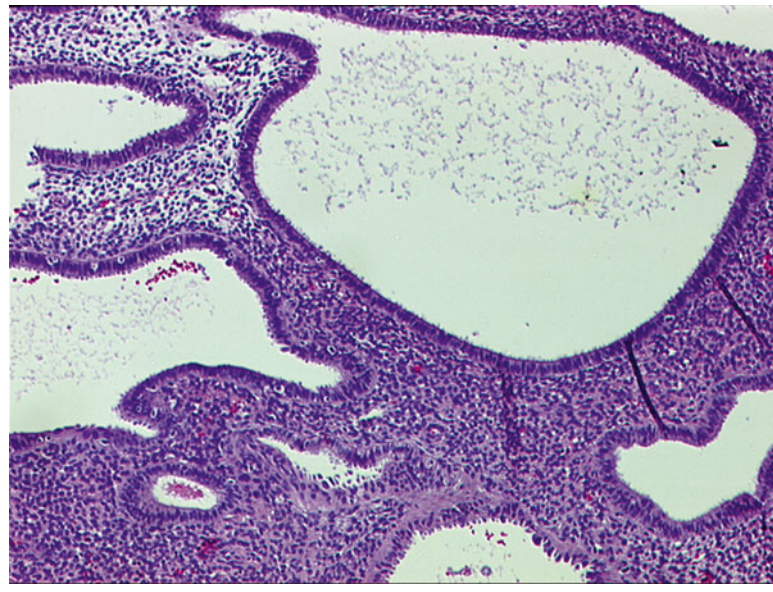

Fig. 10.1 Simple cystic hyperplasia comprising benign-appearing cystically dilated endometrial glands, exhibiting tubal metaplasia (cells with ciliated surface projecting into the lumens) in a compact cellular stroma. Hematoxylin and eosin staining (H&E) ×400

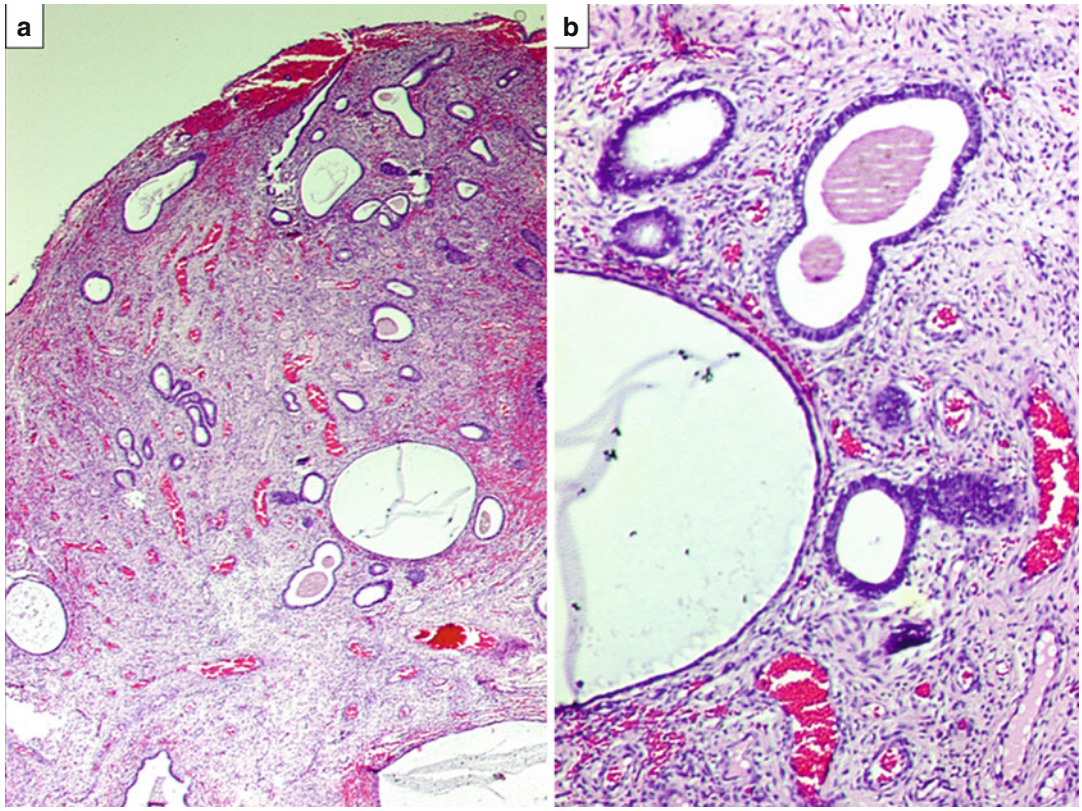

Fig. 10.2 (**a**) Benign endometrial polyp revealing endometrial epithelial lining on three surfaces with variably sized endometrial glands and several blood vessels within stroma. H&E ×40. (**b**) Benign endometrial glands within stroma revealing cystic dilatation with interspersed blood vessels. H&E ×200

who presented with abnormal vaginal bleeding. Invariably these lesions were found to be associated with intake of hormonal medications. Their cases included five of simple papillary proliferations and four of complex papillary proliferations, all associated with metaplastic changes. In another study [8], 59 cases of papillary proliferations of the endometrium without atypia in patients with similar age and symptomatology were analyzed. They classified their study cases as group I lesions (61 %) with localized simple papillae that were further defined as those with short, predominantly non-branching stalks and group II lesions (39 %) comprising complex papillae and/or those with diffuse and crowded intracystic papillae. Complex papillae were defined as those with both short or long stalks and, invariably, secondary and complex branches. These authors [7, 8] concluded that cases with group 2 features were significantly associated with concurrent or subsequent premalignant lesions (non-atypical and atypical hyperplasia) or carcinoma. Furthermore, they suggested that these lesions are analogous to atypical complex hyperplasia, and they termed these as "complex papillary hyperplasia (CPH)" (Fig. 10.4). Recently, a similar case of complex papillary hyperplasia was reported that was initially misdiagnosed as uterine papillary serous carcinoma [9].

Endometrial Adenocarcinoma

Histopathologically, these are classified as villoglandular, secretory, or ciliated cell carcinoma; endometrioid adenocarcinoma with squamous differentiation; and serous, clear cell, mucinous, "pure" squamous cell, mixed, neuroendocrine, or undifferentiated carcinoma. Noteworthy, malignant mixed müllerian tumor (MMMT)/carcinosarcoma is also classified under the rubric of endometrial adenocarcinomas [6].

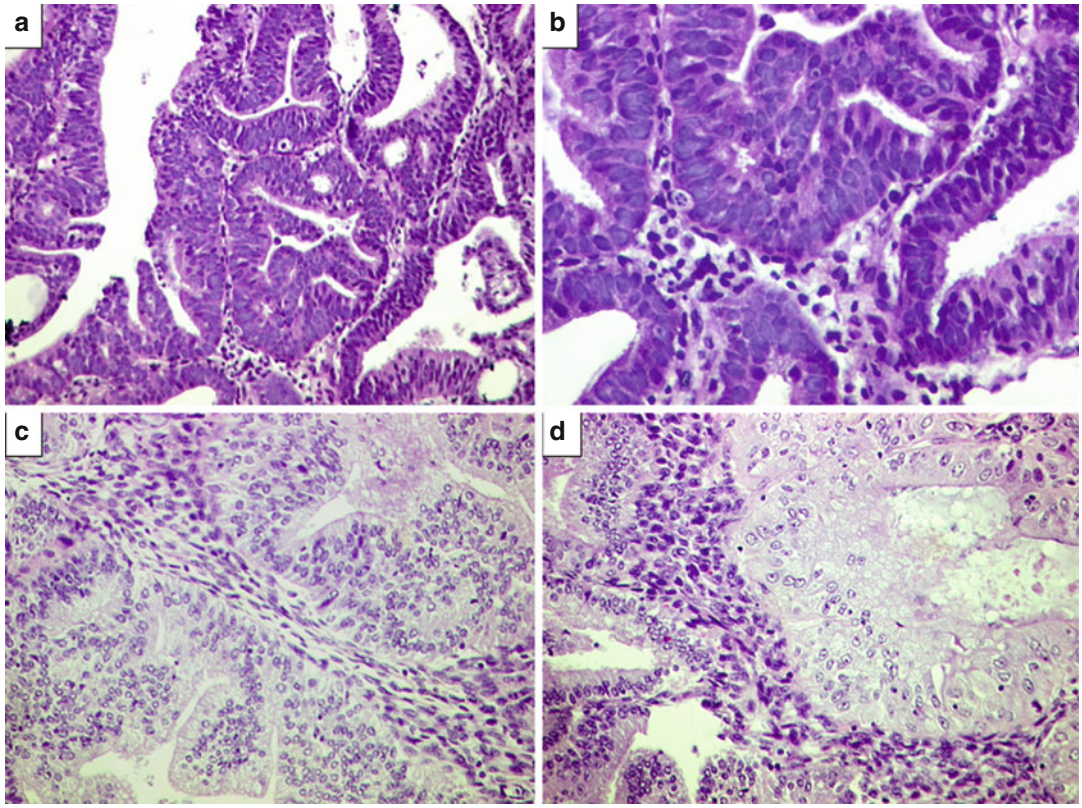

Fig. 10.3 Complex atypical hyperplasia (CAH). (**a**) Atypical endometrial glands exhibiting complex architecture with endometrial stroma between the glands, reported as CAH. H&E ×200. (**b**) The same case at higher magnification revealing complex architecture of glands associated with nuclear atypia. H&E ×400. Diagnosis on hysterectomy was well-differentiated FIGO grade I endometrioid adenocarcinoma. (**c**) Residual CAH reported on hysterectomy specimen in a case wherein curettage specimen revealed well-differentiated FIGO grade I endometrioid adenocarcinoma. Complex architecture of glands with nuclear atypia and conspicuous interglandular stroma. H&E ×200. (**d**) The same case revealing focal eosinophilic metaplasia. H&E ×400

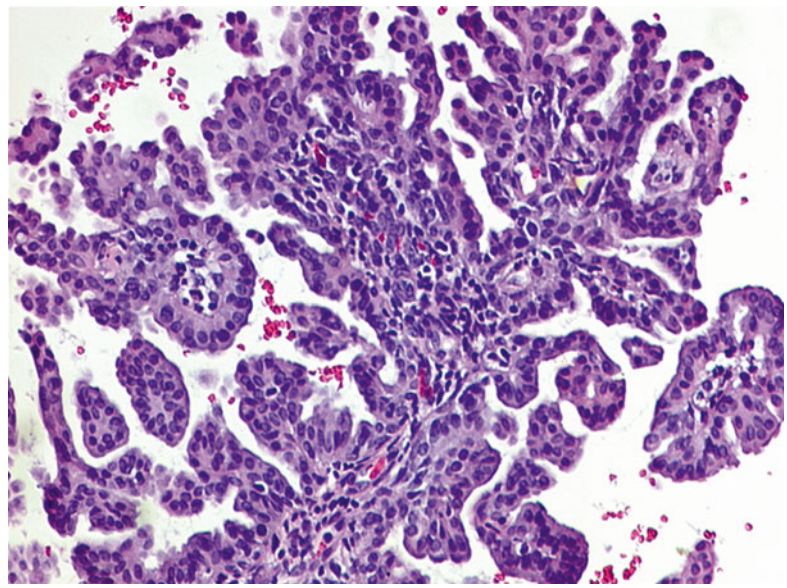

Fig. 10.4 Complex papillary hyperplasia endometrium displaying primary and tertiary ramifications leading to complex papillary formations, lined by "banal" epithelium lacking significant nuclear atypia. H&E ×200

Clinicopathologically, endometrial adenocarcinomas are broadly subclassified as type I and type II adenocarcinomas. Type 1 endometrial adenocarcinomas are generally of low-grade and include secretory, ciliated, and villoglandular variants of an endometrioid adenocarcinoma. These are associated with unopposed estrogen stimulation and arise on a background of hyperplasia.

On the other hand, **type 2** endometrial adenocarcinomas are invariably of high-grade and comprise serous, "pure" squamous, neuroendocrine, undifferentiated, and clear cell types of endometrial adenocarcinomas, along with malignant mixed müllerian tumors (MMMTs)/carcinosarcomas. These, especially serous type, arise on a background of atrophic endometrium and are associated with intraepithelial carcinoma.

The **dualistic classification** also has a molecular basis along with prognostic and therapeutic relevance. Type I cancers are associated with phosphatase and tensin homolog (PTEN) mutation, microsatellite instability, and K-ras mutation, whereas type II adenocarcinomas are associated with p53 mutation. Type I adenocarcinomas are associated with a relatively good prognosis. In some of these cases, "nonsurgical" treatment is opted, such as progesterone therapy. Contrastingly, type II adenocarcinomas are associated with a relatively poor prognosis. In most of these tumors, adjuvant treatment, in the form of chemotherapy (CT) and/or radiotherapy (RT), is included [6, 10].

Endometrioid Adenocarcinoma

Gross appearance of an endometrioid carcinoma includes a variably glistening, shaggy, and/or hemorrhagic external surface. On cutting open, most of the cancers are focally or diffusely exophytic, even when deeply invasive. In cases of serous adenocarcinomas, the uterus is relatively small and atrophic and reveals papillary excrescences on the cut surface. MMMTs are invariably polypoid and extensively fill the endometrial cavity (Figs. 10.5 and 10.6 a, b).

Microscopic examination of endometrioid adenocarcinomas is based upon incorporation of

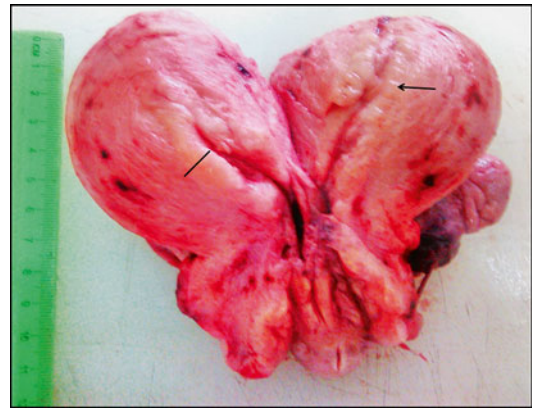

Fig. 10.5 Cut open hysterectomy specimen in a middle-aged lady displaying thickened endometrium (marked) with irregularity on other side (*arrow*). Microscopy showed a well differentiated endometrioid adenocarcinoma (FIGO grade I) arising on a background of complex atypical endometrial hyperplasia

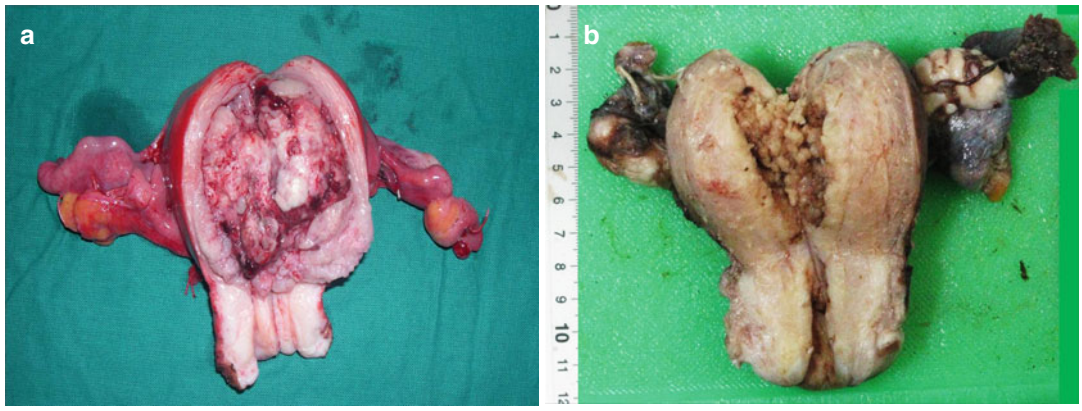

Fig. 10.6 (**a**) Cut open specimen of total hysterectomy with bilateral adnexae/salpingo-oophorectomy (fresh state), showing a proliferative endometrial carcinoma, filling the entire uterine cavity. (**b**). Gross appearance of an endometrioid carcinoma (fixed specimen). Anteriorly cut open total abdominal hysterectomy specimen with bilateral adnexae displaying polypoid tumor in the endometrial cavity. Histopathology revealed well differentiated endometrioid adenocarcinoma

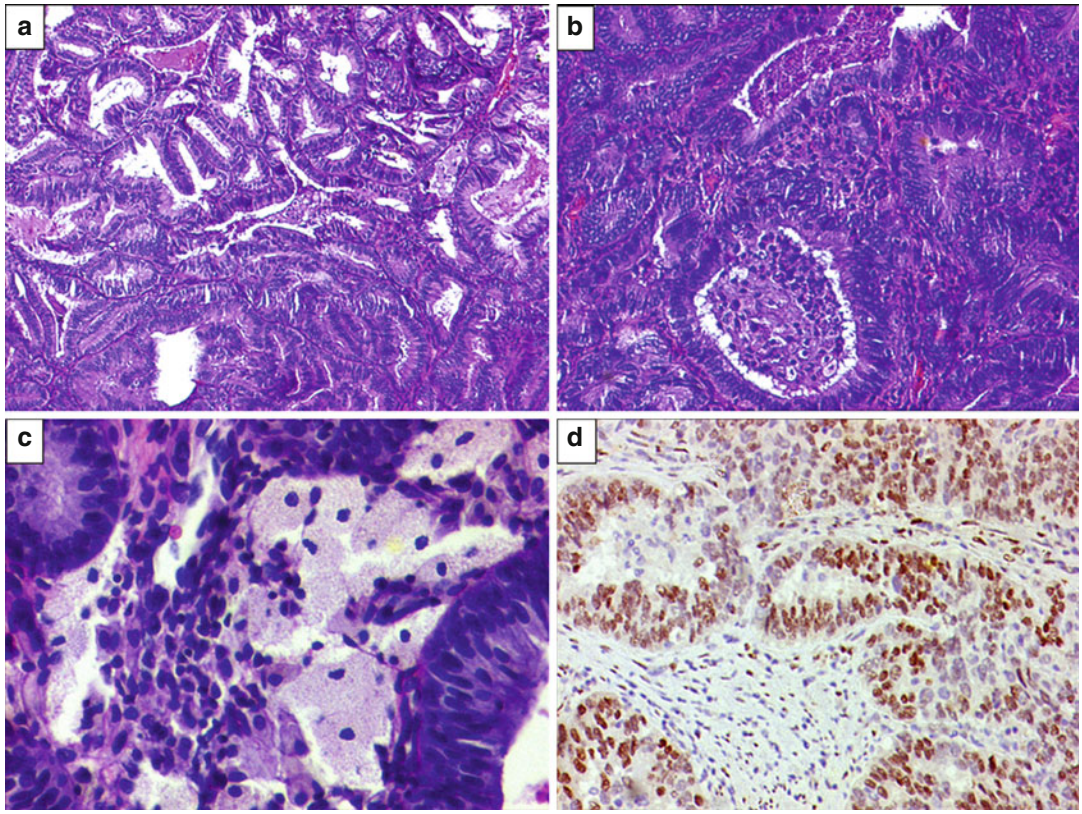

Fig. 10.7 (**a**) Microscopic findings of endometrioid adenocarcinoma. Well-differentiated/FIGO grade I endometrioid adenocarcinoma displaying "back to back" arrangement of endometrial glands with minimal to absent stroma between the tumor glands. Tumor cells exhibit mild nuclear atypia. H&E ×200. (**b**) Same case showing intraluminal necrotic debris and inflammatory cell within one of the atypical glands. H&E ×200. (**c**) Foamy histiocytes within interglandular area, suggestive of well-differentiated endometrioid adenocarcinoma. H&E ×400. (**d**) Diffuse estrogen receptor (ER) positivity (*brown staining* in the nuclei) within tumor glands in a case of well-differentiated/FIGO grade I endometrioid adenocarcinoma. Diaminobenzidine (DAB) immunostaining ×400

architectural patterns and severity of nuclear atypia. Endometrioid adenocarcinomas are classified as grade 1 (not more than 5 % of tumor composed of solid pattern), grade II (6–50 % tumor reveals solid pattern), and grade III (more than 50 % of tumor displays solid pattern). Nuclear grading is based on mild (grade I), moderate (grade II), and marked (grade III) nuclear atypia. In the case of lower architectural grade and higher nuclear grade, the overall grade is escalated. For example, architecturally, grade I endometrioid adenocarcinoma with moderate nuclear atypia is assigned FIGO grade II [6]. Finally, endometrioid adenocarcinomas are graded as well-differentiated (FIGO I), moderately differentiated (FIGO II), and poorly differentiated (FIGO III) carcinomas. On immunohistochemistry, most well to moderate endometrioid adenocarcinomas display positive estrogen receptor (ER) and progesterone receptor (PR) staining (Figs. 10.7 and 10.8). At times, endometrioid adenocarcinomas display squamous differentiation that is a metaplastic change (Fig. 10.9).

Serous Adenocarcinoma

This occurs over a wide clinical age group. Unlike endometrioid adenocarcinomas, in such cases, history of estrogen replacement therapy is

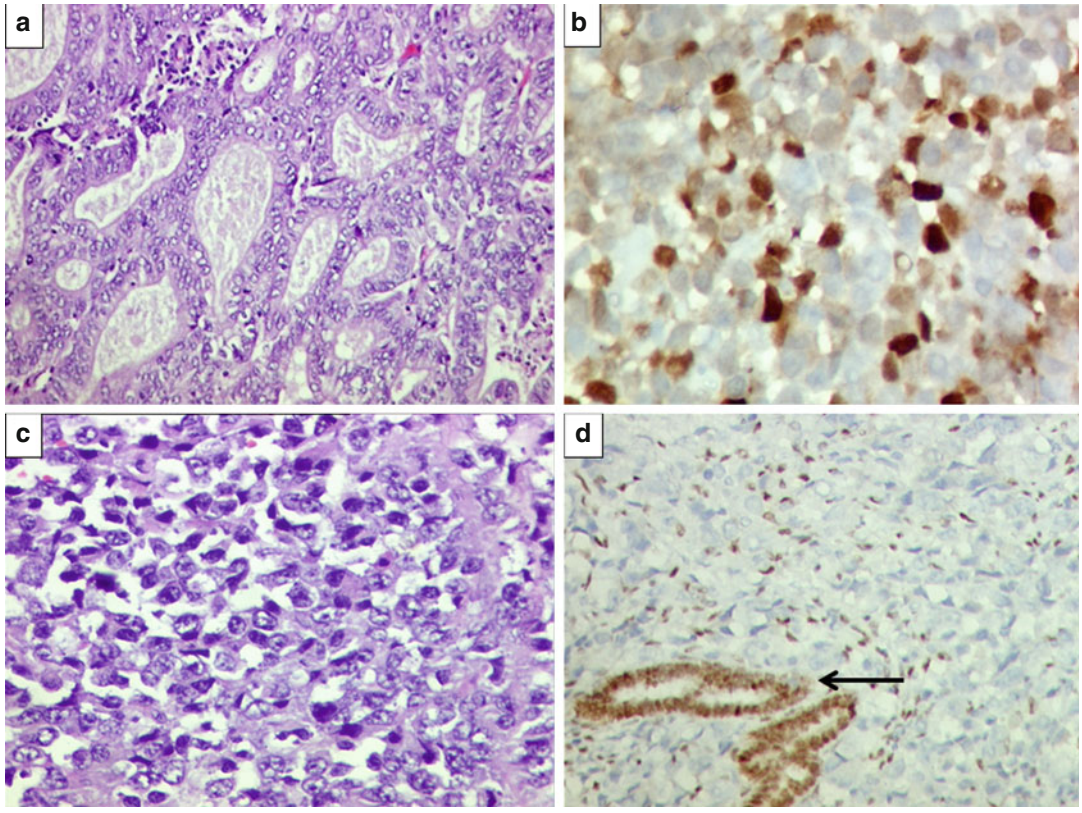

Fig. 10.8 (**a**) Case of a moderately differentiated/FIGO grade II endometrial adenocarcinoma. Tumor seems to retain glandular pattern, but nuclear atypia is moderate. H&E ×200. (**b**) In the same tumor, p53 immunostaining noted in several tumor nuclei. (**c**) Case of poorly differentiated FIGO grade III endometrioid adenocarcinoma displaying solid pattern of cells exhibiting marked nuclear atypia. Glandular differentiation is lacking. H&E ×400. (**d**) Same tumor displaying loss of ER expression. Interspersed are few benign endometrial glands (*arrow*) and interspersed stromal cells displaying positive immunostaining, acting as internal positive control. DAB ×200

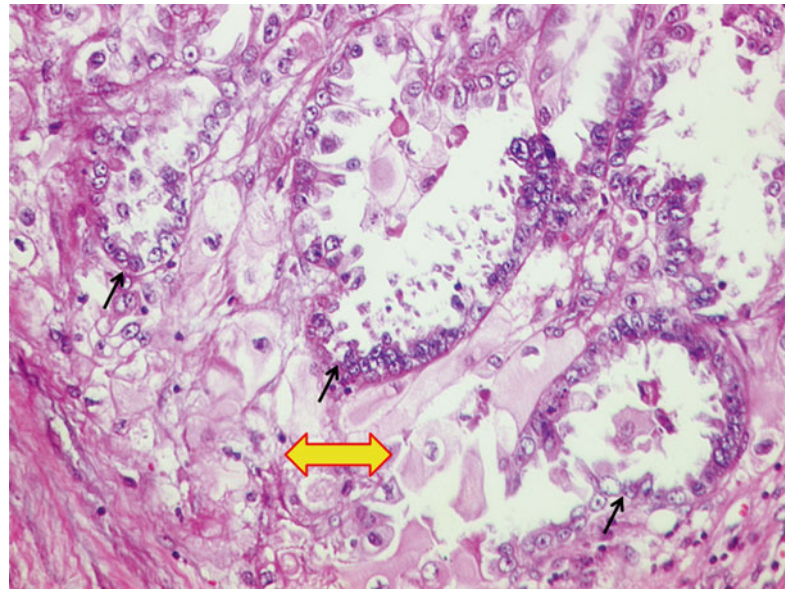

Fig. 10.9 Squamous differentiation in the form of *pink* cells with intercellular bridges (*thick yellow arrow*) in a well-differentiated endometrioid adenocarcinoma (*arrows*). H&E ×200

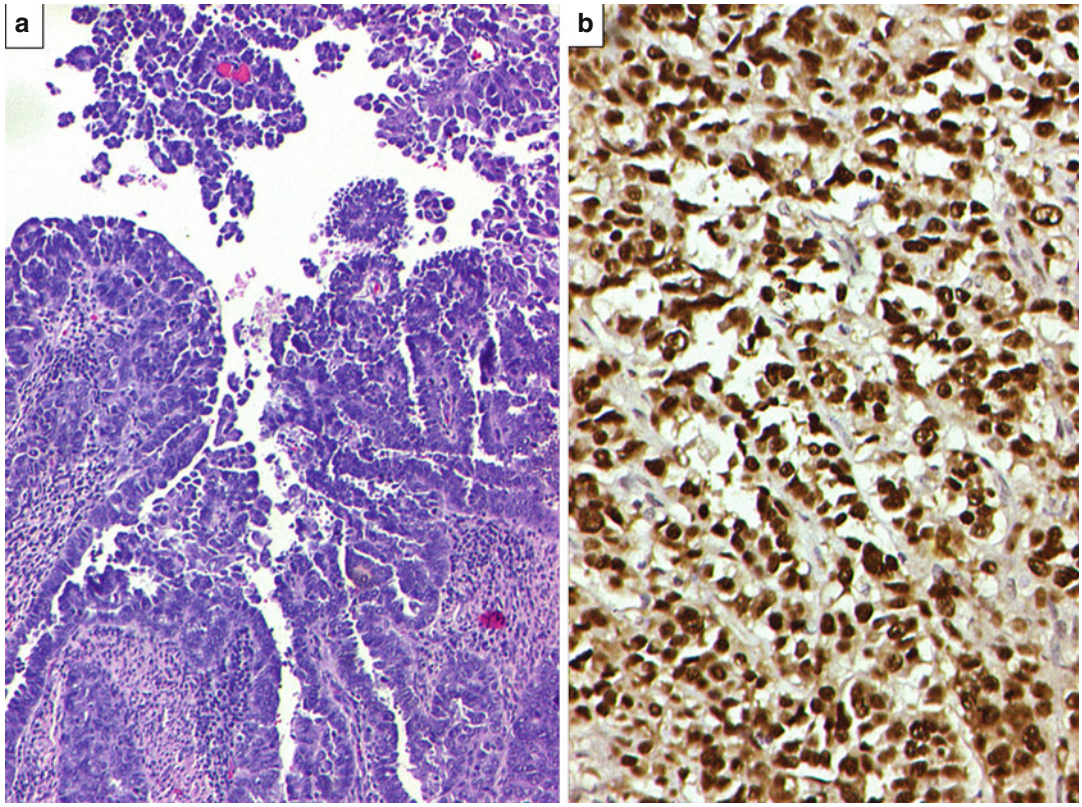

Fig. 10.10 (**a**) High-grade papillary serous adenocarcinoma. H&E ×200. (**b**) Same tumor displaying diffuse p53 immunostaining (*brown staining* in the nuclei). DAB ×400

less likely than abnormal cervical cytology. As aforementioned, the uterus in such cases is small and atrophic. Microscopically, this tumor is characterized by an array of patterns, although papillary pattern is more common. Besides, glandular and solid patterns are also noted. Characteristically, papillary structures lined by markedly atypical cells, exhibiting "hobnail" pattern, are noted with readily identifiable mitotic figures. These are associated with intraepithelial carcinoma along with atrophied endometrium. On immunohistochemistry (IHC), these tumors exhibit diffuse p53 and p16 immunostaining (Fig. 10.10).

Clear Cell Adenocarcinoma

While these tumors have nonspecific gross findings, microscopically they exhibit solid, papillary, tubular, and cystic patterns. Cells exhibit marked pleomorphism, conspicuous hobnail arrangement, variably eosinophilic to clear cytoplasm, and prominent eosinophilic nucleoli in several cells. Stroma is hyalinized leading to formations of eosinophilic bodies. Deep purple psammoma bodies may be identified. The differential diagnoses include Arias-Stella reaction, serous adenocarcinoma, secretory type of endometrioid carcinoma, and yolk sac tumor. On IHC, this tumor expresses CK7 and vimentin and lacks ER, PR, p53, and p16 expression (Fig. 10.11).

An endometrial adenocarcinoma displaying combinations of endometrioid, serous, and/or clear carcinoma is designated as mixed carcinoma.

Malignant Mixed Müllerian (Mesodermal) Tumor (MMMT) (Carcinosarcoma)

These tumors are composed of malignant epithelial and mesenchymal/stromal components.

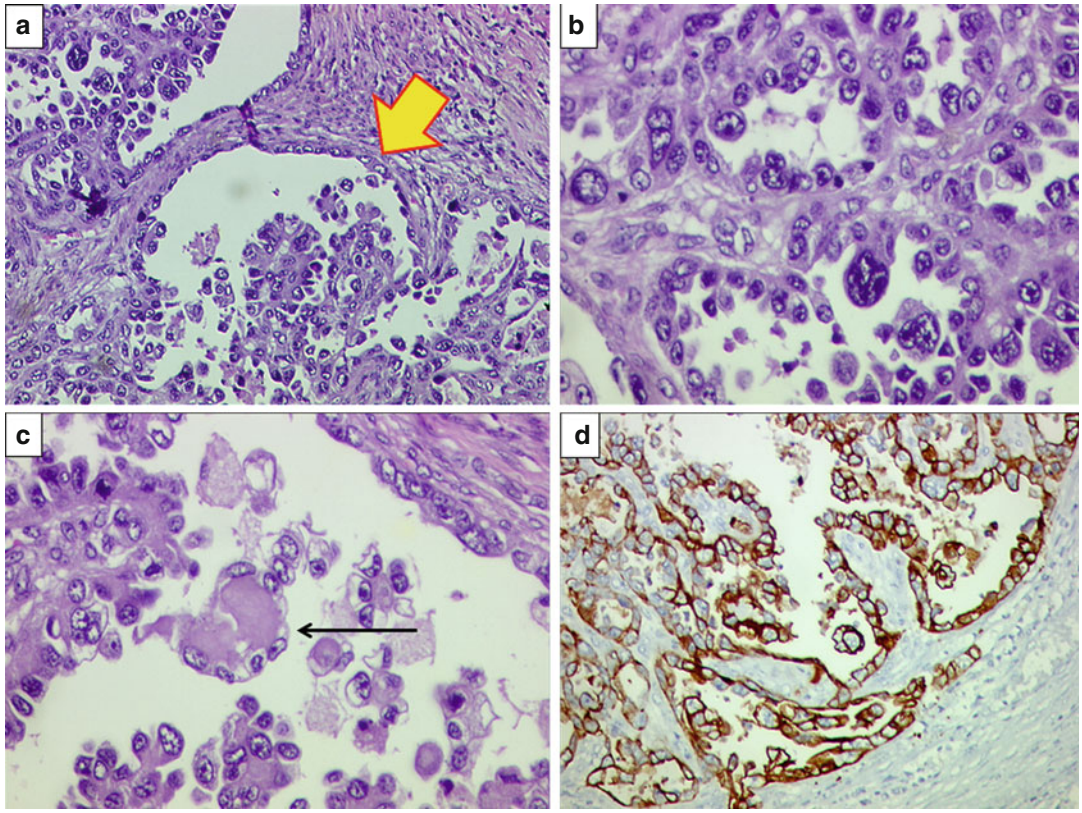

Fig. 10.11 (**a**) Clear cell carcinoma with cells exhibiting papillary and "hobnail" arrangement of markedly atypical tumor cells (*block arrow*). H&E ×200. (**b**) Higher magnification displaying conspicuous "hobnail" arrangement of tumor cells exhibiting marked nuclear atypia, including prominent nucleoli. H&E ×400. (**c**) Tumor displaying hyalinized eosinophilic bodies (*arrow*) detached from the stroma. DAB ×400. (**d**) Same tumor exhibiting diffuse cytokeratin (CK) 7 immunostaining (*brown* intracytoplasmic membranous staining). DAB ×400

Recent studies have shown that MMMTs are likely to be adenocarcinomas, in which malignant mesenchymal elements develop as a result of metaplasia or dedifferentiation [11]. They are also found to be associated with adenosarcomas.

Clinically, these tumors mostly occur in older patients and grossly appear as large polypoid masses filling the endometrial cavity.

Microscopically, MMMTs reveal varying combinations of adenocarcinomatous components and malignant stromal elements that commonly appear as fibrosarcomatous or pleomorphic and sarcomatous (with several giant cell tumors) types. These are designated as homologous components. When the stromal elements reveal rhabdomyosarcomatous, chondrosarcomatous/cartilaginous, or osteosarcomatous elements, these are designated as MMMTs with heterologous components. MMMTs with heterologous components relatively more aggressive[6]. Rhabdomyosarcomatous/malignant skeletal muscle components can be objectively identified with muscle-specific IHC markers, such as desmin, myogenin, and MyoD1 (Figs. 10.12 and 10.13).

Undifferentiated Carcinoma

Tumors that do not display any glandular pattern and characterized by undifferentiated monotonous small- to intermediate-sized malignant epithelial cells exhibiting prominent nucleoli, accompanied by frequent mitoses, are termed as undifferentiated carcinomas. At times, these tumors are accompanied by lymphocytic infiltrate (lymphoepithelioma-like) (Fig. 10.14). In cases of undifferentiated

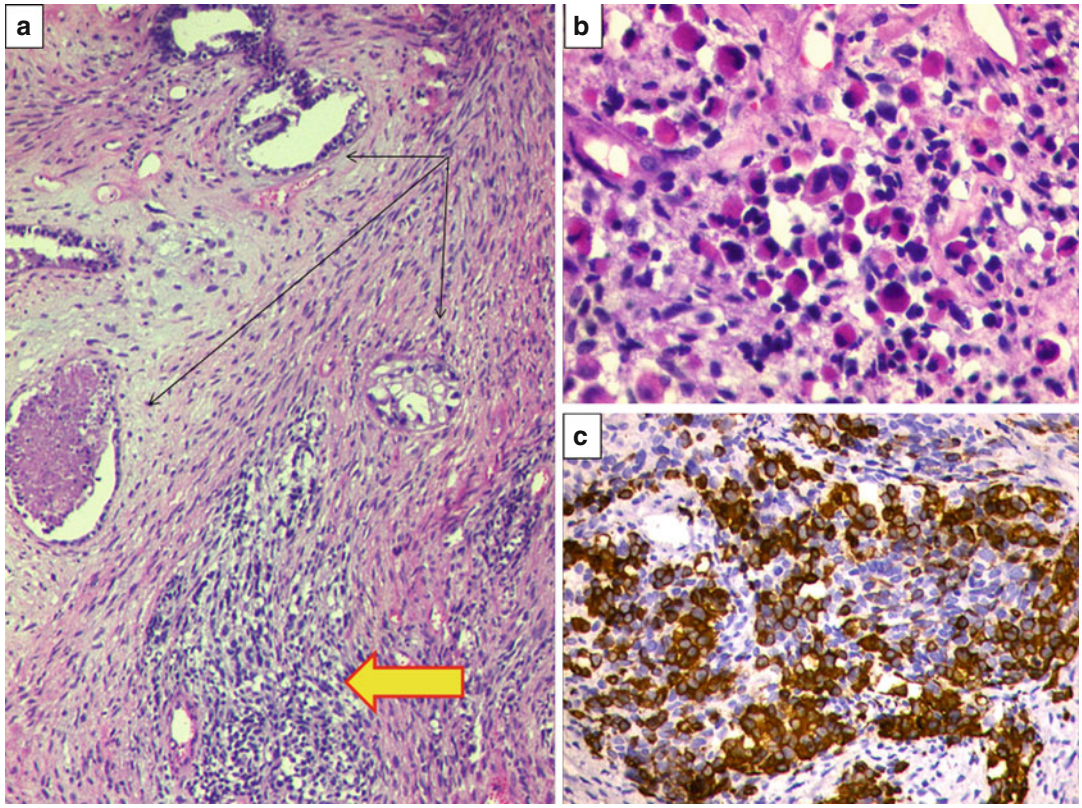

Fig. 10.12 (**a**) Case of malignant mixed müllerian tumor (carcinosarcoma), displaying malignant glands (*arrows*) and malignant stroma/sarcoma (*arrowhead*). (**b**) At higher magnification, stroma displaying several *pink* cells, reminiscent of rhabdomyoblasts/skeletal muscle differentiation (heterologous components). (**c**) Positive desmin immunostaining (*brown* intracytoplasmic staining), reinforcing skeletal muscle differentiation (carcinosarcoma with heterologous differentiation)

carcinomas, lacking cohesion, one has to resort to IHC immunostaining for epithelial markers, such as epithelial membrane antigen and cytokeratin, including AE1/AE3 in tumor cells. This is in view of non-Hodgkin's lymphoma and other round cell tumors that enter as differential diagnoses, wherein treatment modalities differ.

Diagnostic Challenges During Histopathological Evaluation of Endometrial Carcinomas

(i) Complex atypical hyperplasia (CAH) from FIGO grade 1/well-differentiated endometrioid adenocarcinoma
(ii) Identifying aggressive histopathological subtypes/components
(iii) Identification of mesenchymal elements in an otherwise MMMT

These challenges can be overcome by paying careful attention to the histopathological "clues."

Complex Atypical Hyperplasia Versus Well-Differentiated Endometrioid Adenocarcinoma

The objective criterion for diagnosis of carcinoma is myometrial invasion that is best decided on a hysterectomy specimen. However, it has been noted that in 30 % cases of well-differentiated adenocarcinomas, hysterectomy specimens lacked invasion [12]. At the same time, it has been observed that 15–50 % of cases are diagnosed as CAH; on hysterectomies, they revealed adenocarcinomas, including the myoinvasive type [13]. The

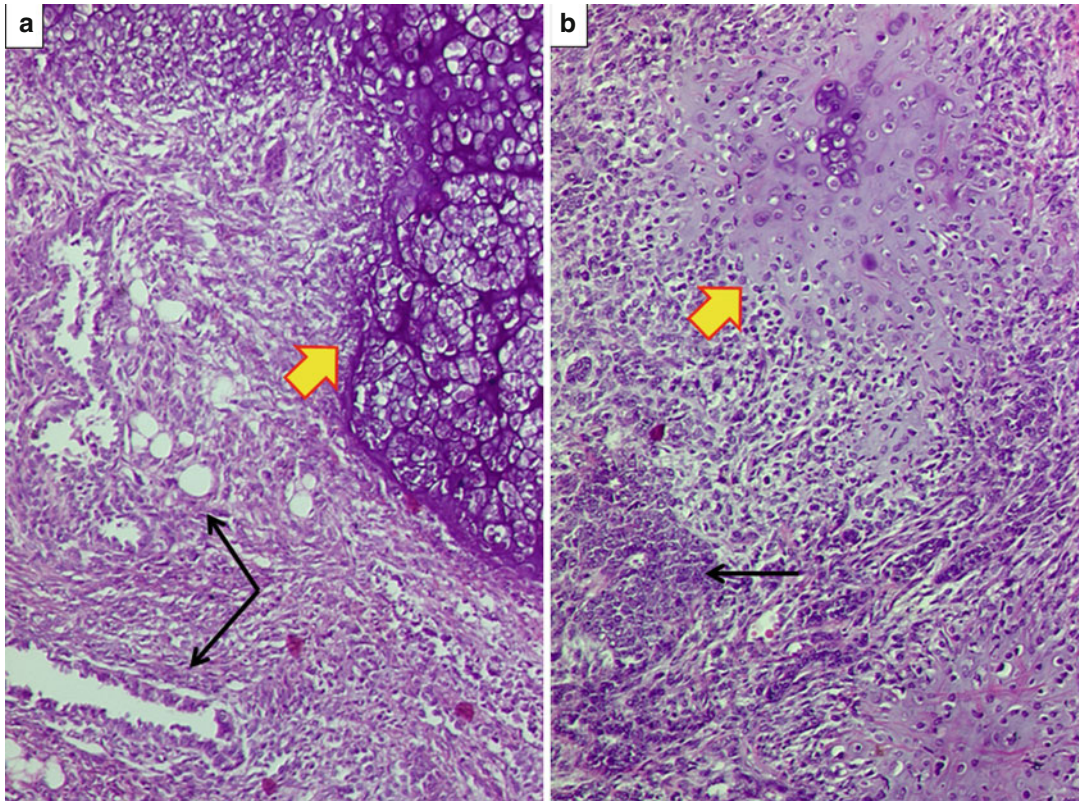

Fig. 10.13 (**a**) Case of malignant mixed müllerian tumor (carcinosarcoma), displaying malignant glands (*double arrows*) and prominent cartilaginous differentiation (*block arrow*) within malignant stroma/sarcoma (*arrowhead*). H&E ×200. (**b**) Same case displaying prominent cartilaginous differentiation (*block arrow*) in close proximity to areas of poorly differentiated carcinoma and sarcoma (heterologous components). H&E ×200

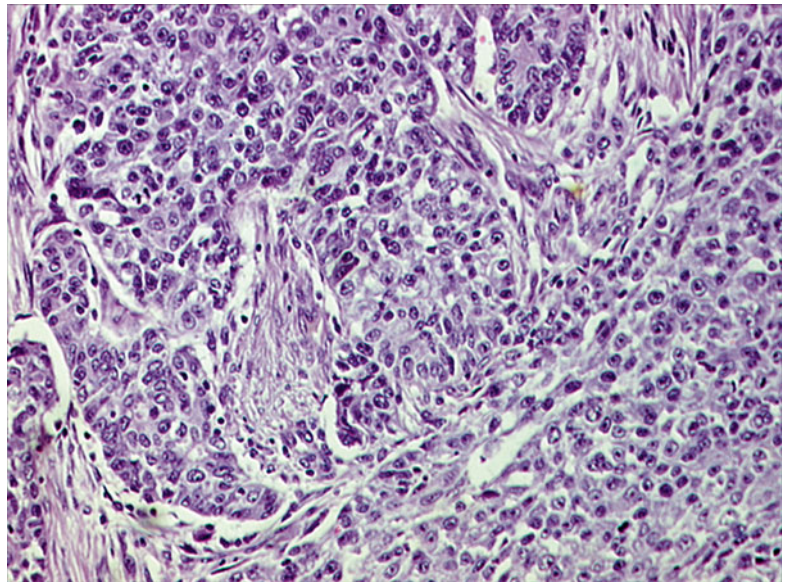

Fig. 10.14 Undifferentiated carcinoma. High-grade malignant tumor displaying focally cohesive tumors cells with marked pleomorphism and prominent nucleoli, arranged in a nondescript manner. H&E ×200

observed risk of progression of a CAH to carcinoma varies from 29 % to 100% [14, 15].

Some of the histopathological "clues" on endometrial biopsy sampling, for diagnosing endometrioid adenocarcinomas, include back-to-back arrangement of atypical endometrial glands without intervening stroma and/or replacement by foam macrophages and luminal bridging, leading to cribriform pattern with intraluminal necrotic debris associated with the presence of acute inflammatory cells (Fig. 10.4).

Squamous Differentiation Versus Adenosquamous Versus Squamous Carcinoma

Squamous metaplasia/squamous "morules" can be identified in cases of hyperplasias, as well as carcinomas. Carcinomatous features in the types of cells (glandular or squamous) indicate the respective types of endometrial carcinomas.

Identification of Aggressive Histopathological Subtypes

In the identification of aggressive histopathological subtypes and malignant mesenchymal/stromal components in an MMMT, the value of adequate tissue sampling cannot be overemphasized during grossing of cancer specimens. Careful attention towards aggressive histopathological subtypes within adequate number of histopathological sections can help in avoiding "missing" of relatively aggressive histopathological subtypes that influence further treatment.

At the same time awareness of various "caveats" or "pitfalls" such as polyps, endometritis, cyclical phase, artifacts (telescoped glands), and atypical adenomyofibroma, including their morphological profile, can help in avoiding overdiagnosis of adenocarcinoma in such cases.

In certain cases of tumor subtyping, one has to resort to ancillary techniques such as immunohistochemistry

Role of Immunohistochemistry (IHC)

Various available IHC markers that are useful in substantiating tumor subtyping in endometrial adenocarcinomas include estrogen receptor (ER), progesterone receptor (PR), β-catenin, p16, etc. It is important to note that expression of IHC markers should be interpreted in a clinicopathological context.

Endometrioid type of endometrial adenocarcinomas is positive for ER, PR, and vimentin. ER and PR are more frequently expressed in FGO grade I and II endometrioid adenocarcinomas [16]. Nuclear β-catenin is positively expressed more in type 1, differentiated endometrioid adenocarcinomas [17]. Endocervical type of adenocarcinoma is more frequently positive for p16/CEA (monoclonal) [18]. p53 is diffusely expressed in high-grade serous adenocarcinomas and also in high-grade endometrioid adenocarcinomas. Noteworthy, IHC markers can differentiate on the bases of cell differentiation (endocervical or endometrial), not site-wise. MUC1 is the "new kid on the block" in the diagnostic armamentarium of endometrioid adenocarcinomas [19].

MIB1/Ki67 (proliferation marker) and p53 are helpful in differentiating high-grade endometrial adenocarcinomas from Arias-Stella reaction as high MIB1 and positive p53 expression are more indicative of high-grade endometrial adenocarcinoma over Arias-Stella reaction [20].

Apart from histopathological subtypes, **various components of a pathology report of endometrial carcinoma** that make it scientifically and clinically viable are as follows:

Gross Description

- Specimen: biopsy
- Type of hysterectomy: measurement in three dimensions
- Description of growth: type (exophytic, polypoid, infiltrative; diffuse or focal), involvement within uterine cavity. Tumor measurement (T)
- Involvement of myometrium (less than, more than, and equal to half)
- Description of myometrium
- Serosa, isthmus, cervix, vagina (if cuff is present); involvement
- Bilateral adnexa (ovaries and fallopian tubes)
- Bilateral parametrium (ovaries and fallopian tubes)
- Lymph nodes (if submitted)
- Sections (labeled and drawn)

Noteworthy, the endometrium should be fixed timely in 10 % neutral buffered formalin after cutting open as the lining surface is fragile. Sufficient, judicious tumor sampling is vital.

Microscopic Description

- Differentiation, FIGO grade (architectural and nuclear)
- Involvement: endometrium and myometrium (less than or more than equal to half)
- Involvement of serosa (distance from growth)
- Lymphovascular emboli, perineural invasion
- Involvement of cervix (glands and/or stroma)
- Vagina and vaginal cut margins (in case submitted)
- Bilateral adnexa (ovaries and fallopian tubes)
- Bilateral parametrium
- Omentum, lymph nodes (if submitted)
- Peritoneal washings [21]

Impression Tumor type, TNM stage (AJCC classification)

As aforementioned, apart from histopathological subtyping, there is significant clinical relevance of mentioning various parameters in the histopathology report of endometrial carcinoma, such as tumor grading and staging [22, 23]. Involvement of deep myometrial invasion (Fig. 10.15a) is indicative of inclusion of adjuvant therapies. It has been observed that in tumors exhibiting more than 50 % myometrial invasion, the patient is at risk for extrauterine metastasis, including lymph nodes, and may require more aggressive surgical staging as well as postoperative adjuvant therapy. One study [24] disclosed that measurement of the distance from the tumor to the uterine serosa correlated better with survival than assessing the percentage of total thickness of infiltrated myometrium.

Nearly 20 % of endometrial carcinomas show lymphovascular invasion (Fig. 10.15b). This cor-

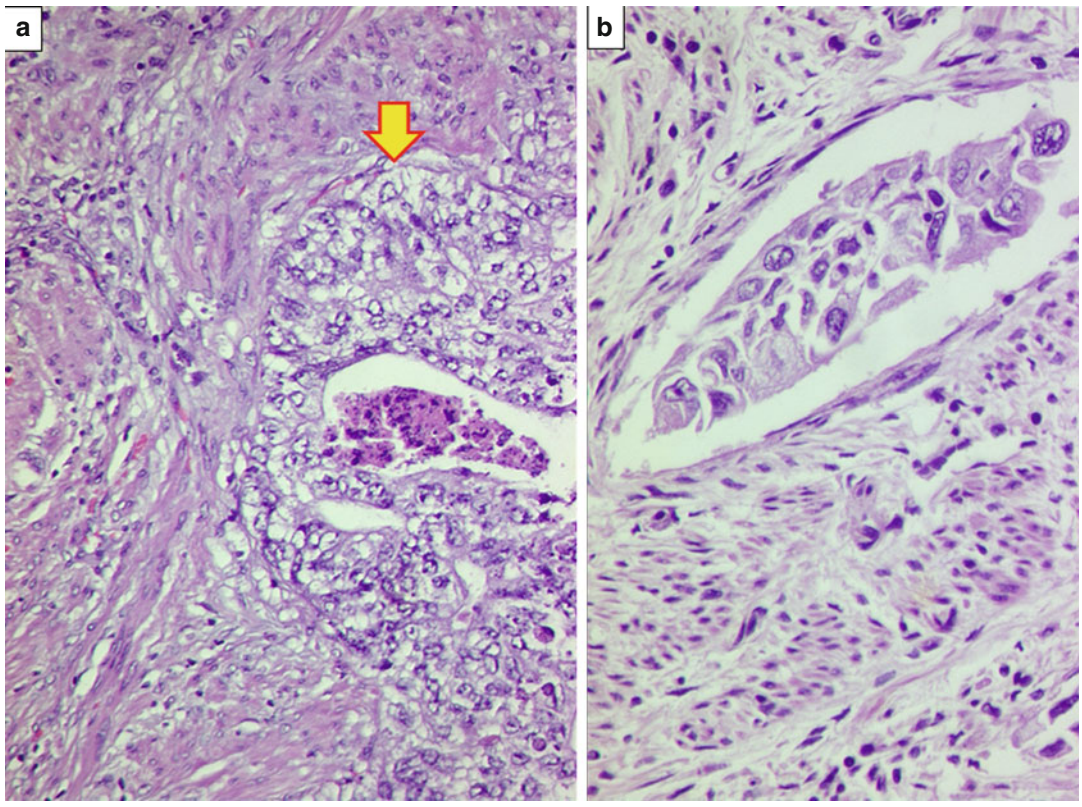

Fig. 10.15 (**a**) Muscle invasion in a high-grade endometrioid adenocarcinoma (adenocarcinoma marked by *block arrow*). H&E ×200. (**b**) Tumor embolus/vascular invasion. H&E ×200

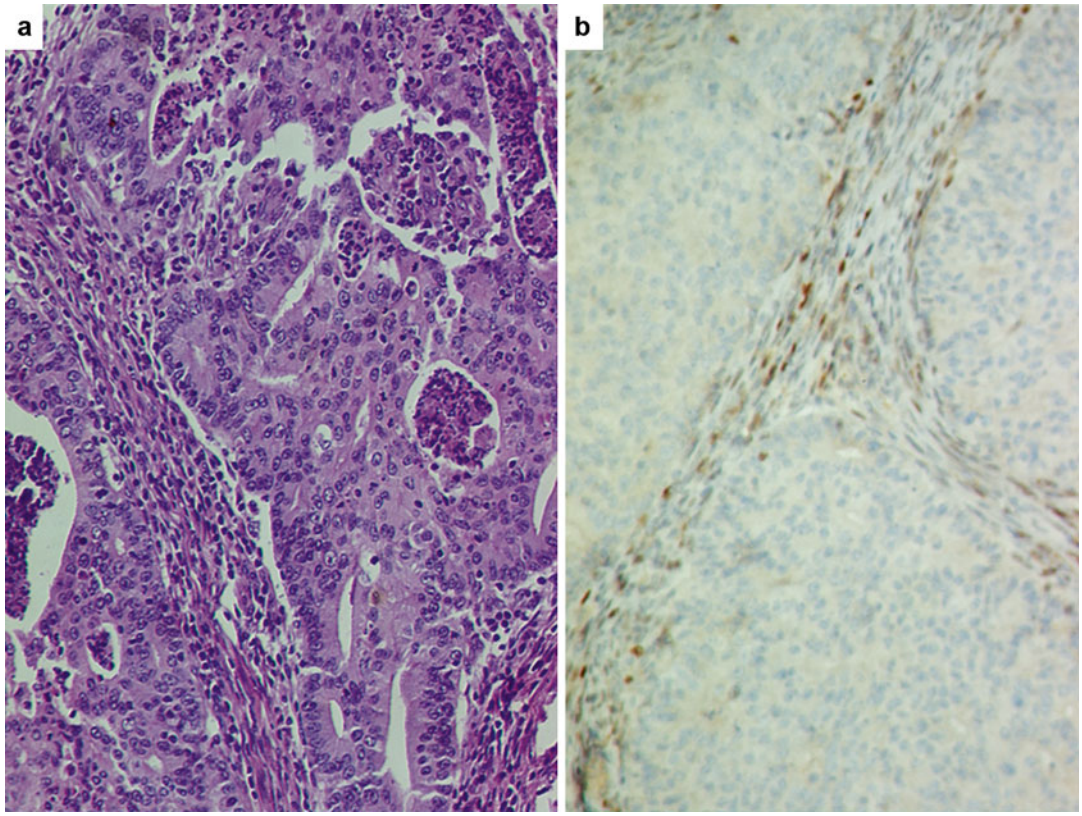

Fig. 10.16 (**a**) Moderately differentiated endometrioid adenocarcinoma in a young female, less than 40 years old. H and E × 200. (**b**). Loss of mismatch repair protein, MSH6 immunostaining within tumor cells. Intervening inflammatory cells and endothelial cells display positive staining (brown intranuclear staining) act as internal controls. DAB × 400. The same tumor was also negative for PMS2, but positive for MLH1 and MSH2

relates with the depth of muscle invasion, tumor grade, and lymph node metastasis and is an independent indicator of risk of recurrence and correlates with a diminished survival in cases with well-differentiated/FIGO grade 1 endometrial adenocarcinoma [25, 26].

Molecular Aspects of Endometrial Carcinoma

It has been identified that tamoxifen treatment of BRCA1 and BRCA2 carriers for prior breast cancer increases the risk of endometrioid subtype endometrial cancer, and there is suggestive evidence that BRCA1 and BRCA2 mutation carriers may be predisposed to EC in the absence of tamoxifen exposure. A study by Duffy et al. [27] has shown a sevenfold increase in endometrial carcinoma risk with tamoxifen exposure for female family members from BRCA1/2 families.

Distinct molecular pathways have been identified for type 1 and type 2 endometrial carcinomas. Whereas type I endometrial carcinomas are characterized by loss of PTEN, followed by PIK3CA and K-ras mutations, type II endometrial carcinomas are characterized by underlying p53 mutations [28]. Inactivation of p16 and overexpression of Her2/neu proteins are also more frequent in aggressive or type II endometrial carcinomas [29–31].

Lately, a subset of endometrial carcinomas has been identified in women younger than 40

years old. Most endometrial carcinomas that occur in this age group are associated with estrogen excess, are usually low-grade type that present at low stages, and are associated with relatively favorable clinical outcomes. Tumors associated with mismatch repair abnormalities and Lynch syndrome appear to be distinct, invariably high grade with worse prognostic factors and possibly aggressive clinical outcome. Conservative hormonal therapy and ovarian conservation are reasonable considerations in the management of these young patients, but carry the risk of tumor progression, recurrence, and an occult synchronous or metachronous ovarian carcinoma [32] (Fig. 10.16a, b).

Summary

Endometrial hyperplasia may be simple and complex, including typical and atypical subtypes. Complex atypical hyperplasia can be differentiated from well-differentiated endometrioid adenocarcinoma in certain cases, in case one pays attention to certain histopathological clues. According to the "dualistic" theory, endometrial carcinomas are of two types, namely, type I and type II. It is vital to identify relatively aggressive tumor subtypes during histopathological assessment that must include optimal tissue sampling. IHC can be helpful in objectively identifying histopathological subtypes of endometrial carcinomas. An optimal histopathology report must include all the predictive and prognostic parameters. Underlying molecular events in cases of endometrial carcinomas are unraveling rather new clinical subtypes of endometrial carcinomas that could have impact on future therapies and prognosis.

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Key Points

1. Endometrial hyperplasias are of simple and complex types. Diagnostic challenge exists in differentiating complex typical versus complex atypical hyperplasia versus well-differentiated endometrioid adenocarcinoma, especially on biopsy. Careful attention towards clinical history, histopathological "clues," and awareness of caveats such as endometritis and polyps all are helpful in resolving these dilemmas.
2. Uncommonly, papillary hyperplasias, especially complex types, can also pose a diagnostic challenge. In such cases, cytopathological features are vital in differentiating a complex papillary hyperplasia from a high-grade serous carcinoma.
3. Endometrioid adenocarcinomas are clinically of type I and type II with their distinct clinicopathological profiles and different underlying molecular events.
4. Adequate tumor sampling is vital for identifying aggressive histopathological subtypes of endometrioid carcinomas that influence treatment and prognosis.
5. Finally, a sufficiently detailed report of endometrial carcinoma should include predictive and prognostic factors, especially tumor-grade stage, myometrial invasion, vascular invasion, etc.
6. Immunohistochemistry is helpful, to an extent, in the identification of certain tumor subtypes of endometrial carcinoma.
7. Recently, endometrial carcinomas in relatively younger women, less than 40 years, have been found to be associated with mismatch repair abnormalities and Lynch syndrome. Such tumors appear to be distinct histopathological group and invariably high grade, including lymphoepithelioma-type, and portend worse prognosis and possibly aggressive clinical outcomes.

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Pathology of Uterine Sarcomas

11

Pushpa Mahadevan

Introduction

Uterine sarcomas are a rare, heterogeneous group of neoplasms, which account for approximately 1 % of all female genital tract malignancies and 3–5 % of malignant uterine tumors [1]. The tumors are derived from the mesenchymal components of the uterus, consisting of endometrial stroma, smooth muscle and blood vessels, or admixtures of these (referred to as homologous elements). Rarely the tumors may contain tissue types not normally seen in the uterus, such as striated muscle, cartilage, or bone (referred to as heterologous elements). Compared with the more common endometrial carcinomas, uterine sarcomas behave more aggressively and are associated with a poorer prognosis with a high rate of local recurrence and/or metastasis. The lack of consensus, on treatment options and risk factors for poor outcome, is largely due to the rarity of these tumors and their histopathological diversity. The classification and staging of these tumors were revised in 2013 and 2009, respectively.

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Classification

Historically uterine sarcomas have been classified into carcinosarcoma, leiomyosarcoma, endometrial stromal sarcoma, undifferentiated sarcoma, and a heterogeneous group of vascular, lymphatic, and heterologic sarcomas. Recently, carcinosarcoma has been reclassified as a dedifferentiated or metaplastic form of endometrial carcinoma. Despite this, and probably because it behaves more aggressively than the ordinary endometrial carcinoma, carcinosarcoma is still included in most retrospective studies of uterine sarcomas[2].

A simple classification of uterine sarcomas based on 2014 WHO Classification of Tumors of Female Reproductive Organs [3] is shown in Table 11.1.

A practical classification of uterine sarcomas excluding carcinosarcoma, with incidence [4], is as follows:

Leiomyosarcoma (LMS 60 %)
Endometrial stromal sarcoma (ESS 30 %)
Undifferentiated uterine sarcoma (UUS 5%)
Adenosarcoma and other uterine sarcomas (5 %)

The 1988 International Federation of Gynecology and Obstetrics (FIGO) criteria for endometrial carcinoma have been used until now for staging uterine sarcomas in spite of the different biologic behavior of both tumor categories. The new FIGO staging system, approved by the FIGO

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Table 11.1 Classification of uterine sarcomas

Endometrial stromal and related tumors
Low-grade endometrial stromal sarcoma
High-grade endometrial stromal sarcoma
Undifferentiated uterine sarcoma
Uterine tumor resembling ovarian sex cord tumor (UTROSCT)
Smooth muscle tumors
Leiomyosarcoma
Epithelioid variant
Myxoid variant
Smooth muscle tumor of uncertain malignant potential
Mixed epithelial and mesenchymal tumors
Adenosarcoma
Carcinosarcoma
Miscellaneous mesenchymal tumors
Rhabdomyosarcoma
Perivascular epithelioid cell tumor ("PEComa")
Other malignant mesenchymal tumors

executive board in September 2008, is specifically designed for uterine sarcomas to reflect different biologic behavior [5]. It includes: (1) staging for leiomyosarcoma (LMS) and endometrial stromal sarcoma (ESS), (2) staging for adenosarcomas (AS), and (3) staging for carcinosarcomas, of which the first two are new, while carcinosarcomas will continue to be staged according to the new classification of endometrial carcinoma.

FIGO Staging System for Uterine Sarcomas (2009)

1. Leiomyosarcomas and endometrial stromal sarcoma

Stage I Tumor limited to uterus
IA Less than or equal to 5 cm
IB More than 5 cm
Stage II Tumor extends beyond the uterus, within the pelvis
IIA Adnexal involvement
IIB Tumor extends to extrauterine pelvic tissue
Stage III Tumor invades abdominal tissues (not just protruding into the abdomen)
IIIA One site
IIIB More than one site
IIIC Metastasis to pelvic and/or para-aortic lymph nodes
Stage IV
IVA Tumor invades bladder and/or rectum
IVB Distant metastasis

2. Uterine adenosarcomas

Stage I Tumor limited to uterus
IA Tumor limited to endometrium/endocervix with no myometrial invasion
IB Less than or equal to half myometrial invasion
IC More than half myometrial invasion
Stage II Tumor extends beyond the uterus, within the pelvis
IIA Adnexal involvement
IIB Tumor extends to other pelvic tissues
Stage III Tumor invades abdominal tissues (not just protruding into the abdomen)
IIIA One site
IIIB More than one site
IIIC Metastasis to pelvic and/or para-aortic lymph nodes
Stage IV
IVA Tumor invades bladder and/or rectum
IVB Distant metastasis

3. Carcinosarcomas

Carcinosarcomas should be staged as carcinomas of the endometrium.

Note: Simultaneous tumors of the uterine corpus and ovary/pelvis in association with ovarian/pelvic endometriosis should be classified as independent primary tumors.

The 2009 FIGO staging systems make no mention of undifferentiated uterine sarcoma or pure heterologous sarcomas, such as rhabdomyosarcoma. These tumors are staged in the same way as leiomyosarcoma and endometrial stromal sarcoma. The term "uterus" includes the uterine corpus and uterine cervix, and the 2009 FIGO staging system is used for all uterine sarcomas, irrespective of whether tumors arise in the corpus or cervix.

Leiomyosarcoma

Leiomyosarcomas are malignant neoplasms that demonstrate either histological or immunohistochemical smooth muscle differentiation. Although

LMSs represent only about 1 % of all uterine malignancies, they are the most common pure uterine sarcomas accounting for 25–30 % of uterine sarcomas. They occur almost exclusively in adults and in an older age group than leiomyomas, with the median age being 50–55 years. LMSs are aggressive tumors that have a tendency to spread locally, regionally, or by hematogenous dissemination, most commonly to the liver and lung. The most common presenting symptoms are abnormal vaginal bleeding and pelvic pain. Local and regional spread may produce an abdominal or pelvic mass with gastrointestinal or urinary tract symptoms or hemoperitoneum. LMSs are generally thought to arise *de novo*, but recent molecular genetic evidence suggests that some of these tumors may evolve from preexisting leiomyomas [6].

Gross Features

LMSs are characteristically solitary, intramural masses and are usually not associated with leiomyomas. The gross appearance of LMSs has significant differentiating features from that of leiomyomas in most of the cases. They are large tumors averaging 10 cm in diameter with poorly circumscribed borders that appear to irregularly infiltrate the adjacent myometrium. Leiomyomas, on the other hand, characteristically have a sharp line of demarcation separating the tumor from the myometrium. LMSs that present as a circumscribed mass are not usually recognized grossly as a malignant tumor because of the overlap in appearance between malignant change and the various forms of degeneration. The macroscopic features that are suspicious of malignancy and require thorough sampling of the tumor are: loss of whorled pattern, heterogeneity, irregular, merging, blurred or poorly defined margins, yellow, tan or gray color, softer tumors that lack a rubbery, resilient feel, and absence of a bulging surface. The cut surface may also show irregular areas of hemorrhage and necrosis.

Microscopic Features

LMSs exhibit hypercellularity, severe nuclear atypia, geographic foci of tumor cell necrosis, and a high mitotic rate including atypical mitotic figures, generally exceeding 15 mitotic figures per 10 high-power fields (Fig. 11.1a). Mitosis is counted in the most mitotically active areas in ten successive HPFs using an 40× objective and a standard 10× eyepiece. The poorly differentiated tumors show nuclear pleomorphism, hyperchromasia, prominent nucleoli, and tumor giant cells, features that indicate increasing anaplasia of the tumor (Fig. 11.1b). Well-differentiated LMS on the other hand consist of elongated smooth muscle cells with regular nuclei that differ little from those of a leiomyoma (Fig. 11.1c). Areas of coagulative necrosis and hemorrhage are seen (Fig. 11.1d). The tumors, in most cases, would have invaded the adjacent myometrial tissue at the time of diagnosis and may have perforated the serosal surface of the uterus with involvement of other pelvic organs. Vascular invasion may also be seen.

If a smooth muscle tumor is well circumscribed, composed of cells that are uniform in size and shape, has no intravascular component, cytological atypia or necrosis, and with a mitotic count of less than 5 mitotic figures per 10 HPFs, then the tumor is a leiomyoma. On the other hand, when a tumor has infiltrative margins (Fig. 11.1e), intravascular growth, marked cytological atypia, coagulative tumor cell necrosis, a mitotic count greater than 10 mitosis per 10 HPFs and abnormal mitotic figures, then the tumor is an LMS. Most of the smooth muscle tumors belong to the two extremes of the spectrum and are either clearly benign or malignant. It is the tumors that fall in the intermediate category that require careful consideration to reliably categorize them, to predict prognosis, and to decide on further treatment. Numerous studies have been undertaken during the past three decades to define the histological criteria that would help to correctly categorize these tumors and to differentiate them from leiomyomas with atypical histological features like the mitotically active leiomyoma, cellular leiomyoma, atypical leiomyoma, myxoid leiomyoma, epithelioid leiomyoma, hemorrhagic leiomyoma, leiomyoma with hormone-induced changes, and from leiomyomas with unusual growth patterns like disseminated peritoneal leiomyomatosis, benign metastasizing leiomyoma, intravenous leiomyomatosis, and lymphangioleiomyomatosis. Of the

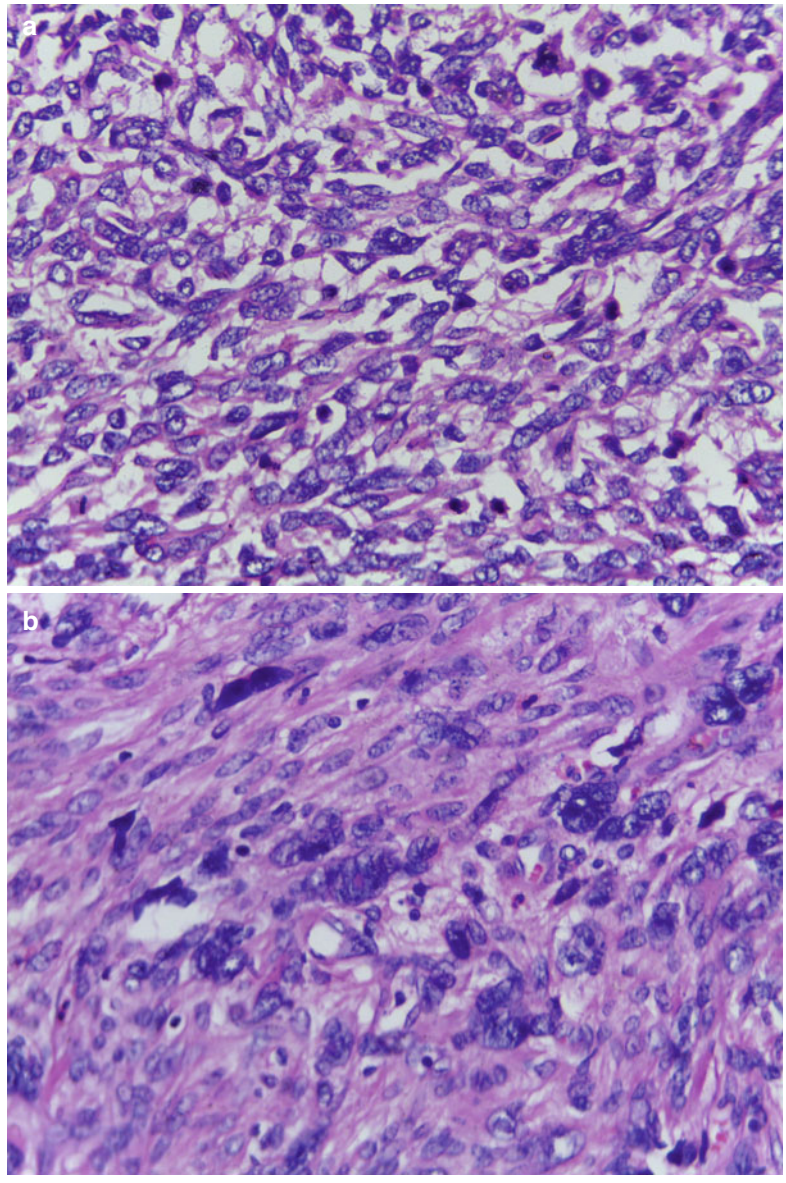


Fig. 11.1 (**a**) Leiomyosarcoma with hypercellularity, hyperchromatism, nuclear atypia, and high mitotic activity. (**b**) Leiomyosarcoma with nuclear pleomorphism and tumor giant cells. (**c**) Leiomyosarcoma with mild nuclear atypia and high mitotic activity. (**d**) Leiomyosarcoma with foci of coagulative necrosis. (**e**) Leiomyosarcoma with infiltrative margins

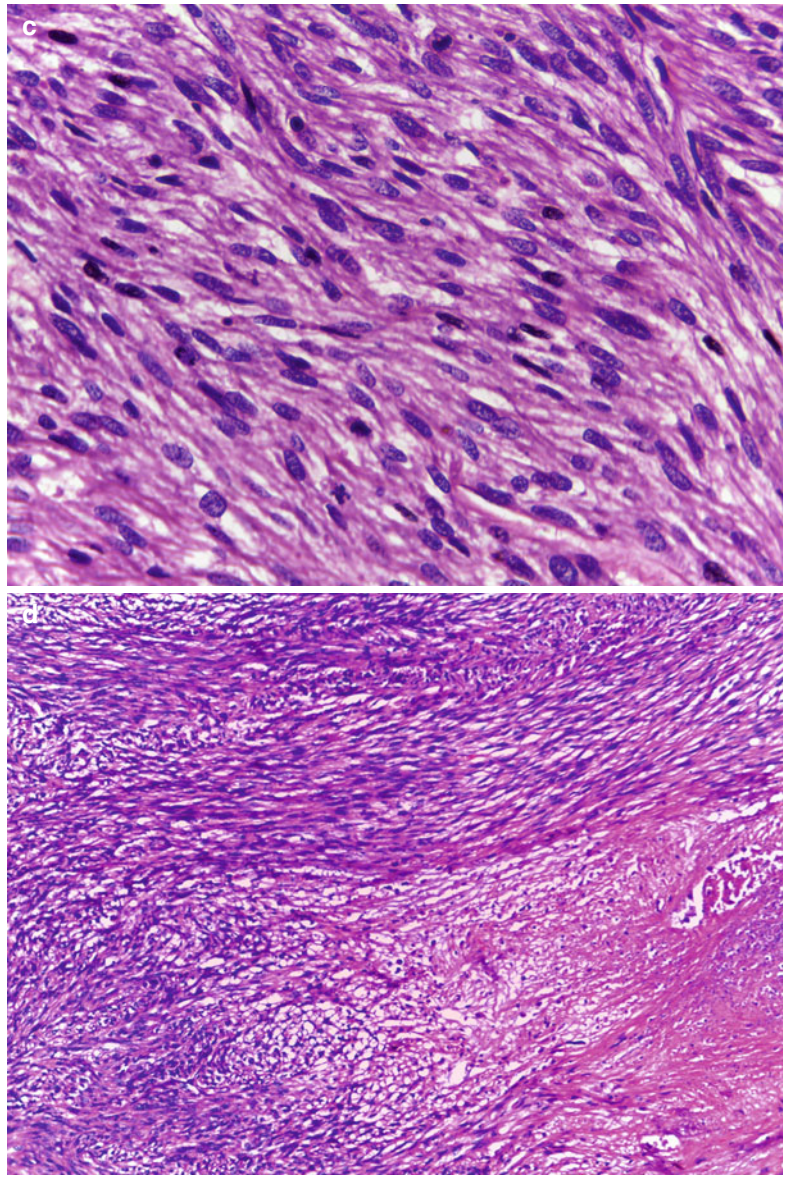


Fig. 11.1 (continued)

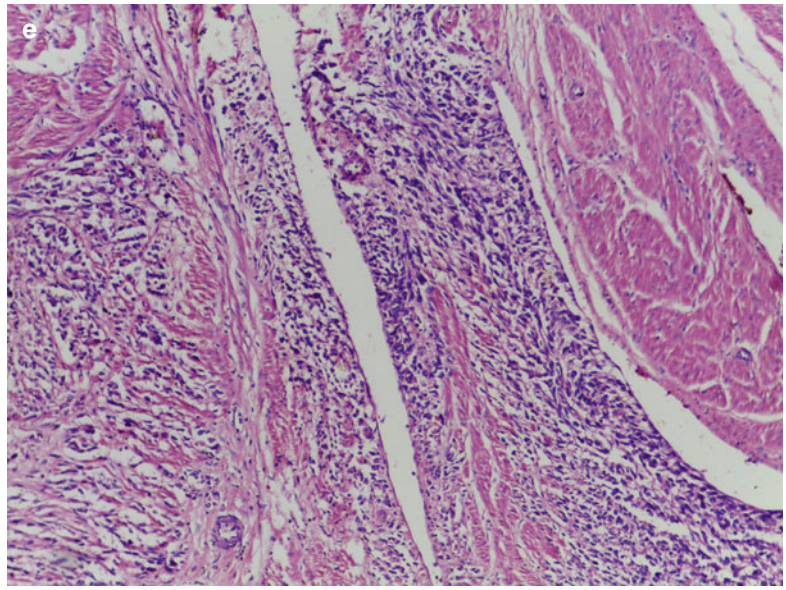


Fig. 11.1 (continued)

many histological features that were assessed, mitotic index, the degree of cytological atypia, and the presence or absence of coagulative tumor cell necrosis have emerged as the most important predictors of behavior [7]. No single histological feature, with the exception of tumor cell necrosis, is diagnostic of malignancy. By employing three variables in the assessment of smooth muscle tumors, this diagnostic strategy moves away from complete dependence on mitotic count [8].

Other features that need to be considered are age of the patient, the size of the tumor and its gross appearance, the tumor's margins, and presence of vascular invasion.

The epithelioid and myxoid variants of LMS are rare tumors that exhibit malignant biologic behavior despite low mitotic counts and mild nuclear atypia.

LMSs are immunoreactive to smooth muscle markers such as smooth muscle actin, desmin, and h-caldesmon and histone deacetylace. Epithelioid LMS can express epithelial markers such as keratin and epithelial membrane antigen and are often immunoreactive to CD10.

Mutation and over expression of p53 and p16 has been described in a significant minority of LMS and in STUMPs that are at an increased risk of aggressive behavior but not in leiomyomas [9]. However other studies have shown that there is significant overlap in the Ki-67, p16, and p53 expression patterns in the atypical leiomyoma to LMS spectrum precluding its routine use for diagnostic purpose.

Smooth Muscle Tumor of Uncertain Malignant Potential

Uterine smooth muscle tumors that show some worrisome histological features like necrosis, nuclear atypia, or mitosis, but do not meet all the generally applied diagnostic criteria for LMS, fall into the category of STUMP. Tumors are categorized as STUMP when: (a) The tumor has a moderately high mitotic count and some nuclear atypia, but it is not clear whether the tumor belongs to the usual, myxoid, or epithelioid type, making it difficult to apply the relevant guidelines to determine malignancy. (b) The tumor exhibits diffuse significant atypia, but the mitotic index is borderline between atypical and malignant categories. (c) The tumor is hypercellular, lacks tumor cell necrosis, has an MI >10, and exhibits borderline nuclear atypia. (d) The tumor

has focal significant atypia, MI > 10, and no tumor cell necrosis. (e) Tumor cell necrosis is present in a hypercellular neoplasm, but there is no significant atypia and the mitotic index is <10. (f) The tumor has diffuse significant atypia or a MI >10, and has necrosis of ambiguous type [10]. When the differential diagnosis is between STUMP and LMS, the diagnosis of STUMP should be favored when the tumor is small (<3 cm), since malignant behavior in a primary smooth muscle tumor <3 cm is yet to be reported. A STUMP diagnosis in a myomectomy specimen allows for flexibility in management that would not be available to patients with a diagnosis of LMS. However, the term should be used sparingly and every effort should be made to classify a smooth muscle tumor into a specific category.

Diagnostic Criteria for Smooth Muscle Tumors [11]

Spindle Cell Smooth Muscle Tumors with Significant Nuclear Atypia

Diffuse or multifocal moderate – severe nuclear atypia + no tumor cell necrosis +>10 mitotic figures/10 high-power fields = Leiomyosarcoma

Diffuse, multifocal, or focal moderate – severe nuclear atypia + tumor cell necrosis +>10 mitotic figures/10 high-power fields = Leiomyosarcoma

Diffuse, multifocal, or focal moderate – severe nuclear atypia + no tumor cell necrosis +< 7 mitotic figures/10 high-power fields = Atypical leiomyoma

Diffuse or multifocal moderate – severe nuclear atypia + no tumor cell necrosis +>7 but < 10 mitotic figures/10 high-power fields = STUMP

Spindle Cell Smooth Muscle Tumors without Significant Nuclear Atypia

No or minimal nuclear atypia + tumor cell necrosis + > 10 mitotic figures/10 high-power fields = Leiomyosarcoma

No or minimal nuclear atypia + tumor cell necrosis +< 10 mitotic figures/10 high-power fields = STUMP

No or minimal nuclear atypia + no tumor cell necrosis +>5 but < 15 mitotic figures/10 high-power fields = Mitotically active leiomyoma

No or minimal nuclear atypia + no tumor cell necrosis + > 15 mitotic figures/10 high-power fields = Mitotically active leiomyoma (uncertain behavior)

Myxoid Smooth Muscle Tumors

<2 mitotic figures/10 high-power + no tumor cell necrosis + no to minimal nuclear atypia + no infiltration of myometrium = Myxoid leiomyoma

>2 mitotic figures/10 HPFs or tumor cell necrosis or moderate to severe nuclear atypia or infiltration of the myometrium = Myxoid leiomyosarcoma

Epithelioid Smooth Muscle Tumors

<3 mitotic figures/10 high-power fields + no tumor cell necrosis + no to minimal nuclear atypia + no vascular invasion + well circumscribed margin = Consider epithelioid leiomyoma

>3 mitotic figures/10 high-power fields or tumor cell necrosis or moderate to severe nuclear atypia or vascular invasion or infiltrative margin = Epithelioid leiomyosarcoma

Endometrial Stromal Sarcoma

Endometrial stromal tumors are rare tumors derived from the endometrial stromal cells and are composed of cells resembling proliferative phase endometrial stroma. The tumors are currently classified by the WHO as endometrial stromal nodule, low-grade endometrial stromal sarcoma, high-grade endometrial stromal

sarcoma, and undifferentiated uterine sarcoma. The tumors account for approximately 0.2 % of all malignant uterine tumors and 10–15 % of uterine sarcomas.

Malignant endometrial stromal tumors were subclassified for many years into low-grade and high-grade ESSs according to their degree of mitotic activity. Tumors with <10 mitotic figures per 10 high-power fields were low grade and tumors with >10 mitotic figures per 10 high-power fields were high grade. However, subsequent studies of uterine sarcomas with recognizable endometrial stromal differentiation failed to confirm the prognostic relevance of this separation based upon mitotic activity, and found surgical stage to be the most powerful predictor of clinical outcome [12]. This resulted in the elimination of the high-grade ESS category based upon a high mitotic rate, and the low-grade ESS were referred to simply as ESS. However, many investigators favored the acceptance of a category of ESS with more than the usual degree of nuclear atypia seen in low-grade ESS and with significant mitotic activity yet retaining some evidence of endometrial stromal differentiation. More recently, some tumors previously considered to be undifferentiated uterine sarcomas have been shown to be of endometrial stromal derivation (often associated with a component of low-grade endometrial stromal neoplasm) and are designated high-grade endometrial stromal sarcomas. The 2014 WHO classification of tumours of the uterine corpus includes the category of high-grade endometrial stromal sarcoma in the endometrial stromal and related tumors group [3].

Significant myometrial invasion and angiolymphatic invasion are the features that distinguish ESSs from ESNs. Patients are usually under 50 years of age and present with abnormal vaginal bleeding or pelvic or abdominal pain.

Gross Features

The tumors are solitary, well-delineated, and predominantly intramural lesions, but extensive myometrial permeation is common with extension to the serosa in approximately half of the cases. They may also present as endometrial polyps or involve both the endometrium and myometrium. Extrauterine primary ESS are also seen and often arise from foci of endometriosis. The tumors are fleshy and yellow or tan, bulging above the adjacent myometrium and lacking the whorled appearance of smooth muscle tumors. Cystic and myxoid degeneration as well as necrosis and hemorrhage are seen occasionally. Some tumors may infiltrate the myometrium with a worm-like appearance. The high-grade tumors usually present as intracavitary polypoid and/or intramural masses and often show extrauterine extension at the time of diagnosis.

Microscopic Features

Low-grade ESS is usually a densely cellular tumor composed of diffuse sheets of uniform, round, oval to spindle-shaped cells of endometrial stromal type. The tumor cells lack significant atypia and pleomorphism (Fig. 11.2a). ESS is a low-grade tumor by definition and mitotic activity is usually low but may be high with mitotic rates of 10 or more per 10 high-power fields. However, the mitotic count is not a criterion for diagnosis. The tumors are supported by a characteristic vasculature composed of a rich network of regularly spaced, thin-walled, elongated, compressed, branching capillaries, and small arterioles resembling the spiral arterioles of the late secretory endometrium (Fig. 11.2b). The arterioles may be surrounded by concentric whorls of tumor cells (Fig. 11.2c). The tumors may have edematous, hyalinized, myxoid, or fibrous areas, clusters of foam cells, rhabdoid cells, endometrial-type glands, and even sex cord-like structures. Focal smooth muscle differentiation may be seen, but is less than 30 % of the tumor. When the smooth muscle component is 30 % or more, the tumors are designated mixed endometrial stromal and smooth muscle tumor. Rarely skeletal muscle, fat, or pseudo cartilage may be seen leading to problems in differential diagnosis.

The term, endolymphatic stromal myosis was formerly used for ESSs with a characteristic type

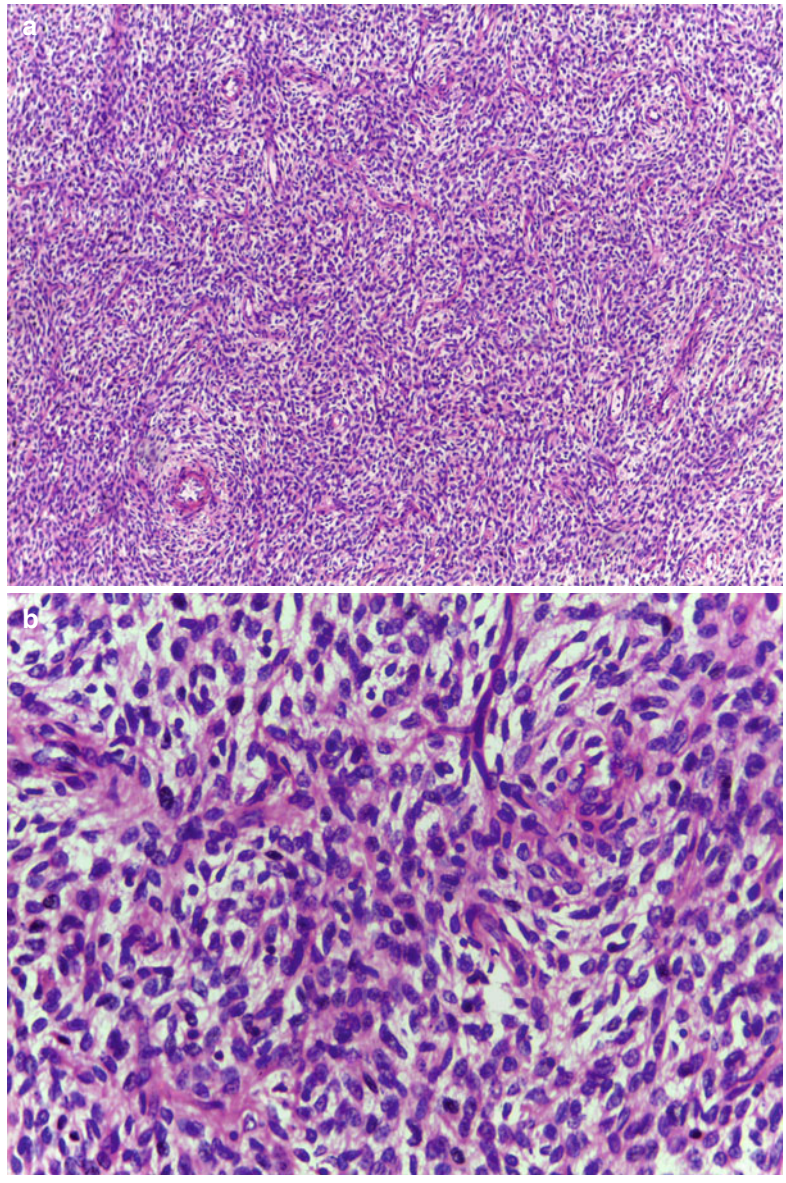


Fig. 11.2 (**a**) Endometrial stromal sarcoma with uniform cells resembling endometrial stromal cells. (**b**) Endometrial stromal sarcoma with rich vascular network. (**c**) Endometrial stromal sarcoma with perivascular whorls of tumor cells and rhabdoid cells

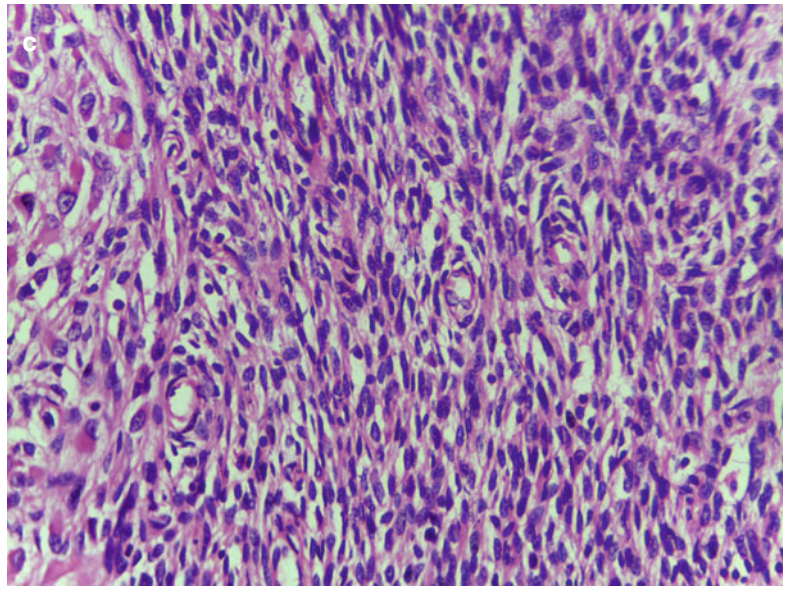


Fig. 11.2 (continued)

of infiltration. In these tumors, broad, rounded bands and serpentine processes of stromal cells infiltrated extensively into the myometrium, between the muscle fibers and particularly into the lymphatic and vascular spaces, sometimes with extension into vessels outside the uterus.

Although the high-grade endometrial sarcomas on low-power examination may reveal a similar pattern of infiltrative growth and vasculature to low-grade endometrial stromal sarcoma, these tumors typically have a confluent, permeative and destructive growth pattern with deep myometrial invasion. There is usually brisk mitotic activity and necrosis. A subset of these tumors displays specific morphological features and genetic abnormalities. There are usually two morphologically distinctive components in these tumors. A (usually predominant) high-grade, round cell tumor component is present in association with a low-grade spindle cell component with fibromyxoid features. The low-grade component is not present in all cases. The high-grade round cell component may be noncohesive or may have a nested, pseudopapillary or pseudoglandular appearance, or rhabdoid morphology.

ESS is immunoreactive to vimentin, CD10, focally for muscle specific actin, alpha smooth-muscle actin, and frequently keratin. They are usually negative for desmin and h-caldesmon. CD10 should not be used in isolation when evaluating the cell of origin in a uterine mesenchymal tumor since smooth muscle tumors, mixed Mullerian tumors, and even rhabdomyosarcomas are immunoreactive to CD10. Low-grade ESSs are usually positive for estrogen and progesterone receptors [13]. ESS often carry the translocation t (7; 17) with involvement of two zinc finger genes, *JAZF1 and JJAZ1*, suggesting a genetic basis for tumor development [14]. The fusion gene product can be detected by fluorescence in situ hybridization or reverse transcriptase polymerase chain reaction.

A distinctive form of high-grade stromal sarcoma, having round cell morphology and a unique t(10;17)(q22;p13), which results in *YWHAE-FAM22* gene fusion, has recently been characterized and is associated with an aggressive clinical course [15]. In this newly described subset of high-grade endometrial stromal sarcoma, the high-grade component is typically CD10, ER, and PR negative, and shows variable, but often high, expression of cyclin D1. The high-grade component is also sometimes CD99 and CD117 (c-Kit) positive but DOG1 negative.

The associated low-grade component is usually, but not always, CD10, ER, and PR positive, negative with CD99 and CD117 and exhibits low expression of cyclin D1.

The differential diagnosis includes ESN, intravenous leiomyomatosis, adenomyosis with sparse glands, and adenosarcoma. ESS is distinguished from ESN by the nature of the interface with the surrounding myometrium. ESS is an infiltrative neoplasm while ESN is well circumscribed, although slight marginal irregularity is allowable. Vascular invasion excludes ESN. Adenomyosis with stromal predominance or adenomyosis with sparse glands may be misdiagnosed as ESS. Further sampling usually demonstrates areas with the typical adenomyosis with glands surrounded by hypertrophied myometrial smooth muscle. **It is difficult to distinguish an ESS from the above lesions in a biopsy or curettage.**

Undifferentiated Uterine Sarcoma

Undifferentiated uterine sarcoma is the term currently used by the WHO for those rare sarcomas without smooth muscle or stromal differentiation and that have a more aggressive histologic appearance than allowed for ESS, but whose topography indicates an endometrial origin. These tumors are formed of anaplastic cells which have no recognizable evidence of a definite endometrial stromal phenotype [16].

UUSs generally occur in postmenopausal women, accounting for approximately 5 % of uterine sarcomas, present with abnormal vaginal bleeding and uterine enlargement, and are associated with a poorer prognosis.

Gross Features

UUSs are usually bulky, polypoid, intracavitary, fleshy, grayish-white tumors with areas of hemorrhage and necrosis. The aggressive growth pattern of UUS typically replaces the myometrium. Angiolymphatic invasion is often present, but the macroscopic plugs of intravascular tumor that are often seen in low-grade ESS are not seen in UUS.

Microscopic Features

The tumors lack the characteristic vascular pattern of low-grade ESS, and the tumor cells bear no resemblance to endometrial stromal cells. The tumor grows as cellular sheets, shows marked nuclear atypia and high mitotic activity, almost always exceeding 10MF/10HPF and sometimes up to 50MF/10HPF, with atypical mitotic figures and/or tumor cell necrosis, resembling the sarcomatous component of carcinosarcomas (Fig. 11.3a, b). Thorough sampling is essential to look for carcinomatous elements to rule out carcinosarcoma and to exclude poorly differentiated or undifferentiated carcinoma, leiomyosarcoma, rhabdomyosarcoma, large cell lymphoma, and granulocytic sarcoma – tumors that have to be considered in the differential diagnosis of an undifferentiated malignant tumor and are excluded by a combination of morphological and immunohistochemical features.

Recent studies suggest that UUS is a heterogeneous group and include a subgroup with uniform nuclei, and having morphologic, immunohistochemical, and genetic features more like low-grade ESS. These findings have reintroduced the term high-grade endometrial stromal sarcoma for those tumors whose cytologic atypia marginally exceeds the limits of that expected for low-grade ESS, exhibit high mitotic activity, including atypical mitotic figures, but still retain some evidence of endometrial stromal differentiation. UUSs are not immunoreactive with ER and PR but a high proportion is EGFR and p53 positive. Smooth muscle markers and myogenin or myoD1 may be used to rule out leiomyosarcoma or rhabdomyosarcoma respectively, or to identify a rhabdomyosarcomatous component of a carcinosarcoma.

The tumors have a poor prognosis and most patients die of disease within 2 years of the diagnosis. Vascular invasion, local recurrence, and distant metastasis are associated with a high mortality.

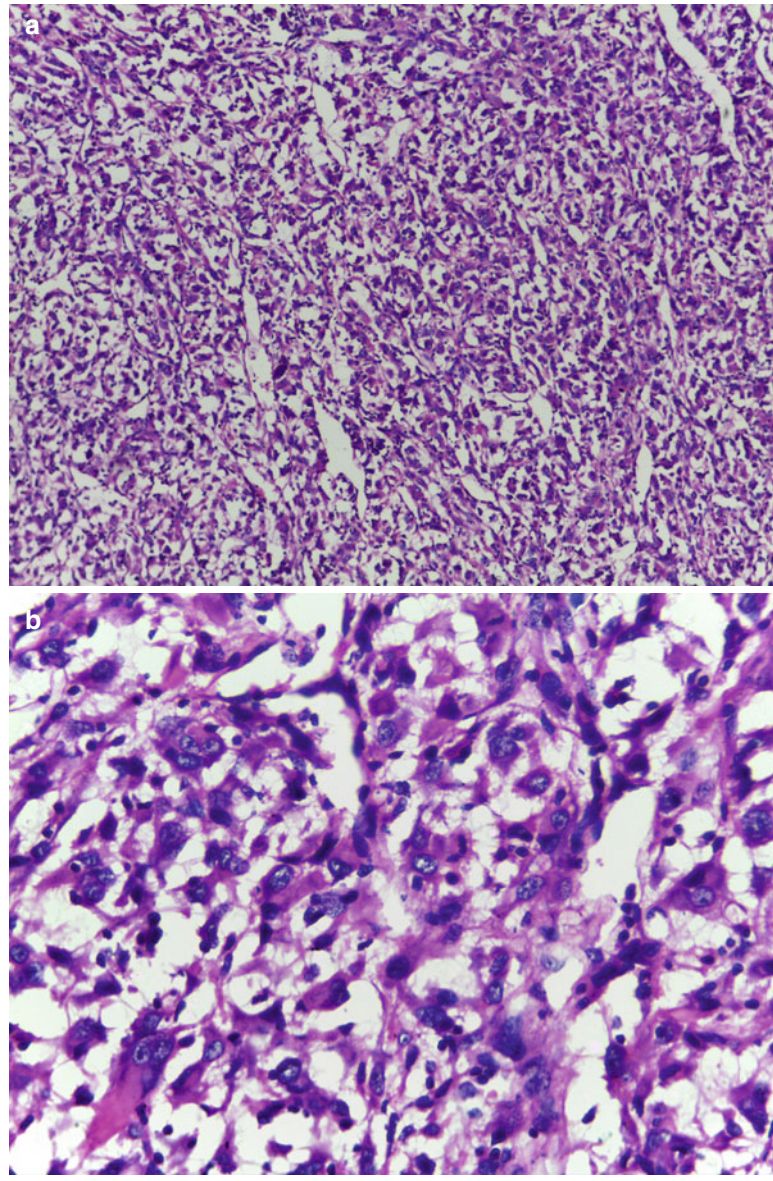


Fig. 11.3 (**a**) Undifferentiated uterine sarcoma resembling the sarcomatous component of carcinosarcomas, LP view. (**b**) Undifferentiated uterine sarcoma, HP veiw

Adenosarcoma

Adenosarcoma is a biphasic neoplasm composed of a benign epithelial component and a sarcomatous mesenchymal component**.** It is a rare tumor that accounts for only about 8 % of uterine tumors with a malignant mesenchymal component. Adenosarcomas are tumors of low malignant potential with distinctive clinicopathological features**.** The tumors occur in women across a wide age range, but mainly in postmenopausal women**.** They present with abnormal uterine bleeding related to a large polypoid tumor (mean diameter of 5 cm) that projects into the endometrial cavity and may protrude through the external os. Patients with repeated episodes

of recurrent endometrial polyps have to be carefully evaluated for the possibility of adenosarcoma, since areas with nondiagnostic or subtle histologic features are common [17]. Adenosarcomas have been reported in women undergoing tamoxifen therapy for breast cancer and occasionally after prior pelvic radiation. There is no association of adenosarcoma with obesity or hypertension.

Gross Features

Adenosarcomas typically grow as exophytic polypoid masses that extend into the uterine cavity. Rarely, they may arise in the endocervix and within the myometrium, from foci of adenomyosis. The tumor may sometimes present as multiple papillary masses protruding into cystic spaces. On sectioning, the surface is tanbrown with foci of hemorrhage and necrosis. Small cysts are frequently present imparting a spongy appearance to the tumor. Most adenosarcomas do not invade the myometrium.

Microscopic Features

On low magnification, the tumor presents a leaf-like pattern closely resembling phyllodes tumor of the breast. The glands form elongated slit-like clefts resembling outlines of leaves, due to compression by polypoid projections of sarcomatous stroma (Fig. 11.4a–c). There is characteristic stromal condensation surrounding the cystic or cleft-like glands. It is in these areas that the stroma shows the greatest degree of atypia or mitotic activity. The glands are usually lined by endometrioid epithelium but may show focal metaplastic changes with mild atypia. The mesenchymal part of adenosarcoma is usually a low-grade homologous stromal sarcoma with varying amounts of fibrous tissue and smooth muscle. Heterologous elements are identified in approximately 10–15 % of cases consisting of striated muscle, cartilage, fat, and other components. Sex cord-like elements resembling those in endometrial stromal sarcoma are found in less than 10 % of adenosarcomas. Typically, mitotic figures are low (usually more than 1 per 10 high-power fields in the hypercellular cuffs) in the mesenchymal component, and cytological atypia is usually mild but occasionally may be moderate. The diagnosis of sarcomatous overgrowth is made when the pure sarcomatous component, usually of high grade, occupies 25 % or more of the total tumor volume. These areas of pure sarcoma are much more likely to exhibit higher nuclear grade with increased mitotic activity and higher Ki-67 proliferation index, more tumor necrosis and loss of immunoreactivity for markers commonly expressed by endometrial stromal cells (CD 10, ER, and PR) than the sarcomatous component of typical adenosarcomas. Adenosarcomas with sarcomatous overgrowth have been found to be more aggressive than the typical adenosarcomas, with recurrences, metastasis, and tumor related deaths occurring at rates similar to leiomyosarcoma or carcinosarcoma.

The immunophenotype of adenosarcomas closely parallels that of endometrial stromal neoplasms when there is no sarcomatous overgrowth. The mesenchymal component typically expresses ER, PR, androgen receptors, CD10, and WT1, while few tumors also express smooth muscle actin and pan-cytokeratins [18]. Cases demonstrating stromal overgrowth generally lose strong and diffuse ER, PR, CD10, and WT1 expression. Tumors containing heterologous elements exhibit an immunophenotype that is similar to eutopic tumors; therefore, the mesenchymal component of an adenosarcoma with rhabdomyoblastic differentiation would be expected to express desmin, myogenin, and myoD1. As with carcinosarcomas, recent work suggests that the presence of rhabdomyoblastic differentiation portends a poor prognosis. The proliferative index, estimated with a Ki-67 immunostain, increases with mitotic rate and the presence of sarcomatous stromal overgrowth.

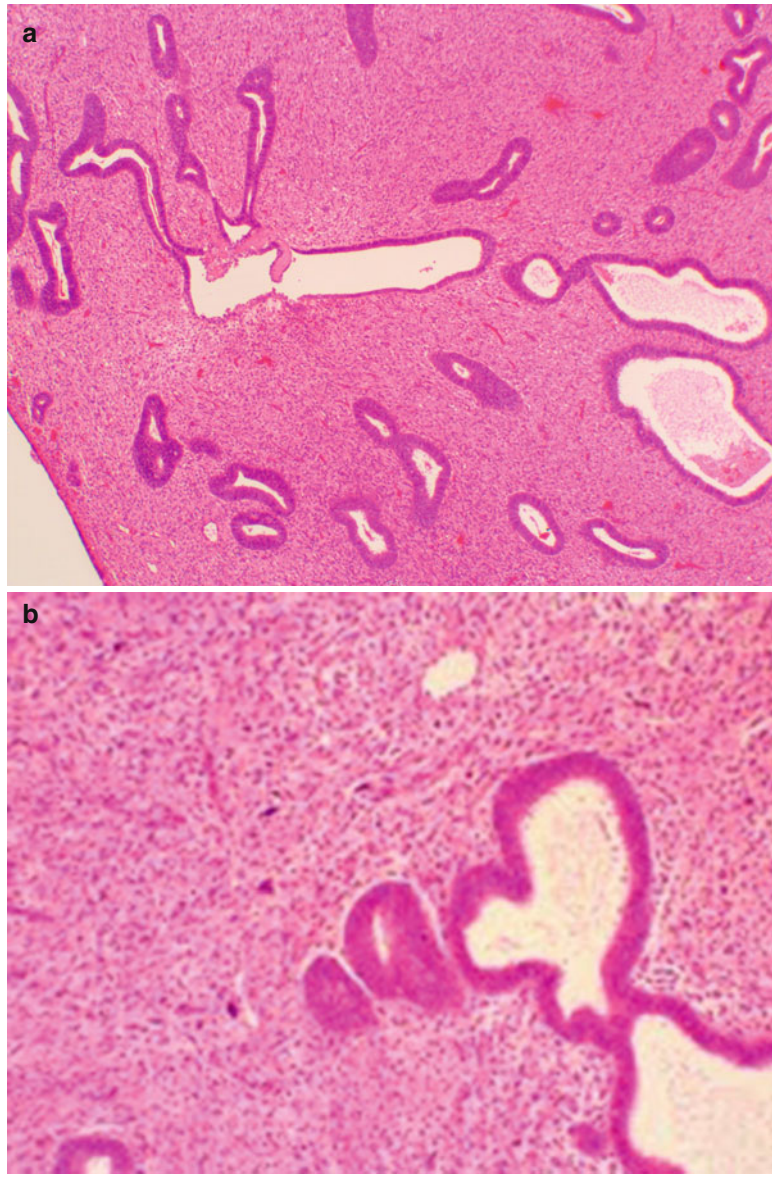


Fig. 11.4 (**a**) Adenosarcoma with slit-like glands in sarcomatous stroma. (**b**) Adenosarcoma with sarcomatous stroma under higher magnification. (**c**) Adenosarcoma with the sarcomatous stroma showing pleomorphic cells

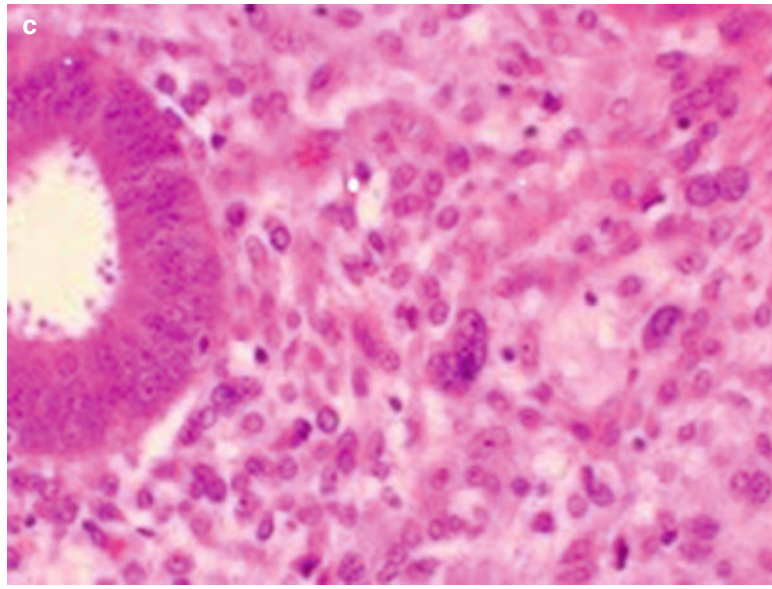


Fig. 11.4 (continued)

Carcinosarcoma

Carcinosarcomas, synonymous with malignant mixed Mullerian tumor and malignant mixed mesodermal tumor (MMMT), were traditionally considered as the most common subtype of uterine sarcomas, accounting for 40–50 % of uterine sarcomas. These tumors are now considered to represent metaplastic carcinomas – a special variant of endometrial adenocarcinoma. However, the tumor is described here in some detail because carcinosarcomas with a predominance of sarcomatous elements are often misdiagnosed as one of the rare heterologous sarcomas. The term carcinosarcoma is now used for all primary uterine neoplasms containing malignant elements of both epithelial and stromal light microscopic appearance, regardless of whether malignant heterologous elements are present.

It is a biphasic neoplasm composed of an admixture of epithelial and mesenchymal elements, both of which are malignant. Though these tumors have traditionally been considered a subtype of uterine sarcomas, mounting clinical, histological, immunologic, and molecular data strongly support the concept that these tumors represent metaplastic carcinomas, hence they are now considered a special variant of endometrial adenocarcinoma [19]. However, though 80–90 % of CSs are monoclonal, 10–20 % of the tumors are biclonal and represent true collision tumors.

Carcinosarcomas typically occur in postmenopausal women who present with abnormal vaginal bleeding, uterine enlargement, and abdominopelvic pain. The serum level of CA125 is elevated in most cases. Rarely these tumors are seen in women less than 40 years. Extrauterine spread (stages III-IV) is present at presentation in up to one-third of cases. Up to 37 % of patients with CSs have a history of pelvic irradiation. These tumors tend to occur in younger women, often contain heterologous elements, and are found at advanced stage.

Gross Features

CSs are large and bulky broad-based, polypoid tumors that distend the endometrial cavity and invade the myometrium. The tumors may protrude through the external os. Cut surfaces are fleshy with hemorrhagic and necrotic areas.

Gritty or hard areas may be present, corresponding to bone or cartilage. Occasional tumors may arise within an endometrial polyp.

Microscopic Features

The carcinomatous component of CS is typically a high-grade adenocarcinoma with endometrioid or serous differentiation and rarely clear cell or other less common carcinomas. The sarcomatous component is also usually high-grade with homologous or heterologous tissues. Homologous sarcoma is usually composed of nondescript spindle, oval, or round cells with significant nuclear atypia and mitotic activity resembling sarcomas derived from endometrial stroma, fibrosarcoma, or rarely leiomyosarcoma (Fig. 11.5a, b). Heterologous sarcomatous

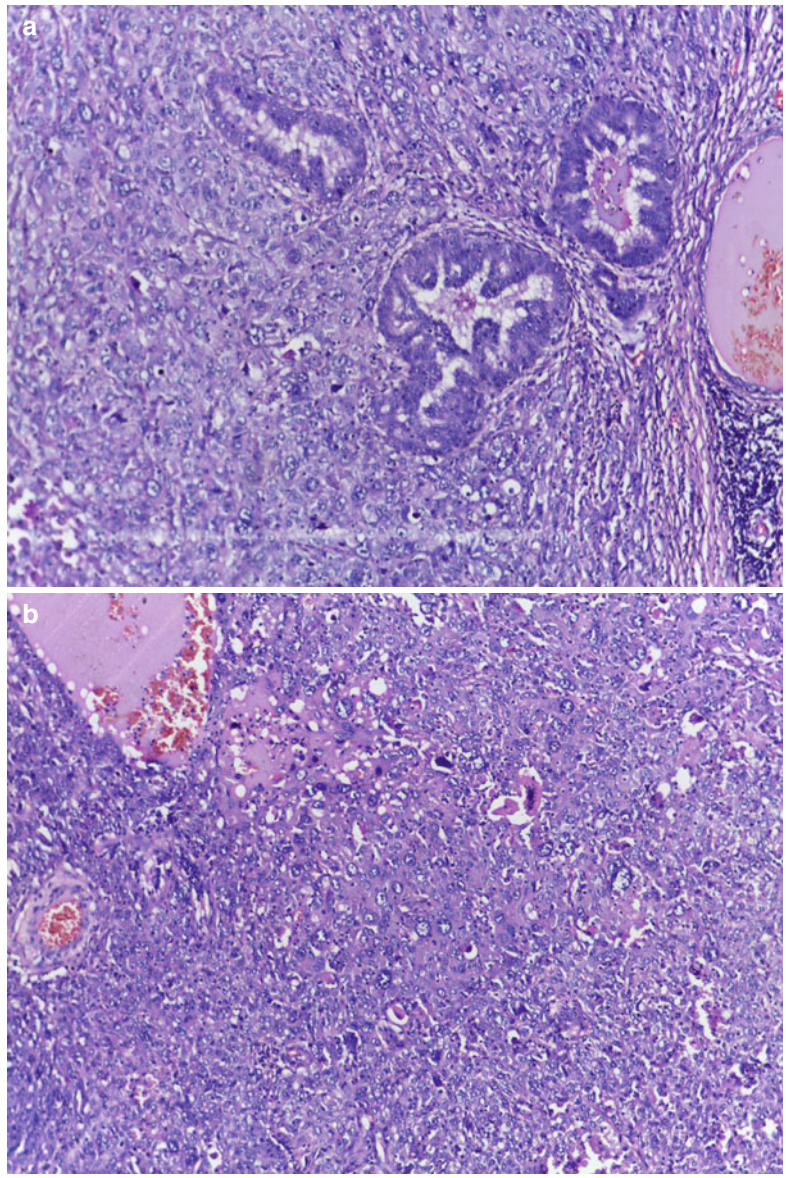


Fig. 11.5 (**a**) Carcinosarcoma with malignant epithelial and sarcomatous stromal elements. (**b**) Sarcomatous stroma of carcinosarcoma. (**c**) Carcinosarcoma with malignant epithelial and heterologous stromal component. (**d**) Carcinosarcoma with chondrosarcomatous areas

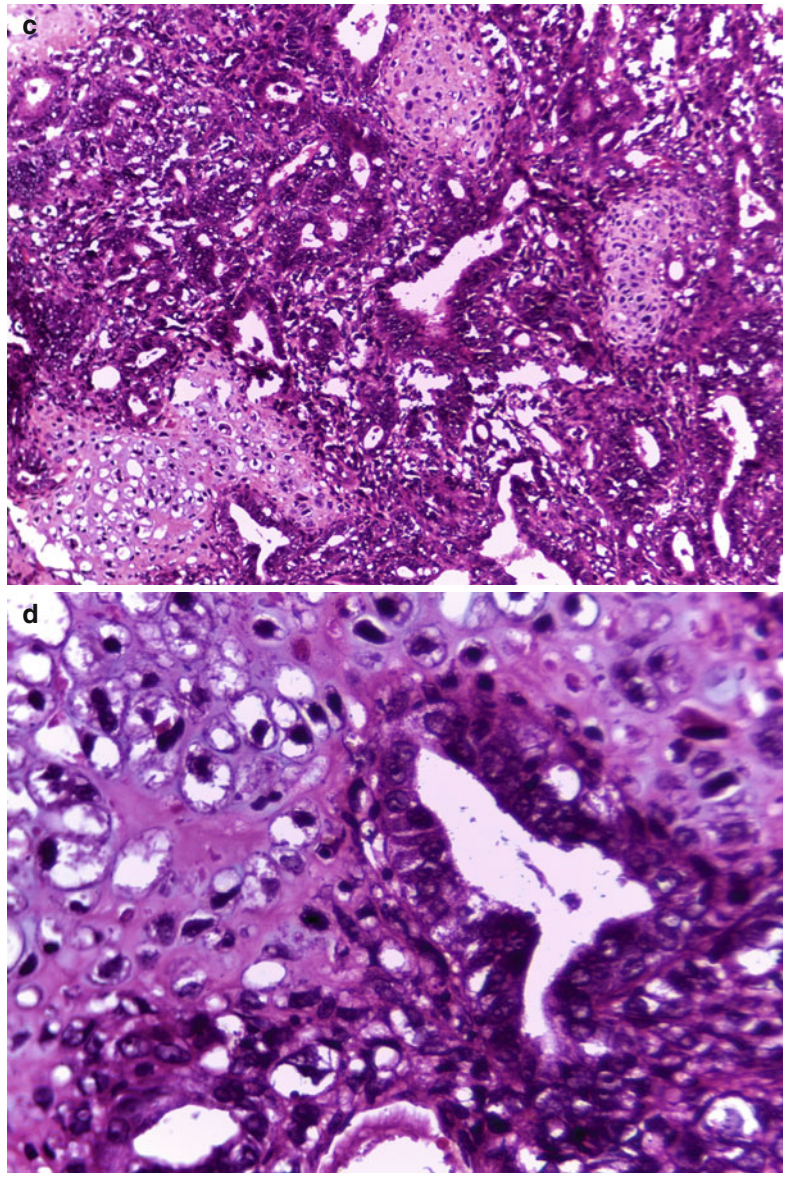


Fig. 11.5 (continued)

elements are usually rhabdomyosarcoma**,** chondrosarcoma (Fig. 11.5c, d), osteosarcoma, and liposarcoma**.**

Carcinosarcomas are aggressive neoplasms that as a group have a prognosis that is worse than both high-grade endometrial adenocarcinoma and the high risk subtypes of serous and clear cell carcinoma, and tumor stage is the most powerful prognostic predictor. The potential prognostic significance of heterologous elements is controversial [20].

Other Rare Sarcomas

Perivascular epithelioid cell tumors ("PEComa") and uterine tumor resembling ovarian sex cord tumor (UTROSCT) (Fig. 11.6a) are rare mesenchymal tumors of the uterus with distinct morphological and immunohistochemical features. These tumors are considered to be neoplasms of low malignant potential.

Sarcomas other than those described above can arise in the uterus from tissues that are not

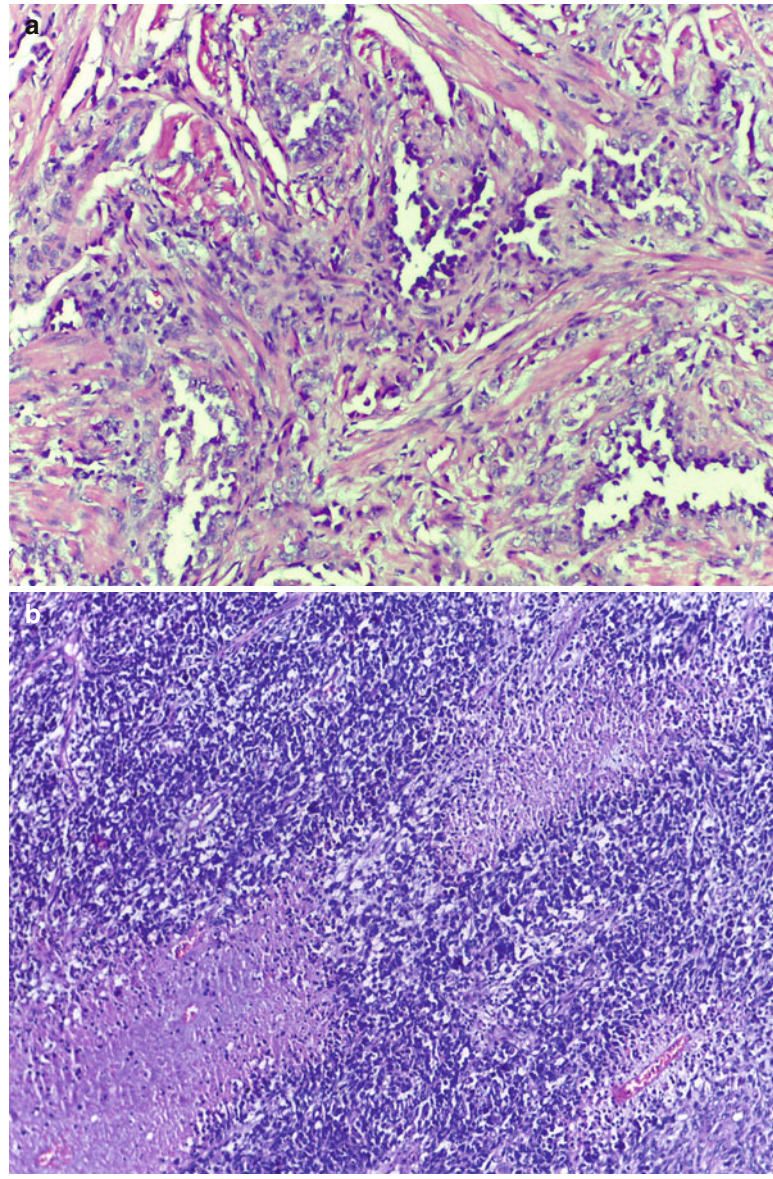


Fig. 11.6 (**a**) Uterine tumor resembling ovarian sex cord tumor. (**b**) Embryonal rhabdomyosarcoma

endometrial stromal or smooth muscle in type. These tumors are rare and are similar to their counterparts arising in more usual sites. They include rhabdomyosarcoma-embryonal in young females (Fig. 11.6b) and pleomorphic in the middle aged and elderly. Liposarcoma, chondrosarcoma, osteosarcoma, malignant peripheral nerve sheath tumor, angiosarcoma, malignant fibrous histiocytoma, malignant mesenchymoma, alveolar soft part sarcoma, GIST, rhabdoid sarcoma, Ewing sarcoma/PNET, and tumors with neuroectodermal differentiation but lacking the EWSRI gene rearrangement [21–23]. In general these tumors are all bulky neoplasms and frequently high stage at presentation. Immunohistochemical studies may assist in establishing a definitive diagnosis of these tumors. However before making a diagnosis of these rare sarcomas, particularly if the tumor is very pleomorphic and includes heterologous elements, the more likely possibility of carcinosarcoma with predominance of the sarcoma-like component should be ruled out with thorough sampling [24].

Conclusion

Uterine sarcomas are a heterogeneous group of rare tumors with aggressive clinical behavior and poor prognosis. The recent changes in the classification and staging of these tumors have helped in understanding the different behavioral patterns of these tumors. Accurate typing of uterine sarcoma is vital since the behavior, management, and patient outcome differ markedly between the different tumor types. Immunohistochemistry and molecular studies can be of use in certain situations in the evaluation of uterine sarcomas. The results of immunohistochemistry should always be interpreted in conjunction with the clinical features and gross and microscopic findings. More knowledge about the genetic aberrations and genomic rearrangements responsible for uterine sarcoma genesis may help in the development of more effective therapies.

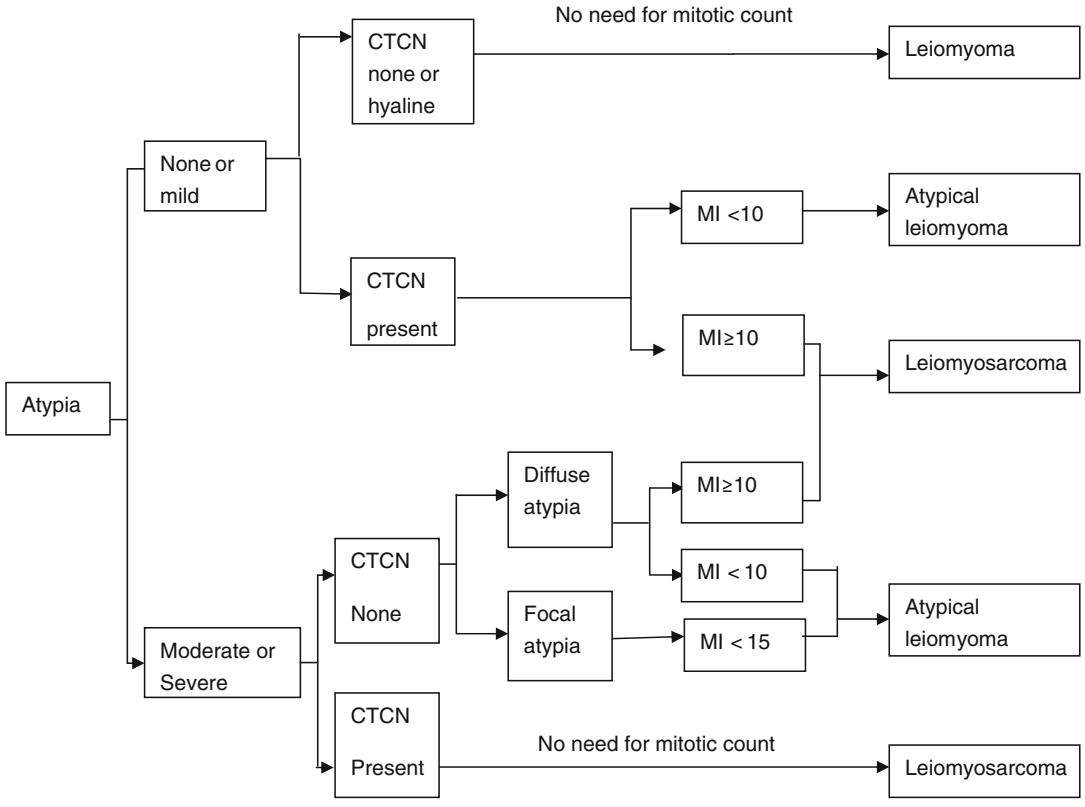
Key Points

1. 3–5 % of malignant uterine tumors contain a malignant mesenchymal component. With the updated classification (excluding CS) LMS accounts for 60 % of the tumors, ESS 30 %, UUS –5 %, and AS and other uterine sarcomas 5 % which includes malignant PEComa, UTROSCT, rhabdomyosarcoma, PNET, angiosarcoma, osteosarcoma, chondrosarcoma, liposarcoma, alveolar soft part sarcoma, malignant rhabdoid tumor, and other very rare tumors.
2. The historic classification of uterine sarcomas which categorized endometrial stromal sarcomas into the low and high-grade ESS based on the mitotic activity had been replaced by ESS and UUS in the (2003) WHO classification of tumours of the uterine corpus. However, recent molecular and morphological data have validated the re-introduction of high-grade endometrial stromal sarcoma, for a specific subset of uterine sarcomas. The latest (2014) WHO classification includes low-grade ESS, high-grade ESS, UUS and UTROSCT in the endometrial stromal group of tumors.
3. Carcinosarcomas are now considered metaplastic carcinomas and the term is now used for all primary uterine neoplasms containing malignant elements of both epithelial and stromal light microscopic appearance, regardless of whether malignant heterologous elements are present.
4. The 2009 FIGO staging system has developed specific staging systems for LMS and ESS and for AS. Carcinosarcoma continues to be staged as an endometrial carcinoma.
5. Leiomyosarcoma, undifferentiated uterine sarcoma, and the heterologous sarcomas are, in general, highly aggressive tumors with a high propensity for extrauterine spread and systemic metastasis while the low-grade endometrial stromal tumors are indolent neoplasms which are compatible with long-term survival despite the tendency for late recurrences or metastatic spread.
6. Adenosarcomas are mixed tumors of low malignant potential containing a benign epithelial and a malignant stromal component, usually of low grade. They are usually polypoid neoplasms that project into the uterine cavity and have a favorable prognosis unless associated with sarcomatous overgrowth or deep myometrial invasion.
7. It is almost impossible to distinguish low-grade ESS from a stromal nodule, a nonneoplastic stromal proliferation or a highly cellular leiomyoma in an endometrial biopsy or a curettage sample since the distinction is mainly based on the appearance of the stromal-myometrial interface.
8. Leiomyosarcoma is only infrequently diagnosed on endometrial samplings.

9. Disease stage is the most important prognostic factor for all types of US. However, the prognosis of stage I LMS is also significantly related to tumor size and mitotic index (MI), and that of stage I ESS is related to MI and tumor cell necrosis (TCN). In adenosarcoma, TCN is the only significant histopathological prognostic factor [25].
10. Molecular studies are proving to be of value in the diagnosis of uterine sarcomas, and these are becoming routinely available in specialist centers. Many, but not all, of the techniques can be performed on formalin-fixed paraffin-processed tissue. A recurrent t (7; 17) (p15;q21) translocation resulting in a JAZF1-JJAZ1 gene fusion has been demonstrated in over 60 % of endometrial stromal tumors, including its variants. A group of high-grade endometrial stromal sarcomas harbors the YWHAE-FAM22 genetic fusion as a result of t(10;17)(q22;p13). Molecular studies may also be useful to confirm the diagnosis in problematic cases. Other sarcomas that occasionally occur in the uterus, like the alveolar rhabdomyosarcoma, desmoplastic small round cell tumor, and neoplasms in the Ewing family of tumors demonstrate consistent molecular abnormalities.

Appendix

The histological diagnosis of leiomyosarcoma



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Prognostic and Predictive Factors in the Management of Carcinoma Endometrium

12

K. Chitrathara

Introduction

Carcinoma Endometrium is the most common gynecological malignancy in the west. It ranks third in India after cervix and ovary. Women with endometrial cancer are usually diagnosed at an early stage, as most present with irregular bleeding or abnormal vaginal discharge and surgery is curative. A few subset of women may present with high risk histological factors or are in an advanced stage of disease. These women will need multimodality treatment to achieve a cure. The overall 5-year survival is 80–90 % in stage 1 tumors. With the advent of molecular and genetic factors further research has to be progressed for the preoperative prediction of bad prognostic group to be selected for neoadjuvant treatment to improve the disease free survival.

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Prognostic and Predictive Factors

Various risk factors have been studied extensively since late 1970s [1, 2] which have a prognostic impact in the management of carcinoma endometrium. A prognostic factor is defined as a measurement taken at the time of diagnosis or surgery that is associated with outcome like overall survival, disease free survival, or local control. A predictive factor is a measurement that predicts response or lack of response to a specific treatment. Various risk factors include:

1. Stage of the disease
2. Type of the tumor
3. Grade of the tumor
4. Myometrial Invasion
5. Tumor site
6. Tumor size
7. Lymphovascular space invasion (LVSI)
8. Positive peritoneal cytology (PPC)
9. Adnexal metastasis
10. Peritoneal implants
11. Age

Stage of Disease

Surgicopathological staging is the most important prognostic factor directly correlating with the survival. However the role of clinicoradiological

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findings in staging is not insignificant. The new FIGO staging for carcinoma endometrium published in NCCN Version 1.2014 [3] is given in the Chap. 6 on Risk factors, diagnosis and staging.

In advanced stages, debulking surgery with radiotherapy with or without chemotherapy is usually done. Five-year survival in carcinoma endometrium is given below and the figures given below are from the National Cancer Database, and are based on women diagnosed with endometrial cancer between 2000 and 2002.

Stage	5 years survival (%)
1A	88
1B	75
11	69
111A	58
111B	50
111C	47
1v A	17
1v B	15

Types of the Tumor

There are two types of tumors.

Type I tumors usually occur in pre- and perimenopausal women, often with a history of unopposed estrogen exposure and/or endometrial hyperplasia. They are often minimally invasive into the underlying uterine wall and are of low grade endometroid type and carry a good prognosis.

Type II tumors occurs in older, postmenopausal, thin women, and are not associated with increased exposure to estrogen; they are more aggressive and less differentiated and carry a poor prognosis. These include clear cell tumor, papillary serous tumors, and carcinosarcomas. These tumors have mainly p53 mutation and ERBb-2 (her 2 neu) expression.

Myometrial Invasion

Depth of myometrial invasion, tumor extension to the cervix, and lymph nodal status are part of FIGO staging, each of the above factor involvement progressively upstages the disease and they are independent prognostic factors themselves. Increasing depth of myometrial infiltration is associated with increasing tendency to extrauterine spread. Superficial or no myometrial infiltration is seen with well differentiated tumors. Deep myometrial invasion is seen frequently in poorly differentiated and undifferentiated tumors and thus is an alarming sign for lymph nodal involvement and distant metastasis and is often independent of degree of differentiation [4, 5]. Patients with >50 % involvement of myometrium is associated with poor prognosis. Patients whose myometrium has not been involved do not have much lymph-vascular space invasion even [6].

Deep myometrial involvement often coexists with cervical involvement by endometrial adenocarcinomas and has an adverse effect on prognosis [7]. Patients with lower uterine segment involvement are more likely to have pelvic and paraaortic nodal disease, and increasing local recurrence [8]. Spread to lymph nodes is associated with poor prognosis and require adjuvant treatment.

Tumor Size

In majority of tumors, T stage includes tumor size, the larger the tumor the more advanced the stage and lesser the survival. In endometrial carcinoma, increasing T stage indicates increasing depth of uterine wall infiltration. However many authors could correlate increasing tumor size with poor outcome in uterine carcinomas [8]. The conventional threshold is a measure of 2 cm [9]. Some have attempted to quantify three-dimensional tumor volume and correlate this risk to metastatic spread and survival [10].

Tumor Site

Tumor location inside the uterus can predict distant nodal disease and indicate chance of recurrence. Tumor involving fundal region has

increased risk of paraaortic lymph node involvement. Tumor occupying the whole endometrial cavity significantly upstages the cancer [11] (Fig. 12.1, and Table 12.1).

Grade of the Tumor

Since long, grade of the tumor has been regarded as an important prognostic factor in endometrial cancer [12]. Adenocarcinomas having 5 % or less nonsquamous or nonmural solid growth are designated as grade 1, those with 6–50 % solid growth as grade 2, and those with more than 50 % solid growth as grade 3. The 5-year survival rate in stage 1 carcinoma endometrium depends on the grade; the higher the grade, the poorer the prognosis (Tables 12.2 and 12.3)

Peritoneal Cytology

Positive peritoneal cytology portends a poor prognostic factor in earlier studies [1, 13]. The impact on survival of positive peritoneal cytology in the absence of other extrauterine disease is unclear and the treatment aimed at this is not well founded [14]. The following mechanisms may be deduced from the literature *for the presence of malignant cells in the peritoneal cavity* [15, 16]. (1) Result of transtubal transport; (2) direct

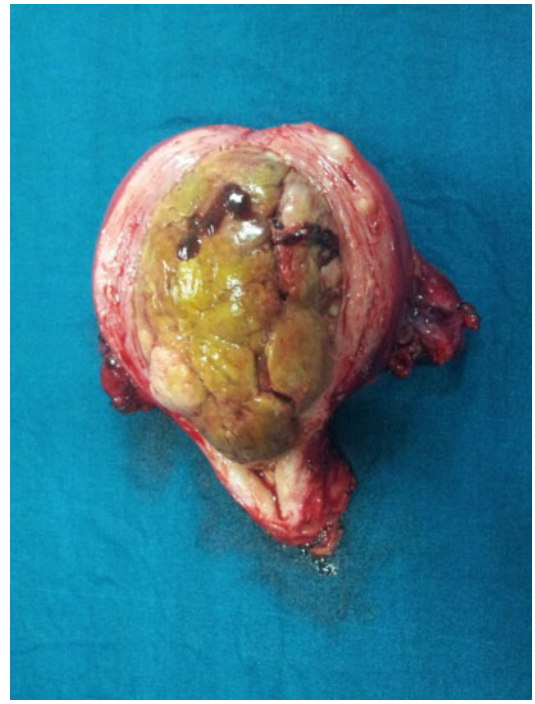

Fig. 12.1 Tumor occupying whole of the endometrial cavity

Table 12.1 Shows the tumor location inside uterus affecting the spread [11]

Tumor Site	Nodal spread (%)	Cervical Stromal Involvement (%)	Regional spread (%)	Metastasis (%)
Anterior (n=5)	0	0	0	0
Posterior (n=7)	0	14.28	0	0
Ant+post (n=3)	0	0	0	0
Fundal (n=5)	20	0	0	0
Ant.Fundal (n=5)	20	0	0	20
Post.Fundal (n=5)	0	0	0	0
Ant.+body (n=1)	0	0	0	0
Full Endometrial.Cavity (n=21)	28.57	14.28	19.04	4.76
Missing (n=7)	0	0	0	0

Table 12.2 Five-year survival in stage 1 endometrial cancer

Grade	Surgical (%)	Clinical (%)
1	93	60
2	90	50
3	79	29

Survival rates based on 5219 patients (Pecorelli S: Int J Gynecol Obstet. 2006;95:S121)

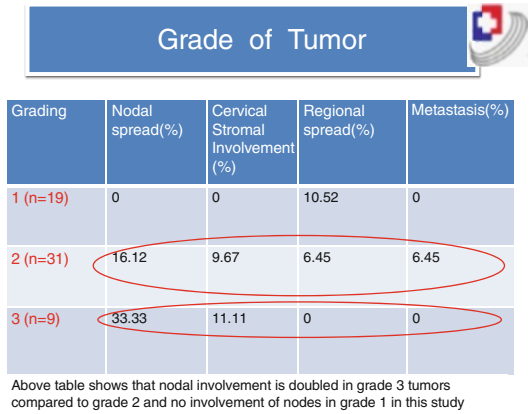

Table 12.3 Grade of tumor and spread [11]

extension of tumor through the myometrium; (3) lymphatic metastasis to the peritoneal cavity; and (4) reflection of multifocal peritoneal occult spread. Transtubal transport seems to be the most logical and popular. In more recent studies the authors are of opinion that the presence of positive peritoneal cytology is not an independent prognostic factor, and that it does not seem to reflect the potential of peritoneal spread in patients with endometrial carcinoma confined to the uterus [17, 18]. **Positive peritoneal cytology** is removed from FIGO Staging now; however it should be documented separately.

Patients having **adnexal metastasis and peritoneal implants** have poor prognosis as they indicate extrauterine spread and have more chances of pelvic and paraaortic lymph nodal involvement.

Age

Endometrial cancer occurs rarely in women under the age of 40. Most cases are found in women aged 50 and over, with more than half of the cases diagnosed in the age group of 50–69. The risk of endometrial cancer increases as the woman gets older. Age is not a significant variable of outcome after adjusting for other poor prognostic factors [19]. One study [20] divided patients to two groups, age in Group A was 59 years (range 50–69) and Group B was 75 years (range 70–92). Patients in Group B were more likely to have hypertension and coronary artery disease. There were no differences in progression-free or disease-specific survival; however, Group B had a worse overall survival proved to be due to associated comorbidities.

Many studies addressed the value of race as a prognostic factor in carcinoma endometrium [21–23]. Analysis of 41,120 cases of endometrial cancer indicated that race was a prognostic factors in addition to FIGO stage, histology, histologic grade, lymph node status, and age at diagnosis [21]. When incorporating the number of poor prognostic factors in a survival model with race and surgical stage, race ceased to be of significant prognostic value [22]. Although the incidence of endometrial cancer is less in Black women, cancer specific survival rates were lower in them when compared to that in white women. This racial difference in survival is multifactorial and include later diagnosis, treatment disparities, comorbid conditions, and genetic differences which result in the occurrence of more aggressive tumors in Black Americans [23].

DNA Ploidy

In a recent study [24], predictive and prognostic factors were analyzed in a consecutive series of 4543 endometrial carcinomas and it was concluded that DNA ploidy was an independent and significant prognostic and predictive factor. Eight predictive and prognostic factors were analyzed in this study with regard to recurrence and survival. The factors analyzed were: age, FIGO stage, histology, FIGO grade, nuclear grade, DNA ploidy, myometrial infiltration, and p53 expression. The 5 years actuarial locore-

gional recurrence rate was 3.6 %, the factors which independently affected the recurrence rate were FIGO grade, DNA ploidy, and depth of myometrial infiltration. The 5 years actuarial overall survival rate in these patients was 73 % and cancer specific survival was 83 %. All the factors studied except p53 expression analyzed with immunohistochemistry were found to be significantly affecting overall and cancer specific survival rates. Tumor stage was the single most important factor with a risk ratio of 4.2 followed by FIGO grade 2.5 and 1.6 for DNA ploidy. Myometrial invasion had the lowest risk ratio of 1.3 in this study with regard to survival.

LVSI

Lymphovascular space invasion is an important predictor for prognosis of disease as these are the patients who are at high risk for recurrences. The risk of pelvic and paraaortic lymph node involvement increases significantly. Gadducci et al. [25] in 2009 reported that their univariate and multivariate analysis on 259 endometroid endometrial cancer patients showed lymphvascular space involvement (LVSI) and deep myometrial invasion as the independent predictive variables for the risk of distant hematogeneous failure. The analysis included 12 patients in stage 1B-2 who developed distant failure compared to 20 randomly chosen control group who were disease free after a median period of 52 months.

In multivariate analysis of 324 high intermediate and high risk endometrial cancer patients (stage 1–3), who came for adjuvant radiotherapy in Maccallum Cancer Centre, for relapse, positive LVSI had a hazard ratio of 4.9, which increased to 8.8 in the presence of positive nodes [26]. For overall survival, only LVSI was significant, with a hazard ratio of 3.02. In particular, in the presence of LVSI and nodes, histological type, grade, and myometrial invasion were not significant factors. Five hundred twenty-five endometrial cancer patients who underwent primary surgery were assessed for the impact of LVSI on recurrence and survival [27].

LVSI in this study was associated with a high risk of recurrence and poor overall survival in early stage endometrial cancer; therefore, it is prudent to include evaluation of lymph vascular space involvement in the clinical decision to decide whether or not a patient with early stage endometrial cancer should receive adjuvant therapy.

Risk group definition [24] is very important in predicting prognosis: apart from pathological factors DNA ploidy is also included in this risk categorization.

The definition of high-risk carcinomas was as follows: (1) FIGO stage I, (2) nonendometrioid histological type, (3) presence of two of the following risk factors: FIGO grade 3 (poorly differentiated), deep (≥50 %) myometrial infiltration, DNA aneuploidy (FCM), (4) nuclear grade 3, (5) pathologically negative lymph nodes, and (6) negative abdominal cytology. Points 5–6 were optional in this study, and data are not available for all cases.

The definition of medium-risk carcinomas was as follows: (1) FIGO stage I, (2) endometrioid histological type, (3) presence of one of the following risk factors: FIGO grade 3 (poorly differentiated), deep (≥50 %) myometrial infiltration, DNA aneuploidy (Flow cytometry (FCM)), (4) nuclear grade 1–2, (5) pathologically negative lymph nodes, and (6) negative abdominal cytology. Points 5–6 were optional in this study, and data are not available for all cases. Lymph vascular space invasion (LVSI) was not regularly included in the pathology reports at the participating centers and was not included in the definition of the medium-risk group.

The definition of low-risk carcinomas was as follows: (1) FIGO stage I, (2) endometrioid histological type, (3) presence of none of the following risk factors: FIGO grade 3 (poorly differentiated), deep (≥50 %) myometrial infiltration, DNA aneuploidy (FCM), or (4) nuclear grade 3. All pathology reports were reviewed by one experienced pathologist at the regional referral center.

It is interesting to note that 54 % of all endometrial tumors will come under the low risk category and 22 % will come under high risk category. The low risk and high risk groups significantly differ in their survival outcomes, with the high risk group getting only 50 % cancer specific survival. The risk grouping helps oncologist to discriminate between patients who require surgery alone (low risk), who require surgery plus brachytherapy (intermediate risk), and those who require external beam radiation and chemotherapy in addition to surgery [28–30].

Tumor Markers as Prognostic Factors in Endometrial Carcinoma

CA 125 as a prognostic factor was studied by Espino-strebel and Luna [31] in 90 patients. They concluded that Ca 125 was significantly correlated with deep myometrial invasion, adnexal metastasis, pelvic and paraaortic nodal involvement, and recommended routine preoperative Ca 125 estimation. A receiver operating characteristic curve (ROC) was constructed to determine Ca 125 cutoff value. A cutoff value of 55 U/ml can predict extrauterine spread with sensitivity of 53.85 %, specificity of 84.38 %, and accuracy of 75.56 %.

Denschlag et al. [32] analyzed 101 patients of stage 3 endometrial cancer to find the prognostic factors of treatment outcome. They observed that an elevated Ca 125 level, adnexal involvement, the final tumor grade, and the lymph node dissection were independent predictors of cause-specific survival.

In multivariate analysis of the results of 100 normal subjects, 47 patients with benign gynecological diseases and 97 patients with endometrial cancer [33] found CA15.3 to be highly significant and had a larger hazard ratio. Univariate analyses showed that the increase of all the three, CA125, CA15.3, and CA19.9, were significantly associated with shorter survival.

Biological and Molecular Prognostic Factors

Among the oncogene expressions, the widely studied one is Her-2neu oncogene expression. Hetzel et al. [34] found Her-2neu oncogene's overexpression to be associated with a poor overall survival. The fraction of cells in S-phase has also been found to be an important prognostic indicator of clinical outcome [35].

Salvesen et al. [36] reported a population based study in 1999 and concluded that in addition to age and FIGO stage, microvessel density and Ki67 and P 53 protein expression were independent prognostic factors in endometrial carcinoma.

A number of authors [37–39] emphasize the prognostic importance of progesterone receptors. Ingram et al. [40] found it to be the most significant prognostic factor in stage 1 and 2 patients. In their series, the 3-year survival tripled (93 %) in patients with progesterone receptor level more than 100 compared to patient with levels less than 100 (36 %).

Lack of PR expression is a strong, independent risk factor for tumor recurrence in patients with stages I–II endometrioid endometrial cancer. The use of this easily measurable biomarker as a prognostic factor in the clinical context should be considered [41]. Molecular markers were detected by the immunohistochemistry on 200 endometrial cancer patients and Yao et al. [42] found the expression rates of ER, PR, PTEN, and p53 were 86.5 %, 85.5 %, 82.1 %, and 49.2 %, respectively. The expression level of Ki-67 in the tumor tissues was 46.9 % ± 24.7 %. The PR expression had a negative correlation with FIGO staging, histological grade, and depth of myometrial infiltration. They concluded that the value of estimating the prognosis using the expressions of ER, PTEN, p53, and Ki-67 was negative, except for the expression of PR.

Alteration of pRb expression is uncommon in endometrial carcinoma and when it does occur, it may represent a late event in carcinogenesis. Loss of heterozygosis (LOH) at the Rb locus

occurs in 10–18 % of endometrial carcinomas; however, there is no significant correlation between Rb LOH and clinicopathological factors.

The role of pRb2/p130 in endometrial carcinogenesis appears more relevant. Reduced expression of pRb2/p130 is a strong independent predictor of poor outcome in endometrial cancer [43]. Increased levels of expression were significantly associated with increased disease free survival. In a multivariate analysis, pRb2/p130 status, tumor stage, and ploidy status were independent predictors of clinical outcome and the risk of dying of disease was increased substantially among patients with loss of pRb2/p130 in tumor cells.

High expression of pRb2/p130 is seen in proliferative endometrium and in hyperplasia without atypia and downregulation in secretory endometrium, atypical hyperplasia and carcinoma [44] suggesting that Rb2 expression might be estrogen-regulated.

In type I endometrial cancer, PARP1(+), ATM(+), and FANCD2(+) were associated with high tumor grade, and γH2AX(+) and ATM(+) with tumor recurrence. In type II endometrial cancer, only PARP1(+) was associated with tumor stage. Endometrial carcinoma patients with p53(+) or FANCD2(+) were more likely to recur with 5-year recurrence free survival (RFS) probability of 71.4 % in comparison to 85.5 % for the other patients and they were more likely to have shorter 5-year overall survival [45].

Phosphatase and tension homology deleted on chromosome ten (PTEN), a new candidate tumor suppressor gene, was the first gene that was found to be phospholipase tumor suppressor gene. Loss of PTEN expression is an early event in endometrial tumorigenesis [46]. Loss of PTEN expression in patients with endometrial carcinoma was significantly related to histological classification and differentiation. PTEN loss was found in 56.8 % of tumors, and occurred more often in EC (60.7 %, 51/84) than in NEC (27.3 %). Loss of PTEN staining was significantly related to the advanced staging in the grade 1 (G1) and grade 2 (G2) endometrioid adenocarcinoma group. PTEN may interfere with the process of apoptosis and cell proliferation by promoting survivin expression [47]. Survivin is a member of the inhibitor of apoptosis proteins, which also has a role in the control of cell division.

High P53 expression correlates with morphological features of aggressiveness. Positive staining was associated with increased surgicopathological staging , histological grade, and lymph node metastasis [48]. p53 staining was largely found in grade 3 (G3) endometrioid adenocarcinoma and other phenotypes of endometrial cancer. Simultaneous abnormality of p53 and PTEN often occurred at a late phase of carcinogenesis [49]. Phosphorylated protein kinase B(p-AKT) was positive in 53.7 % (51/95) of tumors and was found to express almost similarly in endometrioid adenocarcinoma(EC) and nonenometrioid adenocarcinoma (NEC). There was no significant difference of patient survival between p-AKT positive and negative subgroups. p-AKT positive and PTEN loss might have synergic effect on tumor proliferation. On the other hand, as p-AKT expression did not have any correlations with PTEN, P53, and HER-2 status [50]. Ugaki et al. [51] also reported that the patients with PTEN-positive and p-Akt-negative expression clearly showed a higher survival rate than patients in the other groups.

BAF 25 (ARIDIA) is a driver gene; its loss is a frequent event in high grade endometrial carcinoma. The prognostic significance of ARIDIA loss is controversial. ARIDIA loss occurs secondary to deregulated mismatch repair (MMR) mechanism. BAF 25 loss is seen in 29 % of high grade endometrial carcinoma which included high grade endometrial carcinoma, serous carcinoma, and clear cell and carcinosarcomas. Loss of MMR is observed in 33 % of cancers. BAF 25 loss goes hand in hand with MMR deregulation mechanisms. Since MMR deregulation mechanisms represents an alternative oncogenic pathway to P53 alteration, ARIDIA loss is found to be associated with normal P53 expression. BAF 25 loss is associated with superior survival in clear cell and carcinosarcoma [52] (Table 12.4).

Table 12.4 Biological and molecular factors and their effect on outcome of endometrial cancer

	Favorable	Unfavorable
Progesterone receptor	High expression	Reduced expression
pRB	High expression	Reduced expression
PTEN	High expression	Loss
p53 staining	Negative	Positive
Her-2/neu	Reduced expression	Overexpression
pAKT	Negative	Positive
Aridia	Loss	Expression
PARP	Negative	Positive
ATM	Negative	Positive
FANCO2	Negative	Positive

Summary

The classification of Endometrial Carcinoma into Type I and Type II provides a basic criterion to decide the extent of surgical staging procedures and treatment protocols. In FIGO stage I itself, apart from histology which is the basis of Type I and Type II classification many predictive and prognostic factors are incorporated to categorize it into three risk groups for predicting the outcome. CA 125 if elevated indicates extrauterine disease. Progesterone receptor expression in addition to predicting prognosis indicates favorable response to progesterone treatment and is a part of uterine preservation protocol. Many other molecular prognostic factors like PTEN, P53, and Her2neu also provides an insight into the survival outcomes.

Key Points

1. Depth of myometrial invasion, tumor extension to the cervix, and lymph nodal status are part of FIGO staging each of whose involvement progressively upstages the disease and each of which are independent prognostic factors themselves.
2. Grade of tumor and DNA ploidy are significant risk factors which decides intensity of spread and survival.
3. Tumor occupying the whole endometrial cavity significantly upstages the cancer.
4. It is prudent to include evaluation of lymph vascular space involvement in the clinical decision adjuvant therapy in early stage disease since these are the patients at risk of recurrence.
5. The risk grouping helps oncologist to discriminate between patients who require surgery only (low risk), or combined treatment.
6. An elevated Ca 125 was significantly correlated with deep myometrial invasion, adnexal metastasis , and pelvic and paraaortic nodal involvement.
7. Loss of PTEN expression rate is more in endometrioid adenocarcinoma and is associated with advanced stage and poor prognosis.
8. Positive p53 staining is associated with biological aggressiveness.
9. Aridia (BAF 25) loss is a frequent event in high grade endometrial carcinoma. Aridia loss is associated with superior survival in clear cell and carcinosarcoma.

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Part III

Surgical Anatomy and Early Stage Endometrial Cancer

Surgical Anatomy of the Uterus

13

Bhagyalaxmi Nayak and S.K. Giri

Introduction

A thorough knowledge of the anatomy of the uterus and its relationship to neighboring organs is of immense importance to both gynecologic oncologists and radiation oncologists. A good surgical dissection can only be accomplished by an in-depth understanding of the anatomy of the pelvis and retroperitoneum. Laparoscopy and robotic surgery have improved anatomic perception by excellent optics and a 3D depth of vision. The importance of surgical anatomy of the uterus, its blood supply, lymphatic drainage, innervation, and proximity to vital structures such as the bladder and rectum cannot be overemphasized.

Embryology

The uterus develops by fusion of the bilateral paramesonephric ducts. The upper parts remain separate and eventually become the fallopian tubes. Malunion and nonunion of the paramesonephric ducts can lead to various congenital malformations of the uterus like bicornuate uterus, uterus didelphys, etc.

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Anatomy of Uterus

The uterus is a hollow, thick-walled, fibromuscular organ situated in the true pelvis between the urinary bladder and rectum. The shape, weight, and dimensions vary considerably with estrogenic stimulation and previous parturition.

It is divided into two main parts: upper two thirds form the body, which is mainly muscular, and the lower third forms the fibrous cervix. In the reproductive years, the body is considerably larger than the cervix. In the premenarcheal and postmenopausal years, the ratio of the size of body to cervix is 1:1 or even 1:2. The area where the fallopian tubes enter the body of the uterus is the vascular cornual end. The round ligament of the uterus and ovarian ligament are also attached to the cornua inferior to the fallopian tube, the former anteriorly and the latter posteriorly. The part of the uterus superior to the entry point of the uterine tube is the fundus. The body of the uterus extends from the fundus to the cervix. Within the body or corpus, there is a triangular-shaped potential space, the endometrial cavity. Nearly half of the cervix is inserted into the vagina through the uppermost part of its anterior wall and is called portio vaginalis. The supravaginal part of the cervix joins the body at the isthmus.

The cervix contains dense fibrous connective tissue with a small amount of muscular tissue (about 10 %). The scanty smooth muscle is distributed at the periphery of the cervix and is

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continuous with the body of the uterus and the vagina. It is into this layer that the cardinal, uterosacral ligament and the pubocervical fascia are inserted. This layer is easily stripped off while doing an intrafascial hysterectomy.

Relations and Position

Anteriorly, the uterus is separated from the urinary bladder and uterovesical space by loose connective tissue.

Posteriorly, it is related to the rectum and rectouterine pouch.

Laterally, it is continuous with the broad ligaments.

Axis

Long axis of the uterus is at right angle to that of vagina which is called anteversion.

The uterus is bent on itself at the isthmus anteriorly and is called anteflexion.

Uterine Ligaments

They are mostly composed of fibrous tissue and provide support to the uterus. Sometimes few muscle bundles may be found interspersed in the condensed connective tissue.

Round Ligaments

They are extension of the uterine musculature and are mostly composed of smooth muscle and are homologous to the gubernaculum testis. They begin as a broader structure on each lateral side of the corpus, anterior and inferior to the tubes, and assume a more rounded shape before they enter the extraperitoneal space lateral to the deep inferior epigastric vessels. After entering into the internal inguinal ring, they traverse the inguinal canal, through the external inguinal ring, and fuse with the subcutaneous tissue of labia majora. There is less evidence that it acts as a uterine support. Round ligaments are quite stretchable and attain great lengths as the uterus enlarges. It is accompanied by a constant artery on its inferior aspect which needs to be cauterized or ligated when round ligaments are divided.

Uterosacral Ligaments

These are thickening of the endopelvic fascia that form the medial margin of the parametrium and border the pouch of Douglas. It is composed mainly of smooth muscle, autonomic nerves of the pelvic organs, connective tissue, and blood vessels. Transection of these ligaments disrupts the nerve supply to the bladder and rectum leading to bladder atony and constipation. More recently, it has been found that the uterosacral ligaments merge with the rectal fibers on the lateral sides instead of being inserted into the sacrum (Fig. 13.1). Dissection of these during radical hysterectomy calls for a more careful approach in a nerve-sparing surgery (Fig. 13.2). With improved survival rates in cancer endometrium, quality of life issues now take a precedence. The inferior hypogastric plexus and hypogastric nerve are intimately related to the uterosacral ligament. Saving these structures as far as possible and of course with-

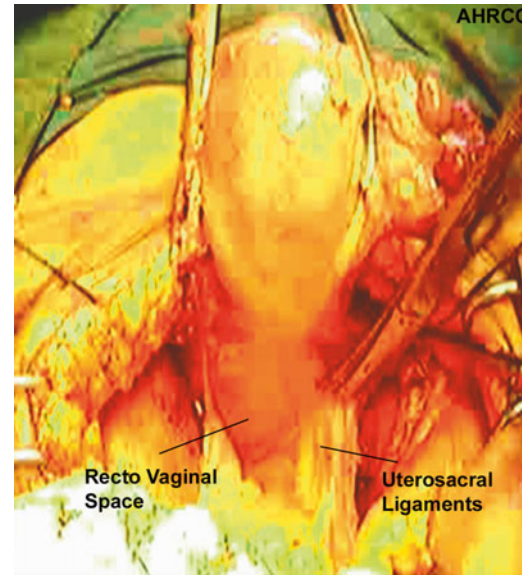

Fig. 13.1 Uterosacral ligaments (AHRCC)

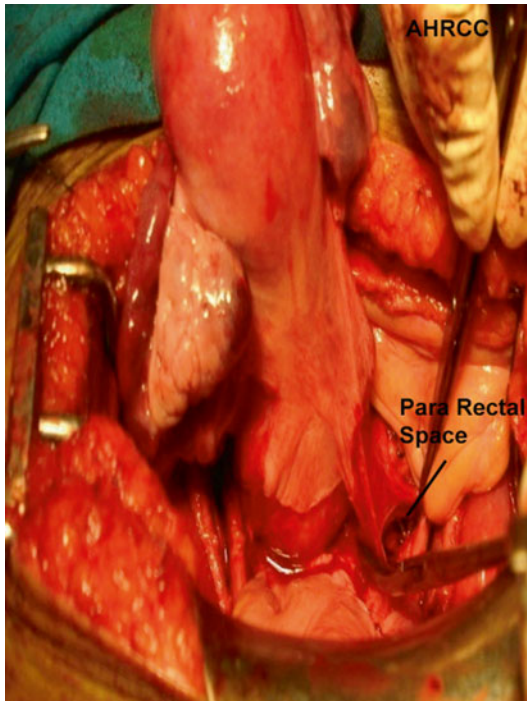

Fig. 13.2 Uterosacral ligaments removed from attachment

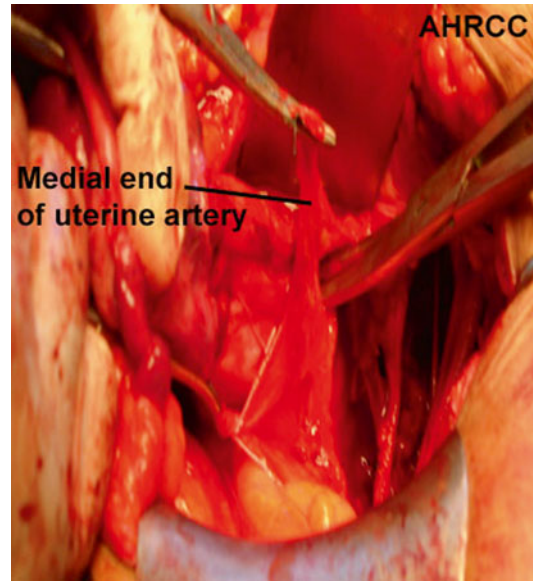

Fig. 13.3 Ureteric tunnel dissection

out sacrificing oncological clearance is of importance [2]. The inferior hypogastric plexus (named after Lee Frankenhauser) gets fibers from the superior hypogastric plexus via the hypogastric nerve and from the roots of S2 to S4 via the splanchnic nerves. It is placed in a sagittal plane and measures about $3 \times 4 \times 0.5$ cm and is a dense triangular neural network with base lying posteriorly. It stretches from the anterolateral wall of the rectum, lateral to the cervix and vaginal fornix, to the lateral vaginal wall and base of the bladder. Its upper limit is in close proximity to the deep uterine vein that serves as a landmark to identify the plexus [3]. Thus, it runs in close proximity to the pelvic connective tissues.

Transverse Cervical (Cardinal/ Mackenrodt's) Ligaments

This serves as the main uterine support. They attach the lateral margins of the cervix and vagina to the pelvic wall. It is important that at the end of hysterectomy, the vault is fixed to these ligaments to prevent future descent of the vault. The cardinal and uterosacral ligaments are simply two parts of a single body of suspensory tissue. It consists mainly of perivascular connective tissue and pelvic vessels.

Though described as extending laterally, these ligaments assume vertical position in erect posture. Each ligament is well defined near the uterine attachment but fans out symmetrically with a broad area of attachment on the second, third, and fourth sacral vertebrae (Figs. 13.3 and 13.4). They help hold the uterus above the levator plate.

The uterosacral and cardinal ligaments provide the greatest support within the pelvis. Fortunately, they are infrequently involved in uterine cancer contrary to cervical cancer where they are frequently involved.

Rectal Pillars

The fibrovascular bundles running from the anterolateral aspects of the rectum to the posterolateral aspect of the vagina are the rectal

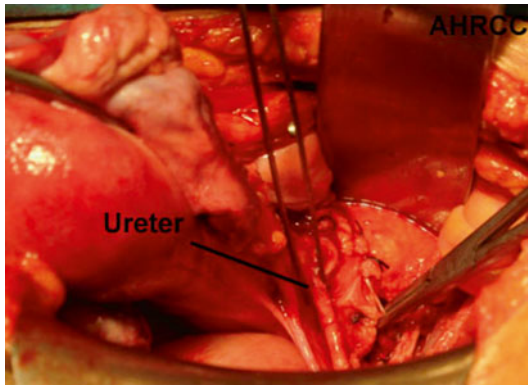

Fig. 13.4 Mackenrodt's ligament (AHRCC)

pillars. They are very vascular and contain the middle rectal arteries, and division may cause unexpected heavy bleeding from the uterine margin. Applying clamps on either side of the division is more esthetic in open surgery.

Bladder Pillars

They are paired fibrovascular bundles that form the lateral limit of the vesicovaginal space. They sometimes are continuous with paracolpos and paravaginal tissue. Condensation of tissue in this area forms the vesicouterine ligament. This houses the ureteric tunnel and is divided into anterior and posterior leaves by the ureter. These two layers have to be dissected off the ureter to visualize its entry into the posterolateral aspect of the bladder [4]. The vesicouterine ligament harbors the cervicovesical veins. Division of these ligaments allows de-roofing of the ureters, and it can be completely mobilized from its attachment to the posterior layer of broad ligament and ureteric tunnel. It is important to know the anatomy of the ureter so that mobilization without ureteric injury is achieved and at the same time preserving its mesentery and vascular supply. The secret to maintaining vascularity of the ureters is to dissect parallel to it and also along the big vessels. The whole purpose of mobilizing the ureter is to place clamps as lateral as required.

Microstructure

Endometrium (Mucosa)

Inside the uterus is a potential triangular cavity lined by endometrium. Endometrium is a unique mucosa. The epithelium is a single-layered columnar and is continuous with tubular uterine glands. The stroma consists of highly cellular connective tissue between endometrial glands and contains blood and lymph vessels. The superficial portion of this layer undergoes cyclic change with the menstrual cycle. Spasm of hormonally sensitive spiral arterioles causes shedding of this layer after each episode of menstruation. A deeper basal layer remains to regenerate a new lining. Separate arteries supply the basal endometrium which explains the preservation of this layer even after shedding.

Myometrium (Smooth Muscle Layer)

The myometrium is fibromuscular in character and makes up most of the uterine corpus. The arrangement of fibers in this layer is complex. This is because the uterus originates from paired paramesonephric primordia, with the fibers from each half crisscrossing diagonally with those of the opposite side. It is composed largely of smooth muscle fascicles mingled with loose connective tissue, blood, and lymph vessels and nerves.

They are arranged in four layers (inner to outer):

1. Submucosal layer (innermost), composed mostly of longitudinal muscles
2. Vascular layer, zone rich in blood vessels and longitudinal muscles
3. Circular muscle layer
4. Thin longitudinal muscle layer

Serosa

It is composed of peritoneum and covers the uterine body and supravaginal cervix posteriorly and only the uterine body anteriorly.

Microstructure of Cervix

Epithelium

The endocervical canal is lined by columnar secretory epithelium and the ectocervix by stratified squamous nonkeratinizing epithelium. The usual prepubertal location of the squamocolumnar junction is at the external os.

At puberty, the endocervical columnar epithelium responds to estrogenic stimulation and extends distally on the ectocervix. This area of columnar cells on the ectocervix is red and raw in appearance and called ectopy. It is then exposed to acidic environment of the vagina, and through a process of squamous metaplasia, a stratified squamous ectocervical epithelium effectively grows over the exposed area resulting in the transformation zone. Other hyperestrogenic states such as pregnancy and use of oral contraceptive pills can also result in ectopy. This area is the site of epithelial abnormalities that may progress to malignancy. In postmenopausal women, the squamocolumnar junction recedes into the endocervical canal.

Spaces Around the Uterus

Knowledge of spaces around the uterus is an absolute necessity to proceed with any kind of uterine surgery and more importantly radical surgery. Pelvic spaces have been created to help us, surgeons, accomplish adequate surgery without blood loss and injury to vital structures. These spaces have loose areolar tissue and are essentially avascular.

The anterior cul-de-sac separates the bladder from the uterus and the posterior cul-de-sac from the rectum. The loose peritoneum of the anterior cul-de-sac helps in filling the bladder without tension. It is this loose peritoneum that helps to create the space between the bladder and uterus during hysterectomy (Fig. 13.5). Posterior cul-de-sac extends lower as the peritoneum covers the upper part of the vagina, unlike anteriorly, where the vagina is bereft of peritoneum. This has to be kept in mind while opening the peritoneal cavity from below in a vaginal hysterectomy. Specialized dense connective tissue between the rectum and the posterior vaginal wall is called the fascia of Denonvilliers and serves as an important landmark while dissecting the rectovaginal space. While dissecting the rectovaginal space, it is also important to remember that the rectovaginal pad of fat should be kept along with the rectum to prevent inadvertent injury to the rectum.

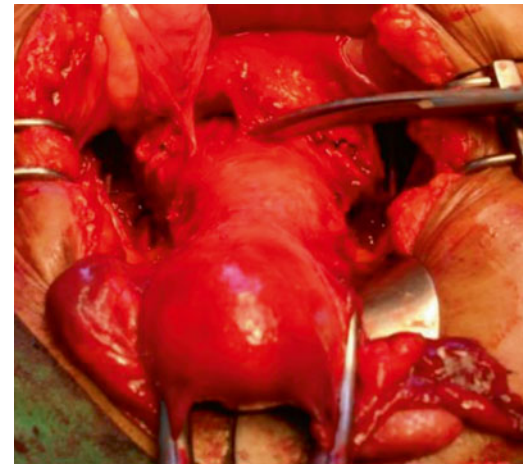

Fig. 13.5 Division of vesicocervical ligament (AHRCC)

Paravesical Space

These are potential spaces on either side of the bladder. The anterior boundary is the pubic arch that is continuous with the lateral pelvic wall as a lateral boundary. It is bounded medially by the bladder and obliterated umbilical artery and posteriorly by the cardinal ligament (Fig. 13.6).

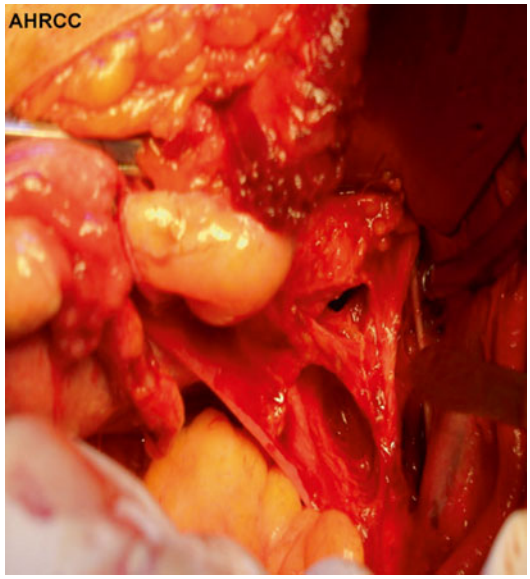

Fig. 13.6 Developing the paravesical and pararectal spaces [1]

Pararectal Space

The cardinal ligament forms the anterior border of this space, the medial border is the rectum, and the lateral limit is the pelvic wall. Posteriorly, it is bound by the presacral fascia. The pararectal space is created easily by dissecting in between the ureter medially and the internal iliac artery laterally (Figs. 13.6 and 13.7).

Peritoneal Folds

These ligaments provide no support to the uterus and only consist of folds of peritoneum.

- Uterovesical fold.
- Rectovaginal fold.
- Broad ligament (mesometrium, mesosalpinx, mesovarium). These folds of peritoneum extend laterally from the uterus and cover the adnexal structures.

Infundibulopelvic ligament contains ovarian vessels.

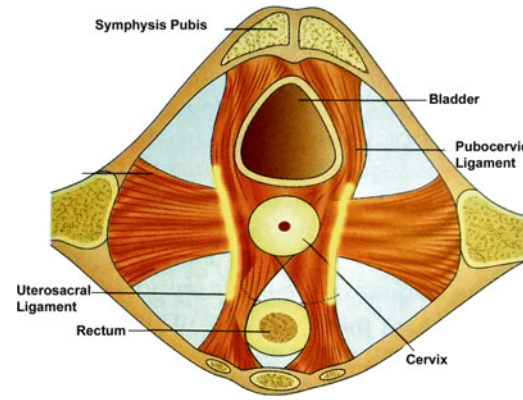

Fig. 13.7 Preserving the hypogastric nerves [3]

Artery Supply

The uterus is abundantly supplied with blood vessels. Uterine artery, a branch of anterior division of the internal iliac artery, supplies the uterus. It usually arises independently or may rarely have a common origin along with the internal pudendal or vaginal artery. It joins the uterus near the junction of the corpus and cervix but may be variable at times. On reaching the uterus, it divides into an ascending and a descending branch. Using injection micrographic and histologic technique to study the vascular anatomy of the uterus, Farrer-Brown et al. [5] showed that the uterine arteries run a tortuous course between the two layers of the broad ligament along the lateral side of the uterus (Fig. 13.8). They turn laterally at the junction of the uterus and fallopian tube, run toward the hilum of the ovary, and terminate by joining the ovarian arteries. At this point, the artery is closely related to the insertion of the uterosacral ligaments to the uterus. Brisk bleeding ensues on inadvertent injury to the vessels while dividing the uterosacrals from the uterus in a Type I hysterectomy. The ascending branch ascends with a tortuous course in the broad ligament and ends by anastomosing with a branch of ovarian artery. A continuous arterial arcade connects the ovarian, uterine, and vaginal arteries. This is a source of collateral circulation after uterine artery ligation done for postpartum hemorrhage.

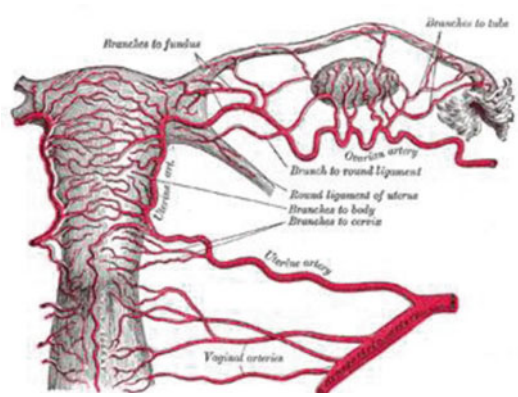

Fig. 13.8 Uterine vasculature [5] (with permission from Tripathy (2009) [13])

Accompanying each uterine artery are several large uterine veins. But uterine veins may not accompany the uterine artery always. Bleeding from uterine veins is low in pressure but high in volume. Attempts to take stitches may result in larger avulsions as uterine veins are very thin walled. Vascular clips would be a better alternative.

The uterine artery crosses the ureter anteriorly. Rotating the uterus and putting it on stretch makes the uterine artery taught and more visible. It is easier to identify the ureter in the posterior layer of the broad ligament, and the entire course may be visible in thin women. Excess of retroperitoneal fat in obese women, adhesion due to inflammation or previous surgery, and needless to say a very deep pelvis and big uterus can sometimes make it difficult to trace the uterine artery and ureter. Exact knowledge of anatomy helps to identify these structures in such difficult situations. Double ureter is another entity that should be kept in mind, and preserving the mesentery is of paramount importance. Each uterine artery gives off numerous branches which enter the uterine wall, divide, and run circumferentially as groups of anterior and posterior arcuate arteries. The arcuate arteries of both sides approach and anastomose at the anterior and posterior midline (Fig. 13.8). Many tortuous radial branches arise from the arcuate arteries and pass centripetally through the deeper myometrial layer to reach the endometrium.

Venous Drainage

Uterine veins are multiple and large. They run in the broad ligament with the uterine artery and drain into the internal iliac vein.

Lymphatic Drainage

Data on the lymphatic vessels of the uterus have been coordinated by Reynolds [6]. The entire uterus has a rich capillary bed as extensive as the blood capillary system. The lymphatic capillary bed is arranged in four zones: (1) the lower uterine segment with its rich supply of fine capillaries, (2) the subserosa of the corpus with a few lymphatics, (3) a deep subserosal network, and (4) a plentiful supply in the muscularis proper. These vessels increase greatly in number and size during pregnancy. The collecting system of the uterine lymphatics is formed from anastomoses of a lateral-uterine descending network of lymph vessels which unites with collecting vessels from the utero-ovarian pedicle and the external iliac area. Lymphatic drainage of the uterus and upper two thirds of the vagina is primarily to the obturator and internal and external iliac nodes. The direction of lymph flow from the uterus tends to follow its attachments, draining along the cardinal, uterosacral, and round ligaments.

Lymphatics from Cervix

The primary cervical drainage is to the paracervical lymph nodes located at the point where the uterine vessels cross above the uterus and then laterally to the external iliac nodes.

Lymphatics from Lower Part of Uterine Body

They drain mostly into internal iliac nodes along the cardinal ligaments and to the presacral and lateral sacral nodes along the uterosacral ligaments. Free communication to the external iliac

nodes leads to further dissemination. The parametrial lymph vessels draining the middle and lower part of the corpus tend to spread in the base of the broad ligaments toward the lateral pelvic side walls and drain into nodes located in the obturator fossa and the internal iliac nodes. Posterolaterally, they drain to internal iliac node, posteriorly to rectal and sacral nodes, and some may drain to obturator or gluteal nodes.

Lymphatics from Upper Part of Body, Fundus, and Tube

Lymph from the fundus drains toward the adnexa and infundibulopelvic ligaments. From there, they drain into lateral aortic and preaortic nodes. Grossly, lymphatics in this region can be divided into left para-aortic, right paracaval, and the aortocaval group of lymph nodes. But Winter and Benedetti-Panici have divided them into more groups: pre-, para-, and retro-aortic; pre-, para-, and retrocaval; and superficial and deep cavo-aortic [7]. The great vessels are covered by the node bearing areolar tissue, and division of this layer exposes the adventitia of the vessels. Once the vessels are exposed, the remaining lymphatics can now be stripped off easily [7]. These ascending lymphatic channels eventually coalesce to form the thoracic duct. Lymphatic channels along the round ligaments may carry the metastatic deposits to the inguinal nodes. Vaginal metastasis in cancer endometrium occurs via lympho-vascular spread. They commonly occur without cervical involvement [8].

The anastomotic connections of the uterine and ovarian vessels have lymphatic connections between these two drainage systems, and metastases in either direction are possible.

Pelvic Blood Supply

A knowledge of the blood supply of the pelvis is essential, because a complete and systematic lymphadenectomy encompasses lymph nodes from the pelvis and para-aortic region up to the renal vessels. Lymphatic channels follow the pelvic vasculature; lymphadenectomy includes stripping off the lymph nodes, lymphatic channels, and fibro-fatty tissue lying along the pelvic vessels.

External Iliac Vessels

After dividing the round ligament and entering the retroperitoneal space, the external iliac artery and vein are seen on the lateral pelvic wall medial to the psoas major muscle (Fig. 13.9). They continue down as femoral vessels after passing under the inguinal ligament. Just before it passes below the inguinal ligament, the external iliac artery is crossed by the deep circumflex iliac vein that marks the lower limit of lymphadenectomy. During its course, it rarely gives out an aberrant obturator artery. It is important to go in between the artery and vein and sometimes behind the vessels to clear all lymphatics.

Internal Iliac Vessels

They remain posteromedial to the external iliac vessels. It divides into anterior and posterior divisions (Fig. 13.9). The pelvic ureter is a close medial relation of the internal iliac vessels. The posterior division supplies the pelvic and gluteal musculature and it's not necessary to trace. The internal iliac vein which follows closely is an important

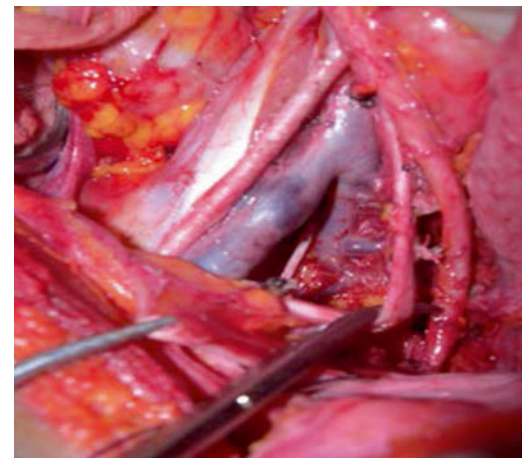

Fig. 13.9 Joining of external and internal iliac veins (AHRCC)

area that should be handled with care. Traction over this area causes avulsion of the vein which has a tendency to retract and cause brisk hemorrhage. The anterior division gives out the uterine artery from its medial aspect. It also gives off the superior and inferior vesical arteries to the bladder that need to be preserved. After giving out the internal pudendal, inferior gluteal, and obturator arteries, it continues as the obliterated hypogastric artery. This serves as an important landmark bordering the medial side of the paravesical space on either side.

Common Iliac Vessels

The external iliac vessels continue above as the common iliac arteries. They are devoid of any major branch except a constant ureteric branch. The common iliac vein lies medial to the artery on the left and lateral to it on the right [9]. The nodes in this area are flattened and hug the common iliac veins snugly. Careful dissection avoids rupture of the veins. Feeding vessels to the nodes bleed briskly as they arise from high-volume vessels. The ureters are a close relation to the common iliac vessels crossing from medial to lateral and need to be protected during lymphadenectomy.

Abdominal Aorta

The aorta divides into two common iliac arteries at the level of L4 vertebra toward the left side. Both common iliac veins join together at the same level to form the inferior vena cava on the right side of the aorta. Rarely, there may be double vena cavae on either side of the aorta necessitating bilateral paraaortic lymphadenectomy. The important anatomical detail to remember is the drainage of the infundibulopelvic vessels. On the left, the ovarian vein drains into the left renal vein, and on the right, it drains into the inferior vena cava. As is obvious, the lymphatics do follow these vascular channels. The ovarian arteries arise from the aorta at the level of L1 vertebra anteriorly just below the renal arteries. The single inferior mesenteric artery arises 3–4 cm above the bifurcation of the aorta and is easily identified as it passes toward the left into the sigmoid mesocolon

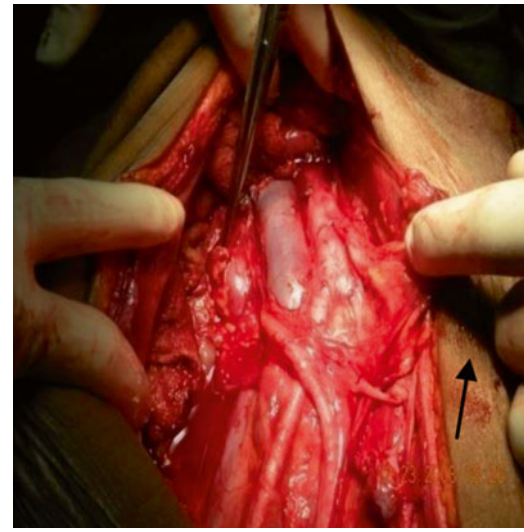

Fig. 13.10 Crossing of the left ureter, inferior mesenteric artery (AHRCC)

(Fig. 13.10). Sacrifice of this vessel may be required at times without much consequence. Destruction of nerve fibers that follow along the inferior mesenteric artery causes prolonged postoperative ileus. But the more important middle sacral artery arising from the V of bifurcation can cause troublesome bleeding if not dealt with care. The left renal vein crosses in front of the aorta to join the inferior vena cava (Figs. 13.11 and 13.12).

Venous Drainage of Pelvis

Veins in the pelvis are thin walled and get easily damaged if one is little careless. They have a tendency to retract and cause troublesome hemorrhage. Of these, the obturator vein in the obturator fossa and uterine veins in the ureteric tunnel need special attention. Sometimes the uterine vein may be difficult to visualize if the uterus is enlarged, and blind entry into the pelvic spaces may cause avulsion and torrential bleeding.

The right external iliac vein is a medial relation of the external iliac artery near the inguinal ligament. As it ascends, it goes behind and passes laterally at its cephalic end. However, the left external iliac vein remains medial to the left external iliac artery throughout its length. They are joined by the

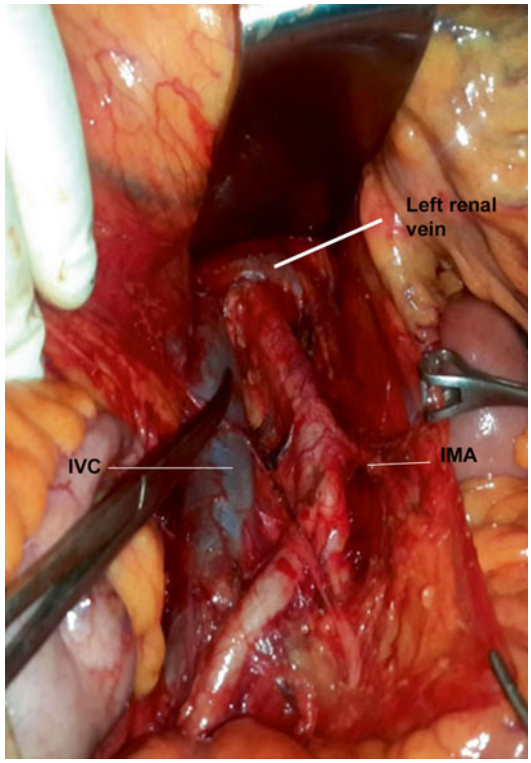

Fig. 13.11 After retro peritoneal dissection [10] (AHRCC)

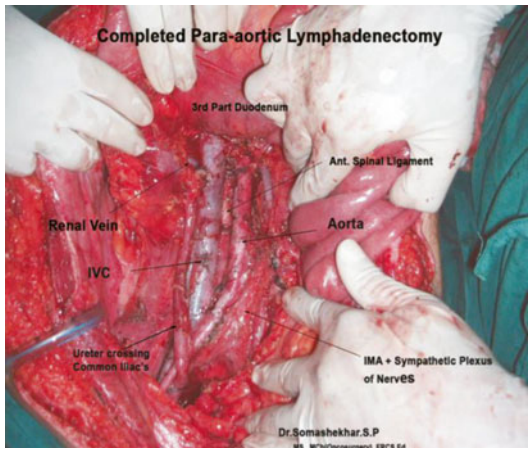

Fig. 13.12 Complete para-aortic lymphadenectomy [10] (with permission from Dr. S.P. Somasekhar)

internal iliac veins to form the common iliac veins on either side. The left common iliac vein crosses behind the left common iliac artery to join the right common iliac vein and form the inferior vena cava. The inferior vena cava ascends along the right side of the aorta (Figs. 13.13, 13.14, and 13.15).

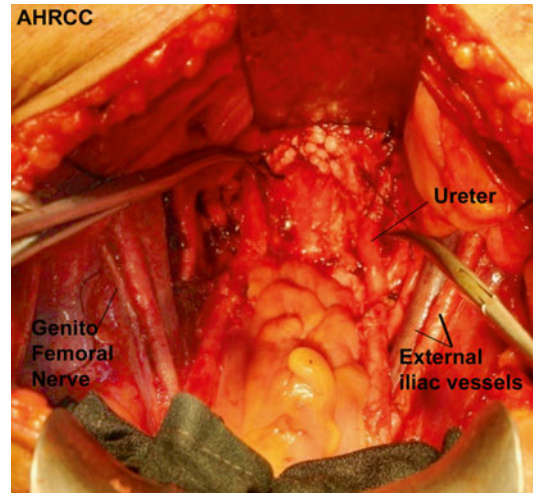

Fig. 13.13 External iliac vessels and ureter after surgery (AHRCC)

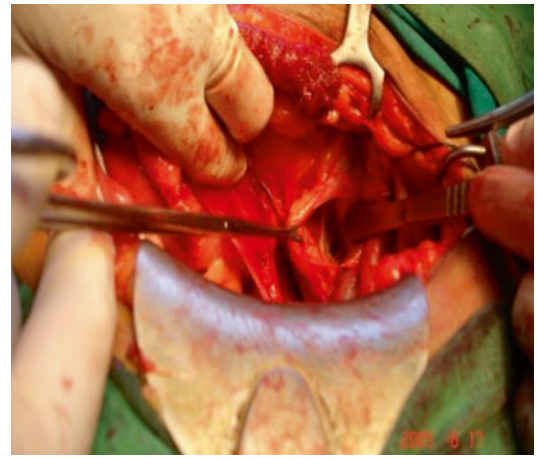

Fig. 13.14 Obturator lymphadenectomy (AHRCC)

Innervation

Knowledge of innervation and nerves running around the uterus during dissection is important to protect them from injury. Nerve-sparing surgery improves sexual and voiding functions. With improved survival rates, the focus is now on improving quality of life [11].

The uterus is supplied by inferior hypogastric plexus. It is a somewhat amorphous concentration of nerve fibers and ganglia. The sympathetic fibers originate in the thoracic and lumbar seg-

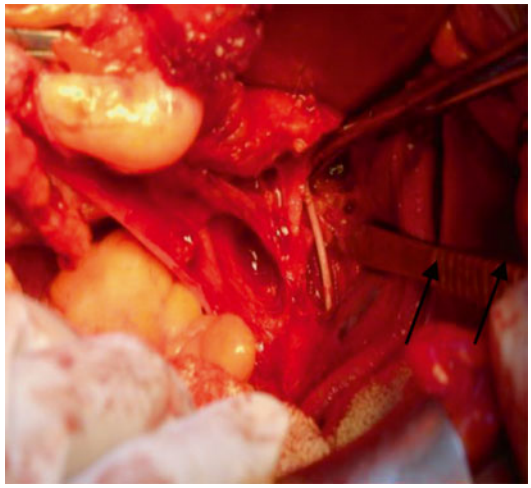

Fig. 13.15 Pararectal space and obturator nerve (AHRCC)

ments (T12 to L1) of the spinal cord and reach the uterus via the hypogastric plexus and are responsible for uterine contraction and vasoconstriction of vessels [12]. The parasympathetic fibers commence from S2, S3, and S4 nerve roots and join the inferior hypogastric plexus. They bring about uterine relaxation and vasodilatation. Inferior hypogastric nerves traverse through the uterosacral ligaments and need to be preserved to maintain smooth functioning of the bowel and bladder.

Genitofemoral Nerve

It arises from L1 and L2 and is a sensory nerve. It passes on the psoas muscle lateral to the external iliac vessels. Attempts must be made to preserve this nerve to avoid numbness of the thigh postoperatively.

Obturator Nerve

Motor nerve from L2, L3, and L4 supplies the adductor muscles of the thigh. It appears as a cordlike glistening structure in the obturator fossa when the external iliac vessels are retracted laterally. The lymphatic tissue in the obturator fossa is attached to the nerve and needs to be teased away gently. Inadvertent injury to the nerve can be repaired with 3–0 Prolene without much consequence.

Conclusion

Surgical anatomy of the uterus involves anatomical description of the uterus along with other pelvic and retroperitoneal structures that are relevant to surgery. Dissection along natural planes and correct development of pelvic spaces are an art to be learned and mastered. Identification of the bloodless planes allows bloodless dissection during simple as well as radical surgery. Knowledge of pelvic anatomy helps surgeons in avoiding injury to vital structures like the ureters, nerve plexuses, and vessels.

Key Points

1. Management of cancer endometrium requires a thorough understanding of the surgical anatomy of the uterus, pelvis, and retroperitoneal spaces.
2. Avoiding injury to ureters and major vessels and preserving the nerve plexuses require a proper and clear understanding of anatomic relationships.
3. Anomalies and variations of vital structures should be understood.
4. Stretching of the ligaments by pulling on the fundus in an opposite direction partially brings into view the paravesical and pararectal spaces.
5. Ureters are loosely attached to the posterior leaf of the broad ligament from where they can be traced upward and downward.
6. The ureteric tunnel is a part of the condensed pelvic connective tissue.
7. The uterine arteries cross the ureters on its superior aspect at almost right angles.
8. The deep uterine vein may not always accompany the uterine artery.
9. The inferior hypogastric plexus is an important relation of the uterosacral ligaments and needs to be identified before transection.

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Endometrial Cancer Staging

14

Simi T.J. Raj and K. Chitrathara

Introduction

Endometrial cancer staging has changed over time to a surgicopathologic staging system. The goal of staging is to have a clinical practice guideline which reduces inappropriate variation in clinical practice and also to have uniformity in reporting results of treatment worldwide. In addition staging intends to prognosticate disease. Presently endometrial carcinoma is surgically staged according to the joint 2010 International Federation of Gynecology and Obstetrics (FIGO)/TNM classification system [1, 2] (see Table 6.3, Chap. 6). The revised staging eliminated the cervical glandular involvement and ascitic fluid cytology from the staging, grouped together both IA and IB of the previous staging as IA, and substratified Stage IIIC. This staging system for endometrial cancers has been found to be highly prognostic in the case of endometrioid tumors [3]. But size of the tumor and LVSI (lymphovascular space invasion), which are also considered as prognostic factors, are not included in the current staging.

Important notes on staging are given below [4].

Rules Related to Staging

1. Corpus cancer is now surgically staged; therefore procedures previously used for determination of stages are no longer applicable (e.g., the findings of fractional curettage to differentiate between Stage I and Stage II).
2. There may be a small number of women with corpus cancer who will be treated primarily with radiation therapy. In these cases, the clinical staging adopted by FIGO in 1971 would still apply, but designation of that staging system would be noted.
3. Ideally, width of the myometrium should be measured along with the depth of tumor invasion.
4. There should be histologic verification of grading and extent of the tumor.

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Notes About the Grading

Histopathology – degree of differentiation. Cases of carcinoma of the corpus should be grouped with regard to the degree of differentiation of the adenocarcinoma as follows:

- G1: <5 % of a nonsquamous or nonmorular solid growth pattern
- G2: 6–50 % of a nonsquamous or nonmorular solid growth pattern
- G3: >50 % of a nonsquamous or nonmorular solid growth pattern

Notable nuclear atypia, inappropriate for the architectural grade, raises the grade of a Grade l or Grade 2 tumor by 1:

- In serous and clear cell adenocarcinomas, nuclear grading takes precedence.
- Adenocarcinomas with squamous differentiation are graded according to the nuclear grade of the glandular component.

Preoperative assessment by endometrial pathology is required to differentiate between tumors at low and high risk of lymph node metastasis, and imaging can be useful in determining depth and cervical involvement and suspicion of involved nodes (Level of Evidence C).

The presence of bullous edema in the bladder is not sufficient evidence to classify a tumor as T4.

AJCC Stage Grouping [2] and FIGO Stages

Extent of the tumor, spread to lymph nodes, and distant cancer spread are combined to assign the stage of disease. This is called *stage grouping*. Omentectomy is also done as a part of staging procedures in Type 2 endometrial cancer.

Stage 0

Tis, N0, M0: This stage is also known as *carcinoma* in situ. Cancer cells are only found in the surface layer of cells of the endometrium, without growing into the layers of cells below. The cancer has not spread to nearby lymph nodes or distant sites. This is a precancerous lesion. This stage is not included in the FIGO staging system.

Stage I (Fig. 14.1)

T1, N0, M0: The cancer is confined to the body of the uterus. It may be involving the glands of the cervix but is not involving the supporting connective tissues of the cervix. The cancer has not spread to lymph nodes or distant sites.

- **Stage IA (T1a, N0, M0):** In this earliest form of Stage I, the cancer is in the endometrium and/or infiltrating less than halfway through the myometrium. It has not spread to lymph nodes or distant sites.
- **Stage IB (T1b, N0, M0):** The tumor involves more than half of the myometrium. The cancer has not spread beyond the body of the uterus.

Stage II (Fig. 14.2)

T2, N0, M0: The cancer has spread from the body of the uterus and infiltrates cervical stroma.

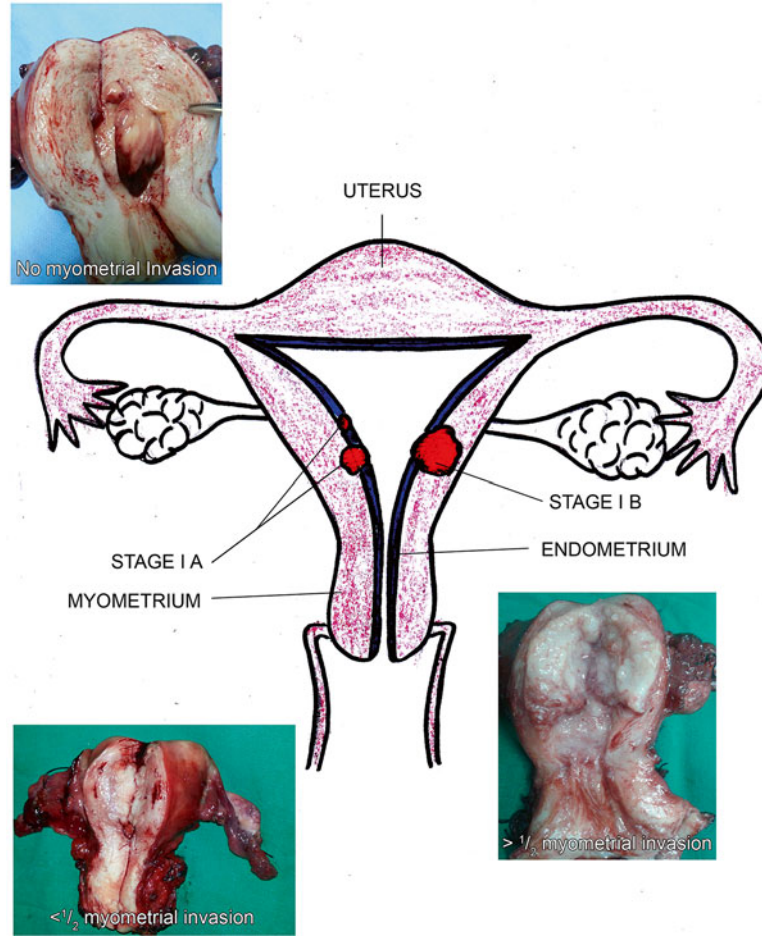

Fig. 14.1 Carcinoma endometrium, Stage 1A (T1a, N0, M0) Tumor Confined to the uterus, no or < ½ myometrial invasion, Stage 1B (T1b, N0, M0) Tumor Confined to the uterus, no or > ½ myometrial invasion

Stage III (Figs. 14.3, 14.4, 14.5, and 14.6)

T3, N0, M0: Either the cancer has spread outside of the uterus or into nearby tissues in the pelvic area.

- **Stage IIIA (T3a, N0, M0):** The cancer has spread to the uterine serosa and/or to the fallopian tubes or ovaries (the adnexa).
- **Stage IIIB (T3b, N0, M0):** The cancer has spread to the vagina and/or to the parametrium.

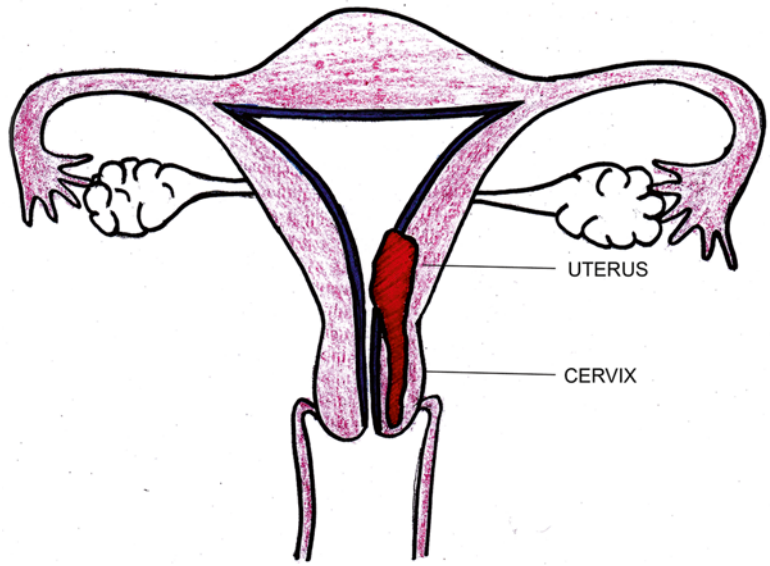

Fig. 14.2 Stage II (T2, N0, M0) Carcinoma endometrium, Cervical stromal invasion, but not beyond uterus

- **Stage IIIC1 (T1 to T3, N1, M0):** The endometrial cancer has spread to pelvic lymph nodes but not to lymph nodes around the aorta or distant sites.
- **Stage IIIC2 (T1 to T3, N2, M0):** The endometrial cancer has involved para-aortic lymph nodes but not spread to distant sites.

Stage IV (Fig. 14.7)

The cancer has spread to the urinary bladder or rectum, or to inguinal lymph nodes, and/or to distant organs, such as the bones, omentum, or lungs.

- **Stage IVA (T4, any N, M0):** Mucosa of the bladder or rectum is involved by the endometrial cancer.
- **Stage IVB (any T, any N, M1):** The cancer has spread to distant lymph nodes, the upper abdomen, and the omentum or to organs away from the uterus, such as the bones or lungs.

Tumor Extent (T)

T0: No signs of a tumor in the uterus.
Tis: Preinvasive cancer (also called *carcinoma* in situ). Cancer cells are only found in the surface layer of cells of the endometrium, without growing into the layers of cells below.
T1: The cancer is only growing in the body of the uterus. It may also be growing into the glands of the cervix, but is not growing into the supporting connective tissue of the cervix.

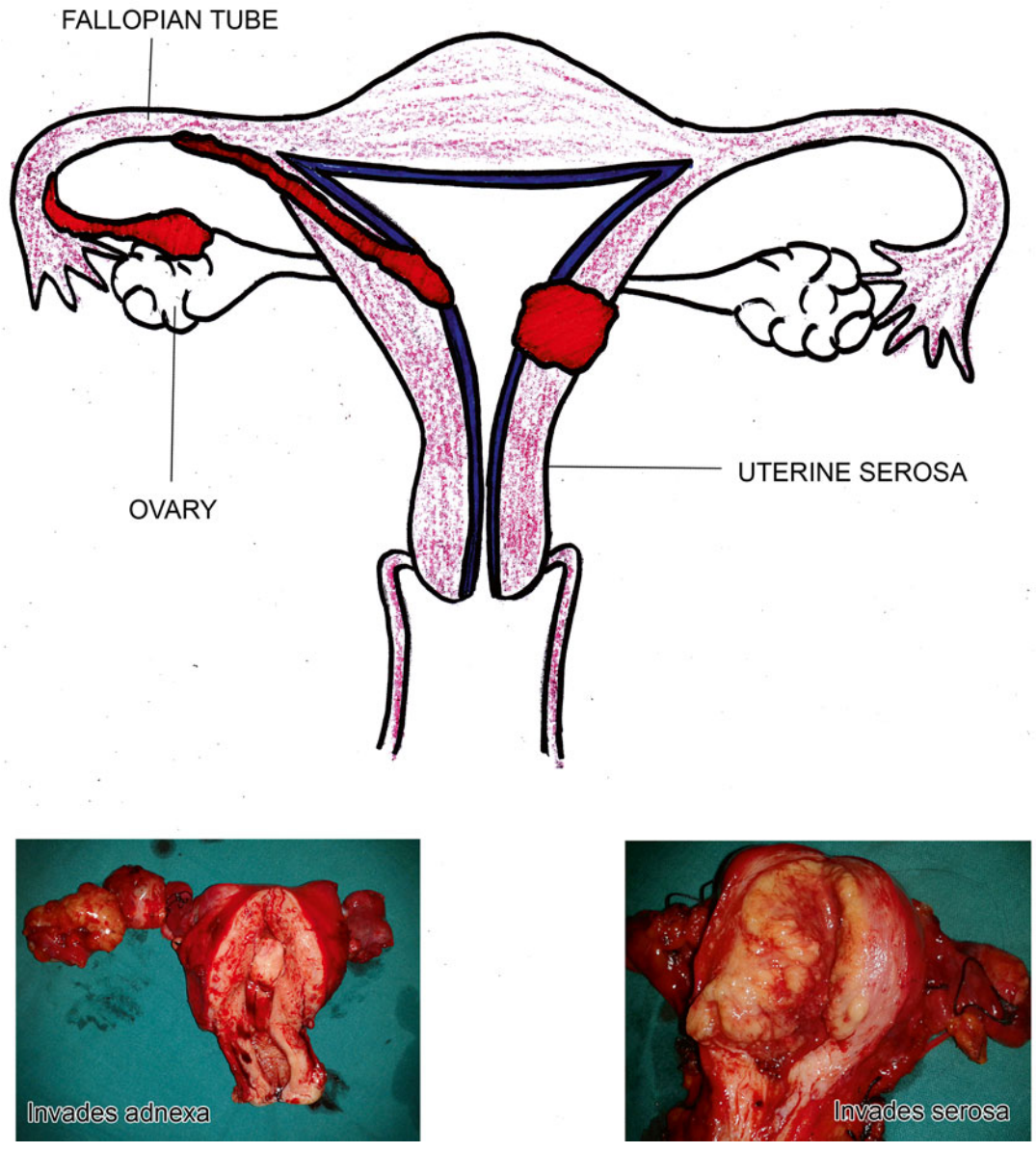

Fig. 14.3 Stage IIIA (T3a, N0, M0) Carcinoma endometrium, Tumor invades serosa or adnexa

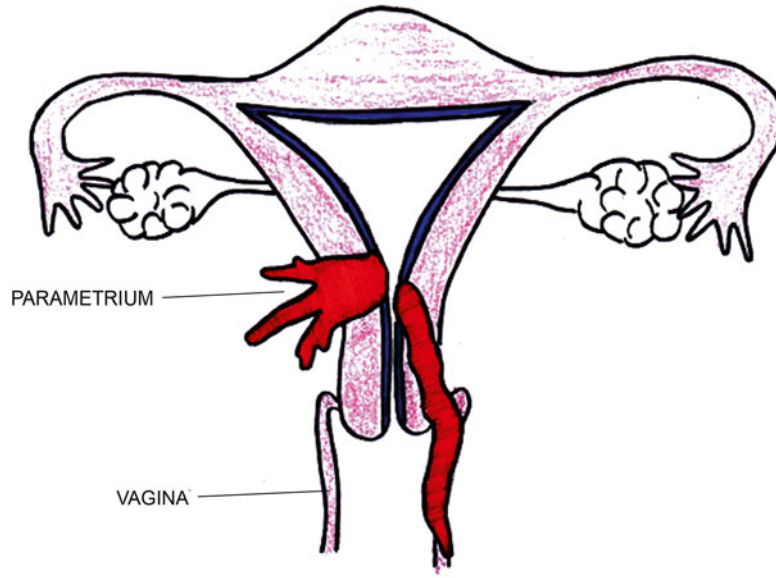

Fig. 14.4 Stage IIIB (T3b, N0, M0) Carcinoma endometrium, Vaginal and/or parametrial involvement

- **T1a:** The cancer is in the endometrium (inner lining of the uterus) and may have grown from the endometrium less than halfway through the underlying muscle layer of the uterus (the myometrium).
- **T1b:** The cancer has grown from the endometrium into the myometrium, growing more than halfway through the myometrium. The cancer has not spread beyond the body of the uterus.

T2: The cancer has spread from the body of the uterus and is growing into the supporting connective tissue of the cervix (called the cervical stroma). The cancer has not spread outside of the uterus.

T3: The cancer has spread outside of the uterus, but has not spread to the inner lining of the rectum or urinary bladder.

- **T3a:** The cancer has spread to the outer surface of the uterus (called the serosa) and/or to the fallopian tubes or ovaries (the adnexa).
- **T3b:** The cancer has spread to the vagina or to the tissues around the uterus (the parametrium).

T4: The cancer has spread to the inner lining of the rectum or urinary bladder (called the mucosa).

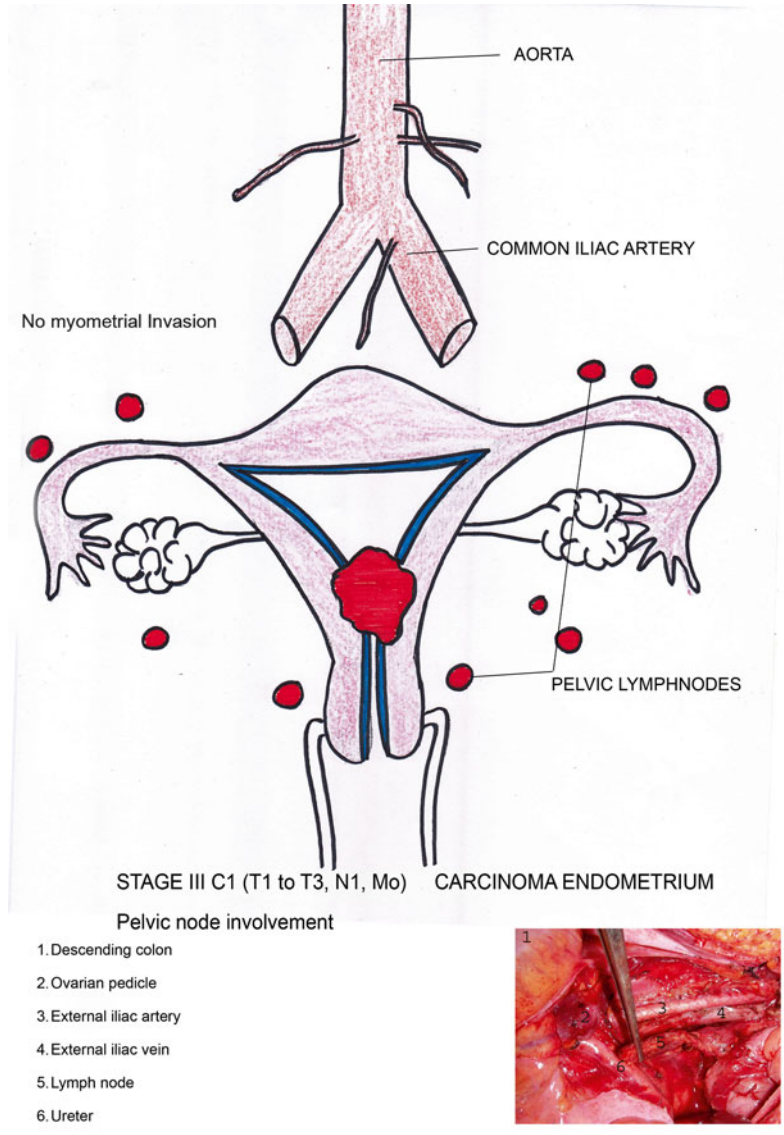

Fig. 14.5 Stage III C1 (T1 to T3, N1, M0) Carcinoma endometrium, Pelvic node involvement

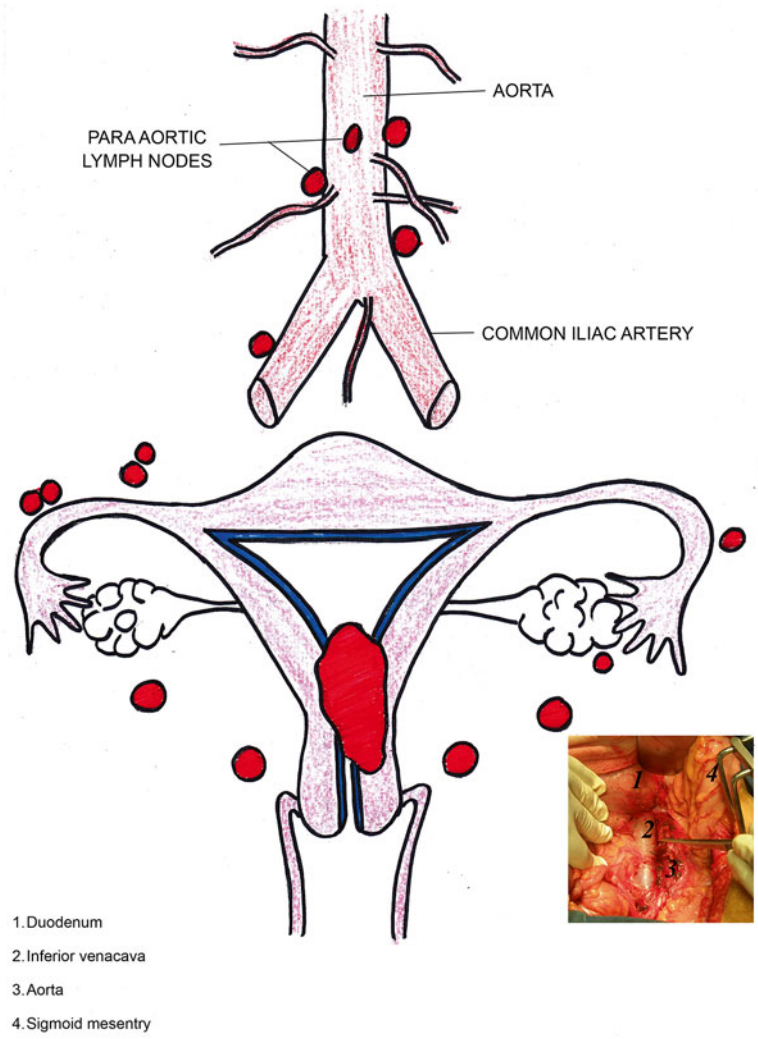

Fig. 14.6 Stage IIIC 2 (T1 to T3, N2, M0) Carcinoma endometrium, Para-aortic involvement

Lymph Node Spread (N)

NX: Spread to nearby lymph nodes cannot be assessed.
N0: No spread to nearby lymph nodes.
N1: Cancer has spread to lymph nodes in the pelvis.
N2: Cancer has spread to lymph nodes along the aorta (periaortic lymph nodes).

Distant Spread (M)

M0: The cancer has not spread to distant lymph nodes, organs, or tissues.
M1: The cancer has spread to distant lymph nodes, the upper abdomen, the omentum, or other organs (such as the lungs or liver).

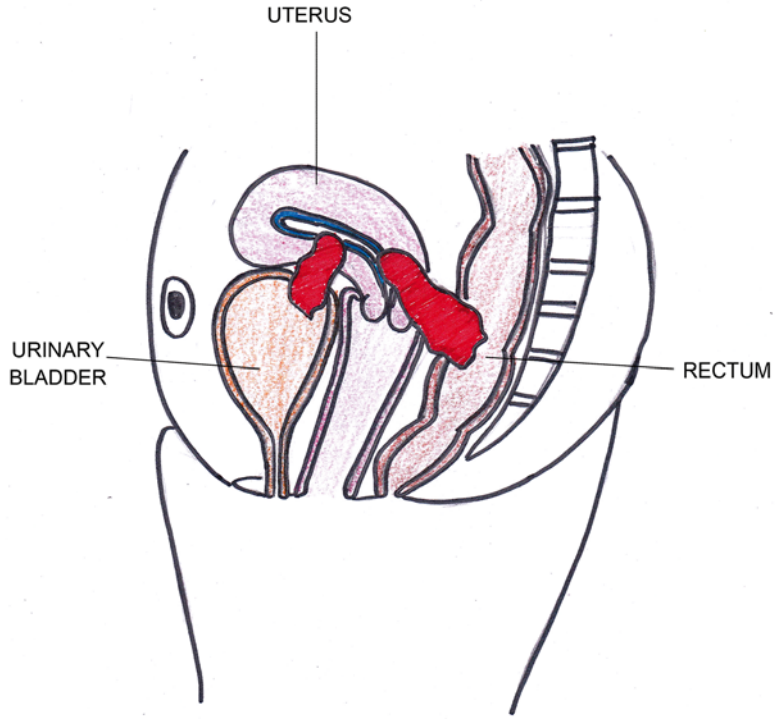

Fig. 14.7 Stage IV A (T4, any N, M0) Carcinoma endometrium, Tumor invasion bladder and/or bowel mucosa

Conclusion

Staging is inevitable in treatment decisions and standardizing treatment. It also helps in prognostication of disease. The two systems used for staging endometrial cancer, the *FIGO* (International Federation of Gynecology and Obstetrics) system and the American Joint Committee on Cancer TNM staging system, are basically the same. They both classify this cancer on the basis of three factors: the extent of the tumor (T), spread to lymph nodes (N), and presence of metastasis (M). The difference between the AJCC system and the FIGO system is that the FIGO system does not include Stage 0. Both the staging systems require surgicopathologic confirmation. However, comprehensive surgical staging in low-grade endometrial cancer still remains controversial.

Key Points

1. Endometrial cancer staging has changed over time to a surgicopathologic classification.
2. The goal of staging is to have a good practice guideline or a clinical practice guideline.
3. Staging also intends to prognosticate the disease.
4. Ideally, width of the myometrium should be measured along with the depth of tumor invasion.
5. There should be histologic verification of grading and extent of the tumor.
6. The difference between the AJCC system and the FIGO system is that the FIGO system does not include Stage 0.

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Sentinel Node Evaluation in Endometrial Cancer

15

Jeffrey Howe and Walter H. Gotlieb

Introduction

In recent years, the role of systematic lymphadenectomy in endometrial cancer (particularly early-stage disease) has been very controversial. The debate originated following the publication of the 1987 Gynecologic Oncology Group study led by Creasman et al. [1]. In their study, complete surgical staging of 621 patients with both grade 1 and clinical stage 1 endometrioid adenocarcinoma revealed that 22 % had lymph node (LN) metastases, adnexal disease, intraperitoneal spread, or positive peritoneal cytology. In addition, they identified risk factors associated with lymph node metastasis. These risk factors included high tumor grade, greater than 50 % depth of myometrial invasion, and the presence of lymphovascular space invasion. In view of the significance of these findings, the International Federation of Gynecology and Obstetrics (FIGO) revised their staging system of endometrial cancer to include surgical dissection and evaluation of pelvic and para-aortic lymph nodes.

Comprehensive surgical staging is meant to serve as a guide to appropriate postoperative adjuvant therapy for endometrial cancer. However, lymphadenectomy is not without complications and has been associated with increased risk of blood vessel and nerve damage, lymphedema, and lymphocyst formation. In addition, some have questioned the therapeutic value of systematic lymphadenectomy. Two recent, large randomized control trials revealed that systematic lymphadenectomy was not associated with improved overall recurrence or survival rates [2–4]. However, the methodologies of both these studies were the subject of criticism [5, 6], and thus, not everyone is quite ready to discontinue lymphadenectomies.

Between the usefulness of the information obtained from the lymph node (LN) dissection and the associated risks, no clear consensus has been reached on the extent of appropriate surgical staging for endometrial cancer [7]. The current practice of LN dissection is heterogeneous among gynecologic oncologists with strategies ranging from complete/radical pelvic and para-aortic lymphadenectomy to complete omission of lymph node sampling. Recently, sentinel lymph node (SLN) mapping has emerged as a promising compromise to the ongoing debate.

The SLN is defined as the first LN in a chain of LNs within a lymphatic basin that receives

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drainage from the primary tumor. Through injection of a traceable dye, these first LNs can be located and examined for histological evidence of metastasis. If the SLNs are found to be negative for metastasis, then similar to the seminal findings in melanoma originally published by the late Don Morton [8], it would imply that the downstream LNs would also be negative, thus obviating the need for further lymphadenectomy in the region. Already well established in melanoma and breast cancer [8, 9], SLN mapping appears promising in gynecologic cancers such as vulvar cancer [10] and cervical cancer [11]. Through SLN mapping, one would be able to obtain information regarding LN status while minimizing the necessity of extensive lymphadenectomy and its associated risks. In this chapter, the current literature regarding detection approaches/techniques and diagnostic accuracy of SLN in endometrial cancer are reviewed.

Limitations of Alternative Methods to Systematic Lymphadenectomy

Current decision-making regarding the extent of surgical staging varies widely (Fig. 15.1). Some surgeons who avoid systematic lymphadenectomy may choose either to completely omit or to perform selective lymphadenectomies. As the name suggests, in complete omission, surgeons abstain from LN dissection and determine the need for adjuvant treatment based on risk for lymph node metastasis and recurrence. Risk is evaluated based on patient age and uterine risk factors such as grade, depth of myometrial invasion, lymphovascular space invasion, and tumor size. It should be noted that suspicious enlarged LNs are still removed in this approach. Other surgeons may choose to perform a selective lymphadenectomy based on intraoperative assessment of grade and depth of myometrial invasion. However, overall, surgeons have

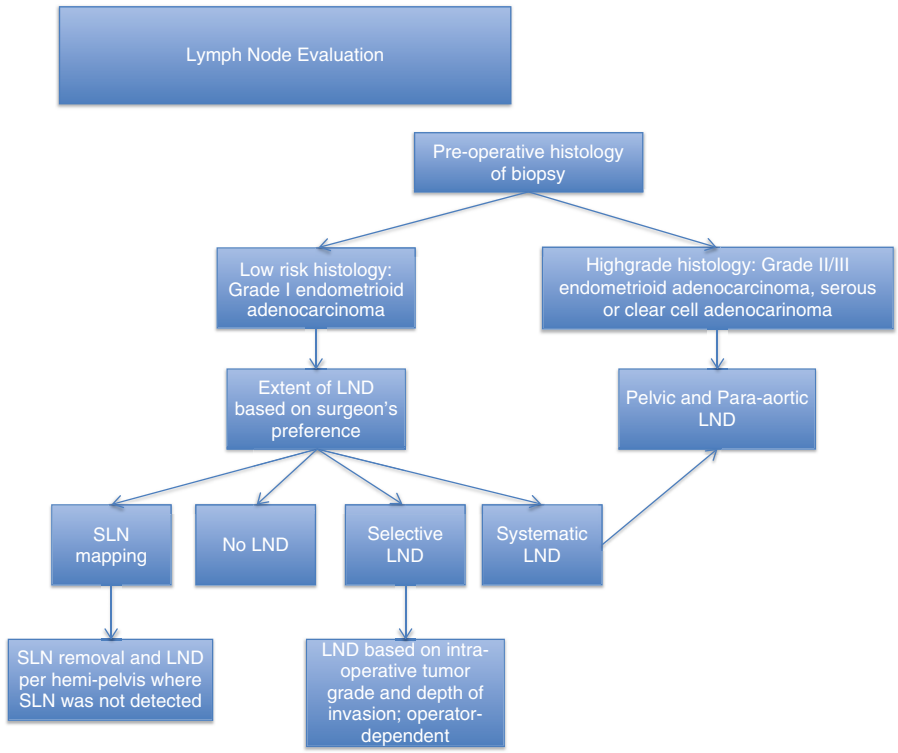

Fig. 15.1 Lymph node evaluation road map. SLN, sentinel lymph node; LND, lymphadenectomy

variable thresholds for performing lymphadenectomies. Considering that patients with grade 1 endometrial cancer still have a risk (though small) of lymph node metastases with approximately 10 % having extrauterine spread, that approximately 20 % of grade 1 tumors observed on preoperative/intraoperative biopsies are upgraded on final pathology [12], and that the frozen section analysis for histological grade and depth of myometrial invasion may not correlate well with the final pathology grade and stage [13], one cannot correctly evaluate the extent of disease in presumed stage I disease. In one study, surgical staging changed management in approximately 29 % of presumed grade 1 endometrial cancer [12]. In view of these challenges, SLN mapping has been investigated as a possible intermediate solution, until better molecular markers are available to predict prognosis and optimal personalized adjuvant therapy.

Sentinel Lymph Nodes and Endometrial Cancer

The first reported use of SLN mapping in endometrial cancer was described by Burke and colleagues in a 1996 pilot study [14]. Numerous studies have followed with varying methodologies for SLN detection. In these studies, the major distinctions are with respect to the type of detection dye used and the location of the injection site (Fig. 15.2).

Detection Methods

In the majority of cases, detection of SLNs is done via visualization of colored lymphatics leading to colored nodes (colorimetric detection), detection of radioactivity in the nodes (isotopic detection), or both.

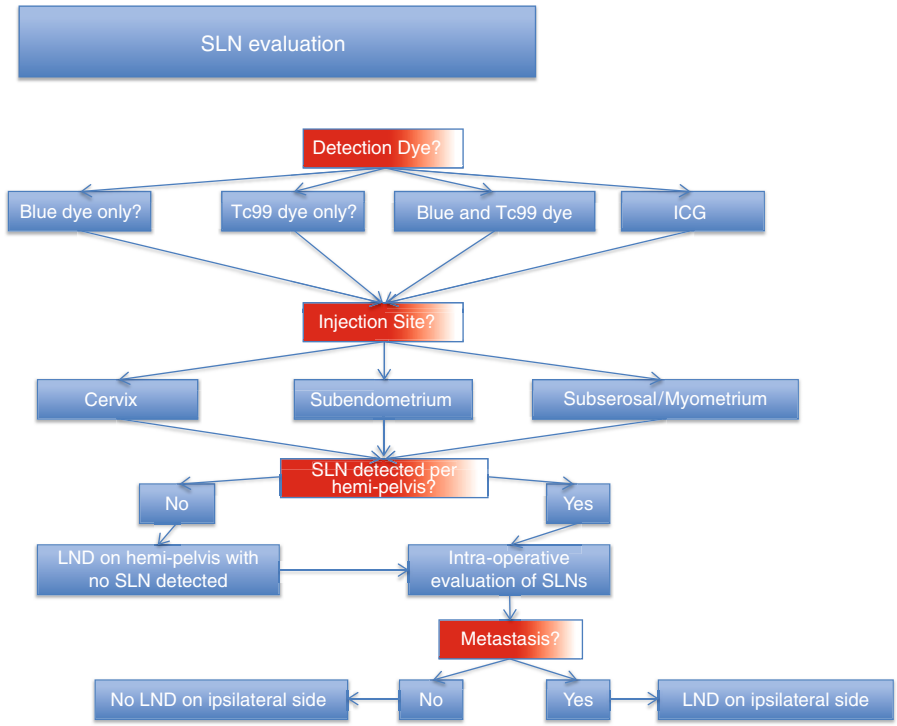

Fig. 15.2 Sentinel lymph node evaluation decision tree. SLN, sentinel lymph node; Tc99, technetium-99 sulfur colloid; ICG, indocyanine green dye; LND, lymphadenectomy

"Blue Dye" Detection

Various blue dyes have been reported in literature and include isosulfan blue, patent blue, and methylene blue. There is no statistically significant difference in the detection rate among the different blue dyes. They will be referred to collectively as "blue dye" in this chapter. Though the injection site may vary, the injection of blue dye always occurs intraoperatively, following induction of anesthesia. After approximately a 10-min delay to allow diffusion of the blue dye, one can visualize the SLN by following blue lymphatic channels to an area of blue collection. The injection of blue dye is deemed safe, but rarely, adverse reactions are reported (e.g., allergic reaction mainly with methylene blue).

Isotope Detection

The patient usually receives a preoperative injection of technetium-99 sulfur colloid on the day prior to or on the morning of surgical staging. Frequently, a lymphoscintigraphy is obtained in order to grossly orient the surgeon to the SLN's location. During the operation, the surgeon utilizes a handheld gamma probe to detect radioactivity. SLNs are identified through the gamma probe by having a tenfold greater radioactive count compared to background radiation. Of note, there is a correlation between the SLNs located via lymphoscintigraphy and during surgical SLN mapping. Ballester and colleagues found 68 % mapping by lymphoscintigraphy vs. 82 % by intraoperative mapping [15]. Improvements are obtained by decreasing the time delay between lymphoscintigraphy and surgical SLN detection [16].

Overall, a combination of both blue dye and technetium produces the highest detection rate and lowest false-negative rate [17] when compared to each individually. It is recommended that surgeons utilize both until technical competency is attained, especially when utilizing blue dye independently. Based on the experience from Abu-Rustum and colleagues, the learning curve for SLN biopsy is approximately 30 cases [18].

Immunofluorescent Detection

Recently, immunofluorescent imaging has been introduced for SLN detection. Rossi and colleagues used indocyanine green (ICG) fluorescent dye injected into the cervix at the 3 o'clock and the 9 o'clock positions in 20 patients [19]. The group utilized the fluorescent imaging mode on the robotic platform of the da Vinci Surgical System in order to visualize the fluorescent green lymphatics and demonstrated a SLN detection rate of 88 % and bilateral detection rate of 60 %. The minimum cervical injection dosage was determined to be 1 mg. Holloway and colleagues utilized a cervical injection of both blue and ICG dye in 35 patients [20]. Utilizing fluorescent imaging, they demonstrated a 97 % bilateral SLN detection rate (100 % bilateral detection rate when using both colorimetric and fluorescent imaging). In both studies, no adverse reactions were noted after ICG injection.

Injection Technique

Three main sites of injection have been utilized for SLN mapping: (1) subserosal/myometrium, (2) endometrium (via hysteroscopy), and (3) cervix.

Subserosal/Myometrial Injection

Subserosal injection was the first technique reported by Burke et al. [14]. In this study, a midline incision was performed, followed by pelvic washings for cytologic analysis and occlusion of the fallopian tubes with hemoclips bilaterally. Next, using 1 ml of 1 % blue dye per syringe (total of 3 syringes), they injected into three uterine locations subserosally: (1) most superior portion of the fundus and on the (2) ventral and (3) dorsal midline 2 cm below the superior injection site. Several studies have replicated this technique [14, 21–23]. Others have followed a similar approach but increased the number of subserosal injection sites [24, 25] and showed an increase in detection rate [24, 25]. Intraoperative injections of technetium at the three previously mentioned

Table 15.1 Studies using subserosal myometrial injection

Study	N	Surgery[a]	Dye[b]	Number of injection sites	Detection rate	Bilateral detection rate	Mean SLN per patient	Sensitivity	NPV	FNR
Burke et al. [14]	15	1	B	3	67 %	NR	3.1	NR	NR	NR
Echt et al. [26]	8	1	B	3	0	0	0	NR	NR	NR
Holub et al. [27][c]	13	2	B	3	62 %	NR	1.15	NR	NR	NR
Gien et al. [28][c]	9	1	B	1	56 %	NR	NR	NR	NR	NR
Li et al. [24]	20	1	B	5	75 %	73 %	4.7	100 %	100 %	0 %
Frumovitz et al. [21]	18	1	B, R	3	45 %	39 %	1.6	NR	NR	NR
Altgassen et al. [25]	23	1	B	8	92 %	NR	3	63 %	93 %	37 %
Lopes et al. [22]	40	1	B	3	78 %	NR	2.0	80 %	96 %	20 %
Robova et al. [29][c]	67	1	B, R	1	73 %	67 %	2.2	100 %	100 %	0 %

N total number of patients, *SLN* sentinel lymph node, *NPV* negative predictive value, *FNR* false-negative rate, *NR* did not report

[a]1 = laparotomy, 2 = laparoscopy, 3 = robotic

[b]B = blue dye, R = Tc99 microsulfur colloid, G = indocyanine green

[c]Study using more than one site of injection and also included in other tables

midline sites have also been used in association with a handheld gamma probe to identify radioactive nodes.

SLN detection rate via this approach has been variable from 45 % to 92 % (excluding one small study of eight patients who did not have any SLN detected) [26] (Table 15.1). Given the small size of studies reported in the literature (largest study having 67 patients) [29], it is difficult to determine the true detection rate of the subserosal approach. Recommendations based on a 2011 meta-analysis [17] are that exclusive subserosal injection should be avoided because it was associated with decreased sensitivity of SLN mapping to detect malignancy.

Of note, a new approach also injecting into the myometrium was reported in a 2013 study by Torné et al. [30]. In their study, transvaginal ultrasonography was utilized in order to identify the uterine tumor and was followed by passing a needle through the anterior vaginal fornix into the anterior uterine wall where 4 ml of technetium was injected into the outer two thirds of the myometrium. A second injection (4 ml of technetium) was given following passing the needle through the endometrial cavity and into the outer two thirds of the myometrium of the posterior wall of the uterus. SLNs were visualized via lymphoscintigraphy and an intraoperative gamma probe. In a cohort of 74 patients, the rate of SLN detection was 74 %. Para-aortic SLNs were detected in 45 % of patients. Sensitivity was 92 %, and negative predictive value was 97.7 %. Disadvantages to this procedure include the technical skill required to ensure adequate injection (without spilling dye into the peritoneal cavity) and detection failure that is associated with tumor size (sevenfold failure rate when tumors were at least 4 cm in size).

Hysteroscopic Endometrial Injection

Hysteroscopy has been utilized in order to inject into the tumor from the cavity. Visualizing the tumor via hysteroscopy, the surgeon injects the traceable dye around the tumor. If the tumor is focal, then it is injected peri-tumorally (2–3 mm away) in four quadrants (3, 6, 9, and 12 o'clock position) into the endometrium. For multiple or diffuse tumors, the dye was injected in five sites: fundus, right mid-lateral wall, left mid-lateral wall, the mid-anterior wall, or mid-posterior wall [28, 31–33]. SLN detection rates range from 33 % to 100 % (excluding a small study of three patients where no SLN was detected) [17]

Table 15.2 Studies using hysteroscopic injection

Study	N	Surgery[a]	Dye[b]	Detection rate	Bilateral detection rate	Mean SLN per patient	Sensitivity	NPV	FNR
Niikura et al. [31]	28	1	R	82 %	50 %	3.1	100 %	100 %	0 %
Fersis et al. [34]	10	1	R	70 %	20 %	1.7	100 %	100 %	0 %
Raspagliesi et al. [35]	18	2	B, R	94 %	56 %	3	NR	NR	NR
Maccauro et al. [32]	26	2	B, R	100 %	18 %	2.5	100 %	100 %	0 %
Gien et al. [28][c]	3	1	B	0 %	0 %	0 %	NR	NR	NR
Delaloye et al. [33]	60	1+2	B, R	50 %	45 %	3.7	89 %	98 %	11 %
Perrone et al. [36]	17	1	R	65 %	27 %	1.3	100 %	100 %	0 %
Feranec et al. [37]	21	1	B, R	81 %	NR	2	100 %	100 %	0 %
Robova et al. [29][c]	24	1	B, R	50 %	NR	2.2	100 %	100 %	0 %
Rossi et al. [38][c]	12	3	G	33 %	50 %	2.5	NR	NR	NR

N total number of patients, *SLN* sentinel lymph node, *NPV* negative predictive value, *FNR* false-negative rate, *NR* did not report

[a]1 = laparotomy, 2 = laparoscopy, 3 = robotic

[b]B = blue dye, R = Tc99 microsulfur colloid, G = indocyanine green

[c]Study using more than one site of injection and also included in other tables

(Table 15.2). Again, this wide range of variability is due to significant influence of the small study effect. Advocates of the hysteroscopic method state that the approach allows for adequate mapping of the para-aortic area; this is aptly demonstrated by a recent study on a cohort of 59 patients [16]. Utilizing only technetium dye, they found a 95 % SLN detection rate with 56 % of patients having a SLN in the para-aortic area. Solima et al. attributed their high SLN detection rate due to the short interval between hysteroscopic injection and SLN detection (approximately 6 h).

In theory, a peri-tumoral injection is most likely to mimic the natural lymphatic drainage of malignant cells. However, the approach does have several drawbacks secondary to utilizing hysteroscopy. For example, given the increased time elapsed from time of injection until access to the abdominal cavity, lower detection rates were seen when using exclusively blue dye [31]. Hysteroscopy is technically challenging and not only prolongs operative time but also may be less reproducible among practitioners compared to other methods. Finally, there is an increased risk of iatrogenic dissemination of malignant cells. Maccauro et al. and Raspagliesi et al. each reported one case of positive peritoneal cytology following hysteroscopic injection [32, 35]. The significance of this positive cytology is controversial, and the risk appears to be reduced if the endometrial pressures remain below 70 mm Hg [39].

Cervical Injection

Most studies evaluating SLN mapping in endometrial cancer have utilized the cervix as the site of injection. For the cervical approach, many of the studies in the literature report the use of both technetium and blue dye [17, 40–42]. In most studies, the technetium is injected preoperatively, and the blue dye is injected in the operating room. Cervical injection sites vary from two (3 and 9 o'clock) to four (3, 6, 9, and 12 o'clock) positions. The blue tracer is injected in the cervix at the 3 o'clock and 9 o'clock positions in the operating room, following general anesthesia immediately prior to the surgical incision. At each cervical injection site, two 25-gauge needles are used to inject superficially (2–3 mm) into the submucosa as well as deeply (1–2 cm) toward the lower uterine segment [40, 41, 43]. Using this approach, SLN detection rates have ranged from 62 % to 100 % [44] with detection rates ranging from 84 % to 92 % for studies with the largest sample populations [40, 41, 45, 46] (Table 15.3).

Another technical variation introduced by How et al. [46] entails dual injection of a mixture of blue and technetium dye intraoperatively into the

Table 15.3 Studies using cervical injection

Study	N	Surgery[a]	Dye[b]	Number of injection sites	Detection rate	Bilateral detection rate	Mean SLN per patient	Sensitivity	NPV	FNR
Holub et al. [27][c]	12	2	B	4	83 %	81	2.5	NR	NR	NR
Gargiulo et al. [47]	11	2	B, R	4	100 %	55 %	NR	100 %	100 %	0 %
Pelosi et al. [48]	16	2	B, R	4	94 %	56 %	1.6	100 %	100 %	0 %
Barranger et al. [49]	17	2	B, R	2	94 %	63 %	2.6	100 %	100 %	0 %
Holub et al. [23]	25	2	B	4	84 %	81 %	2.1	100 %	100 %	0 %
Lelievre et al. [50]	12	1+2	B, R	4	91 %	25 %	3	100 %	100 %	0 %
Bats et al. [42]	43	1+2	B, R	4	70 %	53 %	2.9	100 %	100 %	0 %
Perrone et al. [36]	23	2	R	NR	70 %	38 %	1.7	100 %	100 %	0 %
Mais et al. [51]	34	1+2	B	4	62 %	NR	NR	100 %	100 %	0 %
Ballester et al. [41]	125	1+2	B, R	2	89 %	69 %	1.5	84 %	97 %	16 %
Khoury-Collado et al. [40]	266	1+2	B, R	2	84 %	67 %	3	NR	NR	NR
Rossi et al. [19]	20	3	G	2	85 %	60 %	4.5	50 %	95 %	50 %
Holloway et al. [20]	35	3	B,G	2	100 %	100 %	NR	100 %	96 %	0 %
How et al. [46]	100	3	B,R	2	92 %	72 %	2.0	89 %	99 %	11 %
Rossi et al. [38][c]	17	3	G	2	82 %	57 %	5	50 %	92 %	50 %

N total number of patients, *SLN* sentinel lymph node, *NPV* negative predictive value, *FNR* false-negative rate, *NR* did not report

[a]1 = laparotomy, 2 = laparoscopy, 3 = robotic

[b]B = blue dye, R = Tc99 microsulfur colloid, G = indocyanine green

[c]Study using more than one site of injection and also included in other tables

cervix at the 3 o'clock and 9'oclock positions. When compared to previous studies with cervical injection blue dye and preoperative lymphoscintigraphy [17, 40, 41], the dual injection demonstrated similar results with respect to detection rate (92 %) and diagnostic accuracy of SLN mapping. This approach is simple, cheaper, and performed on the patient under anesthesia and represents an alternative to lymphoscintigraphy in centers which do not have access to these resources.

The most distinguishing advantage of a cervical injection is that it is the most simple and reproducible technique given the accessibility of the cervix for injection. It was demonstrated to have a higher overall bilateral pelvic detection rate (63 %) compared to the other two methods (35 % and 48 % for subserosal and hysteroscopic, respectively) [52]. A recent meta-analysis found that cervical injection was correlated with improved SLN detection rate (although no statistical significance was reached) [17].

A common argument against the use of the cervical approach is the concern that the para-aortic area may not be adequately mapped. Studies examining the cervical approach have reported relatively lower detected para-aortic SLNs (5 % detection in both the Ballester et al. and Khoury-Collado et al. studies and 15 % in the How et al. study) [40, 41, 46]. Interestingly, in a study by Abu-Rustum and colleagues, they examined two cohorts of patients who all received preoperative lymphoscintigraphy with either injection of blue dye into the cervix or into both cervix and fundus. They found no statistically significant difference in the detection of para-aortic SLNs between cohorts. Furthermore, a deep cervical injection at the 3 and 9'oclock positions demonstrated good blue dye spread to the para-uterine lymphatics (a major lymphatic drainage route of the uterine corpus) [53] (Fig. 15.3). As well, blue lymphatics were noted in the infundibulopelvic ligament by How and

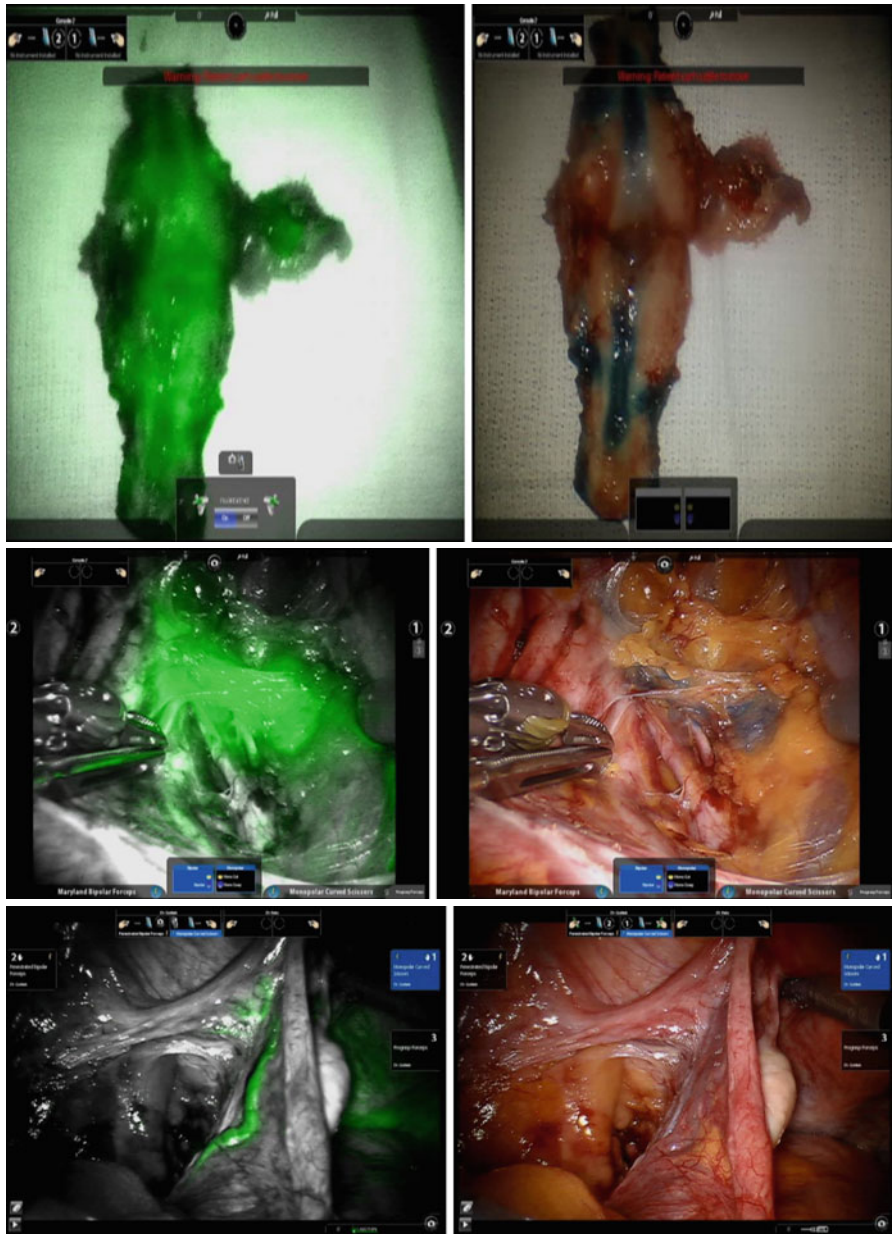

Fig. 15.3 Upper panels: staining of entire uterine cavity following cervical injection of ICG and patent *blue* dye deeply into the stroma of the cervix to reach the lower uterine segment (3–4 cm deeply) and superficially (2–3 mm) to reach to the cervical submucosa. Middle panels: staining of lymphatics and rt obturator lymph node following dual injection of ICG *green* and patent *blue* as above. Lower panels: staining of lymphatics along the IP ligament following dual injection of ICG *green* and patent *blue* as above

colleagues and they suggest that cervical site injections could drain via this pathway [46]. Utilizing the most recent immunofluorescent technique with indocyanine green, Rossi et al. found para-aortic SLNs in a high proportion of patients and the greatest documented detection rate for SLN in endometrial cancer overall [19]. Furthermore, in another related study, the group compared SLN detection rates between two groups receiving an injection of ICG either

through the cervical or hysteroscopic route [38]. Rossi et al. found a higher SLN detection rate in the cervical group and no significant difference in the anatomic distribution of detected SLNs between both groups. Also, one should keep in mind that isolated metastases to the para-aortic area are rare (7–8 %) and typically arise in high-grade tumors or serous and clear cell histologic subtypes. In a Mayo Clinic study, Mariani and colleagues found that even when excluding low-risk patients, isolated para-aortic lymph node metastases are present in only 10 of 281 patients (3.6 %) [54].

Diagnostic Accuracy

In order to function well as a diagnostic test, SLN should have both a high sensitivity and negative predictive value while having a low false-negative rate. It should be noted that false-negative rate should not be confused with failed SLN mapping which refers to failure to detect the SLN. The absence of detection of a SLN on one side of the pelvis warrants a full lymphadenectomy on that side. The presence of metastasis in a SLN warrants a complete lymphadenectomy. Enlarged and suspicious LNs need to be removed as part of every SLN protocol, because it is believed that overtly metastatic nodes might have blocked lymphatic flow that decreases or impedes the uptake of the dye. Overall, the negative predictive value is high, ranging from 95 % to 100 % with a sensitivity and false-negative rate of 93 % and 7 %, respectively, as reported in a meta-analysis of 26 studies [17]. The groundbreaking group from Memorial Sloan Kettering Cancer Center under the leadership of Dr. Abu-Rustum demonstrated the importance of a SLN mapping strategy to maintain low false-negative rates. In their procedural algorithm, they proposed that endometrial cancer patients have (1) peritoneal and serosal evaluation and washings, (2) retroperitoneal evaluation including excision of all mapped SLNs and suspicious LNs (>1 cm) regardless of results of mapping, and (3) side-specific lymph node dissection if there is no mapping on the hemi-pelvis. For example, if the surgeon detected a negative SLN in the right pelvic region only and an enlarged left pelvic non-SLN, then he/she would perform a complete left pelvic lymphadenectomy. When applying the algorithm, the group reduced the false-negative from 15 % to 2 % [45]. As a result, many centers have implemented this approach for SLN mapping.

Ultrastaging and Micrometastasis

As expected, SLNs are three times more likely to have metastasis compared to non-SLNs [40]. However, routine examination of LN with hematoxylin and eosin (H&E) staining and bisection of the SLN at the time of frozen section can miss cases of metastasis. Over the years, ultrastaging has gained popularity in SLN analysis. This procedure entails the use of several techniques in order to identify metastatic cells in lymph nodes to a high degree of sensitivity and accuracy. Many ultrastaging protocols include the use of immunohistochemistry (cytokeratin staining) and serial sectioning. Both allow for better detection of micrometastasis (defined as a focus of disease between 0.2 and 2 mm) or isolated tumor cells (defined as a focus of disease less than 0.2 mm) [55, 56]**.** Though frozen section analysis is capable of detecting the majority of macrometastasis in SLNs, it is inaccurate in detection of micrometastasis and isolated tumor cells [57]. This inaccuracy is mainly due to the metastasis being too small or not sampled on the section plane. Furthermore, 50 % of the SLN metastases in early-stage endometrial cancer patients are micrometastases discovered via ultrastaging [41, 58]. Clinical significance of micrometastasis and isolated tumor cells is not known, but their presence may factor in the physician's decision to administer adjuvant therapy. It should be noted that despite the sensitivity of ultrastaging, it is expensive and time consuming, and it would be impractical to apply this approach for intraoperative frozen section or to patients who undergo comprehensive lymphadenectomy without SLN. In the latter scenario, no data is available on the impact and outcome of these patients who had full lymphadenectomies but without evaluation of micrometastases.

Summary and Conclusion

Although comprehensive surgical staging is accepted by many gynecologic oncologists as the standard of care for the majority of patients with grade II–III tumors and high-risk histologies, it is heavily debated for clinically low-risk endometrial cancer patients. Consensus on treatment is complicated by the failure to reach an appropriate medium between overtreatment of patients with potentially low-risk disease and undertreatment of patients with metastatic disease. On one hand, LN metastasis in these types of patients is uncommon, but on the other hand, without appropriate staging, patients are at risk of inadequate treatment, especially given there is a 20 % risk of tumor upgrade from the preoperative biopsy to the final pathology. Furthermore, surgical staging impacts postoperative treatment decisions in as high as 29 % of patients [12]. Though the therapeutic value of lymphadenectomy has been questionable in endometrial cancer, most would agree that lymph node status influences decisions for adjuvant therapy.

Thus, lymphatic mapping via the SLN procedure appears to provide a promising alternative to the ongoing issue. SLN mapping can help to limit the number of unnecessary lymphadenectomies and its associated complications (especially in women who are obese, elderly, or with multiple comorbidities). Since the first reported study by Burke and colleagues in 1996, SLN mapping has also gained more popularity given the fact there is no consensus on the extent of an adequate lymphadenectomy (e.g., minimum of LNs required to be removed for an adequate dissection) and the optimal anatomic templates (e.g., boundaries for a para-aortic lymphadenectomy).

As well, it is clear that techniques to analyze LNs (such as ultrastaging) are becoming more refined and accurate and play a significant role in detecting metastatic disease. However, these analyzing techniques are exhaustive, and it would be unrealistic to apply ultrastaging to all LNs. Instead, allowing the pathologist to focus his/her attention of a few key LNs that are most likely to harbor disease, i.e., the SLN [40], may help to effectively detect metastatic disease (especially micrometastasis or isolated tumor cells) that would be missed on routine H&E staining of all the lymph nodes. Although the clinical significance of micrometastasis has not been determined, it may alter the patient's prognosis or need for adjuvant therapy.

Despite significant research on SLNs for endometrial cancer, it should still be considered investigational. Widespread clinical implementation and delay in the standardization of SLN mapping in endometrial cancer can be attributed to 1) the lack of consensus on the best route of injection to optimize SLN detection rate, 2) the need for high sensitivity for detecting metastasis together with a low false-negative rate, 3) the requirement to be well tolerated by the patient, and 4) to be easily reproducible. Future research should be comparative and address these issues.

Key Points

1. Extent of lymphadenectomy for early-stage endometrial cancer remains controversial.
2. Current techniques to preoperatively detect metastatic lymph nodes are not reliable.
3. Sentinel lymph node mapping is still investigational but appears to be a promising procedure to minimize complications associated with extensive lymphadenectomy while obtaining information regarding lymph node status that is essential for adjuvant therapy decision-making.
4. Optimal injection site (subserosal/myometrium, subendometrium, or cervix) for sentinel lymph node detection in endometrial cancer is debatable, although the cervical approach with deep lower isthmic injection is the easiest and most reproducible and appears to reliably represent major lymphatic drainage areas.
5. Except for the ICG that is presently restricted to robotics, the utilization of blue dye and technetium is associated with the highest detection and lowest

false-negative rate for sentinel node mapping.
6. Sentinel lymph node is threefold more likely to be a site of metastasis than other lymph nodes.
7. Sentinel lymph node mapping enables ultrastaging with focused, detailed analysis of the most likely lymph nodes involved in metastatic spread.
8. Clinical significance of micrometastasis has yet to be determined, but the presence may factor in the decision for gynecologic oncologists to plan for adjuvant therapy.

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Surgery for Carcinoma Endometrium

16

K. Chitrathara and T.J. Simi Raj

Introduction

There has been a significant change in the management of carcinoma endometrium over the past 50 years. Endometrial cancer was staged clinically in the 1970s. Patients with early-stage disease were treated with preoperative packing of the endometrial cavity with radiation sources, Heyman's capsules, and then followed by hysterectomy. The surgical staging for carcinoma endometrium was introduced by the International Federation of Gynecology and Obstetrics in 1988. The concept of surgery as primary therapy and postoperative adjuvant pelvic radiotherapy for patients at high risk of recurrence emerged after the FIGO surgical staging. There had been a gradual move away from the use of adjuvant pelvic radiotherapy in patients who have been completely surgically staged in the last decade.

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Surgery

Surgery is the primary treatment modality for endometrial cancer and is a surgically staged disease. The procedure includes a thorough exploration of the peritoneal cavity, peritoneal washings, hysterectomy, bilateral salpingo-oophorectomy, and bilateral pelvic and para-aortic lymph node dissection. Conventionally, laparotomy has been used for staging and hysterectomy, but the use of laparoscopy and robotic surgery has been increasing.

Preoperative Assessment and Preparation

A thorough history and physical examination including assessment of medical comorbidities is essential. History should include the length and severity of vaginal bleeding as well as symptoms of metastatic disease like abdominal or pelvic pain, changes in bowel or bladder habits, lower extremity pain, early satiety, dyspnea, or cough. Family history is important as 50 % of women with HNPCC develop endometrial cancer prior to colon cancer. Clinical examination should include assessment of enlarged supraclavicular or inguinal lymph nodes, ascites, abdominal mass, and pedal edema. Per speculum examination is important to look for metastatic vaginal nodules especially in the periurethral region and

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lower one third of vagina and also to rule out any extension to cervix. Vaginal examination is done for uterine size and mobility, adnexal masses, parametrial disease, cul-de-sac nodularity, and extension to cervix and vagina. Routine preoperative laboratory evaluation includes complete blood count, blood group/type and screen, hepatic and renal function tests, and blood sugar estimations. CA-125 level measurement in blood is indicated in women with uterine papillary serous carcinoma. Preoperative serum CA 125 level is a simple test to detect women with more advanced-stage endometrial adenocarcinoma, and its routine use could help triage high-risk patients preoperatively [1].

Women should be counseled on the indications, risks, and benefits of surgery. Written informed consent should be obtained. Mechanical bowel preparation and standard preoperative antibiotic prophylaxis are indicated. As these women are at high risk for deep vein thrombosis, thromboembolic prophylaxis is recommended along with mechanical intraoperative pneumatic compression devices.

Surgical Procedure: Laparotomy

Patients can be positioned supine or in lithotomy. Supine position avoids the risk of neurological injury caused by stirrups. Lithotomy position provides better access to the para-aortic region with surgeon/assistant standing between the patient legs.

A vertical midline lower abdominal incision is preferred to low transverse incision as it allows better access to the para-aortic region. After opening the abdomen, peritoneal washings are taken with 50–100 ml of normal saline. The fluid is gently agitated around the pelvic organs and aspirated from the cul-de-sac and sent for cytologic examination. Washings positive for malignant cells are a poor prognostic factor. Although current FIGO staging disregards positive peritoneal cytology, the Federation insists that it has to be documented separately.

The abdominal cavity should be explored systematically. The pelvis is explored at the end so that the surgeon is not distracted by the findings. The anterior abdominal wall is elevated by the assistant using a Deaver retractor. The omentum, anterior surface of stomach, surface of the liver, and the gallbladder are visualized. Systematic palpation of the abdominal viscera is started on the right side starting with peritoneum of the right anterior abdominal wall and the right paracolic gutter. The surgeon then moves upward in a clockwise direction to palpate the right kidney, gallbladder, right lobe of liver, right hemidiaphragm, left hemidiaphragm, left lobe of liver, spleen, stomach including the pylorus, left kidney, peritoneum of the left anterior abdominal wall, left paracolic gutter, and finally the pelvis. The small bowel is run from the ileocecal valve to the ligament of Treitz. The retroperitoneum including the pancreas, para-aortic lymph nodes, and bilateral pelvic lymph nodes is palpated as the small bowel is brought out of the incision. The cecum and appendix are examined and the large bowel is run. The small bowel is retracted into the upper abdomen, and the pelvis is explored to assess the size and mobility of uterus and pelvic and cul-de-sac peritoneum for implants and ovaries and fallopian tubes for any masses.

Once exploration is complete, bowel is packed into the upper abdomen with moist laparotomy sponges and a self-retaining retractor placed. The blades of the retractor should not be placed over psoas muscle to prevent injury to femoral nerves. The use of Trendelenburg position enables better exposure.

Type 1 Extrafacial Hysterectomy

Long Kelly or straight clamps are used to grasp the uterine cornua bilaterally. This occludes the Fallopian tubes and prevents spill of malignant cells into the peritoneal cavity during uterine manipulation. Uterine fundus should not be grasped with instruments, like vulsellum, tenaculum, or myoma screw. This perforates the uterus and disseminates malignant cells into the peritoneal cavity, an event which must be avoided.

The round ligaments bilaterally are clamped, cut, and ligated. The ligatures on the lateral end

are left long and clipped to the drapes to prevent lateral peritoneum falling into the operative field, since the peritoneum remains stretched. The use of Langenbeck's retractor aids iliac node dissection. Peritoneum posterior to the round ligament is opened one centimeter lateral and parallel to the ovarian vessels till the bifurcation of the common iliac vessels where ureter is seen crossing. The course of pelvic ureter is visualized posteriorly and parallel to the ovarian vessels by blunt dissection of the retroperitoneum. Ureter is identified by its peristalsis. A window is created in the posterior leaf of the broad ligament between the ovarian vessels and the ureter. The ovarian vessels are clamped, cut, and ligated (vessel sealing system or harmonic scalpel can be used). The utero-ovarian ligament is skeletonized till the uterus. The adnexa can be suspended to the clamps placed at the cornua to keep them out of the way. The adnexa should not be excised to prevent tumor spillage into the peritoneal cavity unless it prevents access to the pelvis.

The vesicouterine fold of peritoneum is opened, and bladder is dissected off the uterus and cervix by sharp dissection. Blunt dissection should be avoided to prevent injury to the bladder. The uterine vessels are skeletonized and clamped at the level of the internal os of cervix with the Heaney or curved artery clamp applied perpendicular to the cervix. The uterine pedicle is then transected and ligated. The cardinal ligaments are serially clamped, transected, and ligated bilaterally. Smaller pedicles allow ureter to fall away with each bite and ensure better hemostasis. The uterine and cardinal ligament clamps should be just placed against the cervix and not "rolled off" the cervix to prevent any residual cervix being left behind. Subsequent clamps are placed medially to prevent injury to ureter at the vaginal vault. The uterosacral ligaments can be clamped cut and ligated separately. Upper vagina is cross-clamped one centimeter below the cervix once cervicovaginal junction is reached using a curved Heaney or curved artery clamp. This is to prevent spill of malignant cells into the vagina. The specimen comprising of uterus with both tubes and ovaries is delivered. The vagina is suctioned to avoid any spill of uterine contents into the peritoneal cavity and cleaned with Betadine gauze. The suction tip is irrigated with saline. The vaginal angles are ligated. Vault is closed with continuous sutures and hemostasis is ensured. At the end of the procedure, thorough pelvic wash with saline is given.

Pelvic Lymph Node Dissection

Pelvic lymphadenectomy involves the removal of perivascular lymphatic tissue from common iliac, external iliac, and internal iliac vessels. Internal iliac group of lymph nodes includes obturator nodes (Fig. 16.1).

The bowel is packed to the opposite side of dissection. The colon and ureter are retracted with a large Deaver retractor toward the opposite shoulder. The retroperitoneum is entered by retracting the round ligament and incising the peritoneum lateral to the ovarian vessels up to the pelvic brim. The loose areolar tissue is dissected to identify the pelvic vessels and ureter. The paravesical space is identified by dissecting down into the obturator fossa retracting the obliterated umbilical artery and lateral part of the bladder medially and external iliac vessels laterally. The pararectal space is opened by bluntly dissecting between the ureter and internal iliac artery.

The extent of lymph node dissection is genitofemoral nerve laterally, muscular pelvic wall

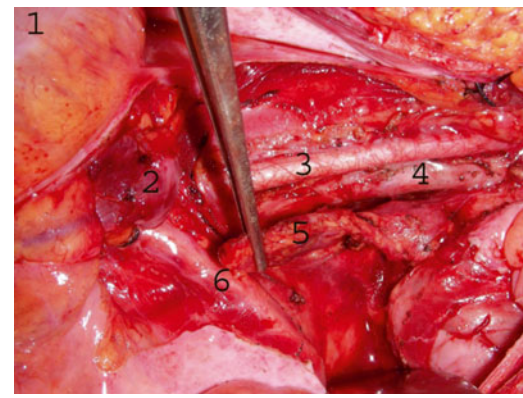

Fig. 16.1 Pelvic lymph node dissection. *1*. Sigmoid-descending colon. *2*. Common iliac nodes. *3*. External iliac artery. *4*. External iliac vein. *5*. Obturator nodes. *6*. Internal iliac artery

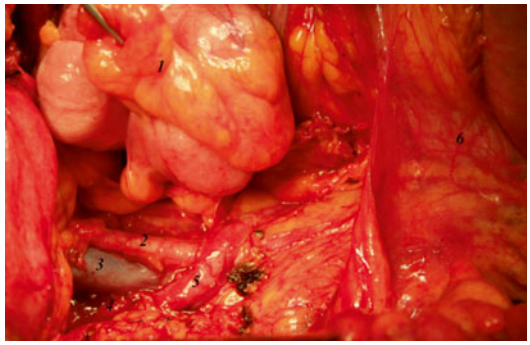

Fig. 16.2 Completed pelvic node dissection. *1*. Cecum. *2*. External iliac artery. *3*. External iliac vein. *4*. Internal iliac vein. *5*. Ureter. *6*. Beginning of jejunum

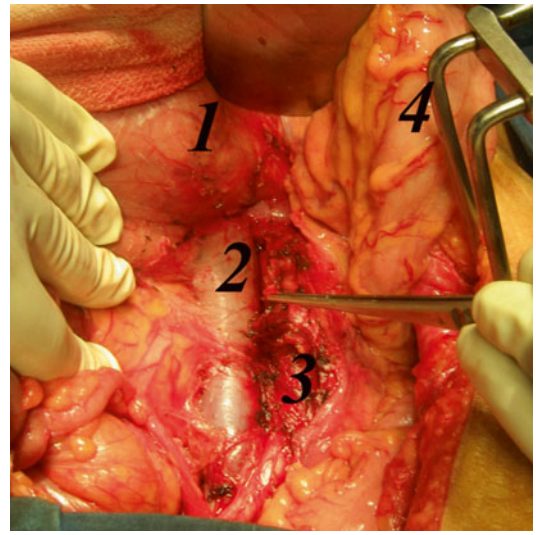

Fig. 16.3 Para-aortic node dissection: *1*.duodenum *2*. inferior venacava *3*. aorta *4*. sigmoid & descending colon mesentry

posterolaterally, obturator nerve posteriorly, and circumflex iliac vein crossing the external iliac artery or the level where the external iliac vessels exit the abdomen distally. Midpoint of the common iliac artery serves as a divide between pelvic and para-aortic nodes. The lymph nodes are dissected using a right angled clamp and feeding vessels cauterized using bipolar cautery and excised. This includes the tissues anterior and medial to the common iliac artery, anterior and medial to external iliac artery, medial to external iliac vein, and anterior to the internal iliac artery extending distally along the superior vesical artery (Fig. 16.2). The external iliac vein is retracted anteriorly with a vein retractor. Blunt dissection is performed within the obturator space to reveal the course of the obturator nerve. The lymph nodes anterior to the obturator nerve are removed.

Para-aortic Lymph Node Dissection

The extent of para-aortic lymph node dissection is from the aortic bifurcation up to either the inferior mesenteric artery or preferably to the level of renal veins.

The small bowel loops are brought out of the incision, packed inside a one meter sheet, and retracted into the upper abdomen using a Deaver retractor. The peritoneal incision is extended along the common iliac vessels up the aorta to the root of the small bowel and on the right side along the paracolic gutter. Midline incision may also be used for aortocaval dissection up to the level of origin of right ovarian vessels. The small bowel loops and right colon are then moved out of the field and right ovarian vessels and ureter freed from the posterior aspect of right colon. On the left side, exposure is attained by extending peritoneal incision through left paracolic gutter and retracting the left colon laterally. The dissection is started from the aortic bifurcation and proceeded in a caudal to cephalad direction.

The lymphatic tissue from anterior surface of vena cava can be removed using sharp and blunt dissection. Care should be taken to prevent tearing of small venous branches entering the vena cava. There is a fairly constant vein within the lymphatics just above the bifurcation named the "Fellow's vein," which when torn can cause unexpectedly large defects in vena cava resulting in heavy bleeding. The inferior mesenteric artery is preserved, and dissection should be continued preferably up to the level of renal veins (Fig. 16.3).

Ligation of lumbar arteries above renal vessels should be avoided to prevent spinal cord ischemia.

The intraoperative complications of retroperitoneal lymph node dissection are injury to ureter, pelvic vessels, obturator nerve, lumbar vein, aorta, and vena cava. Laceration of small veins (Fellow's vein) is the common IVC injury. In case of vascular injury, the site of injury is compressed while sutures are ready. The area above and below is cleared, and the injured area is sutured with 5–0 or 6–0 PROLENE. For aortic rents, it is wise to get the help of a vascular surgeon. The postoperative complications include venous thrombosis, lymphocyst formation, and small bowel obstruction.

Special Considerations

1. Uterine papillary serous carcinomas behave in a manner similar to ovarian cancers demonstrating spread within the peritoneal cavity even when the primary is confined to the endometrium. Hence, staging of uterine papillary serous carcinoma should include hysterectomy with bilateral salpingo-oophorectomy, peritoneal washings and biopsies, bilateral pelvic and para-aortic lymph node dissection, and omentectomy as is typically performed for ovarian cancer. In early-stage endometrial cancer, the majority of omental metastases consist of microscopic disease. Factors significantly associated with omental metastasis were adnexal spread, cul-de-sac implantation, papillary serous carcinoma, positive retroperitoneal lymph nodes, and grade 3 tumor. For patients with high-risk variables, a complete omentectomy should be considered [2].
2. In stage II endometrial cancers with a bulky cervix, there is a risk of parametrial extension as in primary cervical carcinomas. Sometimes, it may be difficult to differentiate a primary endometrial adenocarcinoma with cervical extension from a primary cervical adenocarcinoma. Hence, in such patients, a radical hysterectomy and pelvic and para-aortic lymphadenectomy are done. An alternative for these patients is preoperative external beam whole pelvic radiotherapy and intracavitary brachytherapy followed by completion hysterectomy with bilateral salpingo-oophorectomy. Completion hysterectomy is essential as radiotherapy is not as effective in treating disease in uterine corpus as in uterine cervix. In stage III or IV patients, debulking of the tumor may be of benefit.

Role of Laparoscopy

Current evidence on the safety and efficacy of laparoscopic hysterectomy (including laparoscopic total hysterectomy and laparoscopically assisted vaginal hysterectomy) for endometrial cancer is adequate to recommend the use of this procedure. Patient selection for laparoscopic hysterectomy for endometrial cancer should be carried out by a multidisciplinary gynecological oncology team, and advanced laparoscopic skills are required for this procedure.

Modified Radical Hysterectomy for Carcinoma Endometrium

The author believes that local recurrences are decreased with modified radical hysterectomy when compared to simple extra-fascial hysterectomy for women with carcinoma endometrium.

Although total hysterectomy with bilateral salpingo-oophorectomy was the routine in the initial years, local recurrence was seen in two stage I patients. One patient could be salvaged by radiation, but ever since, a modified radical hysterectomy without ureteric skeletonization is used as the primary surgical procedure. However, surgical procedures are tailored to individual requirements, e.g., in low-risk patients with no lower uterine segment involvement and medically high-risk patients, a routine extra-fascial total hysterectomy with bilateral salpingo-oophorectomy may be sufficient without extensive lymphadenectomy. Ovarian preservation is to be considered in young low-risk women. The advantage of modified radical hysterectomy in stage II endometrial cancer

has been shown in some recently reported studies [3, 4]. This might hold true for stage I endometrial cancer especially when it involves the lower part of the uterus [5]. Ideally, all gynecological cancer surgeries should be done by gynecologic oncologists for better outcome.

Following Are Important Steps of the Author's Modified Radical Hysterectomy

The bladder is dissected down not only in the central part but also laterally. In the lateral part, the ureters can be seen running lateral to medial in the cervicovaginal area (Fig. 16.1). White Waldeyer's fascia is clearly seen during most dissections. On cutting this fascia, the ureter can be identified by peristalsis. After dissection in the groove between the ureter and vagina, the bladder with ureter can be pushed down further.

Then ureter, which is seen above before ligating ovarian vessels, is traced down, and the uterine vessels are transected over the ureter (Fig. 16.4). This is only the extra step required in this method of modified radical hysterectomy.

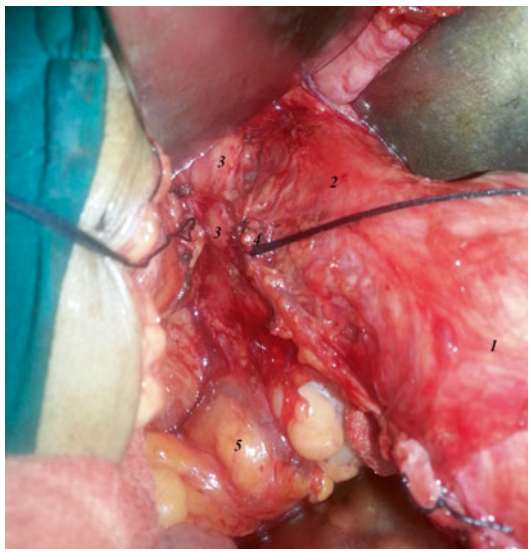

Fig. 16.4 Bladder dissected down to show ureter laterally. Uterine artery is transected over the ureter. *1*. Body of uterus. *2*. Cervix. *3*. Ureter. *4*. Ligated and cut uterine artery. *5*. Sigmoid colon

The ureteric course is now clearly seen, lateral clamps are applied serially, cut and ligated or cut with harmonic instruments (Figs. 16.5, 16.6, and 16.7). Vagina is cross-clamped before opening (Figs. 16.8 and 16.9). This is done in keeping

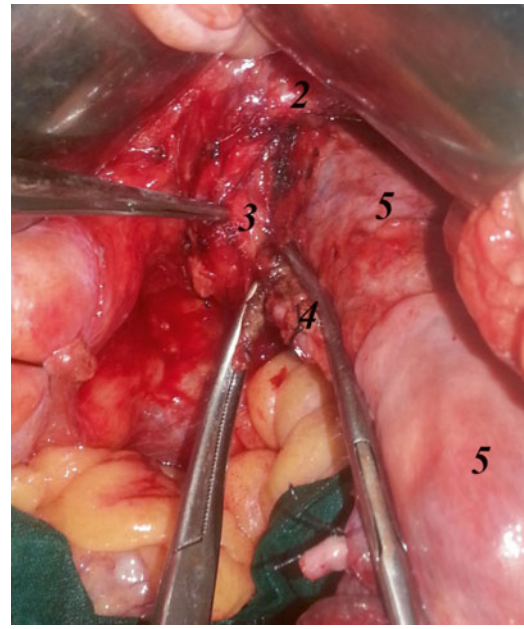

Fig. 16.5 First parametrial clamp at the level of uterine artery. *1*. Ureter. *2*. Bladder. *3*. Parametrium medial to ureter. *4*. Clamp at the level of uterine artery. *5*. Cervix and uterine body

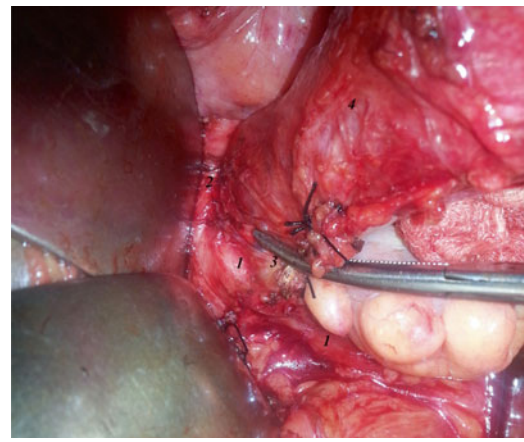

Fig. 16.6 Serial parametrial clamping, clamp below the level of uterine artery reaching close to cervical and vaginal margin. *1*. Ureter. *2*. Bladder. *3*. Parametrium medial to ureter. *4*. Cervix

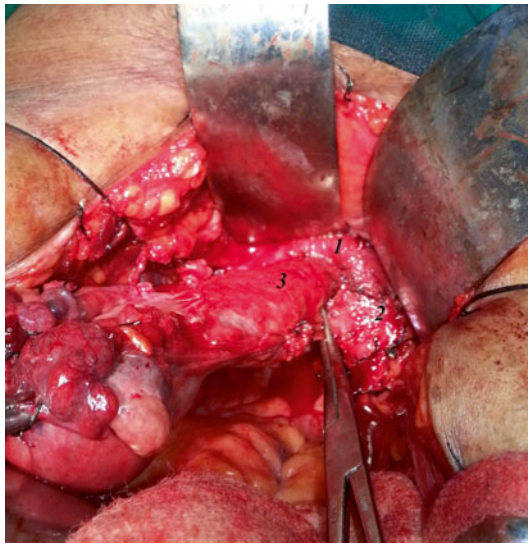

Fig. 16.7 Clamping further down in the lateral vagina. *1*. Bladder. *2*. Ureter alongside bladder. *3*. Cervicovaginal region

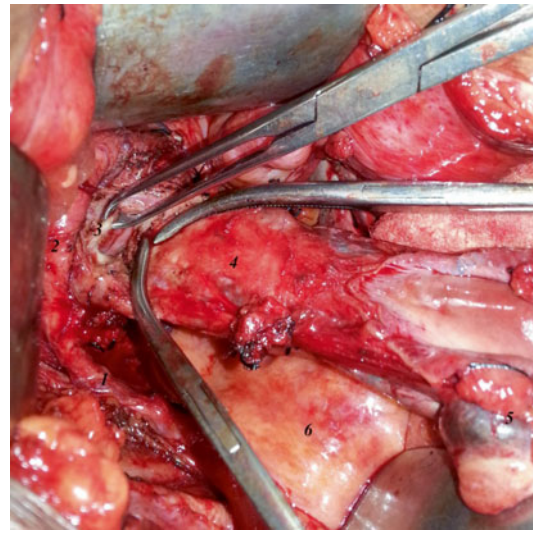

Fig. 16.9 Opening the vagina below the clamp. *1*. Ureter. *2*. Bladder. *3*. Allis forceps in the cut edge of vagina. *4*. Cervix. *5*. Left tube and ovary close to cornu of uterus. *6*. Rectum

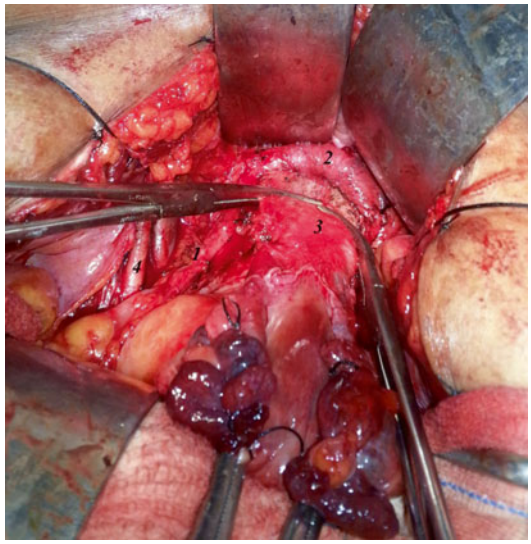

Fig. 16.8 Vagina cross-clamped (overlapping of clamps) to prevent spill. *1*. Ureter. *2*. Bladder. *3*. Cervix

with the oncologic principles of avoiding tumor spill. The vagina is cut below the clamps, length modified according to the preoperative and perioperative findings.

Conclusion

Surgery in carcinoma endometrium has multiple objectives, the most important being that, in majority of cases, treatment is complete with surgery alone. It is also a staging procedure for deciding adjuvant therapy and prognosticating the disease. Lower uterine and cervical involvement predicts metastasis. Modified radical hysterectomy especially in disease involving the lower part of uterus and cervix appears to be important in eradicating local recurrence and in reducing the morbidity of radiotherapy.

Key Points

1. The concept of surgery as primary therapy and postoperative pelvic radiotherapy for women at high risk of recurrence emerged after FIGO surgical staging.
2. There had been a gradual move away from the use of adjuvant pelvic radiotherapy in women who have been adequately surgically staged.

3. Surgery is the primary treatment modality for endometrial cancer. The abdominal cavity should be explored systematically, and the pelvis is explored last.
4. Serum CA-125 measurement is indicated in women with uterine papillary serous carcinoma.
5. According to NCCN guidelines, the extent of para-aortic lymph node dissection is from the aortic bifurcation up to either the inferior mesenteric artery or preferably to the level of renal veins.
6. For patients with high-risk variables, a omentectomy should be considered.
7. The advantage of modified radical hysterectomy in stage II endometrial cancer is shown in recently reported studies.
8. Ovarian preservation may be considered in young low-risk women.

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Ovarian Preservation in Endometrial Carcinoma

17

K. Chitrathara

Introduction

Endometrial cancer is generally a disease of postmenopausal women. However, in recent years, endometrial cancer in younger women is increasing because of lifestyle changes and diseases like diabetes mellitus, obesity, and polycystic ovarian disease. Ovarian preservation must be considered in this group of young premenopausal women. Traditionally, it was thought that metastases to ovaries or synchronous tumors were high, and therefore bilateral salpingo-oophorectomy was advocated. Several factors dictated this thinking, namely:

1. Necessity for documenting ovarian histopathology as an essential part of surgicopathological staging.
2. To exclude synchronous ovarian malignancy or occult metastasis.
3. To remove the source of endogenous estrogen production which may activate potential residual microscopic foci of endometrial cancer. Evidence for this concept is lacking and is not proved in the Gynecologic Oncology group study which evaluated the safety of hormone replacement therapy in postmenopausal women with endometrial cancer [1].

Synchronous ovarian malignancy may occur in 5 % of women with endometrial cancer [2]. Coexisting ovarian cancers are seen in younger age group and have a favorable outcome probably because of favorable histology [3, 4]. Walsh et al. [5] reported a very high (25 %) incidence of coexisting ovarian malignancy in women less than 45 years of age and recommended caution in conserving ovaries in these women. Ovarian metastasis is negligible in stage IA, grade 1–2 tumors [6]. Korea, in its annual statistics (2010), reported a 10.4 % incidence of endometrial cancer in women less than 40 years of age [7]. In the southern Indian state of Kerala, <5 % of the endometrial cancer patients are under 40 years [8]. Changing lifestyle, polycystic ovarian syndrome, and anovulatory cycles increase the risk of endometrial carcinoma, so one can envisage an increasing trend of this cancer in the coming years.

For women under the age of 60 years diagnosed with endometrial cancer, the risk of death from cardiovascular disease is six times greater than the death from endometrial cancer [9]. Endometrial cancer is said to be part of the metabolic syndrome, and the development of fatal cardiovascular disease may be attributed to this rather than the malignancy per se.

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For this discussion on ovarian preservation, we need to study the statistics of ovarian cancer in hysterectomized women for benign disease. 18.2 % of ovarian cancer occurred in women who have had a previous hysterectomy for benign disease with ovarian preservation [10]. Significantly, low bone density and postmenopausal symptoms have been seen in women who had ovarian preservation with hysterectomy [11, 12]. Piver [13] wrote

> it is postulated that prophylactic oophorectomy in women with a history of familial ovarian cancer who have completed their family by age 35 and desire prophylactic oophorectomy and in women age 40 or older who undergo hysterectomy for benign uterine conditions may result in a significant decrease in the death rate from ovarian cancer — a disease in search of a highly sensitive screening test(s) and improved therapy. [13]

No breakthrough in the early detection of ovarian cancer has yet occurred. Advanced ovarian cancer is now considered a chronic disease with all its attendant suffering, mortality, and increasing health burden to the society. Based on evidence, the American Society of Obstetrics and Gynecology stipulated certain guidelines for the prophylactic oophorectomy.

ACOG guidelines and recommendations on ovarian preservation [14] are given below.

The following recommendation is based on limited or inconsistent scientific evidence (Level B):

1. Bilateral salpingo-oophorectomy should be offered to women with BRCA1 and BRCA2 mutations after completion of childbearing.

The following recommendations are based primarily on consensus and expert opinion (Level C):

1. Women with family histories suggestive of BRCA1 and BRCA2 mutations should be referred for genetic counseling and evaluation for BRCA testing.
2. For women with an increased risk of ovarian cancer, risk-reducing salpingo-oophorectomy should include careful inspection of the peritoneal cavity, pelvic washings, removal of the fallopian tubes, and ligation of the ovarian vessels at the pelvic brim.
3. Strong consideration should be made for retaining normal ovaries in premenopausal women who are not at increased genetic risk of ovarian cancer.
4. Given the risk of ovarian cancer in postmenopausal women, ovarian removal at the time of hysterectomy should be considered for these women.
5. Women with endometriosis, pelvic inflammatory disease, and chronic pelvic pain are at higher risk of reoperation; consequently, the risk of subsequent ovarian surgery if the ovaries are retained should be weighed against the benefit of ovarian retention in these patients.

Disadvantages of Prophylactic Oophorectomy

1. Clinical symptoms related to oophorectomy (e.g., hot flushes, vaginal dryness, irritability, mood swings). Other possible disadvantages include changes in self-image and decreased libido attributed to loss of ovarian androgen production (estrogen therapy may relieve most of the symptoms related to oophorectomy).
2. Use of estrogen therapy in women aged 50–79 years (average age, 63 years) who have had a hysterectomy demonstrated an increased risk of thromboembolic disease and stroke.
   In Rocca's [15] series, overall mortality was not increased in women who underwent bilateral oophorectomy when compared to reference women. Mortality was significantly higher in women who had received prophylactic bilateral oophorectomy before the age of 45 years than in reference women, and this was seen in women who had not received estrogen up to the age of 45 years. The risk reduction in breast and ovarian cancer, following salpingo-oophorectomy, is negated by the increase in risk of all-cause mortality, primarily coronary heart disease, lung cancer, and colorectal cancer [16, 17]. At the same time,

another study reiterates that hysterectomy with or without ovarian conservation is not a key determinant of cardiovascular risk status either before or after elective surgery in midlife [18]. These studies should provide reassurance to women and their clinicians that hysterectomy in midlife is unlikely to accelerate the cardiovascular risk.

A Korean Gynecological Oncology group study concluded that ovarian preservation does not appear to have an adverse impact on recurrence and survival in premenopausal women with early stage endometrial cancer [19]. Using medical records of premenopausal women who received primary surgical treatment for stage I and II endometrial cancer, the demographic and survival rates were compared retrospectively for women who had ovarian preservation and those who underwent bilateral salpingo-oophorectomy. A total of 495 women were identified, and 176 had ovarian preservation. The authors enumerated the limitations of the study, like hidden bias inherent to retrospective studies, lack of sufficient follow-up, lack of standardization of lymphadenectomy and adjuvant radiotherapy, and fewer stage IB patients. 75.6 % of women with ovarian conservation and 78.7 % of those who underwent bilateral salpingo-oophorectomy had grade I tumor, and 90.3 % and 88.7 %, respectively, had stage IA disease. High rate of adverse risk factors for adjuvant treatment were present in women with involved ovaries. Despite occult metastasis in preserved ovaries, outcome was not hampered because of adjuvant treatment such as radiation.

The author describes a simple technique of positioning the ovary in the anterior abdominal wall (Fig. 17.1 and 17.2). The ovary can be monitored easily and can be removed as an outpatient procedure whenever required. For this, only one ovary is preserved and is placed over the rectus sheath below the subcutaneous fat. Similar to preparing for ovarian transposition outside the pelvis, ovary with the pedicle is freed up to or beyond the pelvic brim. The peritoneum covering the pedicle has to be preserved and kept out of the pelvic radiation field. Pedicle length should be enough so as to bring it out without tension. The pedicle is brought out lateral to the cecum on the right side and lateral to sigmoid-descending colon on the left side. Care is taken to ensure that the pedicle is not twisted. To facilitate easy bringing out and positioning of ovary in the anterior abdominal wall, the fallopian tube is not removed earlier.

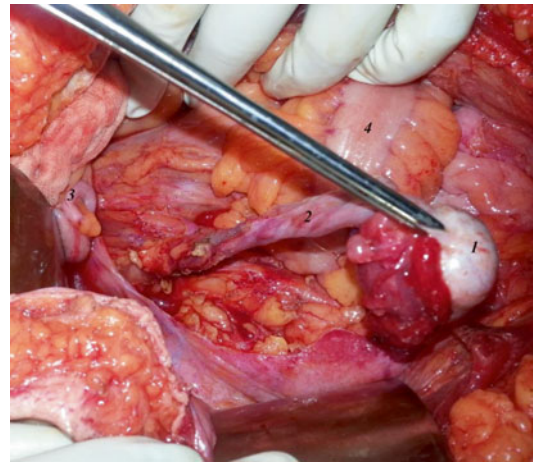

Fig. 17.1 Midline incision. Dissected ovary with the pedicle is shown. Ovarian pedicle is dissected up to just beyond the pelvic brim. *1*. Ovary. *2*. Ovarian pedicle. *3*. Appendix. *4*. Sigmoid colon

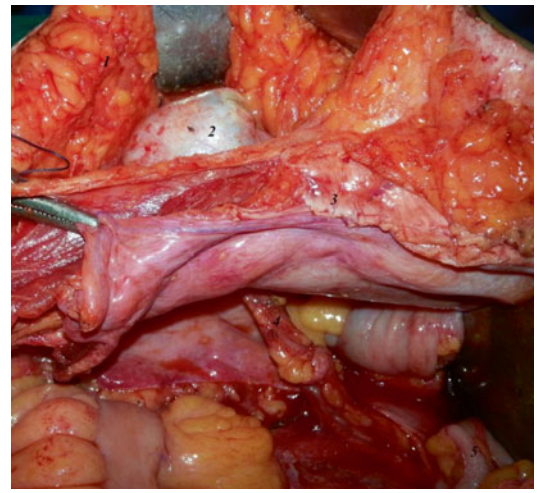

Fig. 17.2 Ovary positioned in the anterior abdominal wall in a space created over the rectus sheath below the umbilicus. *1*. Subcutaneous fat. *2*. Ovary *3*. Rectus sheath with peritoneum. *4*. Ovarian pedicle. *5*. Appendix. The pedicle is seen lateral to appendix

Conclusion

Most current literature shows that coexisting ovarian cancer is low and metastatic ovarian cancer is negligible in low-risk endometrial cancer. More evidence is accruing on the safety of ovarian conservation in hysterectomy. The decision to conserve or remove ovaries should be tailored to individual risks. When ovaries are preserved, salpingectomy is a good option. Placement of ovaries in the anterior abdominal wall appears to be a feasible choice.

Key Points

1. Endometrial cancer is associated with synchronous ovarian malignancy in 5 % of women.
2. In young women, the association of concurrent uterine and ovarian malignancy is high.
3. There is a definite risk reduction in breast and ovarian cancer in women who have undergone prophylactic oophorectomy, but effect is negated by the increase in risk of all-cause mortality.
4. Hysterectomy with or without ovarian conservation is not a key determinant of cardiovascular risk status either before or after elective surgery in midlife.
5. Based on evidence, American Society of Obstetrics and Gynecology specified certain guidelines for the prophylactic oophorectomy.
6. A Korean Gynecological Oncology group study concluded that ovarian preservation does not appear to have an adverse impact on recurrence and survival in premenopausal women with early stage endometrial cancer.

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18 The Role of Lymphadenectomy in Endometrial Cancer: The Mayo Clinic Experience

Mariam M. Al Hilli and Sean C. Dowdy

Introduction

While endometrial cancer (EC) is the most common gynecologic malignancy in the USA, it is the second most common gynecologic malignancy after cervical cancer worldwide and has been responsible for an increasing percentage of cancer deaths in recent years [1, 2]. It is postulated that the obesity epidemic in addition to an aging population has contributed to the remarkable increase in deaths due to EC over the past decade [3].

Despite the wealth of available literature on the etiology and global impact of EC, the fundamental questions regarding the optimal management of EC remain unanswered. As a result, the primary treatment of EC has varied between countries and institutions. There is poor consensus on the extent of surgery needed to treat patients with EC who have no evidence of extrauterine spread. Total abdominal hysterectomy and bilateral salpingo-oophorectomy has been the cornerstone of surgical treatment, while the addition of lymph node evaluation varies according to surgeon and institutional preferences. Comprehensive surgical staging has been traditionally utilized in only 30–40 % of EC patients in the USA [4]. In comparison, lymphadenectomy is performed infrequently in some European countries in women with stage I EC; these patients are treated with hysterectomy and adjuvant radiotherapy if high-risk features are present as described by the Dutch group [5–7].

Surgical staging is the most accurate method of determining EC spread, and an important predictor of patient outcome; women with early-stage disease (approximately 20 %) are unlikely to harbor disease outside the uterus [8–10]. Furthermore, stage, as determined by International Federation of Gynecology and Obstetrics (FIGO) classification, is the strongest predictor of survival [8]. Approximately 82 % of patients with stage I or II disease are alive at 5 years compared to 15 % of patients with stage IV disease [2, 11]. Comprehensive surgical staging for all patients, defined as total abdominal hysterectomy, bilateral salpingo-oophorectomy, and bilateral pelvic and paraaortic lymphadenectomy, has been advocated by many groups who believe that this strategy allows detection of advanced stage disease that may otherwise be undiagnosed and untreated. Yet, variations in the management of EC extend beyond the debate on the requisite for lymphadenectomy to encompass wide variations in the definitions and specifics of comprehensive surgical staging, the optimal number of lymph nodes needed to constitute an adequate lymphadenectomy, and the anatomic boundaries for surgical dissection [12, 13].

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The notion that lymphadenectomy should be reserved for patients with sufficiently elevated risk of nodal spread has become more prevalent in recent years [14]. Yet, the challenge has been to identify patients at risk for lymphatic dissemination before surgery to allow treatment to be tailored to individual patients and risk factors. The contemporary treatment of EC has evolved throughout the last decade and a transition from comprehensive surgical staging for all patients to selective lymphadenectomy has taken place [15]. With a focus on investigating patients who are not likely to benefit from lymphadenectomy or adjuvant therapy (defined as low-risk patients), many institutions have explored alternatives in order to minimize patient overtreatment while preserving oncologic outcomes [16]. This has translated into improvements in surgical outcomes and healthcare costs [16, 17].

Predictors of Lymphatic Metastases

According to the natural history of type I EC, the known potential routes of metastases include direct extension, hematogenous spread, lymphatic dissemination, and intraperitoneal spread [3, 18]. Data have shown that a disease-based approach to treatment that takes into consideration each patient's predicted route of tumor metastases allows effective treatment allocation [3]. For instance, depth of myometrial invasion was found to be independently predictive of hematogenous metastases [19, 20], while lymphovascular space invasion (LVSI) and grade 3 histology were correlated with vaginal recurrences [21]. Peritoneal failures have been found to be associated with stage IV disease (with or without nonendometrioid histology), positive peritoneal cytology, positive lymph nodes, and cervical stromal invasion [22] (Table 18.1). When these criteria were applied to a cohort of 915 patients with EC, tumor relapse rates were significantly higher in the group of patients deemed to be at risk of hematogenous, lymphatic, and peritoneal metastasis in comparison to those not identified to be at risk [18]. In addition, patients who were at risk of recurrence according to the above predictors had a 46 % risk of recurrence in one or more sites, and 27 % had multiple sites of recurrence (Fig. 18.1) [18]. The identification of the pathologic tumor characteristics associated with metastatic disease allows for effective and targeted adjuvant treatment approaches [3]. That is, patients at risk of vaginal recurrences are likely to benefit from vaginal brachytherapy, while patients at risk for hematogenous recurrence require systemic chemotherapy.

Table 18.1 Risk factors for recurrence by site of recurrence

Route of recurrence	Risk factors
Hematogenous	
All stages of disease	Myometrial invasion >50 %
Stage I disease, negative LNs	Myometrial invasion ≥66 %
Lymphatic	
Pelvic/paraaortic LNs	CSI, LN metastases
Peritoneal spread	Stage IV disease
	Stages II-III disease, ≥2 CSI, PPC, LN metastases, or type II histology

Adapted from Mariani et al. [18]
CSI cervical stromal invasion, *LN* lymph node, *PPC* positive peritoneal cytology, type II histo, nonendometrioid subtypes

It is notable that in patients deemed to be at risk for lymph node metastases who undergo staging, the overall rate of lymph node metastasis is 22 % (84 % and 67 % have pelvic or paraaortic lymph node metastases, respectively) [14]. Furthermore, patients diagnosed with retroperitoneal lymph node metastases or cervical invasion have a significantly higher incidence of lymph node involvement and a poorer prognosis than patients with disease confined to the uterus [3, 23, 24]. In a study of 112 patients with positive pelvic and or paraaortic lymph nodes, the external iliac and obturator lymph node basins were the most commonly involved pelvic lymph node sites in patients with disease confined to the corpus, while patients with cervical invasion were significantly more likely to

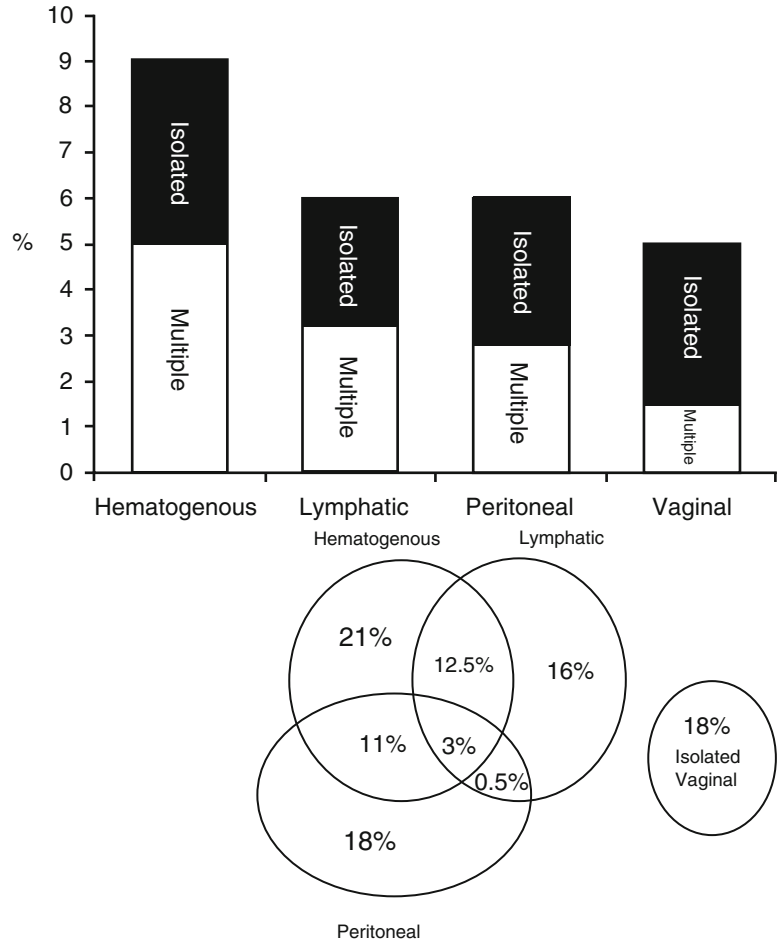

Fig. 18.1 Distribution of sites of recurrence in 915 endometrial cancer patients with 21 % relapse rate (Adapted from Mariani et al. [18]; used with permission)

have positive common iliac lymph nodes [23]. In fact, all patients with both cervical involvement and positive paraaortic lymph nodes were noted to have involvement of the common iliac nodes [23]. Thus, the presence of positive paraaortic lymph nodes correlates highly with common iliac node involvement [25]. Moreover, paraaortic lymph nodes are in direct communication with the external iliac and obturator basins, and drainage into the systemic circulation through the paraaortic lymph nodes is central to disease spread [25–27]. Metastases from the uterine corpus may be associated with direct extension to the paraaortic lymph node basin via gonadal vessels and the infundibulopelvic ligament [23].

Pelvic lymph node status is one of the strongest surrogate markers of paraaortic lymph node involvement [19, 25, 28]. When pelvic lymph nodes are negative, only 2 % of patients are found to have positive paraaortic nodes [19, 29]. In addition, LVSI, which is present in 50–90 % of patients with positive paraaortic lymph nodes, in combination with positive pelvic lymph nodes was found to be highly predictive of paraaortic lymph node metastases [29]. The overall prevalence of positive paraaortic lymph nodes has been described to be between 5 % and 15 % in early-stage disease, and paraaortic lymph nodes may be involved in the absence of pelvic lymph node metastases in 1–6 % of patients [8, 25, 28]. Patients with grade 2 or 3 endometrioid EC,

≥50 % myometrial involvement with or without macroscopic extrauterine disease are most at risk for isolated positive paraaortic lymph nodes [15]. Microscopic paraaortic disease and the presence of isolated tumor cells have additionally been described in up to 73 % of patients with positive pelvic lymph nodes [30, 31].

High tumor grade and deep myometrial invasion have been identified as key factors associated with lymph node metastases [8], while patients with grade 1 or 2 endometrioid tumors and/or superficial myometrial invasion (<50 %) are deemed to be at low risk for lymph node invasion [8, 32]. A rate of lymph node invasion of 4–5 % has been historically described in this group of patients and is considered by most gynecologist to be high enough to warrant lymphadenectomy [33]. However, this rate does not take into consideration tumor diameter, which may potentially lead to an overestimation of risk. Prior observations have shown that patients with primary tumor diameter >2 cm had a 7–8 % risk of regional lymph node involvement in comparison to 0 % in patients with tumor diameter <2 cm [34]. It is recommended that intraoperative tumor diameter be determined through notation of the size of the primary lesion in the three largest dimensions, where primary tumor diameter is defined as the largest of the three dimensions of the tumor. In cases where more than one lesion is present, the lesion with the largest diameter is considered [14, 35, 36]. Furthermore, when the endometrium is diffusely involved by tumor or is abnormal in gross appearance, the size of the tumor is approximated with the aid of microscopic examination of tumor sections [35].

Adequacy of Lymphadenectomy

It has been reported that extensive lymph node resection is associated with improvement in disease-specific survival. In a large cohort of patients with stage I–IV EC with intermediate- and high-risk factors (stage IB, grade 3, or stage IC, II–IV all grades), a 5-year survival benefit of over 30 % was accrued when more than 20 lymph nodes were resected compared to 2–5 lymph nodes [37]. Furthermore, some authors have shown that removal of more than 10 lymph nodes in both low-risk and high-risk patients has diagnostic and prognostic benefits [38, 39]. In a Japanese study of stage IIIC EC patients, patients who had two or more positive pelvic lymph nodes resected had a significantly improved disease-specific survival at 5 years if paraaortic lymphadenectomy was performed compared to pelvic lymphadenectomy alone [40, 41]. This supports the notion that lymphadenectomy may be therapeutic if thoroughly performed. It has been demonstrated that resection of 21–25 pelvic lymph nodes provided an 80 % probability of detecting at least one positive lymph node [42, 43].

Evidence to support performance of comprehensive pelvic and paraaortic lymphadenectomy is limited to patients with intermediate- or high-risk features (FIGO grade 3, deep myometrial invasion, lymphovascular space invasion, or macroscopic extrauterine disease). A significant survival advantage was demonstrated by US and Japanese groups for high-risk patients who underwent paraaortic lymphadenectomy in addition to pelvic lymphadenectomy [18, 44, 45]. In comparison, the initial PORTEC trial demonstrated that patients with stage I disease and high-risk features (deep myometrial invasion and grade 3) who were treated with hysterectomy and adjuvant pelvic external beam radiation alone had a 31 % risk of distant recurrence [46, 47]. Proponents of comprehensive surgical staging for all EC patients believe that full staging precludes the need for postoperative radiotherapy [48, 49]. However, there is currently no precedence for the use of adjuvant external beam radiation therapy in low-risk patients [50]. Thus, the literature suggests that only patients with

substantial clinical and pathologic risk factors are likely to gain benefit from comprehensive surgical staging [45].

The anatomic extent and defining landmarks of paraaortic lymphadenectomy have not been clearly defined among the gynecologic oncology community. According to an SGO survey, 50 % of gynecologic oncologists use the IMA as the upper extent of paraaortic lymph node dissection, and only 11 % perform paraaortic dissection to the level of the renal vessels [13]. It has been shown that in patients with positive paraaortic nodes, positive nodes located above the inferior mesenteric artery (IMA) are prevalent in 73 % of patients [25]. In addition, 77 % of patients with positive paraaortic lymph nodes harbor metastases above the IMA and 63 % of patients with positive lymph nodes below the IMA also have positive nodes above the IMA. Limiting dissection to the IMA may potentially miss up to 46 % of patients with positive paraaortic nodes [15]. We therefore suggest that systematic pelvic and paraaortic lymphadenectomy should include dissection to the renal vessels with at least 22 pelvic lymph nodes and 10 paraaortic lymph nodes removed. These guidelines apply to high- and intermediate-risk patients.

Quality Assessment and Risk Stratification in Endometrial Cancer

Continuous evaluation of the quality of surgical care and the reliance on defined surgical guidelines allows for improved surgical staging [42]. It has been demonstrated that implementation of surgical guidelines and continuous quality assessments results in an improvement in compliance with pelvic and paraaortic lymphadenectomy. The identification of a minimal number of lymph nodes removed has been suggested to be an essential component of clinical trials involving EC staging, and stringent guidelines together with quality assessment are strongly urged to be adopted by other institutions.

Given the lack of well-designed clinical trials investigating the optimal surgical interventions for patients with EC, estimates of overall morbidity related to EC surgery are critical [17]. EC patients with complex underlying comorbidities are most likely to have adverse oncologic outcomes as a result of poor adherence to treatment guidelines in addition to increased surgical morbidity [51–53]. Until recently, however, the relationship between clinical risk factors and surgical outcomes had been inadequately explored. A large prospective study in 2012 reported on predictors of 30-day postoperative morbidity as classified by accordion grade (Box 18.1) and cost [17]. In this cohort, 84 % of 30-day complications were minor or moderate (accordion grade 1 or 2). An analysis of 1,369 patients showed that grade 2 or higher morbidity is independently associated with the following patient risk factors: American Society of Anesthesiologists (ASA) score >2, preoperative white blood count, history of deep venous thrombosis (DVT), minimally invasive surgery, and type of lymphadenectomy. These data were used to develop a "counseling model" that would allow the estimation of risk of operative morbidity preoperatively. Interestingly, a preoperative creatinine more than 1.5 mg/dL was a strong predictor of grade 3 or higher complications. When process of care variables were considered collectively, all previous patient-specific variables in addition to myometrial invasion >50 %, operative time, and increased surgical complexity were used to construct a "global model" (Table 18.2). This model may allow identification of interventions to reduce morbidity.

Table 18.2 Factors associated with grade 2 or higher complications within 30 days of surgery

	Multivariable model of counseling factors*	Multivariable model of global factors*
Patient characteristics		
ASA class higher than 2	2.14 (1.65–2.78)	1.98 (1.50–2.60)
Preoperative WBC ($\times 10^9$/L)[a]	2.06 (1.53–2.77)	1.71 (1.25–2.34)
History of DVT	2.05 (1.28–3.28)	2.10 (1.29–3.41)
Surgical characteristics		
Type of lymphadenectomy		
None	Referent	Referent
Pelvic only	0.85 (0.54–1.34)	1.03 (0.52–2.03)
Paraaortic or pelvic and paraaortic	2.34 (1.71–3.22)	2.06 (1.12–3.79)
Minimally invasive surgery		
Minimally invasive	Referent	Referent
Vaginal only	0.50 (0.16–1.55)	1.46 (0.42–5.07)
Laparotomy	2.84 (1.45–5.54)	4.24 (2.04–8.81)
Tumor characteristics		
Myometrial invasion more than 50 %		2.38 (1.74–3.24)
Process-of-care characteristics		
Operating time, min[a]		1.85 (1.39–2.46)
Surgical complexity[b]		
Grade 1		Referent
Grade 2		0.61 (0.29–1.27)
Grade 3		1.19 (0.65–2.19)
Grade 4		2.67 (1.17–6.11)

Adapted from Dowdy et al. [17]
Data are odds ratio (95 % confidence interval)
The overall biased C-statistic for the models are 0.725 (counseling model) and 0.774 (global model)
ASA American Society of Anesthesiologists, *WBC* white blood cells, *DVT* deep vein thrombosis
*$p < .01$ for all predictors in both models
[a]Odds ratio per doubling in white blood cells and per doubling in operating time
[b]Grade 1: hysterectomy, bilateral salpingo-oophorectomy only; grade 2: hysterectomy, bilateral salpingo-oophorectomy with any lymphadenectomy; grade 3: grade 1 or 2 with additional major procedures unrelated to endometrial cancer (e.g., ventral hernia repair, cholecystectomy); grade 4: grade 1–3 with additional major procedure related to endometrial cancer (e.g., bowel resection, splenectomy, diaphragmatic stripping) [24]

Box 18.1 Accordion Severity Grading System for Postoperative Complications

Severity grade	Grading criteria
1. Mild complication	Requires only minor invasive procedures that can be done at the bedside, such as insertion of– intravenous lines, urinary catheters, and nasogastric tubes, and drainage of– wound infections. Physiotherapy and the following drugs are allowed: antiemetic, antipyretics, analgesics, diuretics, electrolytes, and physiotherapy
2. Moderate complication	Requires pharmacologic treatment with drugs other than those allowed for minor complications, e.g., antibiotics. Blood transfusions and total parenteral nutrition are also included
3. Severe: invasive procedure without general anesthesia	Requires management by an endoscopic, interventional procedure or reoperation without general anesthesia
4. Severe: operation under general anesthesia	Requires management by an operation under general anesthesia
5. Severe: organ system failure	Organ system failure (i.e., ≥1 organ failure)
6. Death	Postoperative death (i.e., 100-day and in-hospital death)

Adapted from Strasberg et al. [54]

Table 18.3 Intra- and postoperative factors stratified by whether lymphadenectomy was performed

	Lymphadenectomy		Total ($N=385$)	
	No	Yes		
Parameters	($N=305$)	($N=80$)		P-value[a]
Surgical approach. N (X)				<0.001
No laparotomy	24 (7.9)	5 (6.3)	29 (7.5)	
Laparotomy	210 (68.9)	75 (93.8)	285 (74.0)	
Vaginal only	71 (23.3)	–	71 (18.4)	
OR time (minutes)				<0.001
Mean(SD)	108.0 (52.9)	150.6 (71.5)	116.8 (59.8)	
Median (IQR)	96.0 (71.0, 130.0)	137.0 (112.5, 170.5)	104.0 (75.0, 143.0)	
Estimated blood loss (ml)				<0.001
Mean(SD)	231.6 (193.7)	309.9 (190.7)	247.9(195.4)	
Median (IQR)	200.0 (100.0, 300.0)	250.0 (200.0, 400.0)	200.0 (100.0, 300.0)	
Length of hospital stay (days)				<0.001
Mean (SD)	3.3 (2.6)	3.7 (1.7)	3.4 (2.4)	
Median (IQR)	3.0 (2.0, 4.5)	3.0 (3.0, 4.0)	3.0 (2.0, 4.0)	
30-Day postoperative complications[b], *N* (%)				0.002[c]
None	246 (80.7)	50 (61.5)	296 (76.9)	
Grade 1	28 (9.2)	17 (21.3)	45 (11.7)	
Grade ≥2	31 (10.2)	13 (16.3)	44 (11.4)	

Adapted from Dowdy et al. [16]
SD standard deviation, *IQR* interquartile range, 25th and 75th percentiles
[a]Parameters were compared using the Wilcoxon rank-sum test for continuous parameters and the chi-square test for categorical parameters
[b]Graded per the Accordion Classification [23]
[c]$P<0.001$ for the comparison of none vs. at least one 30-day postoperative complication

It is notable that surgical approach and use of paraaortic lymphadenectomy were strong predictors of grade 2 or higher complications in both models. Patients undergoing paraaortic lymphadenectomy were twice as likely to experience a complication, while patients requiring complex surgical procedures were also more likely (2.7 times) to experience a grade 2 or higher complication compared to patients undergoing hysterectomy and bilateral salpingo-oophorectomy only [17]. Furthermore, laparotomy was associated with a 4-fold increase in complications compared to minimally invasive surgery [17]. Of the group of patients with low-risk EC who did not require lymphadenectomy, vaginal hysterectomy was only performed in 23.3 % of patients. These patients had favorable outcomes and comparable recurrence-free and disease-specific survival rates compared to patients undergoing laparotomy or laparoscopy. In fact, no patients undergoing vaginal hysterectomy experienced disease recurrence or death secondary to disease [17]. Thus, vaginal hysterectomy was found to be the least invasive of all surgical procedure and the most cost effective procedure, and is the procedure of choice for low-risk patients (Table 18.3). These findings are in concordance with recent advances in the incorporation of minimally invasive surgery into routine gynecologic oncology practice in the USA [50]. The GOG Lap2 data demonstrated that laparoscopic staging for endometrial cancer is feasible and safe from a surgical and oncologic perspective [55]. In addition to a reduction in morbidity, minimally invasive surgery allows greater flexibility in surgical management and ease of modification of treatment planning in cases where intraoperative assessment is inconsistent with final pathology [16, 50].

Regarding cost of care, when modifiable risk factors were considered, only surgical approach was found to influence 30-day cost (Table 18.4) [17]. These data indicate that EC patients undergoing

Table 18.4 30-day cost of care according to accordion grading classification

Complication grade	n (%)	30-d cost
None	775 [56]	$15,236 ± 5,610
		$14,386 ($10,738–18,656)
		($6,466–54,638)
1	196 [14]	$18,211 ± 6,362
		$17,546 ($12,947–21,624)
		($3,189–44,030)
2	303 [22]	$25,725 ± 12,342
		$23,128 ($17,411–31,118)
		($9,843–117,571)
3	46 [3]	$39,201 ± 19,017)
		$35,640 ($25,638–52,698)
		($13,099–91,662)
4	31 [2]	$39,922 ± 21,071
		$33,914 ($21,682–53,533)
		($13,448–90,096)
5	8 [1]	$90,182 ± 55,212
		$74,995 ($45,379–125,734)
		($36,747–192,496)
6 (postoperative death)	10 [1]	$42,702 ± 6,714
		$43,513 ($39,149–47,021)
		($27,992–51,408)

Adapted from Dowdy et al. [17] (Used with permission)
Data are mean ± standard deviation, median (interquartile range), (range [minimum–maximum]) unless otherwise specified
For grade 6 complications (postoperative death, $n = 10$), mean survival was 15.7 [10–23] days from date of surgery. Costs are therefore lower because there are no further medical expenses after death

minimally invasive surgery are likely to have a lower cost-benefit ratio than patients undergoing laparotomy. However, this information is most applicable to affluent societies where surgical resources are available and affordable. Moreover, both pelvic and paraaortic lymphadenectomy were associated with increased cost of care; paraaortic lymphadenectomy was also associated with higher 30-day morbidity [16]. When low-risk patients unnecessarily undergo pelvic and or paraaortic lymphadenectomy, a significant increase in 30-day cost is incurred [17]. These initiatives to explore surgical outcomes and cost provide an opportunity to modify quality of care worldwide and further highlight the merits of selective lymphadenectomy.

Identification of Low-Risk Patients in Whom Lymphadenectomy May Be Omitted

Lymphadenectomy is considered a diagnostic and staging tool for EC patients allowing physicians to define the extent of disease spread, determine the need for postoperative treatment, and determine prognosis [3, 57]. The currently available literature is controversial regarding the therapeutic role of pelvic and paraaortic lymphadenectomy. It has been suggested that lymphadenectomy may reduce the rate of recurrent disease or debulk existing disease [3, 45, 56, 58]. A metaanalysis recently showed that patients undergoing lymphadenectomy do not benefit from improved progression-free or overall survival [59]. Furthermore, two large prospective randomized clinical trials, which included patients with a low probability of lymphatic involvement, failed to show an advantage in disease-free survival in patients with early-stage EC [5, 53]. In contrast, retrospective studies have shown that disease-specific survival is markedly improved in patients undergoing bilateral pelvic and paraaortic lymphadenectomy [60, 61]. This discrepancy in study results can be attributed to differences in the definition of complete lymphadenectomy and the emphasis on low-risk patients in larger studies [45].

In 2004, criteria for surgical management of EC, which emphasized selective lymphadenectomy based on the risk of lymphatic metastases rather than comprehensive staging for all patients, were recommended (Box 18.2) [14, 15, 18]. Using this approach, lymphadenectomy is omitted only in the following circumstances: (1) absence of disease beyond the uterus, (2) endometrioid histology, (3) FIGO grade 1 or 2, (4) myometrial invasion ≤50 %,and (5) tumor diameter ≤2 cm. Using these criteria, approximately 33 % of type I EC patients will be spared lymphadenectomy [14]. A recent study demonstrated in a cohort of 385 patients with stage I endometrial cancer (34.1 % of type I EC patients) of which over 300 patients did not undergo lymphadenectomy, the overall rate of lymph node metastasis was 0.3 % (1/385) over a 5.4 year follow-up

Table 18.5 Overall, recurrence-free and cause-specific survival in low-risk patients undergoing lymphadenectomy vs. no lymphadenectomy

	Lymphadenectomy		
	No	Yes	
Outcome	*(N = 305)*	*(N = 80)*	P-value[a]
Overall survival			0.72
No. of events	25	6	
Estimate at 5 years	92.1 %	94.2 %	
Recurrence-free survival			0.64
No. of events	8	3	
Estimate at 5 years	97.6 %	96.0 %	
Cause-specific survival			0.32
No. of events	3	2	
Estimate at 5 years	99.0 %	97.3 %	

Adapted from Dowdy et al. [16] (Used with permission)
[a]Survivorship curves were compared using the log-rank test

Box 18.2 Mayo Algorithm for Management of Endometrial Cancer

Guidelines for surgical management of endometrial cancer at Mayo Clinic, Rochester, Minnesota (2004–2006)
Hysterectomy
Bilateral salpingo-oophorectomy
Peritoneal cytology
Bilateral pelvic and paraaortic lymphadenectomy
Paraaortic dissection up to renal vessels
Excision of gonadal vessels at insertions (optional)
Omit lymphadenectomy if no disease beyond corpus and
(1) Endometrioid (grade 1 or 2), MI ≤ 50 %, and PTD ≤2 cm; or
(2) Endometrioid and no MI (independent of grade and PTD)
Omentectomy, staging biopsies, or cytoreduction for nonendometrioid or advanced disease

Adapted from Mariani et al. [15]
MI myometrial invasion, *PTD* primary tumor diameter

period [16]. This estimate included low-risk patients who were managed with lymphadenectomy (80 patients, of which 1 patient had lymph node metastasis) and those who were not (304 patients) [17]. Additionally, only 5 disease-related deaths occurred (out of 31 total deaths) yielding a 5-year cause-specific survival of 97.3 % and 99 % in patients who underwent lymphadenectomy and those who did not undergo lymphadenectomy, respectively. Eleven recurrences occurred, none of which were located in the pelvic or paraaortic nodal areas (sites included vagina, inguinal lymph node, peritoneum, and distant sites) [16]. Importantly, recurrence-free and overall survival rates were not influenced by lymphadenectomy in this low-risk cohort (Table 18.5). These data have solidified the validity of the disease-based surgical management criteria for selective lymphadenectomy in the gynecologic oncology community [50]. Furthermore, omission of pelvic and paraaortic lymphadenectomy in type I EC patients with no myometrial invasion, and omission of paraaortic lymphadenectomy in all patients with the exception of the following groups has recently been advocated [15]: (1) patients with positive pelvic nodes, (2) FIGO grade 3 histology, (3) Type II, nonendometrioid, histology, (4) myometrial invasion >50 %.

Findings of the survival effect of paraaortic lymphadenectomy in endometrial cancer (SEPAL) study showed that high-risk patients (but not low-risk patients) who underwent pelvic lymphadenectomy without paraaortic lymph node dissection were at risk of distant recurrences and had a significantly reduced 5-year overall (46.5 % vs. 89 % for pelvic and paraaortic lymphadenectomy) [44, 62]. Furthermore, patients who have extrauterine disease confined to the lymph nodes are unlikely to experience extranodal recurrences, while patients with extrauterine disease in addition to positive lymph node frequently develop nonlymphatic recurrences [29]. These findings collectively indicate that the risk of paraaortic spread should be considered in the context of the presence or absence of additional extrauterine disease, its location, and the number of positive lymph nodes [5].

In the effort to identify a subgroup of EC patients who may potentially forego paraaortic lymphadenectomy, a recent study explored the rate of paraaortic lymph node metastases or recurrence in patients who did not undergo paraaortic lymphadenectomy or had negative lymph nodes in the context of an inadequate paraaortic lymphadenectomy (<5 nodes). This rate was

observed to be 4 % (36 out of 946 patients), where the majority of patients (33/36) had paraaortic lymph node metastases and only 3 patients experienced paraaortic lymph node recurrence (1 with inadequate negative nodes and 2 with omission of paraaortic lymphadenectomy). Independent predictors of paraaortic metastases or recurrence were positive pelvic nodes (odds ratio OR 24.2), myometrial invasion >50 % (OR 5.3), and lymphovascular space invasion [63]. When all three factors were absent, the probability of paraaortic lymph node metastases was only 0.6 %. Thus, caution is recommended in the omission of paraaortic lymphadenectomy in patients with these risk factors. It was further concluded that when myometrial invasion is ≤50 % and intraoperative frozen section is not available, the risk of paraaortic lymph node metastasis is only 1.1 % when paraaortic lymphadenectomy is omitted. Utilizing these recent data, an algorithm that summarizes recommendations for surgical management of EC is illustrated (Fig. 18.2).

Intraoperative Frozen Section in Risk Stratification

Some available surgical guidelines for the management of endometrial cancer necessitate the exclusive use of intraoperative frozen section (IFS). Despite the high accuracy of IFS at some large institutions, there is a lack of uniform quality assurance for frozen section at other centers [16]. Some investigators have shown that IFS correlates poorly with final pathology at institutions with inadequate IFS facilities [65–67]. As a result, large variations in the uptake of IFS exist in the gynecologic oncology community. A recent Society of Gynecologic Oncologists (SGO) survey showed that only 31 % of gynecologic oncologists rely on IFS in determining patient management [13]. There is a strong need to develop guidelines that utilize preoperative and intraoperative parameters without IFS has been well recognized.

To mitigate some of the concerns surrounding IFS, a retrospective study was undertaken where

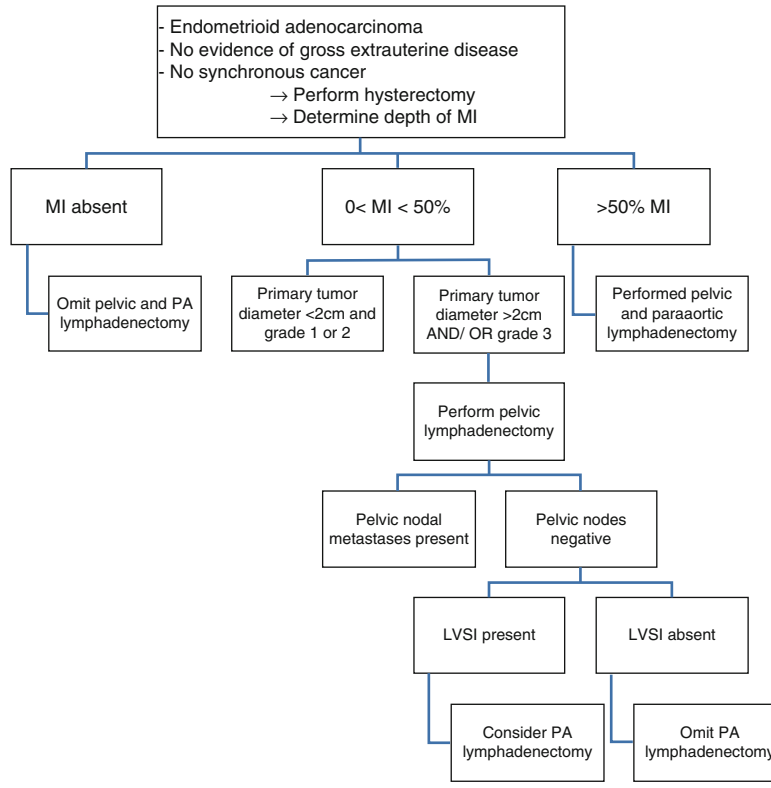

Fig. 18.2 Algorithm for management of type I endometrial cancer according to myometrial invasion and lymphovascular space invasion [64] (Adapted from AlHilli and Mariani; used with permission)

preoperative biopsy results were combined with intraoperative tumor diameter. In this study, patients were stratified into the following three risk groups (Fig. 18.3):

1. High risk: Preoperative grade 3, nonendometrioid histology, or macroscopic extrauterine disease
2. Intermediate risk: Preoperative grade 1 or 2, endometrioid histology, or complex and/ or atypical hyperplasia, tumor diameter >2 cm
3. Low risk: Preoperative grade 1 or 2, endometrioid histology, or complex and/ or atypical hyperplasia, tumor diameter ≤2 cm.

In low-risk patients (based on preoperative biopsy and intraoperative tumor diameter criteria), the risk of lymph node metastases (if lymphadenectomy was performed) and/or lymph node recurrence if lymph nodes were negative or lymphadenectomy was not performed is less than 1 % and the recurrence-free survival at 3 years is 98.7 %. In comparison, high-risk and intermediate-risk patients were found to have a significantly higher rate of lymph node dissemination or recurrence of 27 % and 11 %, respectively, and a lower 3-year recurrence-free survival rate (71.2 % and 92.0 %, respectively) [35]. These finding, after thorough validation, can be applied to countries with low resources or inaccurate IFS. However, IFS remains highly advocated when the IFS resources are accessible and reliable.

Resorting to the use of preoperative diagnostic criteria also appears to be feasible to risk-stratify patients to determine the need for lymphadenectomy. Preoperative imaging studies, specifically pelvic ultrasound or magnetic resonance imaging (MRI), have been utilized preoperatively in the diagnosis of myometrial depth of invasion. The

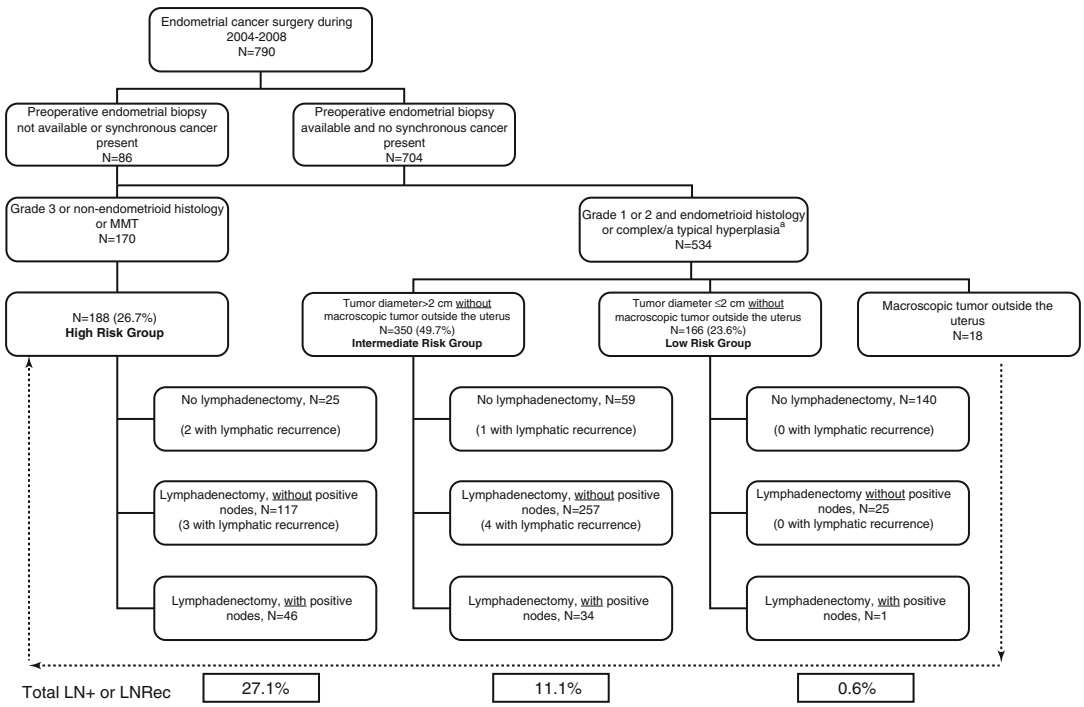

Fig. 18.3 Patient stratification into risk categories based on preoperative biopsy and intraoperative tumor diameter parameters. FIGO indicates International Federation of Gynecology and Obstetrics; *MMT*, mixed Müllerian tumor. *LN+*, lymph node dissemination rate in patients who underwent lymphadenectomy. *LNRec*, lymph node recurrence rates in patients who did not undergo lymphadenectomy or had negative lymph nodes. [a]Grade and histology determined on the basis of preoperative endometrial biopsy (Adapted from AlHilli et al.;used with permission)

sensitivity of MRI criteria was found to be as high as 90 %; however, limitations of this method of myometrial invasion assessment include high cost and poor specificity [68–70]. The use of biologic markers has been additionally proposed. Serum cancer antigen 125 (CA-125) has been found to be predictive of lymphatic metastases and prognosis in EC patients [71, 72]. Todo et al. explored the use of a preoperative scoring system that utilizes uterine volume index (maximum longitudinal diameter along the uterine axis and maximum anteroposterior diameter in horizontal section images), CA-125 and tumor grade/histology all of which were shown to be independent risk factors for lymph node metastases. The actual rate of lymph node metastasis in each patient group (low-risk, intermediate-risk, high-risk, and extremely-high groups) correlated highly with the estimated rate of lymph metastases [31]. Recently, human epididymis protein 4 (HE4) was shown to correlate highly with tumor diameter and myometrial invasion [73]. HE4 can be potentially used as a molecular marker of high- and intermediate-risk EC. As the search for predictive preoperative biomarkers continues, the use of IFS in risk stratification is suggested to be reliable when adequate resources are available. In low-resource settings, information from preoperative biopsy in addition to intraoperative tumor diameter may allow for rational intraoperative decision making.

Summary

While debate continues within the gynecologic oncology community on the fundamentals of EC management, the implementation of surgical guidelines in 2004 has substantially contributed to standardization of care for patients with EC and improvements in clinical outcomes. The focus on investigating patients who are not likely to benefit from lymphadenectomy or adjuvant therapy (defined as low-risk patients) has highlighted the significantly low risk of lymph node metastasis and safe omission of lymphadenectomy. To date, the evidence to support performance of comprehensive pelvic and paraaortic lymphadenectomy is limited to patients with intermediate- or high-risk features. Furthermore, strong evidence is available to support systematic pelvic and paraaortic lymphadenectomy in high- and intermediate-risk patients with dissection up to the level of the renal vessels in order to account for the high rate of positive nodes above the inferior mesenteric artery. Finally, methods to accurately stratify patients into risk groups through the use of accurate pathologic criteria, biologic markers, and radiologic findings are highly sought in order to optimize the management of EC patients in low resource as well as high resource settings.

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19 Extraperitoneal Laparoscopic Para-aortic Lymphadenectomy in Endometrial Cancer: Rationale and Surgical Technique

Jo Marie Tran Janco and Sean C. Dowdy

Introduction

Extraperitoneal laparoscopic para-aortic lymphadenectomy is an increasingly utilized procedure in gynecologic oncology, with advantages over open or traditional laparoscopic surgery, namely, decreased propensity for postoperative adhesions and ability to complete thorough surgical staging in a minimally invasive fashion. For patients with endometrial carcinoma who are at high risk for dissemination to the para-aortic lymph nodes, this technique provides reliable access up to the level of the renal vessels and can be particularly helpful in obese patients.

History

Extraperitoneal laparoscopic para-aortic lymphadenectomy was first described by Querleu and Dargent in 2000, for the evaluation of lymph nodes in the setting of advanced or bulky cervical carcinoma [1, 2]. Prior to this, a technique had been developed for open extraperitoneal lymphadenectomy via a "sunrise" incision – a transverse supraumbilical incision continued laterally to the iliac crests [3]. Despite the adherence to a clinical staging system for cervical cancer, there is benefit to assessing nodal status with bulky or advanced disease, both for prognosis and treatment planning. Imaging is a poor substitute for surgical evaluation, with a prospective study comparing preoperative PET/CT with pathology evaluation of para-aortic lymph nodes finding that imaging has 36 % sensitivity in detecting positive nodes, with a 12–22 % false-negative rate depending on pelvic lymph node positivity on imaging [4]. LeBlanc et al. in a similar study also found a high rate of false negativity for PET/CT of 21 cervical cancer patients with pathologically proven para-aortic disease; 14 (67 %) had a negative PET/CT [5]. More recently, the technique has been advocated for the staging of endometrial carcinoma, as laparoscopic exposure and removal of para-aortic nodes to the level of the renal veins can be limited in the transperitoneal laparoscopic approach [6–8].

Tumor Spread and Staging of Endometrial Cancer

Assessment of nodal status is critical to the staging of endometrial cancer, with positive para-aortic nodes conferring advanced stage at IIIC2. Lymphatic drainage of the uterus typically occurs along channels draining to first the pelvic nodes

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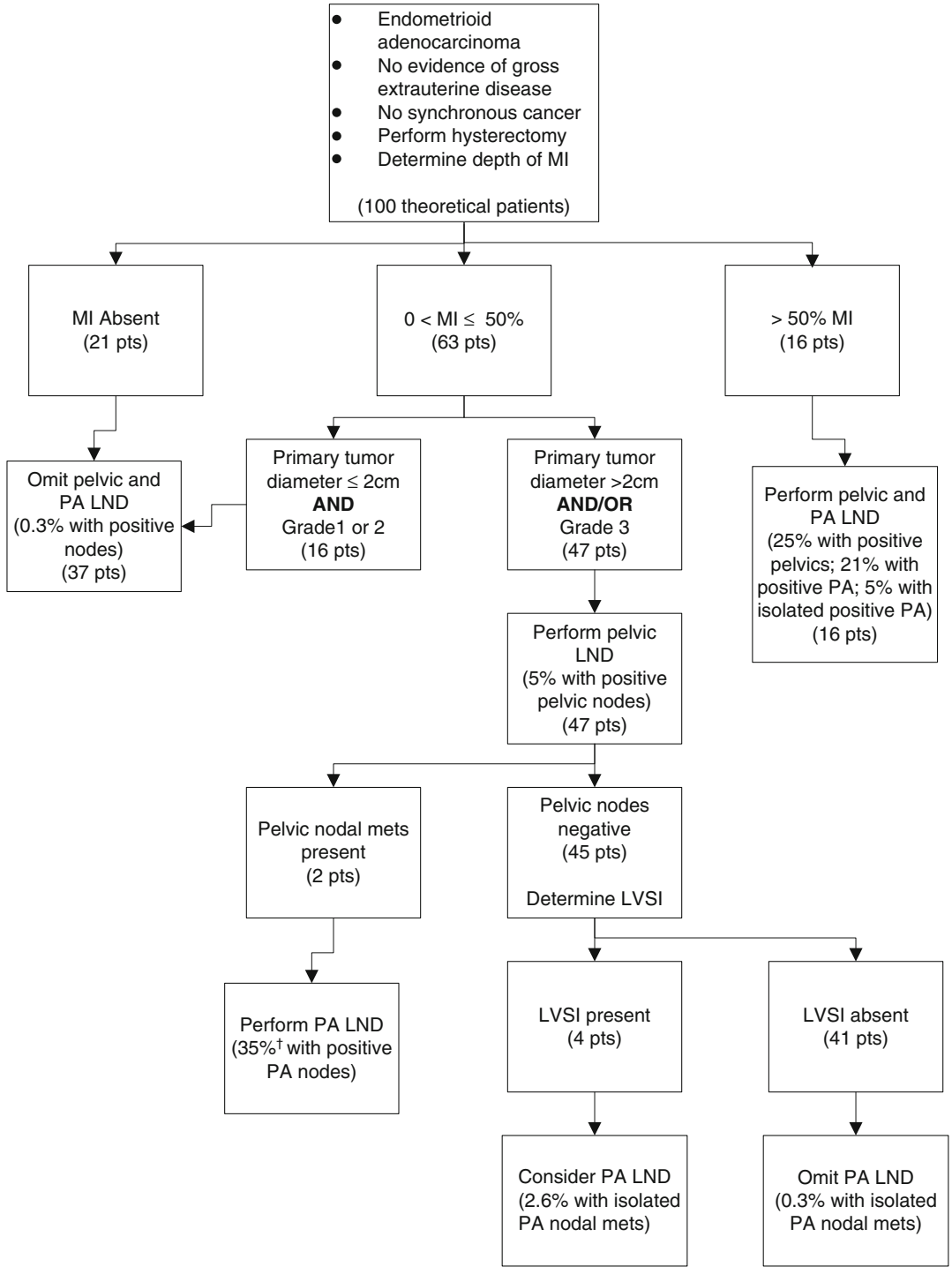
overlying the obturator and iliac vessels and then to the para-aortic nodes. Sentinel lymph node mapping studies in endometrial cancer tend to support this idea, with the majority of sentinel lymph nodes identified in the pelvis [9], but there is a significant proportion of patients that have para-aortic sentinel nodes identified [10, 11], raising the possibility of para-aortic metastasis bypassing the pelvic nodes. In one study examining routes of lymphatic spread in 112 endometrial cancer patients with nodal disease, 9 % of those with positive para-aortic lymph nodes had negative pelvic lymph nodes [12]. In a larger study, 16 % had nodal disease isolated to the para-aortic region [13].

Beyond the prognostic gain of establishing accurate stage, performance of para-aortic lymphadenectomy guides therapy by outlining appropriate radiation fields and can also be therapeutic for patients at high risk of lymphatic involvement. In a retrospective study of 137 patients with deep myometrial invasion, macroscopically positive pelvic nodes, or positive adnexa (excluding stage IV disease) who underwent surgery for endometrial cancer, survival and recurrence rates were compared between those who had undergone para-aortic lymphadenectomy, defined as removal of five or more nodes, and those who had not. Risk factors for recurrence, including age, myometrial invasion, and positive adnexa or cervices, were not significantly different between the two groups. There was a significant difference in overall survival at 5 years – 71.2 % in the group without versus 85.1 % in the group who had received para-aortic lymphadenectomy. There was a 12 % para-aortic recurrence rate among those who had not received lymphadenectomy, in comparison to 0 % of those who had; one of those occurred in a patient who was given extended-field radiation therapy to the para-aortic region. Results were even more striking for those who had positive pelvic and/or para-aortic lymph nodes, with 5-year overall survival of 76.9 % for those with lymphadenectomy versus 42 % without and 76.1 % versus 36.1 % recurrence-free survival for the groups, respectively. Para-aortic lymphadenectomy was the only significant predictor of recurrence-free (odds ratio = 0.28 and overall odds ratio = 0.32) survival. Of note, the number of pelvic lymph nodes dissected was no different between the groups; therefore, therapeutic advantage was derived from the para-aortic component of the lymphadenectomy [14].

Assessment of risk factors for para-aortic disease at the time of staging or risk of recurrence in the para-aortic region is important as many early-stage endometrial cancer patients are at very low risk of para-aortic involvement and may safely have nodal dissection of that region omitted. Appropriate candidates for the procedure are those with high-grade histology, deep myometrial invasion (>50 %), positive pelvic lymph nodes, and lymphovascular space invasion. In a retrospective study of 946 patients undergoing surgery for endometrioid endometrial carcinoma without gross evidence of spread beyond the uterus, 4 % were observed to have para-aortic metastasis or recurrence. On multivariate analysis, positive lymph nodes, lymphovascular space invasion, and deep myometrial invasion were the only independent predictors of para-aortic metastasis or para-aortic recurrence. When all three factors were absent, risk of para-aortic involvement was 0.6 %. Figure 19.1 outlines a flowchart for determination of candidacy for para-aortic lymphadenectomy [15].

Rationale for Use in Endometrial Cancer

The extent to which the para-aortic nodes should be removed remains under some debate; it is our opinion that adequate assessment requires dissection up to the level of the renal veins rather than to the inferior mesenteric artery (IMA). Extension of the para-aortic lymphadenectomy has the potential to double the count of lymph nodes available for evaluation [16] and may detect metastasis in patients without nodal disease below the inferior mesenteric artery. In a study of 281 patients undergoing lymphadenectomy for surgical staging of endometrial cancer, 67 % had para-aortic disease. Of those, 77 % had involvement of nodes above the inferior mesenteric artery. For patients with para-aortic nodal involvement, 46 % were documented to have positive nodes above the



†45% if include patients with evidence of gross extrauterine disease

Fig. 19.1 Algorithm for para-aortic lymphadenectomy in patients with endometrial cancer [15]

inferior mesenteric artery and negative ipsilateral nodes below [13].

However, performing an adequate para-aortic lymphadenectomy to the renal veins can be challenging, particularly in obese patients and when using minimally invasive surgical techniques. In the LAP2 trial conducted by the Gynecologic Oncology Group, comparing laparoscopic to open surgical staging for uterine cancer, risk of conversion to laparotomy increased with higher body mass index (BMI). 26 % of those assigned to laparoscopy required conversion to laparotomy to complete staging. The most common reason for conversion was poor visualization. Across all subgroups, comprising differences in age and metastatic disease, BMI remained an important risk factor for conversion, with an odds ratio of 1.11 for each 1-unit increase in BMI [17]. A study comparing laparoscopic to open surgery with planned pelvic and para-aortic lymph node dissection in obese endometrial cancer patients found similar lymph node counts in both groups (extent of para-aortic dissection was to the inferior mesenteric artery) but noted a 36 % conversion rate, with the most common reason reported as obesity. Again, successful laparoscopic lymphadenectomy was less likely with increasing BMI, particularly greater than 35 [18].

Indications and Technique

Extraperitoneal laparoscopic para-aortic lymphadenectomy may be appropriate for patients at high risk for lymphatic disease or for patients in whom visualization for infrarenal dissection may be challenging (obese, prior surgery, etc.). Using this technique, patients may be staged by vaginal hysterectomy and extraperitoneal pelvic/para-aortic lymphadenectomy. Silver and colleagues argue that the latter approach may arguably be the least invasive method of staging endometrial cancer, as it greatly limits intraperitoneal disruption and subsequent adhesion formation that may contribute to postoperative and post-radiation complications [19]. Contraindications to extraperitoneal laparoscopic para-aortic lymphadenectomy include a history of retroperitoneal surgery (e.g., nephrectomy) or contraindications to laparoscopy such as severe cardiopulmonary disease or closed-angle glaucoma.

Prior to initiation of extraperitoneal laparoscopic para-aortic lymphadenectomy, it is important to assess the intra-abdominal cavity for metastatic disease, which may be performed via a transperitoneal umbilical port. If no metastatic disease is identified, a total of three ports are placed in the left flank, with proper placement critical to the success of the procedure so as not to constrict the operative field or cause perforation of the peritoneum. An initial 2-cm incision is made two fingerbreadths medial and three to six fingerbreadths superior to the left anterior superior iliac spine. Fibers of the oblique and transversalis muscles are split bluntly until the peritoneum is identified. Blunt dissection is continued to develop the retroperitoneal space posteriorly until the left psoas muscle is palpated. A second incision is then made superior and inferior to the first, and a 10-mm trocar is inserted. The retroperitoneal space is insufflated, keeping initial pressures (10 mm Hg) and flow (3 L/min) low to minimize the risk of peritoneal perforation and possible subsequent pneumothorax and hypercarbia. The camera is inserted through this port and additional blunt dissection is performed through the initial incision until the psoas muscles are visualized. A 5-mm trocar is placed under direct visualization further superior and anterior to the second, and a 10-mm port is placed in the initial incision. Port placement is outlined in Fig. 19.2. Pressure may be gradually increased if exposure is inadequate. However, pressures greater than 15 mm Hg should be avoided.

Insufflation pressure generally allows passive retraction of the left ureter and gonadal vessels anteriorly out of the field. Dissection is continued medially with identification of the left common iliac artery and aorta. Following the left gonadal vein into the left renal vein superiorly identifies the superior most limits of the dissection, and para-aortic nodes between the aortic bifurcation and left renal vein are then removed. Dissection is then continued medially to develop the space over the aorta to the inferior vena cava. The right para-aortic lymph nodes are then reflected from the underlying inferior vena cava, with insufflation pressure allowing them to be retracted anteriorly to the roof of the dissection. The inferior mesen-

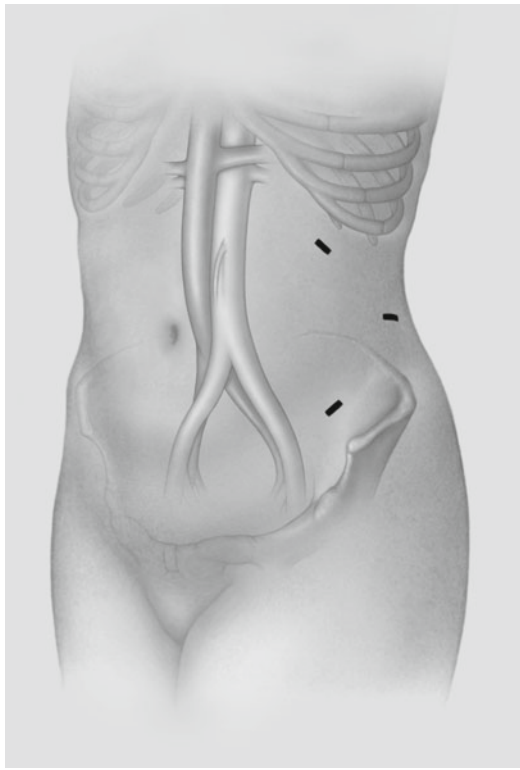


Fig. 19.2 Port placement for extraperitoneal para-aortic lymphadenectomy [23]

teric artery is identified and preserved. Due to the approach from the left side, identification of the right ureter is unnecessary but it may usually be seen along the lateral aspect of the dissection. The nodes are then stripped from the anterior peritoneum. Once all nodal tissue has been removed, the lowermost trocar may be converted to an intraperitoneal port by advancing it through the peritoneum. Transperitoneal pelvic lymphadenectomy may then be performed with placement of additional transperitoneal ports. Use of this technique has been reported using a single-port approach, although this is not widely utilized [20].

Feasibility and Outcomes

As the technique was first described for para-aortic nodal evaluation in the setting of cervical cancer, many of the early studies regarding feasibility arise from that body of literature. In an early paper, Dargent first reported this technique in 44 patients with cervical cancer who underwent laparoscopic para-aortic lymphadenectomy, by either a transperitoneal, bilateral extraperitoneal, or left-sided extraperitoneal approach. Success rates for the respective methods were 78 %, 93 %, and 95 %, although comparison of techniques in this study is limited due to small numbers and the learning curve of the surgeons. Conversion to a transperitoneal approach due to peritoneal perforation occurred in 17 % of extraperitoneal attempts. The extraperitoneal approach was initially pursued because of the difficulty obtaining adequate retraction of bowel and visualization in order to safely perform lymphadenectomy up to the renal veins. The left extraperitoneal approach also yielded equivalent node counts with a shorter operative time [2]. In a larger study by the same group, 53 patients underwent attempted infrarenal para-aortic lymphadenectomy using a laparoscopic extraperitoneal approach, with an overall success rate of 96 % and average nodal count of 20.7. The average procedure time was approximately 126 min [1]. Other groups have reported similar outcomes [21, 22].

The Mayo Clinic experience with laparoscopic extraperitoneal para-aortic lymphadenectomy is one of only a few studies specifying results with regard to successful dissection up to the renal veins. Over 2 years, 38 patients underwent attempted para-aortic lymphadenectomy using the technique, with a 92 % success rate; the mean BMI was 33 and the remainder of the procedure was in most cases performed vaginally. Median operating time for the para-aortic lymphadenectomy portion of the case was 69 min, with an average of 16.5 nodes removed. While not statistically significant, there was a trend toward higher nodal counts for patients with a greater BMI (over 35). An average of 9.5 nodes was harvested above the inferior mesenteric artery. Indeed, in the most obese patient (BMI of 52), 21 of 34 lymph nodes were harvested above the IMA [23].

The technique is neither difficult to adapt nor arduous to disseminate to trainees. In a study reporting outcomes for the procedure when taught to gynecologic oncology fellows, after an average of 5 mentored cases as an assistant

surgeon, 100 % of 22 planned operations were completed successfully, with an average nodal count of 14 and estimated blood loss of 40 mL. Operating times were understandably longer at a mean of 163 min, with an acceptably low complication rate of 6.2 % [24]. In a small study following inexperienced surgeons performing porcine para-aortic lymphadenectomy via either a transperitoneal or extraperitoneal route, the learning curves were similar for both approaches. Ten animals were required for each approach in order for the physician to perform the procedure effectively; one would expect that number to be lower for more experienced laparoscopic surgeons adapting the new technique [25].

Complications

Complications are related to the surrounding anatomical structures in the region and include lumbar artery injury and bowel injury [26], lymphocele [1, 2, 21], and retroperitoneal hematoma [1]. Rates of hypercapnia have been described as being higher with the extraperitoneal approach [27], although this is not a complication we have encountered. While not a complication, if the peritoneum is perforated during port placement, the gradient between extraperitoneal and intraperitoneal pressures will be lost and the approach will not be possible. Small defects may be successfully tamponaded using an inflated Foley catheter balloon [23].

Conclusions

Laparoscopic extraperitoneal para-aortic lymphadenectomy is a useful approach to successfully stage cervical cancer and may be applied to stage patients with endometrial cancer who are at high risk of nodal disease. Use of this technique may enhance adequate evaluation of the para-aortic nodes, particularly in obese patients for whom exposure and dissection of the nodal region between the inferior mesenteric artery and the renal veins can be difficult. Laparoscopic extraperitoneal para-aortic lymphadenectomy is not difficult to adapt for surgeons already practicing laparoscopy and may be advantageous in preventing additional intraperitoneal adhesive disease and subsequent operative and radiation-related morbidity.

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Role of Laparoscopic and Robotic Surgery in Endometrial Cancer: The Inevitable Evolution

20

Alex Rabinovich, Walter H. Gotlieb, and Ido Laskov

Introduction

Surgery remains the cornerstone in the management of patients with endometrial carcinoma. In 1988, the International Federation of Gynecology and Obstetrics (FIGO) implemented a surgical staging system for endometrial cancer that has been updated in 2009 [1]. The transition to surgical staging occurred in part because the clinically defined stage was retrospectively reassigned after examination of the surgical specimen in 25 % of the cases, and 16 % of the women with presumed stage I were found to actually have stage III or IV disease.

This surgical staging includes exploratory laparotomy, peritoneal washings, total abdominal hysterectomy, bilateral salpingo-oophorectomy, pelvic and para-aortic lymphadenectomy, and omentectomy depending on histologic subtypes.

Postoperative treatment recommendations include radiation and/or chemotherapy tailored to the stage of disease, histologic cell type, grade, and presence of lymphovascular space invasion and/or myometrial invasion. Accurate surgical staging adds relevant information toward making adjuvant treatment recommendations, allowing customized adjuvant therapy in patients with high risks for recurrence while minimizing unnecessary therapy in low-risk endometrial cancer, in an attempt to eliminate unnecessary morbidity, improving value for the patient, and reducing cost.

As surgeons, we are figuratively licensed to perform "aggressions" with a scalpel. This comes with an important responsibility to restrain this "aggression" to the minimum necessary. From a patient perspective, the value of the surgery will be a balance between the expected outcome and the extent of the surgical act. The smaller the extent of surgery for an equivalent outcome, the higher the value for the patient. Following this paradigm, healthcare providers have investigated less invasive

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surgical approaches to minimize intraoperative and postoperative complications, without compromising oncologic outcomes. The transition from traditional open surgery to "keyhole surgery" or laparoscopy has opened this path.

Laparoscopy for Endometrial Cancer

Historically, Ephraim McDowell, in 1809, performed the first documented laparotomy for a gynecological tumor. Ernst Wertheim in 1896 introduced and refined the technique for radical gynecologic surgery. The first attempt at laparoscopy was made by George Kelling in 1901, on his dog, but only in the1980s was laparoscopy introduced into the clinical management of gynecological cancers. At first, Dargent used laparoscopy for a presurgical evaluation before Schauta's operation (1987) [2], 2 years later Reich reported a series of laparoscopically assisted vaginal hysterectomies [3], and Querleu introduced laparoscopic pelvic lymph node dissection in patients with cervical cancer [4]. In 1992, Nezhat performed the first laparoscopic radical hysterectomy with pelvic and para-aortic lymph node dissection [5]. A year later, Childers et al. published their description of the laparoscopic lymphadenectomy of pelvic and para-aortic lymph nodes for the staging of endometrial cancer [6].

Compared to laparoscopy, laparotomy allows for increased surgical exposure, three-dimensional vision, direct tissue palpation and manipulation, and ease of suturing. Despite these advantages and the vast experience with laparotomy, the use of minimal invasive surgery is increasing in gynecologic oncology, particularly in endometrial carcinoma. The available randomized controlled trials (RCT) [7–17], comparing laparotomy to laparoscopy, that assessed more than 3,500 patients in total, have shown non-inferiority and often superiority of laparoscopy compared to laparotomy in patients with endometrial carcinoma (Table 20.1).

A striking difference is the significantly shorter postoperative hospital stay after laparoscopy despite longer operative times.

Table 20.1 Summary of available randomized controlled trials comparing laparotomy and laparoscopy for the staging of endometrial carcinoma

Category	Laparotomy	Laparoscopy
Operating room time (min)	113	168
Number of para-aortic LN obtained	6.75	7.58
Number of pelvic LN obtained	19.5	19.6
Estimated blood loss (ml)	305	131
Blood transfusion rate	10.1 % 104/1,022	7 % 128/1,801
Intraoperative complications	6.6 % 93/1,363	8.8 % 201/2,284
Bladder, ureter, bowel, vascular injury	1.2 % 14/1,149	1 % 20/2,020
Postoperative complications	23 % 320/1,389	15.2 % 353/2,310
Early postoperative complications[a]	4.2 % 47/1,097	2.6 % 53/1,965
Postoperative hospital stay (days)	6.2	3.1
Quality of life 6 weeks after surgery	↓	↑
Recurrence-free survival	88 % 154/175	87 % 161/184
Overall survival	88 % 154/175	91.8 % 169/184

[a]Urinary tract infection, vaginal stump infection, hematoma, ileus, deep vein thrombosis, wound infection, wound dehiscence, and temperature >38 °C

The higher rate of intraoperative complications sometimes described in patients who had laparoscopy has been associated with the lack of technical skill and the longer learning curve for laparoscopy compared to laparotomy. Furthermore, more than half of patients included in most of the systematic reviews were derived from the GOG LAP2 trial [15]. This landmark study compared 1,696 patients randomly assigned to laparoscopy to 920 patients assigned to laparotomy for the surgical treatment of endometrial cancer in the United States. Some of these patients were enrolled as early as 1996, when the expertise for laparoscopy was still developing. Despite this, the rate of significant intraoperative complications such as bladder, ureter, bowel, and

vascular injuries was similar in both arms. Total and pelvic lymph node yields and the detection rate of advanced-stage disease, both surrogate markers for surgical completion, were similar in both arms. Para-aortic lymph node counts were equally similar when reported [10–15].

A few concerns remained regarding oncologic outcomes after laparoscopic surgery:

1. The loss of tactile sense during laparoscopy may result in failure to detect metastatic tumor otherwise palpable at laparotomy.
2. Failure to identify and remove high left para-aortic lymph nodes below the renal vein.
3. Potential change in patterns of recurrence associated with the high intra-abdominal pressures resulting from carbon dioxide insufflation.
4. Potential for tumor spill secondary to the use of an intrauterine manipulator and uterine extraction through the vagina.

Most of the concerns faded away following the publication of recurrence and survival in the follow-up publication of the GOG LAP2 study that demonstrated the absence of adverse effects on overall survival, recurrence-free survival, recurrence rate (estimated difference at 3 years, 1.14 %), or the patterns of recurrent disease following laparoscopy [18]. This in combination with the shorter hospital stay, the decreased rate of early and late postoperative complications, the faster recovery, and superior quality of life observed in the laparoscopy cohorts has made minimal invasive surgery the treatment of choice for patients with endometrial cancer.

Special Considerations

Conversion to Laparotomy

Conversions from laparoscopy to laparotomy have been reported from 17 % to 28 % in various series [15, 19]. Higher conversion rates are associated with widespread metastatic disease, increasing BMI and increasing patient age. Conversions may be due to either anatomical difficulties such as dense adhesions, difficult exposure, advanced disease, and a uterus too large to be removed intact through the vagina, or intraoperative complications such as management of intraoperative complications, control of intraoperative bleeding, and intolerance of increased abdominal pressure. The most common reported reason for conversion is insufficient visualization caused by inability to maintain adequate Trendelenburg position. In the LAP2 study, the rate of conversion to laparotomy for women with BMI >40 kg/m^2 was 57 %, and for each 10-year increase in age, the chance of conversion increased by 30 % [15].

Vaginal Cuff Recurrence and Port-Site Metastasis

During laparoscopic staging, the cancer-affected uterus and adnexa are removed through the vagina which may raise a concern for increased vaginal cuff recurrence. Fortunately, no statistically significant difference in the rate of vaginal vault recurrence was noticed between the laparoscopic and abdominal approach [18, 20].

Some have stipulated that the use of uterine manipulator during laparoscopic staging may contribute to dissemination of malignant cell from the uterine cavity thorough the fallopian tubes into the pelvic cavity. A study by Eltabbakh and Mount evaluated peritoneal washings before and after insertion of a uterine manipulator. None of the 42 patients had a change from negative to positive washing results after insertion of the manipulator [21]. Although there is no definitive data to support peritoneal cavity seeding by the uterine manipulator, several authors do advocate sealing the tubes at the start of the case and minimize uterine manipulation [22].

There have been a number of case reports of port-site metastasis after laparoscopic treatment of endometrial cancer. In fact, port-site metastasis has been reported in a small percent of all gynecologic malignancies undergoing laparoscopy [23]. The fact that wound recurrences are not uncommon after conventional surgery clearly attenuates the responsibility of laparoscopic surgery in the occurrence of abdominal wall recurrences [24]. A study from Memorial Sloan

Kettering Cancer Center reported 18 abdominal wall metastases in 1,634 gynecologic cancer patients treated by laparoscopy. Fifteen occurred in 767 patients with adnexal/peritoneal malignancy (2 %), two in 160 cervical cancer patients, and one in 457 endometrial cancer patients. Seventeen out of the eighteen patients had concomitant intraperitoneal disease at the time of diagnosis of the port-site metastasis. Overall, port-site tumor implantation is low and almost always occurs in the setting of synchronous, advanced intra-abdominal, or distant metastatic disease [25].

The presence of port-site implantation is often a surrogate for advanced disease and is not anymore an argument against laparoscopic surgery in gynecologic malignancies including endometrial cancer.

Obesity

Obesity and the concomitant excess of unopposed estrogen are associated with endometrial cancer [26], particularly type 1. These patients frequently suffer from other comorbidities, i.e., diabetes mellitus, hypertension, and/or coronary heart disease. Morbid obesity is considered by some to be a relative contraindication to laparoscopic surgery. Of particular concern are cardiopulmonary compromise and difficulties with ventilation resulting from increased intra-abdominal pressure. These complications may prevent the steep Trendelenburg position sometimes necessary to complete the operation and increase the rate of conversion to laparotomy [27].

In open abdominal surgery, obesity and diabetes mellitus are associated with significantly higher perioperative complication rates such as longer surgery durations, more blood loss, and higher transfusion rates. Postoperative complications, like wound infection and dehiscence or symptomatic ileus, are also increased. Finally, due to prolonged hospital stay, the risks of thrombosis and/or pulmonary embolism rates are higher.

On the other hand, others recommend laparoscopy over laparotomy in obese patients to minimize these peri- and postoperative complications [28]. Vaginal procedures already provide the advantages of reducing total surgery duration and perioperative surgical and anesthetic morbidity. However, during vaginal surgery, neither nodal nor abdominal staging can take place, and safe removal of the adnexa is often compromised. Vaginal approach may be limited by anatomical circumstances as well as patients' parity. Therefore, laparoscopy, even with its limitations, constitutes a valid surgical procedure in obese women. Peritoneal access restrictions, difficulty accessing the pelvic organs and performing adequate lymphadenectomy, as well as the aforementioned anesthetic complications are all associated with the proportional increase in conversion rate to laparotomy with increasing BMI. A recent multicentered study explored the advantages of laparoscopy versus laparotomy in extremely obese women (BMI > 35) with early-stage endometrial cancer. In all cases, systematic pelvic lymphadenectomy was performed. In two women of the laparoscopy group (4.4 %), a port-site hematoma was observed and was resolved without a second surgery. In three women (10 %) of the laparotomy group, dehiscence of the abdominal suture with surgical site infection was observed and was re-sutured [29]. There is no consensus for an upper limit above which laparoscopy should not be considered. The decision is almost entirely surgeon dependent and relies on the experience acquired over the years.

Elderly Patients

Older women constitute another challenge group of patients for laparoscopy.

A number of studies dealt with this issue; in one, 59 women aged 75 years or older who underwent laparoscopy were compared with a cohort of 66 women aged 75 years or older who underwent open staging. Women who underwent laparoscopy had similar operative time ($P = 0.14$), lower blood loss ($P = 0.005$), and shorter length of stay ($P < 0.001$) in comparison with women who underwent open surgical procedure. Overall, women who underwent laparoscopy experienced less postoperative complications than women in the control group ($P < 0.001$). No differences in survival outcomes (including time of recurrence, site of recurrence, disease-free survival, and overall survival) were recorded ($P > 0.05$) [30].

In conclusion, in this population, a minimally invasive procedure will lead to fewer perioperative complications such as myocardial infarction, deep vein thrombosis, and pneumonia without a significant increase in operative time, blood loss, or length of hospital stay. Therefore, laparoscopic staging for endometrial cancer is safe and feasible in the elderly population [30–32].

Quality of Life

The excellent cure rates that are attained for well-differentiated EC have allowed shifting focus from the already high survival toward quality of life issues after treatment. In a recent prospective, randomized study comparing laparoscopy to laparotomy in the management of endometrial cancer, Zullo et al. prospectively demonstrated that patients treated with laparoscopy did indeed have improved quality of life for the first 6 months after surgery [11].

Quality of life up to 6 months after surgery was also assessed in a randomized controlled trial comparing total laparoscopic hysterectomy with total abdominal hysterectomy (TAH) for stage I endometrial cancer [17]. Three hundred and sixty-one participants were enrolled. Three hundred and thirty-two completed the quality of life analysis. Patients who had laparoscopic surgery reported significantly greater improvement in quality of life (QoL) from baseline, in all subscales, apart from emotional and social well-being that are related to dealing with cancer.

GOG LAP2 also required patients to complete quality of life assessment at baseline and then at 1, 3, and 6 weeks and 6 months postoperatively [33]. The first 802 eligible patients randomized in LAP2 participated in the QoL study. Within 6 weeks of surgery, patients assigned to laparoscopy reported significantly better QoL on all scales other than fear of recurrence. In summary, during this 6-week postoperative period, patients assigned to laparoscopy were found to have superior QoL, fewer physical symptoms, less pain and pain-related interference with functioning, better physical functioning and emotional state, earlier resumption of normal activities, earlier return to work, and better body image as compared to those assigned to laparotomy.

The LAP2 QoL study arm completed a self-report QoL survey, which contained sexual function items. Of 752 patients who completed the QoL survey, 225 completed the sexual function items within the QoL survey. No significant differences of sexual function were found between the patients randomized to laparoscopy and to laparotomy. Sexual function scores declined after surgery and recovered to presurgery levels at 6 months. Sexual function was positively associated with better quality of relationship ($P < 0.001$), body image ($P < 0.001$), and QoL ($P < 0.001$) and negatively associated with fear of sex ($P < 0.001$). Younger patients, those who were married, and those who had quality relationships were more likely to answer the sexual function items and have better quality of sexual function. Factors such as age, relationship quality, body image, and pain may place women with endometrial cancer at risk for sexual difficulties in the immediate recovery period; however, sexual function improved by 6 months postoperatively in the cohort of patients with early-stage endometrial cancer [34]. As the concern of recurrence has been addressed by randomized studies, the benefits of minimal invasive surgery in terms of QoL make it the preferred approach.

Robotics for Endometrial Cancer

Although the proportion of endometrial carcinoma patients treated by laparoscopy is slowly increasing [19, 35], many surgeons find the laparoscopic approach difficult to master because of the counterintuitive movements and the fulcrum effect and do not offer it to most of their patients, mainly those who could most benefit from it such as obese and elderly patients with multiple morbidities [36]. A computer-controlled system that assists the surgeon in utilization and manipulation of surgical instruments in minimally invasive surgery was developed. This computer-assisted minimally invasive surgery has been termed "robotic surgery" although it does not fulfill the definitions of a "robot," because it does not perform the surgical procedure on its own nor does it involve any artificial intelligence for the moment

[37]. In April 2005, the FDA approved the only currently available surgical robotic system (Da Vinci Surgical System, Intuitive Surgical, Inc., Sunnyvale, CA, USA) for gynecologic minimally invasive procedures. Over the following years, robotics rapidly gained acceptance by surgeons as an effective tool for performing hysterectomy with staging lymphadenectomy in the management of endometrial cancer. It is estimated that in 2010, more than 50 % of endometrial carcinoma staging procedures in the USA were managed with robotic-assisted surgery, representing a paradigm shift toward minimally invasive surgery not previously achieved with traditional laparoscopic technique. It is expected for this trend to continue as more systems are installed worldwide and more surgeons are trained to use this platform [38].

Robotic surgery has significant technical advantages and some disadvantages compared to conventional laparoscopy [39–42]:

1. Binocular three-dimensional high-definition immersion view of the operative field: the surgeon has full control of the camera. Robotic approach eliminates surgeons' dependence on an assistant that holds a 2D vision camera projected on a screen a few feet away.
2. Seven degrees of freedom permitted with the wristed instruments:
   a. Improved dexterity mimics the freedom of human hand and wrist motion.
   b. Provides a better precision of movement without tremor, which allows superior operative technique, precise dissection, and better exposure.
   c. Intuitive instrument movement enables surgical procedures to be carried out similar to the way they are accomplished during laparotomy.
3. Less torque of the abdominal wall through the operative ports, which results in less postoperative pain.
4. Easier to complete radical and complex gynecologic surgeries thus reducing the need for more morbid laparotomies.
5. Improved ergonomics for the surgeon. Reduces surgeon fatigue and muscle pain thus allowing longer and more complex operations.
6. Easier suturing and knot tying.
7. A shorter learning process.

Disadvantage of the robotic surgical system:

a. Lack of tactile perception
b. Increased cost
c. Need for large operating room (to accommodate the size of the robotic system)
d. Risk of intraoperative mechanical failure
e. Need for additional trained staff

Despite the potential benefits of robotic approach, there have been no prospective RCTs comparing laparotomy, laparoscopy, and robotic-assisted laparoscopic staging procedures for treatment of uterine malignancies. The available studies have been relatively small in size, nonrandomized, and limited to highly experienced surgeons and centers. Still, these studies are informative and demonstrate the feasibility of this technique, its safety, and efficacy [37].

The bulk of retrospective case series and two meta-analyses (eight and nine comparative studies, 1,591 and 1,640 total patients, respectively) [36, 37] indicate similarities with laparoscopy in most categories, except for reduced blood loss and fewer conversions to laparotomy in robotic surgeries (Table 20.2). Robotic and traditional laparoscopic surgeries have better outcomes than laparotomy in terms of blood loss, blood transfusions, peri- and postoperative complications, wound infection, postoperative pain, shorter recovery time, and decreased length of hospital stay. Pelvic and para-aortic lymph node counts, which are a measure of surgical quality, were similar for the three modalities.

The advantages of robotic surgery for the patient compared with traditional laparoscopy are not always evident [39]. Robotic surgery is probably neither safer nor better than laparoscopy

Table 20.2 Summary of meta-analysis comparing laparotomy, laparoscopy, and robotic surgery for the staging of endometrial carcinoma [36, 37]

Category	Laparotomy	Laparoscopy	Robotic
Number	2,555	746	949
Age	61	62	63
BMI	31	29	31
Number of para-aortic LN obtained	10.3	7.8	5.7
Number of pelvic LN obtained	18.5	17.8	14.5
Operating room time (min)	186	211	142
Estimated blood loss (ml)	86	131	227
Transfusion rate (%)	1	4	7
Postoperative hospital stay (days)	1.6	1.9	5.1
Overall complications	13	13	40

in the hands of expert surgeons, but it allows more patients needing complex or radical surgery to benefit from the minimally invasive approach [40, 42].

Disadvantages include present cost associated with purchasing the robotic system and disposable equipment and possibly loss of haptic sensation. Operative times for robotic and laparoscopy cases were similar, but longer than that for laparotomy cases [43].

Recent cost analysis studies indicate that the shorter operating times and the efficiencies gained with robotic surgical experience may translate into significant reductions in operating room costs, such that the widely held belief that robotic surgery is "too expensive" is not true for many institutions [44, 45].

Finally, three recently published retrospective survival analyses of combined 1,054 [46–48] patients provide evidence that robotic-assisted laparoscopy for endometrial carcinoma has similar overall and recurrence-free survival rates to traditional laparoscopy and laparotomy.

Special Considerations

Conversion to Laparotomy

Robotics has become widely used for the hysterectomy and surgical staging of endometrial cancer. Numerous series have reported the success of robotics for endometrial cancer staging and have shown decreased morbidity compared to laparotomy, with low rates of conversion which range from 0 % to 12 % [49, 50], even among subgroups of patients known to be technically challenging for MIS approaches (Table 20.3). Turunen et al. compared surgical outcomes of laparoscopic and robotic hysterectomy for the treatment of endometrial carcinoma in a center with extensive laparoscopic expertise. The robotic cohort ($n = 67$) had a longer operative time than the laparoscopic cohort ($n = 150$), and the rate of overall complications was similar in both groups, but still the rate conversion to laparotomy was higher in the laparoscopic group (3.3 %) compared to the robotic group (0 %) [51].

The reported low conversion rates highlight and reflect the intuitive use of robotics to the surgeon and have helped increase the proportion of women able to benefit from the advantages of MIS, particularly for certain subset of patients, including those with elevated BMI and of elderly age.

Obesity

The challenges associated with obese (BMI 30–39) and morbidly obese (BMI > 40) patients are similar between robotic-assisted and traditional laparoscopy, namely, exposure during aortic lymph node dissection and adequate ventilation related to steep Trendelenburg positioning. Contrary to traditional laparoscopy, modifying the Trendelenburg positioning during robotic surgery is at present impossible without undocking the robotic arms, thus extending the operative time. Yet many believe that the robotic platform enhances the laparoscopic skills of the operator necessary when the patient has a challenging body habitus [52] and that obese and morbidly obese

Table 20.3 Comparison of laparoscopy and robotics in conversion rates to laparotomy

Year	Study	Technique	N	Age	BMI	Conversion rate
2008	Boggess et al. [65]	Laparoscopy	81	62	29	4.9 %
		Robotics	103	62	33	2.9 %
2008	DeNardis et al. [66]	Laparoscopy	–	–	–	–
		Robotics	56	59	29	5.4 %
2009	Seamon et al. [50]	Laparoscopy	76	57	29	26 %
		Robotics	105	59	34	12 %
2009	Holloway et al. [67]	Laparoscopy	–	–	–	–
		Robotics	100	60	29	4 %
2009	Peiretti et al. [68]	Laparoscopy	–	–	–	–
		Robotics	80	58	25	3.8 %
2009	Lowe et al. [69]	Laparoscopy	–	–	–	–
		Robotics	405	62	32	6.7 %
2010	Cardenas-Goicoechea et al. [70]	Laparoscopy	173	60	33	5.2 %
		Robotics	102	62	32	1 %
2011	Paley et al. [71]	Laparoscopy	–	–	–	–
		Robotics	377	62	31	2.9 %
2012	Coronado et al. [72]	Laparoscopy	84	66	27	8.3 %
		Robotics	71	67	29	2.4 %
2012	Backes et al. [73]	Laparoscopy	–	–	–	–
		Robotics	471	60	32	6.4 %
2012	ElSahwi et al. [49]	Laparoscopy	–	–	–	–
		Robotics	155	62	35	0 %
2012	Lau et al. [74]	Laparoscopy	–	–	–	–
		Robotics	143	65	32	4.2 %
2012	Leitao et al. [75]	Laparoscopy	–	–	–	–
		Robotics	347	60	29	11 %
2013	Cardenas-Goicoechea et al. [76]	Laparoscopy	285	61	32	0.5 %
		Robotics	187	62	32	4.1 %
2013	Turunen et al. [51]	Laparoscopy	150	67	29	3.3 %
		Robotics	67	65	28	0 %
2014	Seror et al. [77]	Laparoscopy	106	67	25	4.7 %
		Robotics	40	66	25	0 %
Total		**Laparoscopy**	**955**	**62.8**	**29.1**	**7.5 %**
		Robotics	**2,809**	**61.9**	**30.4**	**4.1 %**

patients could be good candidates for robotic surgery [53, 54]. Figure 20.1 describes the placement and protection of patients with elevated BMIs.

Much like traditional laparoscopy, robotic surgery reduces peri- and postoperative complications, particularly abdominal wound complications, while maintaining adequate pelvic and para-aortic lymph node retrieval counts, overall survival, and recurrence rates when compared to open surgery.

Holloway et al. [38] showed that robotic lymph node yields in obese patients were greater than those of laparoscopic cases and node counts for morbidly obese patients were not greater than laparoscopy, indicating that robotic aortic lymphadenectomy may still have some limitations for this group of difficult patients.

Elderly Patients

Detailed information regarding robotic surgery in elderly and high-anesthesia risk endometrial carcinoma patients is scarce. Lavoue et al. [55] showed that robotic staging of elderly (age ≥70)

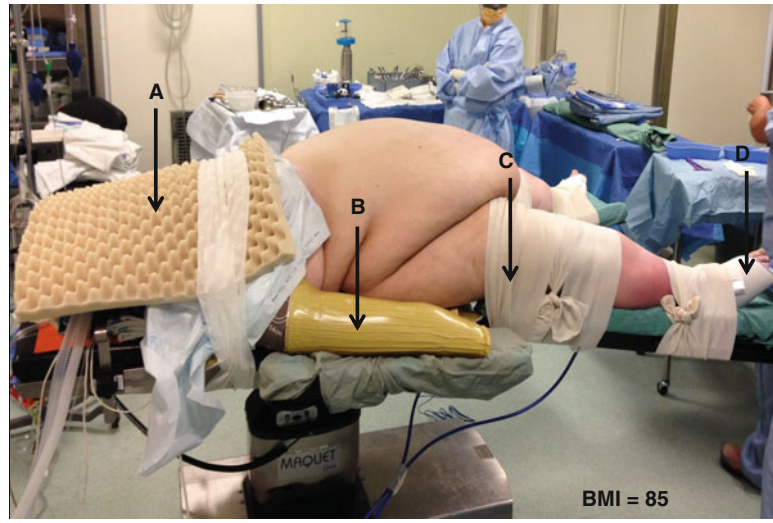

Fig. 20.1 Placement and protection of patients with elevated BMIs. **A.** Protection of the head and chest. **B**. Protection of arms by gel pads. **C**. Protection of legs. **D**. Only intermittent ankle compression stockings could fit the patient

endometrial carcinoma patients is feasible and associated with significant benefits compared to open surgery, including lower minor complication rate, less operative blood loss, and shorter hospitalization, without compromising 2-year disease-free survival. The traditional reluctance to perform radical robotic surgery in medically ill women is not supported by adequate evidence. Siesta et al. [56] examined robotic staging in 66 ASA ≥3 endometrial and cervical carcinoma patients. They concluded that comprehensive robotic staging is feasible and safe in these patients.

Cost Comparison

A major concern voiced against robotic surgery relates to the high costs associated with the operation. The present high cost of robotic surgery is driven by a number of factors, including capital costs for the robotic system, maintenance, the cost of disposable instrumentation, and the generally longer operative times that complex procedures often require, which translates into increased operating room expense.

However, when compared to laparotomy, patients treated for endometrial cancer using robotics are discharged earlier from the hospital, return to normal activity sooner (24 days compared to 52 days), and require less treatment/hospitalization for postoperative complications. These decreased postoperative expenses may quickly offset the financial investment for robotics [57]. Several publications have attempted to quantify the comparative cost per case between laparotomy, laparoscopy, and robotics for endometrial cancer, incorporating both in-hospital and out-of-hospital costs (Table 20.4). Based on these data, the overall cost of robotic surgery for endometrial cancer treatment is significantly less than for laparotomy, but appears more costly than traditional laparoscopy.

Wright et al. performed a national econometric analysis on cost of robotically assisted hysterectomy from 2006 to 2012. A total of 180,230 women, including 169,324 women who underwent minimally invasive hysterectomy for benign indications and 10,906 patients whose hysterectomy was performed for endometrial cancer, were identified. The unadjusted median cost of robotically assisted hysterectomy for endometrial cancer was $9,691 compared with $8,237 for laparoscopic hysterectomy. The cost differential decreased with increasing hospital volume from $2,471 for the first 5–15 cases to $924 for more than 50 cases. Based on surgeon volume, robotically assisted hysterectomy for endometrial cancer was $1,761 more expensive than laparoscopy for those who had performed fewer than five cases; the differential declined to $688 for more than 50 procedures compared with laparoscopic hysterectomy [44].

Table 20.4 Studies analyzing the cost of robotic surgery in endometrial cancer

Year	Author	Average cost per case			Comment
		Laparotomy	Laparoscopy	Robotic	
2008	Bell et al. [57]	$12,943	$7,570	$8,212	–
2010	Barnett et al. [78]	$12,847	$10,128	$11,476	Global cost
2011	Shah et al. [79]	$59,997	$41,339	$54,062	–
2012	Lau et al. [74]	$10,368	–	$7,644	Incorporates the cost of the robotic system and maintenance divided over 10 years
2012	Coronado et al. [72]	€4,681	€4,594	€5,048	Global cost
2012	Wright et al. [80]	–	$8,996	$10,681	–
2013	Desille-Gbaguidi et al. [60]	–	€6,666	€10,816	"Overall care" costs within the 2 months that followed surgery
2014	Leitao et al. [45]	$24,433	$20,289	$20,467	Costs included all aspects of surgical care up to 6 months after discharge
2014	Wright et al. [44]	–	$8,237	$9,691	Median cost for 10,906 endometrial cancer patients

This suggests that costs are reduced with both increased surgeon experience and hospital experience, although the reduction in cost is affected to a greater degree by surgeon rather than hospital volume. Although the cost reduction is multifactorial, the cost savings are likely from a combination of shorter operative times and reduced length of stay. It is notable in that no matter how the two procedures were modeled, in similar circumstances laparoscopic hysterectomy always remained less costly than robotically assisted hysterectomy. Even for very high-volume surgeons and centers, robotically assisted hysterectomy remained more costly. Based on these data, it appears unlikely that robotic-assisted hysterectomy can achieve cost parity with laparoscopic hysterectomy based on surgical experience alone and that reductions in the cost of robotic instrumentation will be required for the procedure to become cost-effective [58–60]. A recent study has assessed the direct costs of three surgical approaches in uterine cancer and the cost-effectiveness of incorporating robotic-assisted surgery and found that laparoscopy is least expensive when including capital acquisition costs. However, laparoscopy and robotic surgery are comparable if upfront costs are excluded [45].

A government-sponsored report created by the Canadian Agency for Drugs and Technologies in Health indicated that the impact of robotic gynecologic surgery on a hospital budget depends on surgical volume. Assuming a robotic system purchased by the hospital can be used for 7 years, robotic surgery for gynecologic surgery becomes cost-effective in Canada after 250 cases, and this decreases to 75 cases if the robot is donated to the hospital as has been the case at most facilities in Canada [61].

The Procedure

1. Bowel preparation is advocated by some to improve visibility in the pelvis and displacement of the bowel for aortic lymphadenectomy.
2. Preventing sliding of the patient on the operating table, the following can be used:
   a. Washable gel pads placed under the sacrum and shoulders and a tension tape positioned over towels on the patients' clavicles and shoulders
   b. Shoulder braces
   c. "Eggcrate" foam or vacuum "beanbag" mattresses
3. The patient's arms should be tucked by her side to allow mobility and ergonomic comfort for the operating surgeon and assistant.
4. Dorsal lithotomy position with adjustable (Allen) stirrups allows for manipulation and extraction of the uterus as indicated.

5. For obese patients or patients with cardiopulmonary disease:
   a. Test ventilatory performance while in steep (30–32°) Trendelenburg position prior to prepping and establishing pneumoperitoneum.
   b. Pressure-controlled anesthesia is required for ventilation in steep Trendelenburg, and neuromuscular blockade must be maintained throughout the procedure.
6. Always have open instruments available in order to avoid delay in the rare events where conversion is necessary.
7. Uterine manipulator insertion:
   According to the surgeon's preference, disposable *VCare* uterine manipulator (ConMed, Utica, NY, USA) or Clermont–Ferrand manipulator is favored; others favor the ZUMI manipulator, KOH ring, or Hohl retractor and a separate pneumo-occluder balloon (CooperSurgical, Trumbull, CT, USA).
8. Placement of a 5–12-mm trocar at Palmer's point and insertion of laparoscopic camera thus allow safe, "under-vision" insertion of the remaining ports.
   a. ENDOPATH® (Ethicon Endo-Surgery, Inc., Ohio, USA) trocar may be used for direct vision of all the layers of the abdominal wall.
   b. Once intra-abdominal placement is confirmed, CO_2 is connected, and the abdomen is insufflated with CO_2 until a pressure of 15 mmHg.
   c. Alternatively, insufflations can be achieved through a Veress needle.
9. Trocar placement – **laparoscopy**:
   Placement of a 10-mm port at the level of the umbilicus for camera placement, a 10- to 12-mm port suprapubically, and a 5-mm port in each of the lateral lower quadrants. Some gynecologic oncologists will usually use a total of 4–6 ports to obtain adequate exposure and accomplish advanced pelvic procedures.
10. Trocar placement – **robotic surgery**:
    a. Port sites are anesthetized with bupivacaine 0.5 %.
    b. 12-mm port for the camera is placed in the midline 23–27 cm above the symphysis pubis, depending on the individual patient's height, torso length, uterine size, and need to perform aortic lymphadenectomy.
    c. Two 8-mm robotic ports for the pro-grasp (right side) and the bipolar grasper (left side) are placed in the lower quadrants at the crossing of imaginary lines through the umbilicus and the superior external iliac crest.
    d. A third 8-mm robotic port for the Endo Shears monopolar scissors is placed 8–12 mm lateral of the camera port in the right upper quadrant.
    e. One 12-mm assistants' port is usually placed at Palmer's point.
11. Visual inspection of the abdominal cavity is undertaken, and the patient is placed in a steep Trendelenburg position.
12. Lysis of any adhesions.
13. The small bowel is carefully placed in the upper abdomen by flipping the bowel cephalad, exposing the mesentery of the small bowel and the aortic bifurcation.
14. Cytology is obtained.
15. The robot is "docked" (term used for attachment to the ports), which is accomplished either between the legs of the patient or recently more frequently from the side (side-docking).
16. Access to the retroperitoneum:
    Open the pelvic peritoneum lateral and parallel to the infundibulopelvic and utero-ovarian ligaments. Dissection is then carried out to develop the pararectal and paravesical spaces. Pararectal space:

    The ureter can reliably be found crossing the pelvic brim at the bifurcation of the common iliac artery. The surgeon/assistant places traction on the broad ligament medially close to the ureter developing the pararectal space with the hypogastric (internal iliac) artery laterally, the sacrum posteriorly, and the uterine artery distally.
17. Paravesical space:

    Dissection is carried along the internal iliac artery to the level of the superior vesical

artery. Retraction of the superior vesical artery in a medial direction exposes the paravesical space between the bladder and superior vesical artery medially and external iliac artery and obturator nodal bundle laterally, with the pubis anteriorly.

a. The uterine artery can be clearly identified originating medially from the internal iliac artery.

18. Dissection of the pelvic lymph nodes[1]:
    a. It is usually done at the level of the common iliac artery, external iliac, internal iliac, and obturator fossa.
    b. The obturator fossa lymph nodes are removed from the pelvic sidewalls, superior to the obturator nerve bordered medially by the superior vesical artery.
    c. The dissection should be completed while paying attention to the ureter, iliac vessels, genitofemoral nerve, and obturator nerve.
19. Right para-aortic dissection:
    a. Ask the anesthetist to adjust the ventilator with reduced tidal volumes and increased rate during the infrarenal portion of the aortic lymphadenectomy.
    b. Incise the peritoneum overlying the right common iliac artery and extend the incision along the aorta to the level of the duodenum.
    c. Elevate the peritoneum overlying the ureter and attach to the base of the cecum in an anterior-cephalad direction, thus providing exposure to the right para-aortic lymph node region up to the level of the insertion of the right infundibulopelvic ligament. The ureter is identified at the crossing of the right common iliac artery and running along the newly formed lateral peritoneal edge. It is mobilized laterally exposing the right psoas muscle, inferior vena cava, genitofemoral nerve, and ovarian vessels.
    d. Skeletonize the nodal bundle over the inferior vena cava, from the bifurcation of the common iliac vessels to just below the right renal vein.
    e. Dissect carefully over the right common iliac artery, the aorta, and the inferior vena cava, creating small pedicles so small perforators can be safely coagulated and sealed before transection.
20. Left para-aortic dissection:
    a. It requires the creation of a window between the aorta and the inferior mesenteric artery, mobilizing the descending colon and rectosigmoid mesocolon anteriorly up to visualization of the left psoas muscle and ureter.
    b. While retracting the inferior mesenteric artery anteriorly, one can identify the lymph nodes on the left side of the aorta. These are dissected carefully considering the presence of short lumbar vessels. This dissection is then extended above the inferior mesenteric artery, to remove the left supra-mesenteric, infrarenal nodes.
21. Hysterectomy and bilateral salpingo-oophorectomy:
    a. Make a fenestration in the posterior broad ligament between the ureter and the infundibulopelvic ligament. Coagulate the infundibulopelvic ligament with bipolar cautery and transect with monopolar scissors.
    b. Cauterize and cut the round ligament.
    c. Reflection of the bladder: lift the bladder flap by incising the vesicouterine fold peritoneum, and dissect the plane between the bladder and the anterior cervix and vagina using both blunt dissection and electrocautery, remaining in intimate contact with the vaginal fascia to avoid injury to the bladder.
    d. Incise the posterior peritoneum and uterosacral ligaments on both sides maintaining the ureters laterally and the rectum posteriorly and away from the vaginal cuff.
    e. Skeletonize the uterine vessels on both sides, cauterize, and cut. Subsequently cauterize and cut the cardinal ligaments at the level of the cervical ring.
    f. Once the bladder and rectum are completely reflected inferiorly, incise the

[1] Sentinel lymph node dissection is discussed in detail in Chap. 15.

vagina around the edge of the retractor placed in the vaginal fornices.

g. Remove the uterus, fallopian tubes, ovaries, and lymph nodes (placed in endobags) through the vagina.
h. Place a sponge in a glove or a balloon in the vagina to maintain pneumoperitoneum, and suture the vaginal cuff paying attention to take enough tissue to avoid dehiscence.
i. The 12-mm trocar sites can be closed by approximating the fascia.

Summary

In recent years, gynecologists have performed comprehensive staging and hysterectomy for endometrial carcinoma by laparotomy, laparoscopy, or robotic-assisted minimally invasive surgery. There is a good body of evidence, based on RCTs, which shows that laparoscopic staging is similar to laparotomy with regard to surgical completion, adequacy of staging, and cytoreduction, survival, and recurrence rates. Patients undergoing laparoscopic staging have lower postoperative complication rates and a faster recovery. Yet, despite nearly 30 years of availability, laparoscopic hysterectomies still comprise only a small percentage of all hysterectomies in the USA and the world [45]. The robotic platform overcomes some of the limitations of standard laparoscopic instrumentation and has dramatically increased the uptake of minimally invasive surgery in gynecologic oncology. Based on multiple retrospective reports, robotic surgery for endometrial carcinoma is at the least noninferior to laparotomy and traditional laparoscopy with respect to adequacy of staging, postoperative complications, and overall and recurrence-free survival rates. Robotic surgery has the advantage of lower rate of conversion to laparotomy and lower blood loss.

The evolution in minimally invasive treatments has transformed the surgical treatment of endometrial carcinoma [62]. Some contend that "the horse is already out of the barn" [63], and minimally invasive surgery, especially robotic surgery, for endometrial cancer has become the dominant paradigm in many centers. Many surgeons adopt robotic surgery because it is easier to master, is less dependent on the availability of a trained assistant, and has ergonomic advantages for the surgeon, but, at least for now, remains more expensive than other modalities. Haptics (tactile feedback) and single-port laparoscopic and robotic instruments are being developed and tested [64]. Improved usage of the robotic computer interface will hopefully allow the use of digital analysis and imaging, overlay of radiological pictures and PET scans, immunofluorescence, and direct feedback to the surgeon, similar to achievements in aviation.

The goal of all gynecologic cancer surgeons should be to perform surgery in a way that minimizes disfigurement and psychological trauma and preserves function. The purpose is not to compete between laparoscopy and robotics but to eliminate as much as possible laparotomy without compromising on the oncological safety.

Key Points

1. Minimally invasive surgery is becoming a standard of care in endometrial carcinoma.
2. Compared to laparotomy, laparoscopic operating room time is longer, but the postoperative hospital stay is significantly shorter.
3. The rate of intraoperative complications with laparoscopy reported in meta-analyses could be attributed to insufficient technical skills in early publications.
4. The rate of significant intraoperative complications such as bladder, ureter, bowel, and vascular injuries is almost equal in laparoscopy and laparotomy.
5. Laparoscopic approach does not compromise the adequacy of staging or cytoreduction in endometrial carcinoma patients and improves quality of life with similar oncologic outcomes compared to laparotomy.

6. Robotic-assisted surgery has allowed a revolutionary increase in the use of minimally invasive surgery for the treatment of endometrial cancer, with most patients in the USA at this time undergoing minimally invasive surgery.
7. Despite the obvious benefits of the robotic approach, there have been no prospective RCTs comparing laparotomy, laparoscopy, and robotic-assisted laparoscopic staging procedures for treatment of uterine malignancies. The available studies have been nonrandomized and limited to highly experienced surgeons and centers.
8. Robotic and traditional laparoscopic surgeries have better outcomes compared to laparotomy in terms of blood loss, blood transfusion rates, peri- and postoperative complications, wound infections, postoperative pain, decreased length of hospital stay, and shorter recovery time. Pelvic and para-aortic lymph node counts, representing a (poor) surrogate for quality, are similar for the three modalities.
9. Robotic surgery, similar in many respects of outcome to laparoscopy, allows to expand the indications for minimally invasive surgery to more surgeons and more complex and radical surgeries.

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Basics of Robotic Instrumentation and Robotic-Assisted Surgery for Endometrial Cancer

21

Somashekhar SP

Introduction

Carcinoma endometrium is a common genital cancer in women worldwide. Surgical management is the mainstay of initial treatment for majority of patients and comprehensive surgical staging guides in the postoperative adjuvant therapy. Minimally invasive surgery has gained acceptance for the surgical treatment of endometrial cancer as it is associated with fewer complications, shorter hospitalization, and faster recovery when compared with laparotomy [1–4]. Adoption of laparoscopic surgery for treatment of endometrial cancer has been slow, primarily because of a steep learning curve and limitations in obese women [5]. The benefits of robotic surgery as a minimally invasive surgical technique parallel those of traditional laparoscopy, with the added advantage of overcoming several barriers to the use of laparoscopy.

Basics of Robot

The surgeon performs a surgery using a computer that remotely controls very small instruments attached to the robot. It allows surgeons to perform delicate operations by manipulating the robotic arms, which translate the surgeon's hand movements into smaller and smoother strokes. It has revolutionized the field of surgery by allowing the surgeon to perform less invasive and complex surgical procedures that was once possible only with open surgery. The robotic machine has three parts, namely, the surgeon console (Fig. 21.1), patient cart (Fig. 21.2), and optical cart. The surgeon console contains 3D monitor and joysticks which control the instruments. Patient cart has four arms for the instrument and camera. With changing technology, improved versions of the robot have better surgeon console and patient cart.

Robotic Technology

It enables the surgeon to be more precise, improve their technique, and enhance their capability in performing complex minimally invasive surgery.

1. Binocular stereoscopic 3D vision (Fig. 21.3) with stability of camera and 10× magnification.

   The robotic system also allows the surgeon to better visualize anatomy, which is especially

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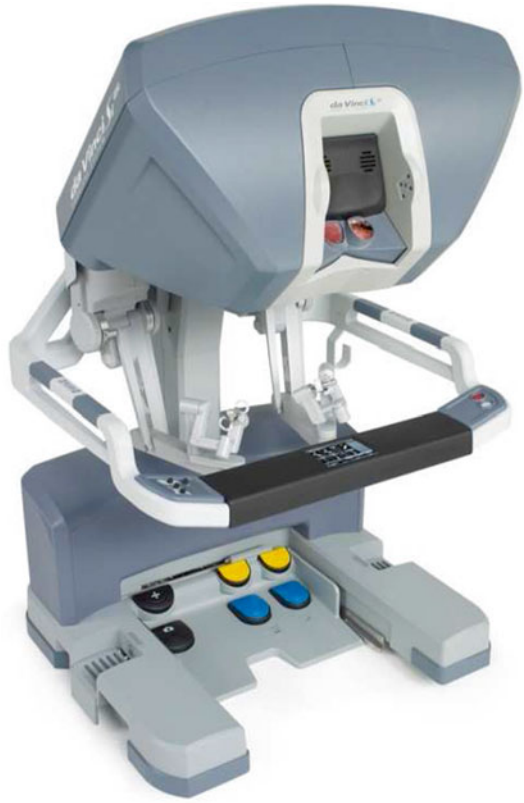

Fig. 21.1 Surgeon console

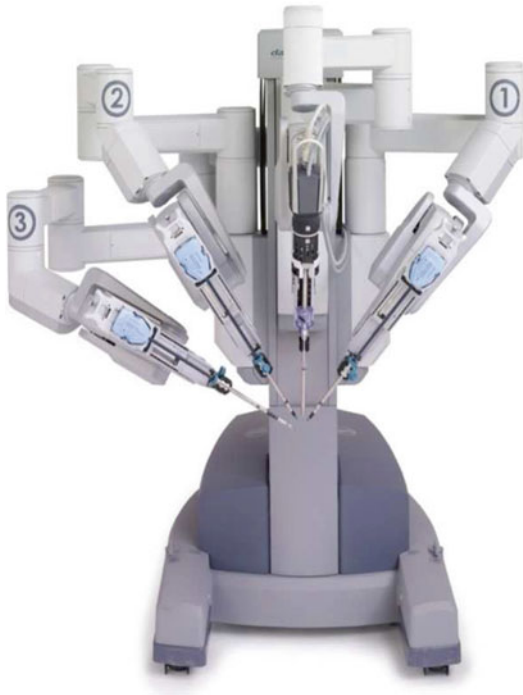

Fig. 21.2 Patient cart

critical when working around delicate and confined structures like in the pelvis, chest, or abdomen. This allows surgeons to perform radical cancer surgeries with superior oncological outcome.

2. EndoWrist instrumentation technology (Fig. 21.4).

   It mimics the human hand in its flexible movement and also overcomes its limitations, like elimination of hand tremors. Despite the widespread use of laparoscopic surgery, adoption of laparoscopic techniques, for the most part, has been limited to a few routine procedures. This is due mostly to the limited capabilities of traditional laparoscopic technology, including standard video and rigid instruments. Surgeons have been slow to adopt to laparoscopy for complex procedures because they generally find fine-tissue manipulation such as dissecting and suturing to be more difficult (Table 21.1). Intuitive technology, however, enables the use of robot for complex procedures (Table 21.2). The robot allows for seven degrees of motion vs. the limited 4° of motion in laparoscopy. Robotic technology eliminates the fulcrum effect of laparoscopy (the robotic arms imitate the movements of the surgeon's hand).
3. Motion scaling and precision surgical movements improve the quality of surgery.
4. Extremely easy and allows fast suturing and knotting.
5. Multitasking instrumentation decreases operative time.
6. Surgeon sits and operates at ease which decreases fatigue, translating to safe surgery.

Surgical Technique

Preoperative Preparation

Patient takes clear liquids a day prior to surgery. On the night before the surgery, proctoclysis enema and two Dulcolax (bisacodyl) tablets are given per oral. We do not administer polyethylene glycol with electrolytes (Peglec) for bowel preparation as it causes dilatation of bowel.

Fig. 21.3 Binocular stereoscopic vision and camera

Fig. 21.4 EndoWrist instrumentation

Table 21.1 Disadvantages of laparoscopy

Steep learning curve
Limited dexterity
Counterintuitive motion
Two-dimensional field
Limited depth perception
Ergonomic difficulty

Table 21.2 Advantages of robotic technology

Binocular stereoscopic 3D vision
Stable high-definition camera with 10× magnification
EndoWrist instrumentation – increased dexterity
Extremely easy and fast suturing and knotting intracorporeally
Surgeons sit and operate at ease with arms rested
Multitasking instrumentations
Option of harmonic scalpel
Three arms in addition to the camera arm
Filters human tremor
Ergonomics with equal access with both left- and right-sided ports

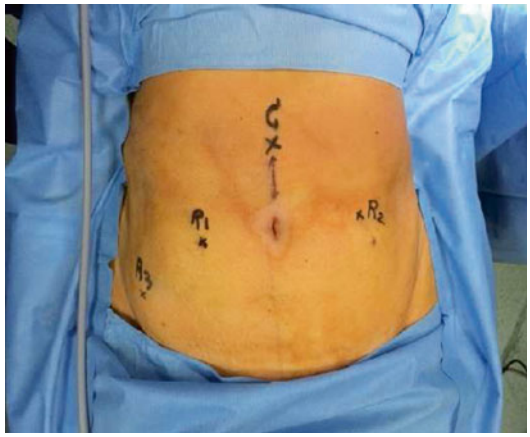

Fig. 21.5 Abdominal marking of port placement

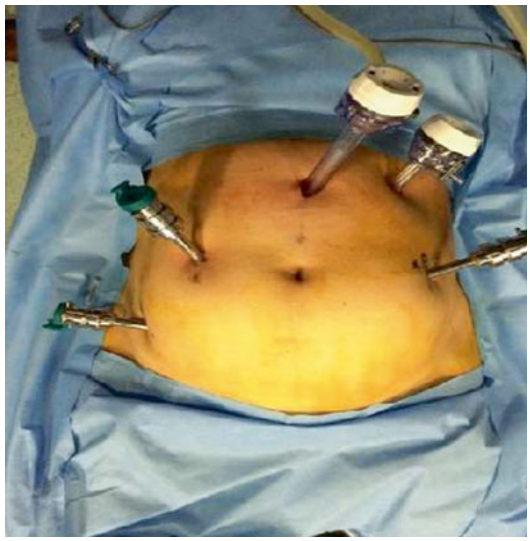

Fig. 21.6 Port placement

Port Placement and Instrumentation

Port placement and instrumentation are shown in Figs. 21.5, 21.6, and 21.7, respectively. VCARE (Vaginal–Cervical Ahluwalia Retractor–Elevator) uterine manipulator is fixed to the cervix after placing the patient in lithotomy position. Intraoperatively, it helps in manipulating the uterus. A 12 mm camera port is placed 3 cm above the umbilicus in the midline with optical trocar. The rest of the ports are placed after insufflating the abdomen with gas and marking the port measurements. Arm one (8 mm) port is placed on the patient's right side, 3–5 cm below and at least 8 cm lateral to the camera port. Arm two (8 mm) port is placed on the patient's left side, 8 cm lateral and 3–5 cm below the level of the camera port. The third arm (8 mm) port is placed on the patient's right side, 2 cm above anterior superior iliac spine and 8 cm away from the first port. The assistant port (12 mm) is placed on the patient's left side, slightly cephalad to the camera port on an arc at the midpoint between the camera port and the instrument arm two port.

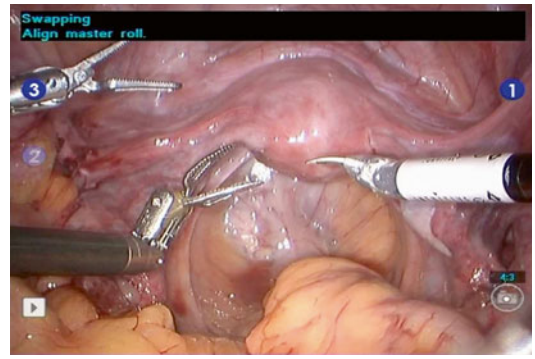

Fig. 21.7 Robotic instruments showing dexterity

Zero degree scope is used for all the steps, except for para-aortic lymph node dissection where 30° down scope is used. In arm one, hot shears (monopolar curved scissors) are used; in arm two, fenestrated bipolar forceps; and in arm three, prograsp forceps.

Patient positioning is shown in Fig. 21.8, and docking of the patient cart is shown in Figs. 21.9 and 21.10.

After placing all the ports, the patient is positioned before docking the robot. Head end is lowered completely, and all the bowel loops are taken toward the upper abdomen. Pelvic wash is given, and fluid is taken for cytological examination.

Surgical Steps

Dissection is done in a circular fashion from one round ligament to the other.

Step 1: The uterus is retracted to the patient's left side with the help of the uterine

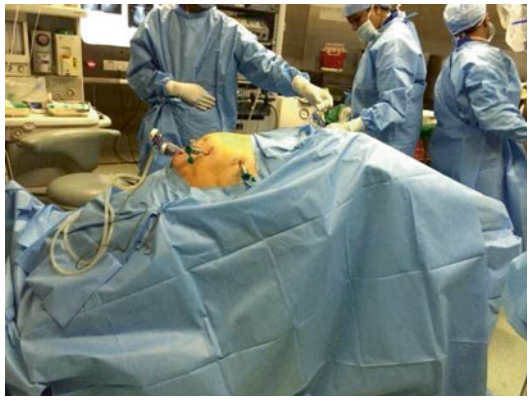

Fig. 21.8 Patient positioning: head end lowered to 45°

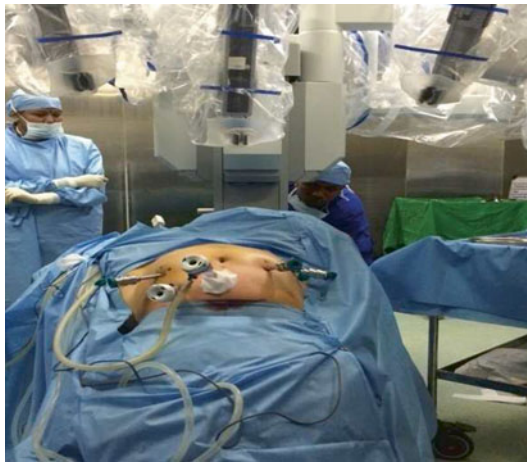

Fig. 21.9 Robot (patient cart) is docked

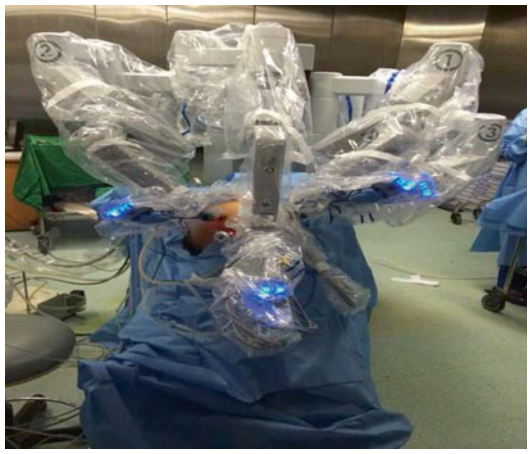

Fig. 21.10 Widely spaced arms after docking between legs

manipulator. Dissection starts with incising the peritoneum over infundibulopelvic triangle, isolating the ureter and ovarian pedicle. Then, the round ligament is transected near the inguinal ring with hot shear (monopolar diathermy). Incision is extended anteriorly into the anterior leaf of the broad ligament up to the lateral uterovesical junction. Coagulate and transect the right uterine pedicle and cardinal ligament. Careful attention to the course of the ureter at all times must be kept in mind.

Step 2: The urinary bladder is lifted up with the third arm, and the uterus is retroverted with the help of the uterine manipulator and second arm. The vesicouterine groove is identified, and the bladder is dissected away from the uterus, and adhesions if any are dissected with the cold knife (hot shear).

Step 3: Left side isolation of the ureter and dissection of the round ligament are done similar to Step 1. Both side ovarian pedicles are coagulated with bipolar diathermy but not divided until complete dissection is done.

Step 4: Posterior part dissection is done by separating the rectum from the uterus with the division of uterosacral ligaments on either side. The course of the ureter must be noted during this step.

Step 5: Anterior and posterior colpotomies are done by incising over the colpotomy ring. Finally, both the ovarian pedicles are divided. Specimen is delivered through the vagina by pulling out the uterine manipulator, and abdominal pneumatic pressure is maintained by packing the vagina with an adequate-sized mop inside a surgical hand glove.

Step 6: Bilateral pelvic lymphadenectomy (Figs. 21.11, 21.12, and 21.13) is done by exposing pararectal and paravesical spaces. A separate specimen bag is used for lymph nodes of either side, and specimen is delivered through the vagina. Para-aortic lymph node dissection is done when indicated. Vaginal cuff is closed with a 15 cm long self-retaining polydioxanone (monofilament, violet) barbed suture, and uterosacral ligaments are included laterally.

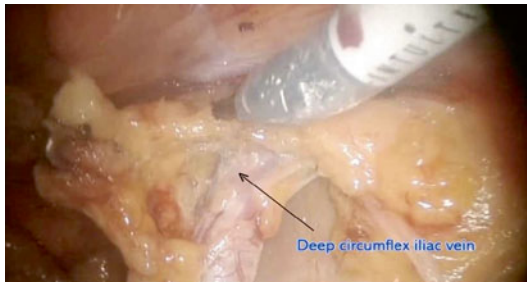

Fig. 21.11 Pelvic lymphadenectomy: distal boundary

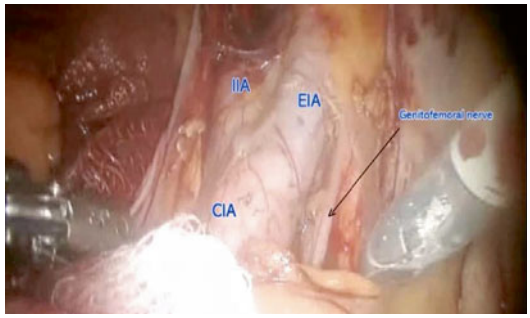

Fig. 21.12 Pelvic lymphadenectomy: lateral and proximal boundary

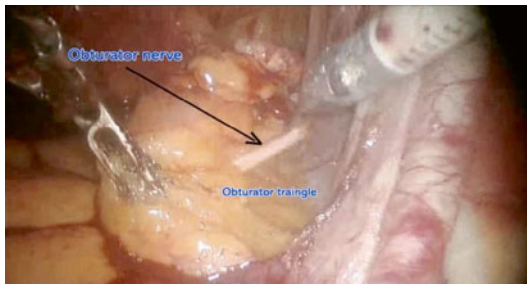

Fig. 21.13 Pelvic lymphadenectomy: inferior boundary

The role of systematic pelvic lymphadenectomy is an issue of current debate. Excision of suspicious or enlarged nodes is important to exclude metastasis. A more selective and tailored lymphadenectomy approach is now recommended to avoid systematic overtreatment [6]. No randomized trial data supports full lymphadenectomy [7] although some retrospective studies have suggested that it is beneficial [8]. A subset of patients may not benefit from lymphadenectomy, but it is difficult to preoperatively identify these patients because of the uncontrollable variable of change in grade and depth of invasion in final histopathology.

As the grade of the tumor increases, accuracy of intraoperative evaluation of myometrial invasion by gross examination decreases. Therefore, frozen section examination for evaluation of the histology, size of primary, grade, and depth of invasion is important. Pending further trials, pelvic lymphadenectomy is done in all patients. Para-aortic lymphadenectomy is indicated in high-risk patients. High-risk patients are with tumor size >2 cm, deep myometrial invasion, positive pelvic nodes, Grade 3 tumor, and high-risk (clear cell, papillary serous, squamous, or undifferentiated) histology.

Anatomical spaces in pelvic dissection:

1. Paravesical space
2. Pararectal space

Pelvic lymphadenectomy: anatomical boundaries

Distally – deep circumflex iliac vein
Proximally – common iliac vessels
Laterally – genitofemoral nerve
Inferiorly – obturator fossa

Para-aortic lymphadenectomy

Boundaries

Superiorly – renal vein
Inferiorly – common iliac vessels
Laterally – ureter

Efficacy of Laparoscopy

The Gynecologic Oncology Group (GOG) has completed a phase III randomized study (lamina-associated polypeptide (LAP) 2) comparing laparoscopy vs. laparotomy in endometrial cancer [9]. Patients with clinical stage I to IIA uterine cancer were randomly assigned to laparoscopy ($n=1,696$) or open laparotomy ($n=920$), including hysterectomy, salpingo-oophorectomy, pelvic cytology, and pelvic and para-aortic lymphadenectomy. Laparoscopy was initiated in 1,682 patients and completed without conversion in 1,248 patients (74.2 %). Conversion from laparoscopy to laparotomy was secondary to poor visibility in 14.6 %, metastatic cancer in 4.1 %, bleeding in 2.9 %, and other causes in 4.2 %. Laparoscopy had fewer moderate to severe postoperative adverse events than laparotomy (14 % vs. 21 %, respectively; P=.0001) but similar

rates of intraoperative complications, despite having a significantly longer operative time (median, 204 vs. 130 min, respectively; P = .001). Hospitalization of more than 2 days was significantly lower in laparoscopy vs. laparotomy patients (52 % vs. 94 %, respectively; P = .0001). They concluded that laparoscopic surgical staging for uterine cancer is feasible and safe in terms of short-term outcomes and results in fewer complications and shorter hospital stay. Time to recurrence was the primary end point, with non-inferiority defined as a difference in recurrence rate of less than 5.3 % between the two groups at 3 years. The recurrence rate at 3 years was 10.24 % for patients in the laparotomy arm, compared with 11.39 % for patients in the laparoscopy arm, with an estimated difference between groups of 1.14 % (90 % lower bound, −1.278; 95 % upper bound, 3.996) [10]. Although this difference was lower than the prespecified limit, the statistical requirements for non-inferiority were not met because of a lower-than-expected number of recurrences in both groups. The estimated 5-year overall survival was almost identical in both arms at 89.8 %. These results, combined with previous findings from this study of improved QOL and decreased complications associated with laparoscopy, are reassuring to patients and allow surgeons to reasonably suggest this method as a means to surgically treat and stage patients with presumed early-stage endometrial cancers.

Another prospective randomized trial is ongoing at Australian and UK institutions. The Laparoscopic Approach to Cancer of the Endometrium (LACE) trial is anticipated to randomize 590 patients to total laparoscopic hysterectomy and lymph nodal staging vs. standard, open surgery [11].

Evidence for Robotic-Assisted Surgery

Obesity

Endometrial cancer is particularly suited for robotic surgery for several reasons. The majority of women with endometrial cancers are obese and at greater risk for postoperative wound complications and would benefit from a minimally invasive procedure with smaller incisions, resulting in less risk for wound breakdown. However, at the same time, obesity increases the degree of difficulty via laparoscopy to the extent that accomplishing the operation may be jeopardized. In a retrospective comparison of obese women and morbidly obese women undergoing traditional laparoscopic approach vs. robotic-assisted approach, better surgical outcomes were observed in the group undergoing robotic-assisted laparoscopy [12]. The group who underwent the procedure robotically had significantly shorter operating time, less blood loss, improved lymph node count, and shorter hospital stay suggesting that robotic-assisted laparoscopy greatly facilitates laparoscopic surgery in obese patients. In obese patients with greater abdominal surface area, adequate spacing between the ports and in turn clashing of the arms are seldom a problem.

Bernardini et al. [13] studied women with clinical stage I or II endometrial cancer and a BMI greater than 35 kg/m^2 treated with robotic surgery at their institution between November 2008 and November 2010 and compared the results with a historical cohort of similar patients who underwent laparotomy. A total of 86 women were analyzed in this study (robotic surgery, 45; laparotomy, 41). The overall intraoperative complication rate was 5.8 %. There was no statistical difference in age, number of comorbidities, BMI, prior abdominal surgery, and operative complications between the women who underwent robotic surgery and laparotomy. Postoperative complication rates were higher in the laparotomy group (44 % vs. 17.7 %; P = 0.007), and hospital length of stay was also higher in the laparotomy group (4 vs. 2 days; P G 0.001). There was no difference in rates of (pelvic) lymph node dissection; however, para-aortic node dissection was more common in the robotic surgery group.

Learning Curve

An analysis of robotic-assisted hysterectomy with lymphadenectomy vs. total laparoscopic hysterectomy with lymphadenectomy and

laparotomy with total abdominal hysterectomy with lymphadenectomy was done by Lim PC et al. [14] Data was categorized by chronologic order of cases into groups of 20 patients each. The learning curve of the surgical procedure was estimated by measuring operative time with respect to the chronologic order of each patient who had undergone the respective procedure. Analysis of operative time for robotic-assisted hysterectomy with bilateral lymph node dissection with respect to the chronologic order of each group of 20 cases demonstrated a decrease in operative time: 183.2 (69) minutes (95 % CI, 153.0–213.4) for cases 1–20, 152.7 (39.8) minutes (95 % CI, 135.3–170.1) for cases 21–40, and 148.8 (36.7) minutes (95 % CI, 130.8–166.8) for cases 41–56. For the groups with laparoscopic hysterectomy with lymphadenectomy and traditional total abdominal hysterectomy with lymphadenectomy, there was no difference in operative time with respect to the chronologic group order of cases. It was concluded that the learning curve for robotic-assisted hysterectomy with lymph node dissection seems to be easier compared with that for laparoscopic hysterectomy with lymph node dissection for surgical management of endometrial cancer.

Survival Analysis

Retrospective study was conducted at two academic centers to compare the survival of women with endometrial cancer managed by robotic- and laparoscopic-assisted surgery [15].A total of 183 women had robotic- and 232 women had laparoscopic-assisted surgery. With a median follow-up of 38 months (range, 4–61 months) for the robotic and 58 months (range, 4–118 months) for the traditional laparoscopic group, there were no significant differences in survival (3-year survival 93.3 % and 93.6 %), DFS (3-year DFS 83.3 % and 88.4 %), and tumor recurrence (14.8 % and 12.1 %) for robotic and laparoscopic groups, respectively. Univariate and multivariate analysis showed that surgery is not an independent prognostic factor of survival. Robotic-assisted surgery yields equivalent oncologic outcomes when compared to traditional laparoscopic surgery for endometrial adenocarcinoma.

A retrospective chart review was performed for all consecutive endometrial adenocarcinoma patients surgically staged with robotic-assisted laparoscopy at the University of North Carolina Hospital from 2005 to 2010 [16]. Demographic data, 5-year survival, and recurrence-free intervals were analyzed. Assisted surgical staging was 85.2 % for stage IA, 80.2 % for stage IB, 69.8 % for stage II, and 69 % for stage III. Projected 5-year survival was 88.7 % for all patients included in the study. Nearly 82 % of cases were endometrioid adenocarcinoma, with papillary serous, clear cell, or mixed histology comprising 17.4 % of cases. Median follow-up time was 23 months, with a range of 0–80 months. Among stage IA, IB, II, and III patients, projected overall survival was 94.2 %, 85.9 %, 77.4 %, and 68.6 %, respectively. The results from this study demonstrate that robotic-assisted surgical staging for endometrial cancer does not adversely affect rates of recurrence or survival. These findings provide further evidence that robotic-assisted laparoscopic surgical staging is not associated with inferior results when compared to laparotomy or traditional laparoscopy.

Efficacy of Robotic Surgery

In our prospective randomized study [17] of 50 consecutive patients with carcinoma endometrium, estimated blood loss (81.28 ml), hospital stay (1.94 days), and perioperative complications were significantly less in robotic-assisted group in comparison to open method ($n=50$ patients, 25 in each arm). The mean number of lymph nodes removed was 30.6 versus 27.6 in open arm vs. robotic arm, which was statistically significant (P value, 0.071). Operative time decreased as the experience of the surgeon increased but remained higher than the open procedure after 25 robotic-assisted surgeries (mean operating time in robotic vs. open arm was 142.5 min and 117 min, respectively; P value <0.001). Mean hospital stay for open vs. robotic was 5.54 vs. 1.94 days with P value <0.001, and mean

estimated blood loss for open vs. robotic was 234 ml vs. 81.28 ml (P value < 0.001 significant). All robotic surgeries were completed successfully without converting to open method. Robotic-assisted staging procedure for endometrial carcinoma is feasible without converting to open method, with the advantages of decreased blood loss, short duration of hospital stay, and less postoperative complications.

A cohort study [18] was performed by prospectively identifying all patients with clinical stage I or occult stage II endometrial cancer who underwent robotic hysterectomy and lymphadenectomy from 2006 to 2008 and retrospectively comparing data using the same surgeons' laparoscopic hysterectomy and lymphadenectomy cases from 1998 to 2005, prior to their robotic experience. Patient demographics, operative times, complications, conversion rates, pathologic results, and length of stay were analyzed. One hundred and eighty-one patients (105 robotic and 76 laparoscopic) met inclusion criteria. There was no significant difference between the two groups in median age, uterine weight, bilateral pelvic or aortic lymph node counts, or complication rates in patients whose surgeries were completed minimally invasively. Despite a higher BMI (34 vs. 29, P < 0.001), the estimated blood loss (100 vs. 250 mL, P < 0.001), transfusion rate (3 % vs. 18 %, RR 0.18, 95%CI 0.05–0.64, P = 0.002), laparotomy conversion rate (12 % vs. 26 %, RR 0.47, 95%CI 0.25–0.89, P = 0.017), and length of stay (median, 1 vs. 2 nights; P < 0.001) were lower in the robotic patients compared to the laparoscopic cohort. The odds ratio of conversion to laparotomy based on BMI for robotics compared to laparoscopy is 0.20 (95 % CI 0.08–0.56, P = 0.002). The mean skin to skin time (242 vs. 287 min, P < 0.001) and total operating room time (305 vs. 336 min, P < 0.001) were shorter for the robotic cohort. The study concluded that robotic hysterectomy and lymphadenectomy for endometrial carcinoma can be accomplished in heavier patients, in shorter operating times, and in lesser hospital stay. In addition, transfusion rates were lower with fewer conversions to laparotomy when compared to laparoscopic hysterectomy and lymphadenectomy.

Magrina JF et al. [19] did a prospective analysis of 67 patients undergoing robotic surgery for endometrial cancer between March 2004 and December 2007. Comparison was made with similar patients operated between November 1999 and December 2006 by laparoscopy (37 cases), laparotomy (99 cases), and vaginal/laparoscopy approach (vaginal hysterectomy, bilateral adnexectomy/laparoscopic lymphadenectomy) (47 cases) and matched by age, body mass index (BMI), histological type, and International Federation of Gynecology and Obstetrics (FIGO) staging. Mean operating times for patients undergoing robotic, laparoscopy, vaginal/laparoscopy, or laparotomy approach were 181.9, 189.5, 202.7, and 162.7 min, respectively (P = 0.006); mean blood loss was 141.4, 300.8, 300.0, and 472.6 ml, respectively (P < 0.001); mean number of nodes was 24.7, 27.1, 28.6, and 30.9, respectively (P = 0.008); mean length of hospital stay was 1.9, 3.4, 3.5, and 5.6 days, respectively (P < 0.001). There were no significant differences in intra- or postoperative complications among the four groups. The conversion rate was 2.9 % for robotics and 10.8 % for the laparoscopy group (0.001). There were no differences relative to recurrence rates among the four groups: 9 %, 14 %, 11 %, and 15 % for robotics, laparoscopy, vaginal/laparoscopy, and laparotomy, respectively. It was concluded that robotics, laparoscopy, and vaginal/laparoscopy techniques are preferable to laparotomy for suitable patients with endometrial cancer. Robotics is preferable to laparoscopy due to a shorter hospital stay and lower conversion rate and preferable to vaginal/laparoscopy due to a reduced hospitalization.

Ran L et al. recently reported a meta-analysis which included 22 studies [20]. These studies involved a total of 4,420 patients, 3,403 of whom underwent both robotic surgery and laparoscopy and 1,017 of whom underwent both robotic surgery and laparotomy. The estimated blood loss (P = 0.01) and number of conversions (P = 0.0008) were significantly lower, and the number of complications (P < 0.0001) was significantly higher in robotic surgery than in laparoscopy. The operating time (OT), length of hospital stay (LOHS), number of transfusions, and total

lymph nodes harvested (TLNH) showed no significant differences between robotic surgery and laparoscopy. The number of complications ($P<0.00001$), LOHS ($P<0.00001$), EBL ($P<0.00001$), and number of transfusions ($P=0.03$) were significantly lower, and the OT time ($P<0.00001$) was significantly longer in robotic surgery than in laparotomy. The TLNH showed no significant difference between robotic surgery and laparotomy. The study concluded that robotic surgery is generally safer and more reliable than laparoscopy and laparotomy for patients with endometrial cancer. Robotic surgery is associated with significantly lower EBL than both laparoscopy and laparotomy, fewer conversions but more complications than laparoscopy, and shorter LOHS, fewer complications, and fewer transfusions but a longer OT time than laparoscopy.

Limitations of Robotic Surgery

Apart from the absence of level 1 evidence regarding robotic-assisted surgery for endometrial cancer, there are other limitations of robotic-assisted surgery to consider. These limitations can be categorized as physical limitations of the da Vinci system and cost considerations.

The limitations of robotic technology include: [21]

1. Additional surgical training
2. Increased costs and operating room time
3. Bulky devices
4. Instrumentation limitations (e.g., lack of a robotic suction and irrigation device, size, cost)
5. Lack of haptics (tactile feedback)
6. Risk of mechanical failure
7. Limited number of energy sources (i.e., less than with conventional laparoscopy)
8. Not designed for abdominal surgery involving more than two quadrants (the device needs to be re-docked and repositioned to operate in the quadrants it is not facing)

The development of the da Vinci Xi, with a longer reach and improved range, has in general enabled para-aortic lymph node dissection without much difficulty.

Robotic surgical systems are designed with features intended to minimize the potential effects of mechanical failures on patients [21]. Such features include system redundancy, the so-called "graceful" performance degradation or failure, fault tolerance, just-in-time maintenance, and system alerting. In simplified terms, there are several mechanical checks and balances built into current robotic surgical systems so that the risk of mechanical failure is minimized.

Also as a result of the robotic arms being limited in its ability to reach away or in the cephalad direction, the placements of the laparoscopic ports are typically higher in a patient than compared to traditional laparoscopy in order to have access to both the pelvis and the upper abdomen. These incisions, some of which are placed above the umbilicus, may be a cosmetic concern for some patients.

The absence of haptics or tactile feedback is also an important consideration in robotic-assisted surgery. Currently, there is no ability for the surgeon at the surgeon console to receive tactile feedback regarding the "firmness of tissue" or the degree of tension one is exerting on tissue as would be the case in an open laparotomy or traditional laparoscopy procedure in which the surgeon is actually touching the tissue or holding instruments that are in direct contact with the patient; however, most surgeons would agree that as one gains more experience with the robot, the surgeon is able to use visual cues which enable a "virtual" tactile feel.

Another limitation of the robot already discussed has been in the bulkiness of the arms of the robot holding the robotic instruments. These have a greater propensity to clash if not positioned with adequate spacing in between, a situation that sometimes cannot be avoided in small, petite patients, but is seldom a problem for most endometrial cancer patients. Truncal obesity resulting in a greater abdominal surface area ironically results in an advantage, overcoming this limitation for many patients with endometrial cancers. The recent-generation da Vinci Xi system which has a longer reach and thinner arms has improved many of the limitations discussed above.

Summary and Conclusion

Robotic-assisted surgery for endometrial cancer has brought in a new revolution in the technique of surgery. Laparoscopic method is established as a standard method with the landmark GOG LAP2 trial. Robotic surgery has overcome the deficiencies of laparoscopic method with comparable results. However, randomized trials are awaited. The only Indian study, randomized trial comparing robotic with open surgery for endometrial cancer [17], shows that robotic endometrial surgery and pelvic and high para-aortic lymphadenectomy are highly feasible and oncologically not inferior to gold standard open surgery and robotic surgery is superior, in terms of postoperative hospital stay, and has significantly less blood loss and better cosmetic outcome and shares all advantages and benefits of minimally invasive surgery. Larger multi-institutional multicentric similar studies are required.

Objectives in improving cancer treatment can be categorized as those that improve efficacy and those that lessen morbidity. Minimally invasive surgery seeks to decrease morbidity from surgery while maintaining at the very least equivalent efficacy. Robotic-assisted laparoscopic surgery has been able to further advance laparoscopy by greatly facilitating the learning curve, enabling surgeons to gain sufficient proficiency in cases that otherwise would have been problematic for mainstream surgeons.

Key Points

1. Binocular stereoscopic 3D vision with 10× magnification, EndoWrist instrumentation, and ergonomics have brought about a huge advantage in surgical technique.
2. Robotic technology has overcome major limitations of rigid laparoscopic instrumentation.
3. Head end is tilted down to 45°, and modified central docking is used.
4. The right hand handles two instruments namely monopolar diathermy and prograsper while the left hand uses one instrument, the fenestrated grasper with bipolar diathermy.
5. Identification and separation of the ureter in infundibulopelvic triangle is important before securing ovarian pedicle.
6. The urinary bladder is separated from the uterus and cervix, beyond uterine manipulator cup.
7. Para-aortic lymph node dissection can be done in the same docking position with 30° down camera and by placing the camera port higher than is done routinely, i.e., above the umbilicus.
8. Land mark GOG LAP2 trial has proved the efficacy of laparoscopy as the minimally invasive surgery in the management of carcinoma endometrium.
9. Many studies have proven the efficacy of robotic surgery; however, level 1efficacy data is awaited.

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22 Adjuvant Radiation in Early-Stage Endometrial Cancer: Evidence, Principles, and Techniques

Umesh Mahantshetty, Shirley Christabel, Reena Engineer, Supriya Chopra, and Shyamkishore Shrivastava

Introduction

Endometrial cancer is a common gynecological cancer and is mainly seen in postmenopausal women. Early-stage endometrial cancer includes stage I and stage II where the disease is confined to the uterus and cervix and comprises 75 % of patients [1]. Sixty-eight (68 %) percent of women have localized disease at the time of diagnosis [2]. In India, incidence of endometrial cancer is low. There are 0.88 million cancer cases with an incidence rate (ASR) of 105.5 per 100,000 in women with the highest rates seen in Bangalore (ASR = 4.2) and in Delhi (ASR = 4.3), while in Mumbai it was 2.8 per 100,000 [3]. Sixty-seven to seventy-three percent of patients have stage I–II disease [4, 5]. The primary treatment of endometrial cancer is total hysterectomy with bilateral salpingo-oophorectomy. The role of pelvic and/or para-aortic lymphadenectomy to determine the need of adjuvant treatment is a matter of debate. Two major trials have not found evidence supporting the use of routine lymphadenectomy in early-stage endometrial cancers in terms of overall survival or recurrence-free survival [6, 7]. The purpose of this chapter is to discuss various factors associated with endometrial cancers which are vital for treatment decisions and clinical outcome and provide guide for appropriate adjuvant radiation in early endometrial cancers.

There are two types of endometrial cancer based on clinical history, molecular profile, and histology, which differ widely in their prognosis and are an important factor for treatment decisions and outcomes. Type I includes endometrioid adenocarcinoma which is diagnosed early and has a good prognosis. Type II consists of clear cell, papillary serous adenocarcinoma and carcinosarcomas which fare poorly and have a high distant metastasis rate.

Early-stage endometrial cancer has good outcome with reported 5-year overall survival rates of 80–90 %, cancer-specific survival rates of 90–95 %, and locoregional relapse rates of 4–8 % only [8]. Since the majority of recurrences are locoregional, treatment should be directed appropriately to reduce risk. Adjuvant radiation therapy plays an important role in improving locoregional control rates.

The diagnosis of endometrial cancer depends on clinical presentation, history, and physical examination including a thorough gynecological examination, endometrial biopsy, and imaging studies like chest X-ray and MRI. Surgery is the mainstay of diagnosis and staging. A detailed

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histopathology report to identify various prognostic factors and risk stratification is vital to decide on further adjuvant therapy. Hence, it is important to know and understand the prognostic factors and definition of risk stratifications.

Prognostic Factors

There are various factors which determine the risk of recurrence that adversely affect local control and survival. They influence decision for adjuvant treatment.

Histology and Cell Type

The most common type is endometrioid adenocarcinoma. Clear cell and uterine serous papillary types have a poorer prognosis compared to adenocarcinoma.

Depth of Myometrial Invasion (Ratio of Invasion to Total Myometrial Thickness)

The incidence of lymph node involvement increases with depth of infiltration. According to Creasman et al., incidence of lymph node involvement with deep infiltration is 43 % [9].

Lympho-Vascular Space Invasion (LVSI)

It is an adverse risk factor, and as per GOG 33, the presence of LVSI has 27 % incidence of pelvic lymph node involvement [9].

Grade

Grade of tumor is given by the percentage of non-squamous non-morular growth pattern. Higher grade with outer one third of myometrial invasion signifies high risk with higher rates of lymph node involvement.

Age

Older patients have poorer prognosis. They are more likely to have higher grade and deep infiltrating tumors.

Lymph Node Status

The approximate incidence of pelvic lymph node involvement is for FIGO stage IA, 5 %; IB, 10 %; IC, 15 %; II, 20 %; and III, 55 % [1].

Cervical Involvement (Glandular or Stromal) and DNA Ploidy

Cervical involvement by endometrial adenocarcinomas has an adverse effect on prognosis, Patients with lower uterine segment involvement are more likely to have pelvic and paraarotic nodal disease, and increasing local recurrence. Spread to lymph nodes is associated with poor prognosis and require adjuvant treatment. DNA ploidy is an independent significant prognostic and predictive factor (see Chap. 12).

The staging of endometrial cancers is as per the FIGO classification (2009). It is a surgicopathologic classification. However, most of the trials on adjuvant treatment have been based on FIGO classification 1988 version and very few reports validating the revised version [5].

Risk Stratification

The definition and inclusion criteria for selection of patients with high-risk factors vary in different studies. Basically, patients are stratified in three risk categories: low, intermediate, and high risk as per ESMO and SOGC guidelines using FIGO 2009 staging system [1, 10].

Low Risk (LR)

Patients with grade I or II disease (histological type I) and myometrial invasion less than 50 %

(IA). The 5-year risk of recurrence is 2–10 % after surgery.

Intermediate Risk (IR)

Patients with stage IA grade III (histological type I) and myometrial invasion more than 50 % (IB) with grade I–II (histological type I). The 5-year risk of recurrence is 20–25 % after surgery.

High Risk (HR)

Patients with stage IB grade III (histological type I); deep cervical stromal involvement; LVSI irrespective of stage IA or IB, in advanced stage; and serous papillary and clear cell histology (histological type II) irrespective of being stage IA or IB. The 5-year risk of recurrence is between 30 % and 65 % after surgery.

Not all patients can strictly be classified into these risk types; so many groups defined a "high-intermediate risk." This risk grouping was not uniform, e.g., GOG and PORTEC had different definitions which are as follows:

1. In GOG 99, the risk factors which were considered are increasing age, grade III, stage IC (1988 FIGO staging), and presence of lymphovascular invasion [11]. GOG (GOG 99 study) defined a high-intermediate-risk category which is as follows:
   - Patients 70 years of age or older with only one risk factor
   - Patients 50 years of age or older with any two of the other risk factors
   - Any age with all three of the other risk factors
2. PORTEC criteria for high-intermediate risk [8]:
   - Stage I–IIA, endometrioid type, grade I or II with >50 % myometrial invasion
   - Age >60 years, grade III with no or <50 % MMI

Since there is no uniform definition and enough evidence for high-intermediate-risk grouping, the latest ESMO/SOGC guidelines for risk stratification using FIGO 2009 staging do not define the high-intermediate-risk group. Subsequent to surgery and thorough histopathological staging followed by risk stratification for early endometrial cancers, appropriate adjuvant therapy treatment should be decided in a multidisciplinary team approach comprising the gynecologic oncologist/surgeon, radiation and medical oncologist, and the reporting pathologist. The following section deals with evidence for adjuvant radiation therapy and type of radiation (external/vaginal brachytherapy).

Adjuvant Radiation Therapy: Evidence and Rationale

Radiation plays an important role in adjuvant treatment of early endometrial cancers. Adjuvant external beam radiation therapy (EBRT) alone, vaginal brachytherapy (VBT), and combination of both have been used in the treatment of early endometrial cancers. However, in recent past, there has been a decline in the use of EBRT with increasing use of VBT. Since both EBRT and brachytherapy lead to acute and late effects, the need and the clinical benefit of radiation should strongly outweigh the side effects.

Initial results of studies of EBRT versus no EBRT showed that adjuvant EBRT resulted in reduction in locoregional recurrence; however, there was no impact on overall survival (OS) or cause-specific survival (CSS). The large randomized studies evaluating the role of adjuvant radiation in early-stage cancer have shown excellent local tumor control with vaginal brachytherapy (VBT) alone even in high-risk patients.

The studies evaluating the role of radiation have been summarized in subsequent sections.

EBRT With/Without VBT Versus No Adjuvant Treatment

In the Norwegian trial by Aalders et al., 540 stage I endometrial cancer patients underwent surgery (TAH + BSO) and vaginal brachytherapy 60 Gy to the vaginal surface followed by further randomization to pelvic EBRT versus no additional

treatment. No difference in survival or recurrence rates was found between the treatment groups. A subgroup of patients who were high risk (grade III and >50 % MMI), benefited from adjuvant radiation with pelvic relapses reduced from 20 % to 4.4 % and a 10 % survival advantage [12].

In the PORTEC trial by Creutzberg et al., 715 patients with stage I endometrial cancer after surgery were randomized to pelvic radiation (46 Gy) or no further treatment. The survival rates were similar between the two groups (85 % vs. 81 %), but the locoregional recurrence rates were reduced to 4 % compared to 14 % in the control group. Seventy-three percent of recurrences were limited to the vagina which underwent salvage treatment. Complete remission rate was 85 %. The 2-year and 3-year survival after vaginal relapse were 79 % and 69 % when compared to 21 % and 13 % for pelvic or distant relapse [8].

Creutzberg et al. reported on the survival rates after vaginal relapse in PORTEC patients which showed that 5-year survival rates were significantly better in the control group compared to the radiation group (65 % vs. 43 %). Treatment of relapse was effective with complete remission rates of 89 % with EBRT and VBT [13].

Fifteen-year follow-up results of PORTEC 1 trial showed that there was no difference in survival rates but with reduction in locoregional recurrence rates with EBRT (5.8 % vs. 15.5 %). However, patients treated with adjuvant EBRT had significantly higher rates of symptoms like urinary incontinence, diarrhea, and fecal leakage with limitations in activities of daily living. They also had lower scores of physical and role physical functioning [14].

Keys et al. reported the results of GOG 99 in which 292 intermediate-risk stage IB, IC, and II (occult) endometrial cancer patients with negative lymph nodes after surgery were randomized to pelvic radiation (50.4 Gy) or no adjuvant treatment. Factors considered for increased rates of recurrence were increasing age, moderate to poorly differentiated tumor grade, presence of lympho-vascular invasion, and outer third myometrial invasion.

At a follow-up of 2 years, there was statistically significant reduction in cumulative recurrence rates with EBRT (3 % vs. 12 %). In the high-risk group, radiation had a substantial effect on recurrence rates (6 % vs. 26 %) compared to low risk. However, there was no difference in survival rates [11].

In the UK MRC ASTEC/EN.5 study, 905 women with intermediate- or high-risk early-stage disease were randomized after surgery for observation or pelvic radiation (40–46 Gy). Brachytherapy was allowed as per institutional protocol and similar proportions in both the groups received VBT. Five-year survival was 84 % in both groups. EBRT was associated with a small reduction in isolated local recurrence (3.2 % vs. 6.1 %). It was concluded that adjuvant radiation is not recommended as adjuvant treatment in this subgroup [15].

The updated Cochrane review in 2012 suggested that adjuvant EBRT showed a statistically significant reduction in locoregional recurrence but not OS, endometrial CSS (cause-specific survival), or distant metastases in stage I patients. There were no survival benefits from EBRT for women in any of the risk subgroups either. EBRT was associated with statistically significantly more severe acute toxic effects and late complications (grade III and IV) compared with no EBRT [16].

These studies have shown that the majority of the initial recurrences for patients with stage I cancer were limited to the vagina, thus suggesting that vaginal vault brachytherapy alone could be used as an adjuvant treatment.

EBRT Versus VBT

PORTEC 2 study was aimed at evaluating effectiveness of VBT versus pelvic radiation in patients with high-intermediate-risk factors. Four hundred and twenty-seven patients of stage I and IIA with high-intermediate-risk factors were randomized to pelvic EBRT (46 Gy) or VBT (21 Gy in 3/HDR or 30 Gy LDR). There was no difference in overall survival and disease-specific survival between VBT and EBRT. Vaginal recurrence rates are similar in both groups (1.8 % vs. 1.6 %), and locoregional relapse rates are 5.1 % with VBT and 2.1 % with EBRT. Gastrointestinal

toxicity was reduced in the VBT arm from 54 % (with EBRT) to 13 % only. The conclusion of PORTEC 2 study was that VBT should be the adjuvant treatment of choice for endometrial cancer with high-intermediate risk [17].

Sorbe et al. evaluated the role of vaginal brachytherapy alone versus the combination of pelvic radiation and brachytherapy in medium-risk stage IA–C endometrial cancer. There was no difference in survival benefit, but locoregional and pelvic recurrences were more in the brachytherapy arm (6.8 %, 5.3 %) compared to the combined arm (2.3 %, 0.4 %). Treatment toxicities of all grades involving the intestine, bladder, and vagina were more with the combined arm (14.5 % vs. 2.7 %). Combined RT should be reserved for high-risk cases with two or more high-risk features due to increased toxicity despite local benefit [18].

VBT Alone

In women who are at low risk, EBRT may have an adverse effect on CSS. Because the locoregional recurrence rate in this subgroup is low and not significantly improved by VBT, VBT is not required in treatment of low-risk women.

Sorbe et al. studied VBT versus no additional treatment in low-risk groups (stage IA, IB; grade I–II). In this trial, there was no difference in overall survival or cause-specific survival between VBT and control, and the vaginal recurrence rates were also similar (1.2 % vs. 3.1 %, $P=0.07$) [19].

There are no large series or studies reported from developing countries. Patients are often diagnosed with incidental endometrial cancers after simple hysterectomy or often undergo incomplete surgical staging. This is a common situation in routine clinical practice and poses a dilemma in management. There are no guidelines or literature addressing further management after inadvertent surgery. We reported our experience and outcome of such patients in a large series of 249 patients treated from 1988 to 2004. The 1988 International Federation of Gynecology and Obstetrics (FIGO) staging and risk stratification was used. Of the studied population, low risk (LR) comprised 60 women, intermediate risk (IR) 124, and high risk (HR) 65. Adjuvant radiation treatment was offered to 18 (LR), 85 (IR), and 57 (HR) patients. In this study, DFS and OS were 80 % and 95 %, respectively, at 5 years. The DFS and OS rates at 5 years were 84 % and 97 %, 85 % and 98 %, and 60 % and 85 % for the LR, IR, and HR groups, respectively, which are comparable to western literature including the validation of FIGO 2009 staging with reported literature. Also, out of 249 patients, 131 (52.6 %) patients underwent TAH BSO alone of which 27 were LR, 58 were IR, and 46 were HR. Forty percent of patients in LR, 62 % in IR, and 69 % in HR received adjuvant EBRT with VBT. Twenty-six (26) of 37 (68 %) recurrences were seen in women who underwent incomplete surgery. Disease-free survival was significantly poor for patients undergoing incomplete surgery (95 % vs. 70 %, $P=0.008$). However, OS was not significantly better whether lymph node dissection was performed (100 % vs. 92 %, $P=0.217$) suggesting that there is no benefit of lymph node dissection on OS and DFS for patients in the IR and HR group [5].

Other Histologies

Papillary serous, clear cell carcinomas and carcinosarcomas are aggressive histologies with a high propensity for local recurrence and distant metastatic spread. Patients with these unfavorable histologies should undergo aggressive surgical staging including omental/peritoneal biopsies. Carcinosarcomas are usually treated as high-grade adenocarcinomas. There is lack of sufficient evidence to support therapeutic options in this subgroup of patients. However, pelvic EBRT and vaginal brachytherapy are safe and a commonly practiced option. Reed et al. compared adjuvant radiation to observation in stage I and II carcinosarcoma and showed that radiotherapy was associated with fewer local recurrence rates (19 % vs. 36 %, $P=0.001$). However, there was no survival advantage [20]. Adjuvant ifosfamide–paclitaxel- or paclitaxel–carboplatin-based chemotherapy has shown some benefit in outcome [21].

David Ly et al. studied impact of adjuvant radiation on recurrence and survival in 125 patients with early-stage IA unfavorable histology (clear cell, papillary serous, or grade III endometrioid). The 5-year local–regional control in patients who received radiation was 97.8 % versus 80.1 % in patients who did not receive radiation ($P=0.018$). The 5-year overall survival rate in patients who received radiation was 84.9 % versus 68.1 % in patients who did not receive radiation ($P=0.0062$) [22].

Summary of Adjuvant Treatment Strategies According to ESMO and SOGC Risk Stratification (Table 22.1)

Low Risk

These patients have excellent prognosis. The Cochrane review in 2007 concluded that pelvic radiation has deleterious effects on survival in low-risk patients [23]. VBT has not affected survival or recurrence rates compared to observation alone. Hence, observation after surgery is recommended for this group of patients.

Intermediate Risk

Based on the results of the three major randomized trials [8, 11, 15], adjuvant brachytherapy alone should be offered to all intermediate-risk patients. Brachytherapy showed equivalent results in terms of local, locoregional survival to pelvic radiation and significant reduction in radiation-related toxicities.

PORTEC 1 study with 15-year follow-up and GOG 99 study suggested a significant improvement in locoregional control rates of approximately 10 % with the use of postoperative adjuvant radiation (EBRT) without any overall survival benefit. Also, the morbidity associated with adjuvant EBRT was significantly higher especially GI complications. The GI complications were 20 %, mainly diarrhea, abdominal cramps, and frequency of bowel movements. GU symptoms were urgency, frequency, and mild incontinence [24]. PORTEC 2 study suggested that adjuvant EBRT can be replaced by VBT without compromising the outcomes and significant reduction in toxicities and better QOL as reported by patients [25].

Table 22.1 Treatment options as per risk and stage

Risk stratification	Factors	Treatment
Low risk	Stage IA, grade I–II	Observation
Intermediate risk	Stage IA, grade III; stage IB, grade I–II	Vaginal brachytherapy (VBT)
High risk	Stage IB, grade III; stage II	EBRT + VBT

High Risk

Pelvic radiation with or without brachytherapy is the recommended treatment.

In a subgroup analysis by Aalders et al. in high-risk group patients, pelvic radiation with brachytherapy had lower rates of cancer-specific deaths (18 % vs. 31.4 %) and pelvic and vaginal recurrences (4.8 % vs. 19.6 %) as compared to brachytherapy alone [12].

Prophylactic vaginal brachytherapy is considered after EBRT in the case of cervical involvement (stage II).

Role of Adjuvant Chemotherapy/ Chemoradiotherapy in High-Risk Patients

In high-risk patients even after adequate therapy, 88 % of all recurrences are distant failures, and less than 30 % develop local recurrences. Hence, adjuvant chemotherapy, radio-chemotherapy, etc., have been attempted. The NSGO EC 9501 and MaNGO ILIADE studies evaluated adjuvant radiotherapy versus adjuvant chemoradiotherapy in high-risk women. Their pooled data showed an

improvement in 5-year failure-free survival of 13 % from 71 % to 84 % [26].

Currently, there are ongoing prospective phase III randomized trials to evaluate the role of adjuvant chemotherapy and radiotherapy like PORTEC 3, GOG 249, and GOG 248. Completion of these studies and mature data is essential to establish further the role of adjuvant chemo-/radiotherapy in high-risk endometrial cancer patients.

Patients Undergoing Inadvertent Surgery or Incomplete Surgical Staging

In patients who undergo incomplete surgical staging/incidental finding of endometrial cancer, an attempt should be made to stratify them into various risk stratification categories. All patients are usually subjected to imaging at least CT of the abdomen and pelvis to rule out residual disease in the abdomen, peritoneal/omental surfaces, pelvic/para-aortic lymph nodal regions, etc. In general, if imaging is negative, then either VBT (in low and intermediate risk) or EBRT ± VBT (in high risk) is offered. If there are positive findings on imaging, surgical re-exploration for appropriate staging and further adjuvant therapy is offered.

Low-Risk Patients

Observation or VBT alone

Intermediate-Risk Patients

EBRT ± VBT (imaging negative) or surgical re-exploration (imaging positive)

High-Risk Patients

EBRT ± VBT (imaging negative) or surgical re-exploration (imaging positive) and adjuvant therapy according to final staging

Other Histologies: Clear Cell, Papillary Serous, and Carcinosarcomas

Stage IA: Observation or chemotherapy or pelvic RT

Stage IB–II: Chemotherapy with or without pelvic RT ± VBT

Radiation Therapy for Endometrial Cancer

External Radiation Planning

In post-operative settings, aim is to treat upper 3 cm of vagina including vault, para-vaginal soft tissues and draining lymph node regions including common, external, and internal iliac lymph node regions [Clinical Target Volume (CTV)] and achieve optimal sparing of various neighboring structures like bladder, small bowel, rectum, bone marrow, and the femoral heads.

Conventional

The radiation portal is usually two-field (AP/PA) or four-field (box) arrangement. Shielding to minimize dose to neighboring structures (bowel, bladder, and rectum) can be used. The radiation portals are usually marked using fluoroscopy/CT guidance. The radiation field is fixed based on bony landmarks with superior border at L5-S1 and inferior border below the obturator canal to include upper 1/2–1/3 of the vagina, and the lateral borders are placed at 1.5–2 cm lateral to the pelvic brim for two-field AP/PA technique. Dose is prescribed in the midplane (Fig. 22.1).

In the four-field technique (AP/PA and bilateral), apart from AP/PA portals as described above, two additional lateral (right and left) fields with anterior border anterior to pubic symphysis and posterior border at S3 are placed. Customized blocks to shield the small bowel anterosuperiorly and the low ano-rectum inferiorly to reduce radiation toxicities are attempted (Fig. 22.1).

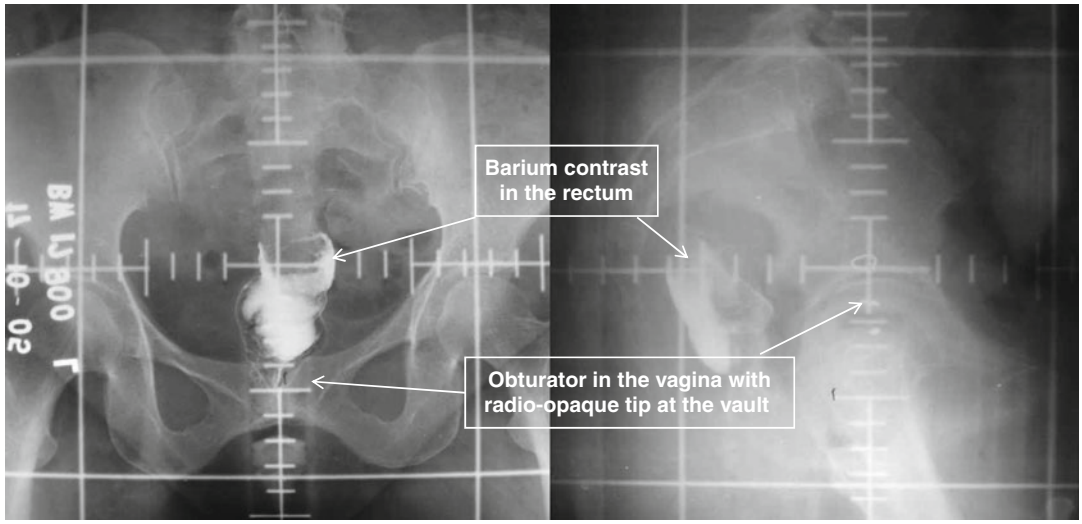

Fig. 22.1 Anteroposterior and lateral EBRT planning X-ray illustrating standard pelvic portals marked by lead wires and scale

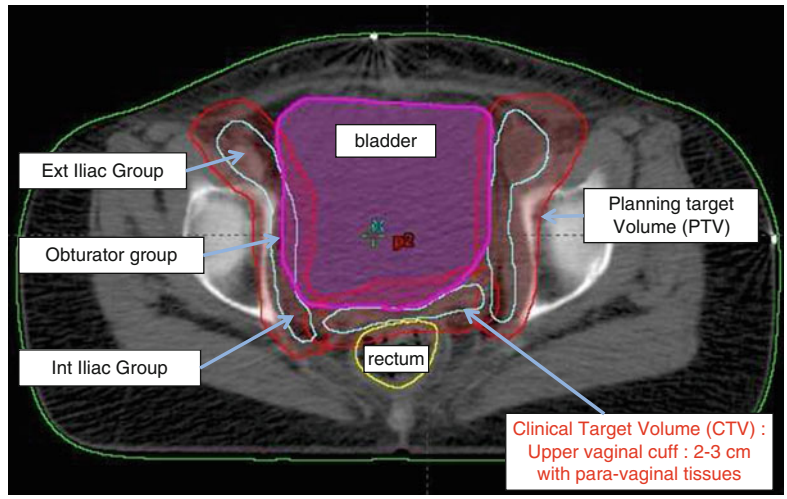

Fig. 22.2 Representative axial CT slice showing various target volumes (CTV and PTV) and organ definitions for conformal/IMRT planning

Conformal and Newer Techniques

More conformal techniques like three-dimensional conformal radiation techniques (3DCRT) and intensity-modulated radiation therapy (IMRT) are used to reduce normal tissue toxicities. These techniques involve the use of CT imaging, delineation of various targets and organs, planning, and dosimetric evaluation. 3DCRT uses fixed beams shaped to the target volume with uniform dose intensity, while IMRT uses optimized nonuniform dose intensities to deliver conformal radiation to the target to minimize doses to surrounding normal tissues. IMRT studies have shown a significant reduction in doses to the small bowel, bladder, and rectum which translated into reduction in radiation-related acute and chronic toxicities as compared to conventional/3DCRT techniques [27, 28, 29].

Various guidelines are available which define in detail concepts and contouring of the target and OARs [30] (Fig. 22.2).

In a retrospective review by Shih et al., the outcomes with postoperative pelvic IMRT in high-risk endometrial cancer were excellent with 5-year DFS and OS >88 % with a favorable

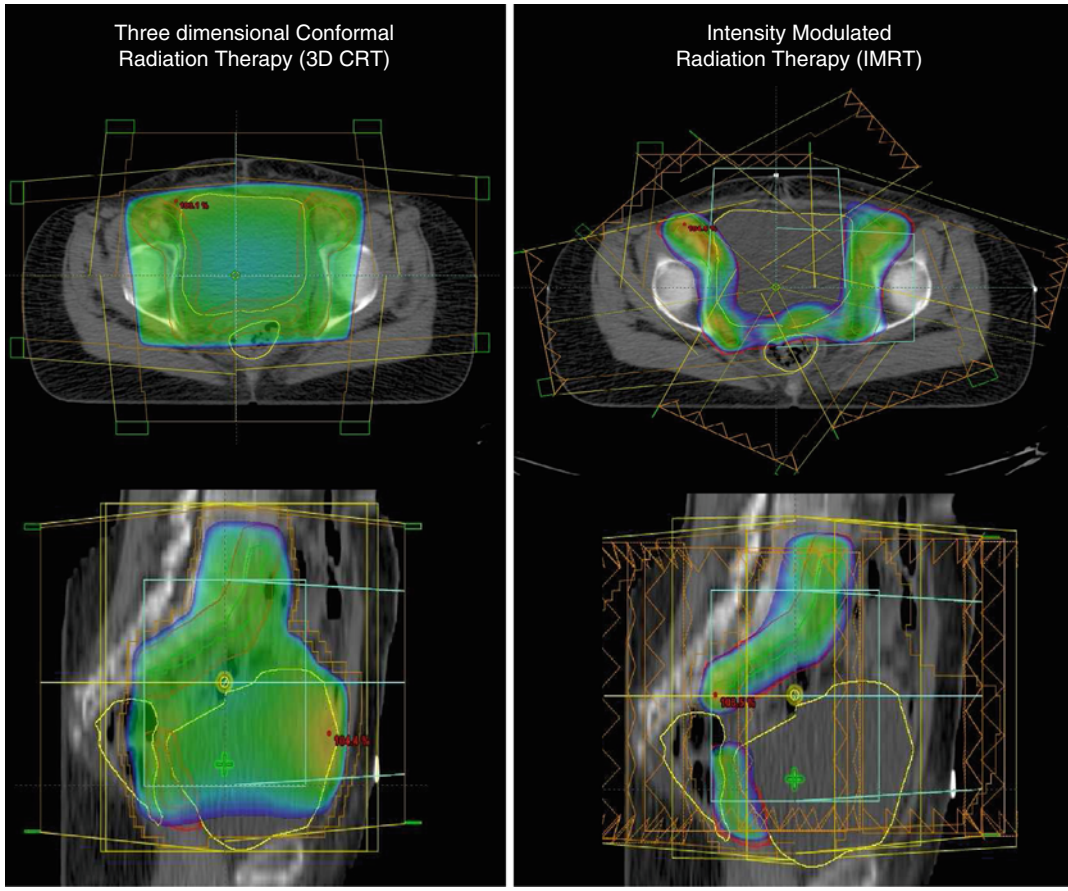

Fig. 22.3 Axial and sagittal CT comparison of dose distribution: 3DCRT (*left panel*) versus IMRT plan (*right panel*) illustrating sparing of organs at risk with IMRT

toxicity profile [31]. The preliminary data from phase II RTOG 0418 trial highlights the advantages of IMRT. Forty-three patients of endometrial cancer (93 % stage I–II) treated with adjuvant IMRT showed a 3-year DFS and OS rates of 91 % and 92 %, respectively [32] (Fig. 22.3).

External Radiation Doses

An external radiation dose of 45–50.4 Gy in 25–28 fractions in 5–5.5 weeks is recommended.

Brachytherapy

Vaginal brachytherapy (VBT) is effective with <5 % recurrence rates and low toxicity. Care should be taken to choose the appropriate applicator to adequately treat the vaginal mucosa. Adjuvant brachytherapy is performed at least 4 weeks after surgery. Vaginal cylinders or ovoids are commonly used. The aim is to radiate proximal 3–5 cm of the vagina including the vault.

Vaginal cylinders are the standard applicators used. They are available with a diameter of 20, 25, or 30 mm. According to ABS guidelines for vaginal brachytherapy, the size of the cylinder should be carefully chosen to ensure good contact between the cylinder and the vaginal mucosa [33]. The largest size which fits snugly to the vagina should be chosen. This is to avoid any air gaps and prevent underdosage of the vaginal mucosa. Radiopaque markers or clips may be placed at the vaginal apex to confirm that the applicator is in contact with the mucosa. The length of the vagina should be measured from the vault to the level of the introitus. Plain X-ray

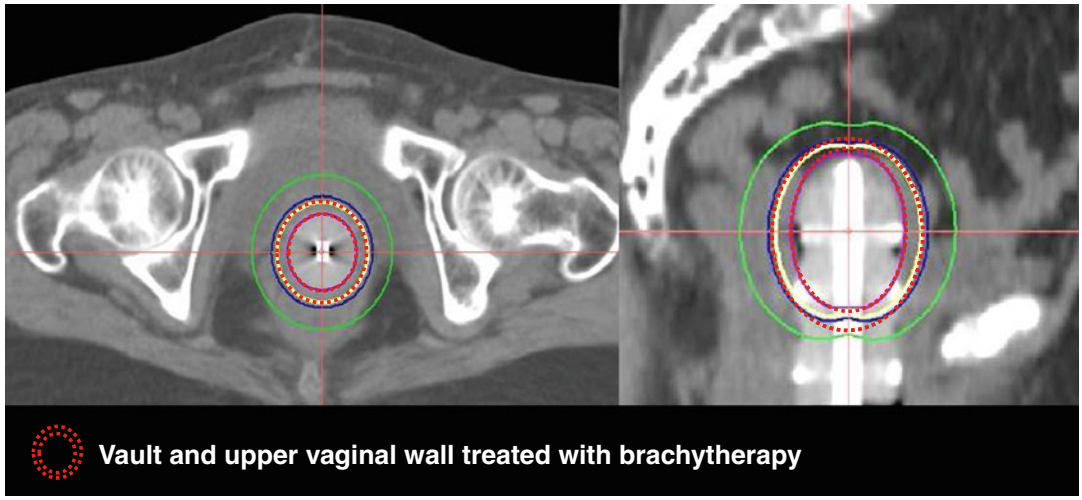

Fig. 22.4 Axial and sagittal CT images showing intravaginal brachytherapy cylinders, brachytherapy doses to vault, and upper vaginal wall

film- or CT imaging-based planning is done. The proximal 3–5 cm of the vagina with 5 mm thickness is treated with VBT. The dose should be prescribed to a depth of 5 mm from the vaginal mucosa or at the vaginal surface. More than 95 % of lymphatic channels are located in the first 3 mm of the mucosa. Brachytherapy can be delivered with high dose rate (HDR) or low dose rate (LDR) and rarely with pulse dose rate (PDR).

Brachytherapy Doses

LDR prescription is 50–60 Gy to the surface over 60–70 h when used alone. However, HDR brachytherapy is preferable. The common fractionation schedules used are, for brachytherapy alone, 4 Gy×6, 6 Gy×5, 7 Gy×4, and 8 Gy×3 at the vaginal surface or 7Gy×3 fractions at 5 mm depth when VBT alone is planned. If VBT boost is planned after EBRT, 4Gy×4 and 6 Gy×3 at the vaginal surface or 5 Gy×3 fractions or 6 Gy×3 fractions at 5 mm are delivered (Fig. 22.4).

Clinical Outcome and Survival

Patients with early endometrial cancer have excellent outcomes, with 5-year disease-free and overall survivals of 93 % and 98 %, respectively, for stage I patients and 70–80 % for stage II [34]. The survival outcomes according to risk stratification for early endometrial cancers are as follows:

Low Risk

The risk of recurrence is low, with 5-year cancer-specific and overall survival of 98 % and 96 %, respectively, and progression-free survival in the range from 90 % to 99 % [19].

Intermediate Risk

The risk of recurrence after adjuvant therapy is 2–10 %, with 5-year disease-specific and overall survival of 90–97 % and 88 %, respectively, and progression-free survival of 86 % [18, 35].

High Risk

The risk of recurrence is high especially distant failures with locoregional control rates of 92 % and 5-year disease-specific and overall survival of 74 % and 63–78 %, respectively [35, 36].

Morbidity of Adjuvant Radiation Therapy

The side effects of pelvic radiation are due to irradiation of the small bowel, bladder, rectosigmoid, femoral heads, and bone marrow which are in close proximity to the target volume. The toxicities seen depend on the tolerance of these organs. Reactions are broadly classified acute and late. The frequency and severity depend on the total dose, dose fractionation, volume of the organ irradiated, concurrent chemotherapy, previous abdominal surgery, and presence of other comorbidities like diabetes, hypertension, or inflammatory bowel disease. The toxicities especially in the small bowel are more pronounced due to small bowel adhesions in the true pelvis and receive relatively high-dose gradients.

Acute reactions are seen during treatment or within 3 months. The common toxicities are diarrhea, abdominal pain, cramps, vomiting, hematochezia, dysuria, frequency of micturition, skin erythema, dry desquamation, moist desquamation, and ulceration. These are commonly mild (grade I–II) reactions. These are treated with appropriate symptomatic medications and are self-limiting.

Late reactions are those which are seen 6 months after treatment. Their incidence varies from 9 % to 20 % and is commonly seen between 1 and 5 years but may even manifest up to 10–20 years after radiation. The late sequelae of the bowel are chronic intestinal dysfunction with changes in bowel habits, abdominal pain, and bowel obstruction. The rectal toxicities include tenesmus, hematochezia, bleeding, ulceration, and rectovaginal fistula. These are managed with corticosteroid enemas, argon plasma coagulation, and hyperbaric oxygen in severe cases.

Bladder toxicity includes dysuria, urgency, and frequency due to reduction in bladder storage capacity. These are managed with urinary analgesics and antispasmodics. Urethral stricture and severe hemorrhage are also seen. Bleeding is treated with cystoscopy, bladder irrigation, cauterization of bleeding points, and hyperbaric oxygen. Vaginal toxicity manifests as atrophy, decrease in vaginal pliability, shortening, and fibrosis. Sexual activity, regular use of vaginal dilators, and maintenance of vaginal hygiene help to reduce majority of symptoms.

With advanced conformal technologies like 3DCRT and IMRT, the complication rates have decreased without compromising tumor control.

Follow-Up

Patients should be followed up at regular intervals for early detection of recurrence and to monitor early and late reactions. Follow-up schedule varies as per institutional protocol. Patients are reviewed at 3 monthly interval till 2-year posttreatment period, thereafter 6 monthly until 5 years, and beyond 5 years at yearly intervals. At every visit, history and physical and vaginal examinations should be done. Further investigations like examination under anesthesia, biopsy, or imaging tests like CT, MRI, or PET may be considered in the event of high clinical suspicion of recurrence. There is an increased risk of cancer of the breast and ovary in these patients. Appropriate tests like CA 125 and annual mammograms help in the surveillance [37].

Conclusion

Radiation therapy plays a vital role in the adjuvant treatment of early-stage endometrial cancers. Surgical staging and risk stratification should be done to decide on the need for further adjuvant therapy. Adjuvant radiotherapy in intermediate- and high-risk patients after adequate surgical staging and in patients undergoing suboptimal surgical staging significantly reduces locoregional recurrences. Adjuvant radiation therapy in the form of external therapy, brachytherapy, or combination should be tailored according to surgical staging and the risk criteria.

Key Points

1. Surgical staging and risk stratification is mandatory in early-stage endometrial cancers.

2. Adjuvant radiation therapy is an established treatment modality for early-stage high-risk and intermediate-risk endometrial cancers.
3. Adjuvant radiation therapy should be tailored according to surgical staging and risk stratification.
4. Adjuvant radiation therapy can be in the form of external beam radiation alone, vaginal vault brachytherapy alone, or combination of both.
5. After adequate surgical staging, low-risk patients do not benefit from adjuvant radiation therapy, while vaginal vault brachytherapy alone is recommended for intermediate-risk patients. Most patients with high-risk factors after adequate surgical staging or suboptimal surgical staging for early endometrial cancers should undergo external beam radiation with or without a brachytherapy boost.
6. Vaginal brachytherapy is effective treatment with minimal toxicity. External beam radiation should be delivered with newer radiation techniques to minimize toxicity.
7. Unfavorable histology (clear cell, papillary serous, and carcinosarcomas) should undergo aggressive surgical staging including omental/peritoneal evaluation and observation (stage I) or further adjuvant therapy (chemotherapy ± radiation).
8. Regular follow-up and early detection of relapse and salvage treatment are effective.

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23 Therapeutic Options for Early-Stage Uterine Papillary Serous Carcinomas, Carcinosarcomas, and Clear-Cell and Mixed-Cell Histologies

Rachel Brightwell and Shashikant Lele

Introduction

Cancer of the uterus is estimated to result in the death of 8,190 women and will account for 49,560 new diagnoses of cancer in the USA in 2013 [1]. Approximately 1 in 37 women will be diagnosed in their lifetime based on data analysis from 2008 to 2010 [1]. Endometrial cancer is the most common gynecologic malignancy in the USA and developed countries and second only to cervical cancer in underdeveloped nations. Endometrioid type, or type I, is the most common type of uterine cancer, accounting for approximately 80 % of endometrial cancers. It is also the most curable, with a 5-year survival of approximately 85 %. This is due to the fact that most women are diagnosed with either a precursor lesion or at an early grade and stage secondary to symptomatic complaints and subsequent investigation. However, type II endometrial carcinomas, accounting for 10–20 % of women diagnosed, are typically higher grade, diagnosed at a later stage of the disease, and with precursor lesions rarely identified. Type II endometrial carcinomas include uterine papillary serous carcinoma, carcinosarcoma, and clear-cell, mixed, mucinous, squamous, mesonephric, undifferentiated, and grade III endometrioid type carcinomas. Type II tumors are more aggressive, proposed to develop from endometrial intraepithelial carcinoma, a malignant transformation from atrophic endometrium or benign polyp epithelium, secondary to mutations in p53. Though uterine papillary serous carcinoma (UPSC) accounts for only 10 % of endometrial carcinomas, it accounts for nearly 40 % of endometrial cancer deaths [2]. Although vaginal bleeding is still the most common presenting symptom, it typically manifests in the UPSC patient at a much later stage, and other common presenting complaints include bloating and increased abdominal girth, early satiety, and other symptoms typical to epithelial ovarian cancer presentation.

Preoperative detection of UPSC, when suspected, can be aided by both pap smears and CA-125. Abnormal pap smears were the only clinical finding at presentation in asymptomatic women in 51.5 % of UPSC patients and 25 % of clear-cell carcinoma patients [2]. Olawaiye et al. correlated CA-125 levels with disease stage at the time of surgery. Elevated CA-125 (>35 U/mL in a postmenopausal patient) had almost four times greater risk of cancer-related death than those without [3].

Type II tumors are more common in African-American women and in parous individuals. The increased rate of finding type II carcinoma may account for why African-American females tend to have a poorer overall survival (OS) with a generic diagnosis of endometrial cancer.

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In stage I and II disease, staging and treatments vary greatly than that of later-stage disease. The "Efficacy of Systematic Pelvic Lymphadenectomy in Endometrial Cancer" (ASTEC) trial did not demonstrate a significant increase in survival for early-stage patients with lymphadenectomy. However, the majority of patients enrolled in the study were those with type I endometrioid carcinoma. Another criticism of the ASTEC trial was that pelvic and para-aortic lymphadenectomy was not performed in a uniform or systematic fashion. A subsequent study, "Survival effect of para-aortic lymphadenectomy" (SEPAL), demonstrated that patients with intermediate or high recurrence risk receiving either pelvic (PLND) or pelvic plus para-aortic lymph node dissection (PPLND) elicited a longer OS in the PPLND group. Factors such as tumor size, grade, and depth of myometrial invasion direct the surgeon to elect or abstain from doing a pelvic/para-aortic lymphadenectomy in type I endometrial adenocarcinoma. Type II carcinoma management is not as easily deciphered. This is because they are more likely to have features such as lymphovascular space invasion, microscopic or grossly visible metastatic disease, and is due to the fact that myometrial invasion and tumor grade are not predictive of extrauterine spread.

Uterine Papillary Serous, Clear-Cell, and Mixed-Cell Carcinomas

Pathology and Pathogenesis

While type I endometrial carcinomas are estrogen related and generally seen in a relatively younger, obese population with a good prognosis, type II tumors are not associated with high levels of estrogen and have a poor prognosis similar to that of epithelial ovarian cancer. Uterine papillary serous carcinomas have a papillary architecture very similar to serous ovarian carcinoma, with very atypical nuclei [4]. Thirty to sixty percent of tumors are noted with psammoma bodies [4]. By definition, all UPSC is high grade. Additionally, upon presentation, approximately 70 % of women will have extrauterine disease (Fig. 23.1).

Clear-cell cancers are more varied, often characterized by tubulocystic, solid, and papillary patterns. The name clear cell is given due to the increased percentage of glycogen within the cell. Because of the varied histology of clear-cell carcinoma, diagnosis requires at least 25 % of the tumor to illustrate a clear-cell component [5]. Clear-cell endometrial adenocarcinomas are histologically similar to those arising from the

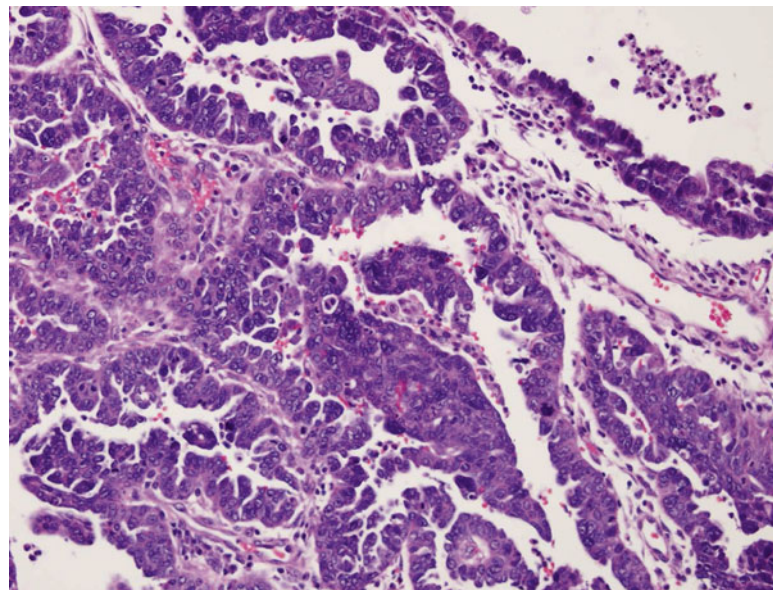

Fig. 23.1 Uterine papillary serous carcinoma. Note the fibrovascular core lined by stratified, pleomorphic cells, forming secondary papillae and cellular buds

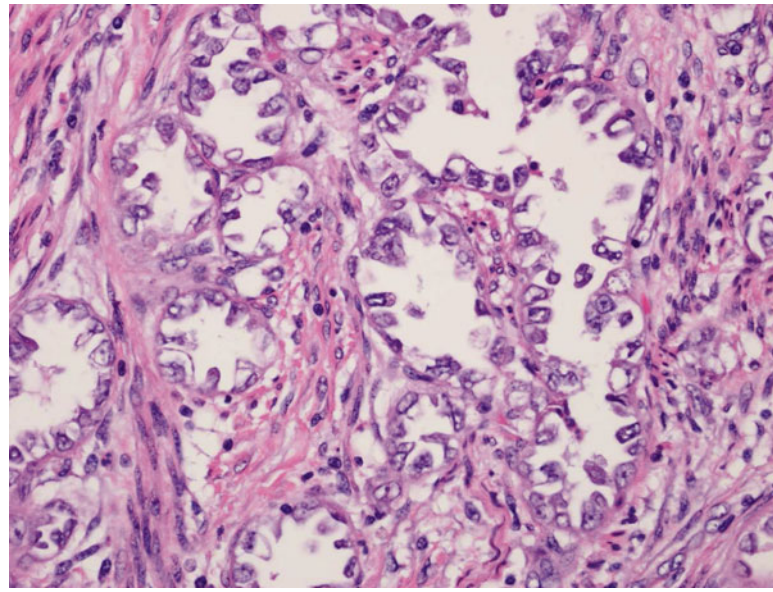

Fig. 23.2 Clear-cell uterine carcinoma. Note the clear, glassy cytoplasm, enlarged angulated nuclei with enlarged irregular nucleoli, and hobnail appearance

ovary, vagina, and the cervix [4]. As in UPSC, clear-cell carcinomas are high grade and tend to be deeply invasive (Fig. 23.2).

If the serous component of a tumor is greater than 10 % but less than 90 %, the tumor is considered mixed serous histology. Typically, the other fraction of the tumor is endometrioid histology. Once thought to have similar survival, a multi-institutional review compared patients with UPSC to those with mixed UPSC and found that the pure UPSC group had an almost threefold risk of recurrence and death than the mixed-cell histology [5]. This holds true for pure clear-cell versus mixed clear-cell histology. These patients historically do relatively the same with regard to survival [6].

While type I tumors are associated with mutations in PTEN, K-ras, and microsatellite instability [7], type II are most commonly found to have p53 mutations and/or Her-2/neu overexpression [8, 9]. P53 is a tumor suppressor gene that regulates transcription and initiates apoptosis in the event of DNA damage. When a mutation or defect in p53 occurs, proliferation of tumor cells occurs. It is thought that approximately 50 % of cancers arise from this defect. It is still currently scrutinized whether BRCA1/2 mutation carriers have an increased risk for UPSC; however a recent study by Pennington et al. did demonstrate a higher than expected BRCA1 mutation rate at 2 % [10]. Given this finding, it has been suggested that women with a diagnosis of UPSC be offered genetic counseling and testing. Additional data suggests that epidermal growth factor receptor (EGFR) expression correlates with a poorer prognosis in both type I and II endometrial carcinoma, reducing survival in UPSC and clear-cell carcinomas from 86 % to 27 % [11]. While Her-2/neu is thought to play a role in UPSC, Herceptin use has not been studied extensively in recurrent or metastatic disease, and successful treatments have only been reported in case reports [12]. Current studies are underway, particularly a phase II study of carboplatin/paclitaxel with or without trastuzumab for advanced or recurrent UPSC patients with 3+ IHC for Her2/neu. Other molecular targets include PPP2R1A, FBXW7, and PIK3CA. Mutations in the regulatory unit of PPP2R1A's serine-threonine protein phosphatase 2 are reported in as high as 32 % of UPSC [10]. This enzyme is responsible for control of cell growth and division and is located downstream of Her2/neu, which may prove a potential target for treatment of UPSC. FBXW7 is an F-box protein important in targeting tumor-promoting proteins, including cyclin E. Cyclin E upregulates the cell cycle, particularly in the transition from G1 to S phase, in a dose-dependent manner that increases

oncogenic potential [13]. A genome-wide analysis of UPSC by Kuhn et al. demonstrated that PIK3CA was mutated and/or amplified in 48 % of the sequenced patients, supporting the PIK3CA/AKT/mTOR pathway is one from which USC arises. Therefore, findings to support this notion will likely lead to adjuvant treatment with mTOR inhibitors such as rapamycin.

Surgical Management

For the majority of endometrial carcinoma patients, the first-line treatment is comprehensive surgical staging. This includes total hysterectomy, bilateral salpingo-oophorectomy, and pelvic and para-aortic lymph node dissection per the International Federation of Gynecology and Obstetrics (FIGO) 2009 guidelines. Although it is common practice to collect peritoneal cytologic washings, this was not included in the 2009 FIGO recommendations. The role of lymphadenectomy is still under investigation for type I endometrioid adenocarcinoma, though recent studies support the omission of routine lymphadenectomy for superficial grade 1–2 endometrioid carcinoma in light of associated complications and lack of survival benefit [14]. In contrast, regarding grade 3 and type II carcinomas, combined pelvic and para-aortic lymphadenectomy has been shown to improve survival [15]. The therapeutic value of removing normal-appearing, normal-sized lymph nodes has been disputed, except to provide the most accurate staging to optimize postoperative treatment modality. Fader et al. also recently performed a multicenter study demonstrating that for early-stage endometrial cancer, regardless of histology, there was no significant difference in overall survival if patients were staged with a minimally invasive approach versus open laparotomy [16].

Though studies are still ongoing, initial data suggest that use of sentinel lymph node mapping may reduce morbidity associated with full lymphadenectomy (lymphedema, increased operative time), while detecting lymph node involvement at the same rate of fully staged carcinomas [17]. Further investigation over time will yet determine optimal placement and type of dye used and the extent of any long-term complications and outcomes.

For early stage I and II type II cancers, lymphadenectomy is thought to help tailor postoperative adjuvant therapy. However, when the histology indicates a high-grade tumor, these women are likely to receive adjuvant treatment regardless of lymph node status. Additionally, as ASTEC did not guide management of type II carcinomas and given the results of SEPAL, it is still recommended that comprehensive staging with PPLND is performed. Until the results of GOG 249 (Radiation vs Brachytherapy for Endometrial Carcinoma: A Phase III Trial of Pelvic Radiation Therapy Versus Vaginal Cuff Brachytherapy Followed By Paclitaxel/Carboplatin Chemotherapy in Patients With High Risk, Early Stage Endometrial Carcinoma) are available, these are still standard, and additional procedures such as abdominopelvic washings, omentectomy, and peritoneal biopsies are still incorporated at the surgeon's discretion due to lack of convincing evidence in favor of or against it.

Adjuvant Therapy

There is no standard adjuvant radiation therapy for early-stage endometrial carcinoma that has been set for comprehensively staged patients. However, it has been noted that with observation alone, recurrence risk in women with early UPSC and no myometrial invasion was 0–30 %. Recurrence rates in this population increased dramatically with myometrial invasion, from 29 % to 80 % [18]. Whole-abdominal radiation with and without pelvic boost has been studied, specifically in GOG 94 (a phase II study of whole-abdominal radiotherapy in patients with papillary serous carcinoma and clear cell carcinoma of the endometrium or with maximally debulked advanced endometrial carcinoma). Of 19 patients, 7 recurred. 71 % of the recurrences were within the irradiated field.

A Cochrane review by Kong et al. also concluded there was no demonstrable difference in survival with whole pelvic radiation for stage I high-risk endometrial carcinoma [19]. In early-stage patients with comprehensive staging performed, adjuvant chemotherapy is also of no proven benefit. However, recurrences have been reported in disease solely confined to a polyp that did not receive adjuvant chemoradiation [20]. Therefore, in the early-staged population, treatment decisions should still be tailored to the individual, discussing the risks of recurrence versus those associated with chemoradiation, so that the physician and patient are making the most informed and responsible decision. The standard of care for patients with any evidence of remaining disease in the uterus at the time of hysterectomy should be offered adjuvant chemotherapy [2].

Standard first-line treatment for UPSC is chemotherapy with carboplatin and paclitaxel with or without vaginal brachytherapy based on GOG 209. This non-inferiority trial demonstrated that the doublet of carboplatin and paclitaxel was just as efficacious but less toxic than the triplet of doxorubicin, cisplatin, and paclitaxel. "Sandwich therapy" has also demonstrated survival rates of 75 % in early-stage disease in a phase II trial by Fields et al. [21]. In this therapy model, patients receive three cycles of carboplatin and paclitaxel with whole pelvic radiation subsequently given and then receive an additional three cycles of carboplatin and paclitaxel. Additionally, Kiess et al. demonstrated that the use of six cycles of IV carboplatin and paclitaxel with only vaginal brachytherapy still elicited 85 % 5-year progression-free survival and 90 % overall [22]. A 2009 Society of Gynecologic Oncology (SGO) consensus statement supported chemotherapy with or without radiation for early UPSC with any residual disease in the uterus at the time of hysterectomy. The recurrence risk for IA UPSC is 8.7 % for those receiving chemotherapy, while radiation-only patients have a recurrence as high as 25 %. For Stage IB and IC disease, a similar threefold increase in recurrence risk is seen with radiation or observation alone is seen [2].

Uterine Carcinosarcoma

Uterine carcinosarcoma, formerly known as malignant mixed Mullerian tumor (MMMT) is a rare neoplasm accounting for only 1–2 % of cancers of the uterus. The dedifferentiated tumors arise from the endometrium and are also considered to arise from uterine epithelial carcinoma, rather than from a true sarcoma [23, 24]. Due to the rarity of the disease, large, prospective studies have not been performed. The most common presenting complaints are a triad of vaginal bleeding, lower abdominal pain, and a rapidly growing uterus [25, 26]. The median age at diagnosis is approximately 62–67 years, with blacks affected at twice the rate of non-Hispanic whites [27]. On presentation, 60 % of patients will have extrauterine spread [28].

Evaluation both pre- and postoperatively with CA-125 has proven beneficial to identify more advanced and aggressive disease status, correlated with metastases and tumor volume. It is highly correlated with disease stage, serous component, and myometrial invasion of more than 50 % with a "positive cutoff value" of more than or equal to 30 U/mL [29] (Figs. 23.3 and 23.4).

Surgical Management

Surgical management is the mainstay of treatment for early-stage carcinosarcoma diagnosed by preoperative biopsy that is by definition without evidence of metastatic spread. Surgical staging should be performed, including total hysterectomy, bilateral salpingo-oophorectomy, PPLND, omentectomy, and peritoneal washings for cytology. However, if complete cytoreduction can be performed with no gross visible residual disease, patients with limited peritoneal spread (stage IVB) may still also benefit from surgical management. In patients that were diagnosed during postoperative review of the pathological specimen, a second surgery usually is warranted to perform lymphadenectomy and completes the surgical staging. Carcinosarcoma falls under the umbrella of FIGO staging for endometrial carci-

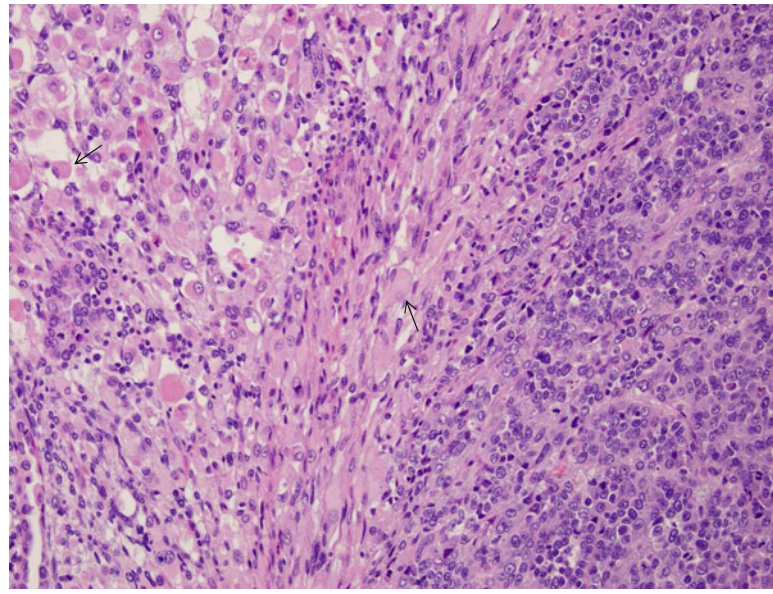

Fig. 23.3 Uterine carcinosarcoma. Heterologous MMMT with rhabdoid features. Heterologous tumors typically have mesenchymal elements such as bone, fat, skeletal muscle, or cartilage within them. Note the large, anaplastic, racquet-shaped cells with abundant cytoplasm (*arrows*)

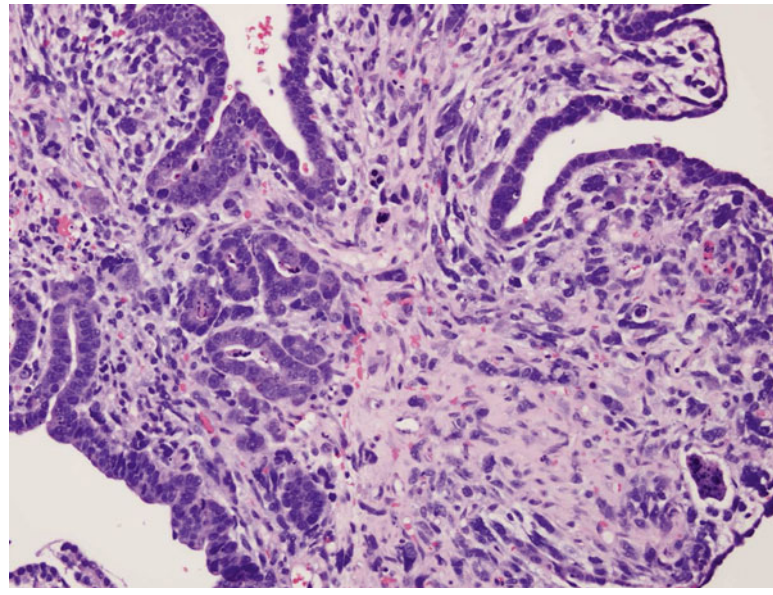

Fig. 23.4 Uterine carcinosarcoma. Homologous MMMT. Note the glandular epithelial component and the stromal sarcomatous component throughout

noma. In one of the largest studies of carcinosarcoma to date, the median survival was improved from 25 to 54 months in the patients who underwent complete staging procedure including lymphadenectomy [30].

Adjuvant Therapy

Adjuvant treatment is tailored to stage at time of diagnosis. For stage IA patients (less than half of the myometrium invaded by tumor), there is limited evidence to support for adjuvant chemotherapy or radiation [31, 32]. However, in all early-stage patients (I and II), adjuvant treatment has been shown to improve progression-free survival, though without an increased overall survival [33]. Treatment decisions for stage IA patients should then be tailored to the specific desires of the patient, so long as she is well-informed of the risks versus benefits and the lack of overall survival benefit. Furthermore, due to the lack of evidentiary support for treatment of these patients, they become attractive candidates for randomized clini-

cal trials. Currently, one such trial is underway, GOG 261, comparing ifosfamide plus paclitaxel to carboplatin plus paclitaxel for primary uterine carcinosarcoma, stages I–IV OR chemotherapy-naïve recurrence patients. The European Organization for Research and Treatment of Cancer (EORTC) trial 55874 showed that although adjuvant pelvic RT resulted in significantly lower local recurrence rates, it had no effect on progression-free or overall survival [31]. Currently, there is a paucity of reliable prospective data to support chemoradiation for treatment of carcinosarcoma and thus far is used only in clinical trials. For stage IB–IV disease, chemotherapy is the cornerstone of treatment [34, 35, 36]. Clinical trials are also underway exploring the role of PI3K/AKT/mTOR in carcinosarcoma because mutations are often found in this type of cancer [37].

Conclusion

Type II endometrial carcinomas have a very aggressive behavior and have different genetic mutations compared to type I tumors. Complete staging followed by chemoradiation is warranted for improved survival in early stages. Optimal cytoreduction when possible with chemotherapy in advanced disease is recommended.

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Chemotherapy for High-Risk Early-Stage Endometrial Cancer: Current Evidence

24

Seema Gulia and Sudeep Gupta

Introduction

Endometrial cancer (EC) is the third common gynecological cancer affecting women in the Western world. By contrast, the incidence in developing countries is approximately tenfold lower [1]. The incidence in India is 2.3 per 100,000 women. Around 80 % of patients are diagnosed in early stages (FIGO stages I and II) and have good prognosis (5-year survival ~90 %). Currently patients with early-stage endometrial cancer are treated with primary surgery, which includes hysterectomy, bilateral salpingo-oophorectomy, and pelvic and para-aortic node dissection with or without omentectomy. The histopathological information obtained from the pathology specimen is used to identify patients with adverse prognostic features who may benefit from adjuvant therapy. Several factors have been associated with the risk of recurrence including older age, higher grade, histologic type (i.e., serous or clear cell type), deep myometrial invasion, lymphovascular space invasion (LVSI), involvement of the cervical stroma, and large tumor size (>2 cm) [2–4]. The indication of adjuvant chemotherapy or radiotherapy is based on the aggregate risk conferred by these factors.

Patients with endometrial cancer could be divided into three risk groups based on these factors [2, 5]:

1. **Low risk** – stage IA, grade 1 (G1) or grade 2 (G2), and stage IB, G1 with no adverse prognostic factors
2. **Intermediate risk** – is further divided into low and high-intermediate risk
   (a) **Low-intermediate risk** – age less than 70 years, superficial myometrial invasion (less than 2/3)
   (b) **High-intermediate risk**
      (i) 70 years of age with only one of the other risk factors (i.e., moderate to poorly differentiated tumor grade, presence of LVSI, and deep (>2/3) myometrial invasion)
      (ii) 50 years of age with any two of the other risk factors
      (iii) Any age with all three of the other risk factors
3. **High risk** – clear or serous cell type, gross involvement of the cervix (gross stage II), stage III, or stage IV

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Adjuvant Therapy for Low- and Low-Intermediate-Risk Groups

The risk of locoregional recurrence for EC patients with G1and G2 endometrioid-type carcinoma and superficial (<50 %) myometrial invasion is about 5 % or less [6, 7]. There is no proven benefit of adjuvant therapy for low- and low-intermediate-risk groups, and therefore these patients can be safely treated by surgery alone [7]. It was concluded from the PORTEC-1 trial (external beam radiotherapy 46 Gy versus observation) that postoperative radiotherapy is not indicated in stage I patients <60 years of age and patients with G2 tumors with superficial invasion [8].

Adjuvant Chemotherapy for Early-Stage Endometrial Cancer Patients with High-Risk Features: The Evidence

Lessons from of Radiation Therapy Literature: Adjuvant Radiation Therapy Versus Observation Trials

In PORTEC-1 (postoperative radiation therapy in endometrial carcinoma) trial, patients with stage I (G1 with outer-half myometrial invasion, i.e., >50 % myometrial invasion, G2 with any invasion, or grade 3 with superficial myometrial invasion, i.e., <50 % myometrial invasion) were randomized to pelvic EBRT (46 Gy) or no further treatment after surgery (total abdominal hysterectomy and bilateral salpingo-oophorectomy without lymphadenectomy). At a median follow-up of 52 months, 5-year locoregional recurrence rates were 4 % in the radiotherapy group and 14 % in the control group ($p<0\cdot001$), while the 5-year overall survival rates were similar in the two groups: 81 % (radiotherapy) and 85 % (controls), $p=0\cdot31$. Most (73 %) of the local recurrences were restricted to the vagina. The overall incidence of distant metastases was similar in both groups: 8 % in the radiotherapy group and 7 % in the control group. Treatment-related complications occurred in 25 % of radiotherapy patients and in 6 % of controls ($p<0\cdot0001$). It was concluded from this trial that postoperative EBRT for stage I patients (with high-risk features for locoregional relapse) reduced locoregional recurrence but has no impact on overall survival (OS) [8, 9]. Additionally, EBRT increased treatment-related morbidity [9].

In the GOG 99 (Gynecologic Oncology Group) trial, adjuvant whole pelvic EBRT (50.4 Gy) for stage IB, IC, and II (occult) patients had a substantial positive impact on 2-year cumulative recurrence (12 % in the observation group and 3 % in the EBRT group; $p=0.007$). The treatment difference was particularly evident among the high-intermediate-risk group subgroup (2 years in cumulative recurrence was 26 % in the observation arm versus 6 % in the RT arm). Thus adjuvant radiation resulted in 58 % reduction in the hazard for any relapse in high-intermediate-risk group. The estimated 4-year OS did not differ between the observation and the EBRT groups (86 % versus 92 %; $p=0.56$) [5].

In the ASTEC/EN.5 trial, patients with high-intermediate and high risk (including stages IA and IB grade 3, IC of all grades, and serous or clear cell histology) were randomized to receive postoperative adjuvant EBRT (40–46 Gy) or observation. At a median follow-up of 58 months, the overall survival with EBRT was no better than observation with a hazard ratio $1\cdot05$ (95 % CI $0\cdot75$–$1\cdot48$; $p=0\cdot77$). Despite randomizing high-risk group women, the isolated locoregional recurrence rate in ASTEC/EN.5 (5-year cumulative incidence $6\cdot1$ % in observation versus $3\cdot2$ % in external beam radiotherapy arm) is similar or lower than that seen in other trials recruiting low-risk/intermediate-risk women. Only 35 % (42 of 120) of the total recurrences were isolated local recurrence, and the small reduction in isolated local recurrence (absolute difference of 2.9 %) did not translate into an effect on overall or recurrence-free survival [10]. The ASTEC/EN.5 findings suggested that brachytherapy might be an effective strategy for local control with less toxicity compared to EBRT, and this formed the basis of PORTEC-2 trial.

In PORTEC-2 trial, patients with high-intermediate risk (age >60 years and stage IC G1 or G2 disease, stage IB grade 3 disease, or any

age and stage IIA disease) were randomized to receive pelvic EBRT (46 Gy) or VBT (21 Gy high-dose rate or 30 Gy low-dose rate). Five-year locoregional recurrence rate (EBRT versus VBT = 2.1 % versus 5.1 %; $p = 0.17$), OS (79.6 % versus 84.8 %; $p = 0.57$), or disease-free survival (DFS, 78.1 % versus 82.7 %; $p = 0.74$) did not differ between the two groups. This trial concluded that VBT is effective in ensuring vaginal control and a better quality of life, with fewer gastrointestinal toxic effects (12.6 %) than with EBRT (53.8 %) [11, 12].

The updated systematic review and meta-analysis confirms that adjuvant EBRT reduces locoregional recurrence but does not improve CSS (cancer-specific survival) or OS in stage I endometrial carcinoma. EBRT is associated with statistically significantly increased morbidity and a reduction in quality of life [13]. Despite the inclusion of differing risk profiles of patients, the rates of death from disease were similar in women participating in the PORTEC-1, PORTEC-2, and ASTEC/EN.5. These unsatisfying outcomes are the rationale for the adjuvant systemic therapy in early-stage endometrial cancer with high-risk factors.

Thus it can be seen that adjuvant radiation therapy in early-stage endometrial cancer reduces locoregional recurrence rates but has no impact on overall survival. This is at least partly attributable to the excellent outcome of majority of early-stage patients such that any benefits are incremental and hard to prove and one of the reasons why there are continuing questions about the role and place of this modality in the management of these patients. This has also stimulated continuing interest in exploring systemic therapy options in order to impact survival outcomes.

Role of Chemotherapy in Early-Stage Disease: Adjuvant Chemotherapy Versus Observation Trials

Hirai et al. assessed the efficacy of adjuvant chemotherapy in stage I endometrial cancer; 251 primary surgically treated stage I patients were studied [14]. Of 54 patients with lymphovascular space invasion, 10-year survival rate in patients who had surgery followed by adjuvant chemotherapy ($n = 23$) was 86 %, while in patients who had surgery alone ($n = 31$), it was 59 %. This difference in outcome was statistically significant ($p = 0.02$). This trial also indicated that lymphovascular space invasion is the most significant prognostic factor in both 5- and 10-year survival rates ($p = 0.001$ at both times), and stage/depth of invasion is significant for the 10-year survival rate ($p = 0.04$).

A retrospective analysis of 170 cases with endometrioid histology, FIGO stage I or II, was done by Akoi et al. Non-endometrioid histologic subtypes such as serous and clear cell subtypes were excluded. Surgery was followed by adjuvant postoperative chemotherapy, consisting of intravenous cisplatin (70 mg/m^2), doxorubicin (40 mg/m^2), and cyclophosphamide (500 mg/ m^2) (CAP) given every 4 weeks for three courses in 41 patients. No whole pelvic or vaginal radiation was given in these patients. To select a high-risk subgroup that might benefit from adjuvant systemic therapy in patients with FIGO stage I or II, the investigators divided early-stage patients into low-risk group and high-risk group based on four prognostic factors (LVSI, tumor grade, cervical invasion, and depth of myometrial invasion). Five-year disease-free survival and overall survival in the low-risk group (with 0 or 1 prognostic factor) were 97.4 % and 100 %, respectively. In the high-risk group, disease-free survival and overall survival rates were significantly lower as compared to the low-risk group ($P < 0.001$). Among high-risk patients, the 5-year DFS and OS were 88.5 % and 95.2 % in 26 patients treated with adjuvant chemotherapy and 50.0 % and 62.5 % in eight cases who underwent only surgery ($p = 0.0150$ and $p = 0.0226$, respectively). This trial concluded that the high-risk group of patients should be treated with postoperative adjuvant CAP to decrease distant failure and improve prognosis [15]. The relatively small number of patients and the retrospective nature of this study limit the power of these conclusions.

Kodama et al. conducted a retrospective study in 167 patients with surgically staged IB–II and IIIA (positive peritoneal cytology only) to assess

the efficacy of adjuvant chemotherapy [16]. Of these, 58 patients (34.7 %) underwent combination chemotherapy comprising cyclophosphamide-epirubicin-cisplatin or paclitaxel-pirarubicin-carboplatin. Adjuvant chemotherapy was administered to 14 of 23 patients with histologic grade 3 tumors. The 5-year OS rate for these patients was 92.3 %, significantly higher than that in patients who had not received chemotherapy (50.0 %). The authors concluded that histologic grade 3 is an independent prognostic factor in patients with endometrial cancer and adjuvant chemotherapy might improve survival in these patients.

The abovementioned studies suggest that adjuvant chemotherapy might improve survival in early-stage endometrial cancer patients with high-risk factors. However, these studies lack a well-designed control arm, trials subdivided early-stage patients in different ways, and the numbers of patients included are small. Because of this heterogeneity, it is difficult to confidently recommend adjuvant chemotherapy in early-stage patients.

Role of Chemotherapy in Early-Stage Disease: Trials Evaluating Combination or Sequential Radiation Therapy and Chemotherapy

In a Finnish trial, patients with stages IA–IB G3 ($n=28$) or IC–IIIA grades 1–3 ($n=128$) were randomized to receive pelvic EBRT (56 Gy) or chemoradiotherapy [EBRT combined with three courses of cisplatin (50 mg/m^2)-epirubicin (60 mg/m^2)-cyclophosphamide (500 mg/m^2)]. The first cycle was given immediately after the surgery. The second one was carried out during the pause in radiotherapy and the last within 2 weeks after the completion of the second radiation course. The disease-specific 5-year OS was 84.7 % in the EBRT group versus 82.1 % in the CTRT group ($p=0.148$). The median disease-free survival was 18 (range 9–36) months with EBRT and 25 (range 12–49) months with CTRT ($p=0.134$), respectively. The addition of CT failed to improve OS or the recurrence rate, but the patients in RT group lived a median of 23 months as compared to 37 months in CTRT group ($p=0.148$). Chemotherapy was reasonably well tolerated. Grade 3/4 leucopenia was seen in 50 % patients but only 6.2 % of the patients had grade 3 infection. While designing this trial, it was presumed that the 5-year survival rate in the radiation-only group would be 60 %, and the study was powered to detect a 20 % difference in the 5-year survival in favor of the chemotherapy group (i.e., from 60 % to 80 %). In fact, the 5-year disease-free survival in the radiotherapy-only group was 25 % better than expected (84.7 %). Thus this trial was underpowered for the actual survival differences between the arms and a smaller, but clinically meaningful, benefit of adjuvant chemotherapy cannot be ruled out [17].

The EORTC 55991 trial included stage I–IIIC patients and compared EBRT with or without VBT plus cisplatin-based multi-agent chemotherapy versus EBRT with or without VBT. Several CT regimens were allowed – CAP, AP, or paclitaxel plus carboplatin for a total of four cycles. RT was given before CT in the sequential radiotherapy and chemotherapy arm. The 5-year PFS and OS were better for the combined radiotherapy plus chemotherapy arm (HR = 0.62, 95 % CI = 0.40–0.97, $p=0.03$, and HR = 0.65, 95 %CI = 0.40–1.06, $p=0.08$, respectively). Despite the fact that 27 % of the patients who were randomized to CT-RT arm did not received chemotherapy, radiotherapy plus chemotherapy was still found to be better than RT alone as adjuvant therapy for patients with high-risk early endometrial cancer [18]. Similar trial (ILIADE-III) was performed by the Gynecologic Oncology Group at the Mario Negri Gynecologic Oncology group (MaNGO) which compared pelvic RT with combined radiotherapy plus chemotherapy in stage IIB and IIIA–C disease. In this trial chemotherapy was given before radiation therapy and consisted of three courses of cisplatin (50 mg/m^2) and doxorubicin (60 mg/m^2) at 3-week interval. Since neither trial was large enough to show a statistically significant benefit, the results were combined for a total of 534 patients randomized to receive pelvic radiotherapy with or without chemotherapy. In the combined

analysis, the estimate of risk for relapse or death was similar but with narrower confidence limits (HR 0.63, CI 0.44–0.89; $p=0.009$). Overall survival approached statistical significance (HR 0.69, CI 0.46–1.03; $p=0.07$). Combined modality seems better from these trials, but these studies had few limitations – the eligibility criteria allowed inclusion of patients with several risk levels of the disease, different CT regimens were used, and lymphadenectomy was optional and performed in a fraction of the patients [18].

These studies suggest that addition of adjuvant chemotherapy to radiation therapy improves progression-free survival in early-stage endometrial cancer with high-risk features.

Role of Chemotherapy in Early-Stage Disease: Trials Evaluating Radiation Therapy Versus Chemotherapy

In the Japanese Gynecologic Oncology Group (JGOG) randomized trial, stage IC–IIIC patients with deep (≥50 %) myometrial invasion and <75 years of age received adjuvant pelvic RT (45–50 Gy EBRT) or cyclophosphamide (333 mg/m^2)-doxorubicin (40 mg/m^2)-cisplatin (50 mg/m^2) for three or more courses. The majority (77.4 %) of patients had stage IC or II lesions. The 5-year PFS in the EBRT and chemotherapy groups was 83.5 % and 81.8 %, while the 5-year OS was 85.3 % and 86.7 %, respectively. These rates were not significantly different in intermediate-risk group defined as stage IC patients under 70 years old with G1/2 endometrioid adenocarcinoma. However, among 120 patients in high-intermediate-risk group defined as stage IC in patients over 70 years old or with G3 endometrioid adenocarcinoma or stage II or IIIA (positive cytology), the chemotherapy group had a significantly higher 5-year PFS rate (83.8 % versus 66.2 %, log-rank test $p=0.024$, hazard ratio 0.44) and higher 5-year OS rate (89.7 % versus 73.6 %, log-rank test $p=0.006$, hazard ratio 0.24). Moreover, adverse effects were not significantly increased in the CAP arm when compared with those in the EBRT arm. The authors concluded that adjuvant platinum-based combination chemotherapy is a suitable alternative to radiotherapy for intermediate-risk endometrial cancer. In patients with high-intermediate-risk endometrial cancers, the adjuvant chemotherapy improved the prognosis significantly compared to pelvic radiation. The above results were derived from post hoc analysis, and hence the validity is limited [19]. Demonstration of a true advantage of chemotherapy requires a large-scale randomized controlled trial with stratification for risk factors prior to randomization.

Maggi et al. [20] included patients with high-risk early disease (stage IC–II, grade 3 tumors with >50 % myometrial invasion, stage III) and compared EBRT alone (45–50 GY) versus adriamycin and cisplatin every 28 days for five cycles. The primary end points were overall and progression-free survival. After a median follow-up of 95.5 months, there was no difference between chemotherapy and radiation therapy with respect to OS (HR = 0.95, 95 % confidence interval (CI), 0.66–1.36; $p=0.77$) and PFS (HR = 0.88, 95 % CI, 0.63–1.23; $p=0.45$). Radiotherapy tended to delay local relapses and chemotherapy distant metastases, but these trends did not achieve statistical significance. Overall, both treatments were well tolerated. The above randomized trials are listed in Table 24.1.

A meta-analysis was done by Park et al. to define the role of adjuvant chemotherapy combined with postoperative radiotherapy in patients with endometrial cancer. The analysis included three observational studies and three randomized clinical trials. It showed that the combined modality group had a significant survival benefit compared to radiation alone in advanced-stage endometrial cancer (OS HR = 0.53, 95 % CI 0.36–0.80; PFS HR = 0.54, 95 % CI 0.37–0.77), but no benefit in early-stage endometrial cancer (OS HR = 0.96, 95 % CI 0.70–1.32; PFS HR = 1.00, 95 % CI 0.39–2.58) [21]. The limitations of this analysis include lack of comprehensive surgical staging (pelvic lymph node dissection) in all cases, heterogeneity in chemotherapy regimens, small sample sizes, and inclusion of non-randomized observational studies.

To definitively address whether chemotherapy improves survival in early-stage uterine cancer,

Table 24.1 Randomized trials in early-stage endometrial cancer

Study	Study population	Control arm	Experimental arm	Outcome
Kuoppala et al. [17]	Stage IA–B G3, IC–IIIA	$n=72$ Pelvic RT	$n=84$ Pelvic RT+ CEP	5-year PFS: CT-RT – 82 % RT – 77 % (NS) 5-year DSS: CT-RT – 85 % RT – 82 % (NS)
Maggie et al. [20]	FIGO stage IC grade 3 or stage IIA/B grade 3 with >50 % myometrial invasion or FIGO stage III Non-serous/non-clear cell carcinoma	$n=166$ Pelvic RT ± PART	$n=174$ CAP every 4 weeks × 5	5-year OS CT 66 %, pelvic RT 69 % 5-year PFS CT 63 %, pelvic RT 63 %
JGOG 2033 [19]	Stages IC–IIIC with >50 % myometrial invasion	$n=192$ Pelvic RT ± VBT	$n=193$ CAP every 4 weeks × 3	5-year PFS: 84 % vs. 82 % (NS) HIR: 66 % vs. 84 % ($p=0.024$) 5-year OS: 85 % vs. 87 % (NS) HIR: 74 % vs. 90 % ($p=0.006$)
NSGO/ EORTC [18]	Stage I–III (high-risk profile) serous/ clear cell histology included	$n=196$ Pelvic RT ± VBT	$n=186$ CAP, AP, PC,PEC – 3–4 weekly × 4 #	5-year PFS: 72 % vs. 79 % ($p=0.04$) 5-year OS: 76 % vs. 83 % (NS)
MaNGO ILIADE-III [18]	Stages II–IIIC Serous/clear cell histology excluded	$n=76$ Pelvic RT	$n=80$ Pelvic RT + AP	5-year PFS: 61 % vs. 74 % (NS) 5-year OS: 73 % vs. 78 % (NS)
PORTEC-3 [22]	Stages I–III (high-risk profile)	Pelvic RT	Pelvic RT/cisplatin + PC (4 cycles)	Ongoing study
GOG 249	Stage I with HIR with (±) cytology Stage II any histology Stage I–II serous or clear cell and (–) cytology	Pelvic RT	VBT plus PC	Ongoing study

PART para-aortic RT, *VBT* vaginal brachytherapy, *CAP* cyclophosphamide/doxorubicin/cisplatin, *CEP* cyclophosphamide/epirubicin/cisplatin, *PC* paclitaxel/carboplatin, *AP* adriamycin/paclitaxel, *HIR* high intermediate risk

protocols PORTEC-3 and GOG 249 were designed. PORTEC-3 randomized patients with high-risk early disease (stages I–II, grade 3) and patients with locally advanced disease (stages IIIA–IIIC) to EBRT versus concurrent cisplatin and EBRT followed by carboplatin and paclitaxel [22]. GOG 249 randomized early-stage HIR (high-intermediate-risk) patients to EBRT versus VBT followed by three cycles of carboplatin and paclitaxel. The results of these studies will definitively answer whether or not systemic chemotherapy has a place in the management of high-risk early-stage EC.

Role of Chemotherapy in Early-Stage Disease: Studies in Early-Stage Endometrial Cancer of Non-endometrioid Histologic Types

It is well known that papillary serous carcinomas (PSC) and clear cell carcinomas (CCC) have a poorer prognosis even in the early stages and most relapses are outside the pelvis [16]. These histologic types have been included together with stages III and IV as high-risk groups in many, but not all, studies. In a large population-based study, Hamilton et al. compared the survival of PSC or

CCC patients with that of grade 3 endometrioid carcinomas (G3EC) patients [23]. Of 4,180 women, 1,473 had PSC, 391 had CCC, and 2,316 had G3EC. A higher proportion of patients with PSC and CC had stage III–IV disease compared to those with G3EC (52 % and 36 % versus 29 %; $p=0.0001$). The 5-year disease-specific survivals for women with UPSC, CC, and G3EC were 55 %, 68 %, and 77 %, respectively ($P=0.0001$). In multivariate analysis, advanced stage, PSC or CCC cell types, and old age were found to be the independent predictors of poor survival.

A GOG phase II trial evaluated the outcome of whole abdominal radiotherapy (WAR) in patients with clinical stage I–II PSC or CCC [24]. After surgery, patients received radiotherapy to the abdomen (3,000 cGy at 150 cGy/day) along with a pelvic boost (1,980 cGy at 180 cGy/day). The 5-year PFS for PSC and CCC were 38.1 % and 53.9 %, respectively. More than half of treatment failures were within the radiation field. It was concluded that other adjuvant approaches such as chemotherapy or chemoradiotherapy are required in stage I and II cases of PSC or CCC.

Kelly et al. evaluated the efficacy of adjuvant platinum-based chemotherapy and vaginal cuff radiation in 74 surgical stage I patients with PSC who underwent complete surgical staging [25]. Twenty of 43 (47 %) patients who did not receive platinum-based chemotherapy recurred compared to 1 of 32 (3 %) who received platinum-based chemotherapy. None of the 43 patients who received radiation to the vaginal cuff showed local recurrence compared to 6 of 31 (19.4 %) patients who did not receive this treatment. The authors highlighted the effectiveness of platinum-based chemotherapy in patients with stage I UPC and the importance of high-dose-rate vaginal cuff radiation in these patients.

PSC and CCC are clearly distinct tumors with poorer prognosis compared to endometrioid tumors. Adjuvant therapy should be offered for these types of tumors even in the early stages. A prospective randomized study is required to investigate the role of radiotherapy, chemotherapy, and chemoradiotherapy in these histologic subtypes.

Which Chemotherapy Regimen for Endometrial Cancer Patients?

The active chemotherapy drugs in endometrial cancer include platinums (cisplatin, carboplatin), anthracyclines (doxorubicin, epirubicin), and taxanes (paclitaxel, docetaxel). When used as single agents in advanced/recurrent disease, these drugs have response rates of more than 20 %. A GOG study showed that doxorubicin-cisplatin combination resulted in a significantly higher response rate compared to single-agent doxorubicin (43 % versus 17 %; $p=0.004$) while showing only modest OS benefit in patients with good performance status (median OS 9 months versus 7 months; $p=0.014$) [26]. Another GOG study (protocol 163) showed equivalent response rates (40 % versus 40 %) and OS (13.6 months versus 12.6 months) between 24-h paclitaxel-doxorubicin and doxorubicin-cisplatin [27]. Yet another GOG trial (protocol 177) randomized 263 patients to doxorubicin 60 mg/m^2 plus cisplatin 50 mg/m^2 (AP) or doxorubicin 45 mg/m^2 (day 1), cisplatin 50 mg/m^2 (day 1), and paclitaxel 160 mg/m^2 (day 2) with filgrastim support (TAP). Both regimens were repeated every 3 weeks to a maximum of seven cycles. TAP significantly improves RR, PFS, and OS compared with AP but was associated with increased grade 3 peripheral neuropathy (12 % versus 1 %, respectively) [28]. However, both doxorubicin-cisplatin and TAP cannot be recommended as standard chemotherapy regimens.

Hidaka et al. conducted a retrospective study to compare the efficacies of paclitaxel-carboplatin and CAP in patients with advanced endometrial cancer. They concluded that paclitaxel-carboplatin is a promising regimen with major activity and an accepted toxicity profile, and it could be substituted for CAP [29]. A randomized phase II trial confirmed that paclitaxel-carboplatin is superior to doxorubicin-cisplatin with regard to the patients' quality of life [30]. JGOG (protocol 2041) conducted a randomized phase II trial with docetaxel-cisplatin compared to docetaxel-carboplatin or paclitaxel-carboplatin in women with advanced or recurrent endometrial cancer. There was no difference in tumor response rates

among the three arms, but a favorable toxicity profile was reported for paclitaxel and carboplatin arm [31]. Based on above trials, combination of paclitaxel and carboplatin is now the recommended adjuvant therapy in early-stage high-risk and advanced-stage endometrial cancer patients.

The Tata Memorial Centre Policy on Adjuvant Treatment of Endometrial Carcinoma [32]

1. Type I histology (endometrioid adenocarcinoma)
   (a) Stage IA, grade 1 with no adverse risk factors – no adjuvant treatment
   (b) Stage IA, grade 1 with one or more adverse risk factors – vaginal brachytherapy
   (c) Stage IA, grade 2/3 (irrespective of adverse risk factors) – vaginal brachytherapy
   (d) Stage IB, grade 1 with no adverse risk factors – no adjuvant treatment
   (e) Stage IB, grade 1 with one or more adverse risk factors – vaginal brachytherapy
   (f) Stage IB, grade 2/3 – external beam pelvic radiation therapy + vaginal brachytherapy
   (g) Stage II – external beam pelvic radiation therapy + vaginal brachytherapy
   (h) Stage III A – chemotherapy, four cycles of paclitaxel (175 mg/m^2) + Carboplatin (AUC 5–6)
   (i) Stage IIIB – Pelvic radiation therapy + Vaginal brachytherapy
   (j) Stage IIIC – four cycles of paclitaxel + Carboplatin followed by Pelvic +/– paraaortic radiation therapy + vaginal brachytherapy
2. Type II histology (papillary serous, clear cell, adenosquamous, undifferentiated)
   (a) Indicated in stages IA/IB/II/III – four cycles of paclitaxel (175/m^2) + carboplatin (AUC 5–6) followed by external beam pelvic radiation therapy + vaginal brachytherapy

Conclusions

Adjuvant therapy in endometrial cancer is planned according to patient's performance status, disease stage, and pathological variables predictive of high risk of local or distant failure. Randomized trials and meta-analysis suggest that adjuvant pelvic irradiation significantly reduces locoregional recurrences without impacting overall survival. Although relapses occur in less than 20 % of patients with clinically early endometrial cancer, many involve distant sites. Adjuvant chemotherapy is now routinely utilized in the management of patients with advanced-stage disease. It is being increasingly evaluated and used after surgery in patients with early-stage disease who have adverse pathological prognostic factors such as deep myometrial invasion, serous or clear cell subtypes, and grade 3 endometrioid histology. Nevertheless, many questions remain unanswered in terms of patient selection, combination with adjuvant radiotherapy, and optimization of cytotoxic regimens. Phase III trials of adjuvant chemotherapy, alone or combined with sequential and/or concomitant external pelvic irradiation, will establish firm evidence on which to base therapeutic decisions.

Key Points

1. Endometrial cancer is the third common gynecological cancer affecting women. Most of the patients (around 80 %) are diagnosed in early stages (FIGO stages I and II) and have good prognosis (5-year survival ~90 %).
2. Comprehensive surgical staging which includes hysterectomy, bilateral salpingo-oophorectomy, and omentectomy with or without pelvic and paraaortic node dissection (when indicated) remains the first step in successful management of endometrial cancer.
3. Decisions regarding adjuvant therapy in endometrial cancer are dependent on histopathological risk factors for recurrence.
4. Adjuvant radiation therapy in early-stage endometrial cancer reduces the locoregional recurrence but has no impact on overall survival.
5. There is an emerging role of adjuvant chemotherapy in early-stage disease with adverse prognostic factors. It has

been shown to improve progression-free survival, but there is no definitive evidence of improved overall survival with its use.

6. Demonstration of advantage of chemotherapy requires well-designed randomized controlled trials with stratification for risk factors prior to randomization.

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Diagnosis and Management of Stage II Endometrial Cancer

25

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Introduction

Current staging guidelines define stage II endometrial carcinoma as a tumor that invades the cervical stroma but does not extend beyond the uterus. If the patient is deemed medically operable, surgical management remains the primary treatment modality with the goal of removing all gross diseases. Pathologic evaluation of the surgical specimens can help tailor adjuvant chemotherapy. Previously, adjuvant radiation was a mainstay of treatment, but controversies exist about this given the lack of data to support improved overall survival. High-risk histologic subtypes (serous, clear cell, carcinosarcoma, high-grade endometrial sarcoma, and leiomyosarcoma) should receive adjuvant chemotherapy with or without tumor-directed radiation.

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Incidence and Historical Significance

Stage II endometrial carcinoma comprises 11 % of endometrial cancer cases [1]. The relative rarity of stage II endometrial cancer made early understanding of the best approach for evaluation and management challenging. Previously, the limits of preoperative imaging and assumptions about the pattern of metastasis precluded accurate diagnoses. The extent of cervical and extrauterine involvement often went undetected until the time of exploratory laparotomy. The clinical staging system adopted by the International Federation of Gynecology and Obstetrics (FIGO) in 1971, which simply included stage II disease as carcinoma that involved the corpus and cervix, was ultimately replaced with the 1988 surgical staging system after clinical staging was found to be incorrect in about 40 % of cases [2]. The 1988 FIGO staging system further classified stage II disease into stage IIA (disease involving the endocervical glands) and stage IIB (cervical stromal invasion). Even with further classification, inaccurate staging continued as evidenced by a retrospective analysis of 174 patients that reported a false positive endocervical curettage rate of 44 % [3]. Despite this modification of the surgical staging system, clinicians continued to rely heavily on radiation therapy as primary treatment for patients with cervical involvement without an adequate assessment of extrauterine spread.

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A shift toward primary surgical management began in the early 1990s when several reports emerged regarding the impact that the sequence of surgery and radiation had on survival. A multi-institutional analysis of 184 patients with clinical and surgical stage II disease suggested that timing of radiotherapy was not an independent predictor of outcome, and surgical staging prior to radiation would provide additional pathologic information that could be used to tailor treatment [4]. Mannel et al. found in a series of 70 patients that only 37 % of patients had operative findings consistent with suspected, preoperative stage II clinical disease and suggested upfront surgery in cases of cervical involvement [5]. Supporting these findings is a study of 202 patients with endometrial carcinoma and cervical involvement. Five-year actuarial survival in patients with surgical stage II endometrial cancer was 76 %, compared to 65 % of women with clinical stage II disease [6]. These findings validated the surgical approach to diagnosis, which provided more accurate diagnoses and avoided overtreatment with radiation without compromising recurrence risk and survival.

FIGO further revised surgical staging for the primary treatment of endometrial carcinoma in 2010 [7]. Stage II endometrial carcinoma now includes any grade tumor that invades the cervical stroma, but does not extend beyond the uterus. The message from these differing staging guidelines for stage II disease remains that patients with involvement of the endocervical glands should not be upstaged and should be considered as stage I disease. Procedures prior to definitive surgical management such as fractional dilation and curettage no longer apply [8].

Preoperative Work-Up

Definitive surgical management remains the gold standard for most early stage endometrial cancer patients, but alternative treatments warrant consideration for patients with medical comorbidities. Management of patients with stage II disease begins with a thorough history and physical examination including a detailed pelvic examination with endometrial and/or cervical biopsies to determine histology if not previously obtained. Additional laboratory testing should include a CBC and chest imaging to rule out metastatic disease. Optional testing that should be considered if a patient presents with symptoms for metastatic disease include a basic metabolic profile, liver function tests, and CA125. A detailed family history must not be overlooked, and genetic counseling prior to testing should be offered in patients that present younger than 50 years old or have family members previously diagnosed with endometrial or colon carcinomas [9, 10]. Approximately 3–5 % of endometrial cancers are attributable to Lynch syndrome, and those patients with germline mutations in DNA mismatch repair genes (MLH1, MSH2, MSH6, and PMS2) have a 40–60 % lifetime risk of endometrial or colon cancers [11, 12].

Management of Endometrioid Histology

On pelvic examination, if the clinician suspects or finds gross cervical involvement, additional preoperative work-up is warranted and may include an endometrial biopsy, cervical biopsy, endocervical curettage, or MR imaging to determine histology and primary disease site and to further guide treatment planning [13, 14]. The high rate of false positives associated with endocervical curettage has challenged the value this information contributes to the preoperative work-up, but it still may be necessary if a patient has suspected cervical involvement.

If after careful preoperative work-up, there does not appear to be cervical stromal involvement, surgery including a hysterectomy, bilateral salpingo-oophorectomy, and staging should be performed by a gynecologic oncologist [15] with the goal of surgery to remove all tumors to no gross residual disease.

Complete surgical staging may be performed by a variety of approaches including laparotomy or by a minimally invasive approach. The GOG-LAP2 randomized phase III trial evaluated the ability of a surgeon to comprehensively stage patients with clinical stage I to IIA disease and found a 26 % conversion rate to laparotomy. There was no significant difference between the ability

of a surgeon to identify advanced disease by either a minimally invasive or open approach. Limitations of traditional laparoscopy were demonstrated by differences in the ability to remove lymph nodes; 8 % could not be removed via a minimally invasive approach as compared to 4 % during laparotomy ($p<0.0001$). However, there were shorter hospital stays and less postoperative events in the minimally invasive group [16]. Recurrence rates were similar: 11.4 % in the laparoscopy arm and 10.2 % in the laparotomy arm. Both groups had a 5-year overall survival of 84.8 % [17]. Robotic-assisted surgery has been increasingly adopted as another form of minimally invasive surgery. A retrospective chart review of all consecutive endometrial cancer patients was conducted for 499 patients, and projected overall survival was 77.4 % for patients with stage II disease. Results from this study as a whole demonstrated that robotic-assisted surgical staging for endometrial cancer did not adversely affect rates of recurrence or survival and that robotic-assisted laparoscopic surgical staging is not associated with inferior results when compared to laparotomy or traditional laparoscopy [18].

The surgeon should visually inspect all aspects of the peritoneum, diaphragms, and serosal surfaces and biopsy any areas suspicious for extrauterine metastasis. While obtaining peritoneal cytology does not affect the stage, current recommendations by FIGO and the American Joint Committee on Cancer (AJCC) recommend obtaining washings upon entry and reporting them [19]. In high-risk subtypes, including serous, clear cell, and carcinosarcoma, surgical staging should include an omentectomy. A pelvic lymph node dissection and/or sentinel lymph node mapping should be performed to assess for lymph node involvement. An evaluation of the para-aortic lymph nodes should be considered and/or performed between the infrarenal and intramesenteric arteries for tumors that invade greater than one-half of the myometrium are of high-grade histology. The surgeon's discretion should ultimately determine whether or not a woman may safely undergo surgical staging. Factors for consideration include length of surgery, obesity, ability for safe ventilation, blood loss, functional status, and ability to safely complete the staging from a technical standpoint.

Adjuvant Radiation Treatment for Surgically Staged

In the patient who has undergone surgical staging, adjuvant therapy depends on intraoperative findings and thorough pathologic assessment of submitted tissue. Radiation therapy remains a mainstay of adjuvant therapy in the stage II endometrial cancer patient, but controversies given the lack of data exist. Each patient should be counseled about the risk of recurrence, ability to salvage in the event of a recurrence, risk of side effects, and impact on progression-free and overall survival. A summary of the PORTEC-1, PORTEC-2, GOG 99, and ASTEC/EN.5 trials revealed that radiation administration in the adjuvant setting improved pelvic control in women with certain high-risk features but did not improve overall survival in any of these trials. The major limitation of these trials rests in that they were underpowered for patients with high-risk factors such as grade 2 and 3 disease, deep myometrial invasion, presence of lymphovascular space invasion (LVSI), and high-risk histological subtypes including serous and clear cell histologies.

PORTEC-1 included patients with grade 1 disease with greater than or equal to 50 % invasion, grade 2 with any invasion, and grade 3 with superficial or less than 50 % invasion. Stage II disease was not specifically evaluated. Findings included improved locoregional recurrence in patients with stage I disease that received postoperative radiation, but no impact on overall survival [20].

The GOG published a phase III trial in 2004 that included 448 "intermediate"-risk women with stages IB, IC, and II endometrial adenocarcinoma. Following surgery, women were randomized to receive no additional therapy or whole pelvic radiation (50.4 Gy). The difference in overall survival was not statistically significant, but there was a statistically significant difference in the cumulative incidence of recurrence (3 % in radiation arm versus 12 % in no additional therapy arm; $p=0.007$). A high-intermediate-risk group was defined as those with moderately to poorly differ-

entiated tumors, presence of LVSI, outer-third myometrial invasion, age greater than 50 with two risk factors listed previously, or age at least 70 with any above risk factor. All of the remaining women were considered to be in the low-intermediate-risk group. There was a 2-year cumulative incidence of recurrence of 26 % versus 6 % in the no additional treatment and radiation groups, respectively (relative hazard = 0.42) [21].

ASTEC/EN.5 divided 905 patients into intermediate- and high-risk groups. The intermediate-risk group included cancer confined to the uterus (stage I) or endocervical glands (IIA), with pathological features suggestive of an intermediate or high risk of recurrence including FIGO stage IA and IB grade 3, stage IC (all grades), or serous or clear cell histologies (all stages and grades). Patients were randomized after surgery consisting of hysterectomy and bilateral salpingo-oophorectomy with or without lymph node dissection to external beam radiation (target dose of 40–46 Gy in 20–25 daily fractions delivered to the pelvis five times a week) or observation. Vaginal brachytherapy was permitted in either group for all women that had stage I or IIA disease, so that 52 % and 54 % received brachytherapy in the observation and radiation groups, respectively. Five-year survival was 84 % in both groups. The 5-year local regional recurrence rate was lower in the radiation arm (3.2 % vs. 6.1 %, 95 % CI: <0.1–5.9 %) [22].

To address whether vaginal brachytherapy (delivered as 21 Gy high dose rate in three fractions or 30 Gy low dose rate) was equally effective as pelvic external beam radiation (46 Gy in 23 fractions) in the prevention of vaginal recurrence, the PORTEC-2 trial included 427 patients with stage I or IIA endometrial cancer with features of high-intermediate risk defined as age greater than 60 years, stage IC, grade 1 or 2, or stage 1B, grade 3 disease, or stage IIA disease in any age woman (apart from grade 3 with greater than 50 % myometrial invasion). All high-risk histologic subtypes including serous and clear cell carcinomas were excluded and lymphadenectomy was not required. Five-year rates of vaginal recurrence were 1.8 % and 1.6 % ($p = 0.74$) for the vaginal brachytherapy and external beam radiation therapy arms, respectively. There was no statistically significant difference between 5-year rates of local regional relapse, isolated pelvic recurrence, rates of distant metastases, overall survival, or disease-free survival. The rate of grade 1–2 gastrointestinal toxicity was lower in the arm that received vaginal brachytherapy (12.6 % vs. 53.8 %) [23].

The controversy from these four trials results because the majority of patients treated were relatively low risk based on their intrauterine pathologic risk factors. The studies did not routinely require lymphadenectomy for disease assessment, included different radiation treatment doses, and included different patient populations in their study designs.

According to the National Comprehensive Cancer Network (NCCN) guidelines, the role of adjuvant therapy should be considered in patients with stage II disease and an invasive cervical component. The extent and route of administration of radiation varies depending on grade, but other factors including age, performance status, volume of tumor, involvement of lower uterine segment, and extent of invasion into the myometrium or cervix must be considered [24]. In patients with grade 1 disease, the radiation oncologist should be consulted for administration of vaginal brachytherapy and/or pelvic radiation therapy. Patients with grade 2 disease should receive pelvic radiation therapy with vaginal brachytherapy. Pelvic radiation with vaginal brachytherapy and consideration given to concomitant chemotherapy is reserved for patients with grade 3 disease.

In a GOG study of 895 evaluable women with clinical stage I or II endometrioid adenocarcinoma, overall survival was correlated with grade. For patients with grade 1, 2, and 3 disease, 5-year relative survival was 94 %, 84 %, and 72 %, respectively [25].

The NCCN also recommends upfront radiation therapy for patients with cervical involvement that may initially have unresectable disease. In this patient population, women are typically treated with radiation therapy and/or brachytherapy with or without chemotherapy. Recommended dosages range between 75 and

80 Gy to point A followed by reconsideration of surgical management with hysterectomy, bilateral salpingo-oophorectomy, and staging if residual tumor remains and the patient is a candidate for surgery [19].

Role of Radical Hysterectomy

In the past, treatment recommendations for patients with cervical involvement included a radical hysterectomy due to the metastatic potential of the tumor given its proximity to the vasculature of the cervix and lower uterine segment. This practice pattern reflected an accepted assumption that endometrial cancer followed the same pattern of spread as cervical carcinoma, thereby involving the parametria [26]. Retrospective series reported longer survival in patients treated with radical hysterectomy [27, 28]. Publication of a retrospective study of 334 endometrial cancer patients who underwent radical hysterectomy found that LVSI better predicted involvement of the parametrium rather than of the cervix [29]. In the 28 women with histologically confirmed parametrial involvement (8.4 %), 26 cases had LVSI with one or more histological findings including the presence of invasion in greater than half of the myometrial depth; cervical invasion; metastasis to the ovary, pelvic, and/or para-aortic involvement; or positive cytologic washings [13]. These data suggested that cervical involvement alone cannot accurately predict parametrial spread.

The primary objective of primary surgical management in patients deemed to be operable candidates is the removal of all gross residual diseases. Therefore, radical hysterectomy, bilateral salpingo-oophorectomy, and complete surgical staging should be primarily reserved for those patients in whom a simple hysterectomy would cut through the primary tumor. If the pathologic diagnosis remains uncertain after a thorough preoperative review about whether the etiology is cervical or uterine, radical hysterectomy may also be warranted and may improve local control and survival when compared to extra-fascial hysterectomy [30, 31]. NCCN guidelines support management of stage II patients who have undergone radical hysterectomy with negative margins and no evidence of metastasis to be managed with observation alone or to offer radiation. This was reported in 2002 after 170 total patients with surgicopathologic stage II endometrial cancer patients were analyzed: 120 received postoperative external beam radiation and brachytherapy; 18 received external beam therapy alone; 5 received brachytherapy alone; and 27 received no radiation. Five-year overall survival and disease-specific survival were 77 % and 68 %, respectively. Prognostic factors included age ($p = 0.0008$), histologic grade ($p = 0.01$), and capillary-lymphatic space invasion ($p = 0.0007$) [32].

In patients with mucosal involvement alone, adjuvant therapy can be considered after surgical staging [33, 34]. On final pathological assessment, however, those with stromal disease, close surgical margins, or a high burden of cervical disease should be offered whole pelvic radiation with or without brachytherapy. A final treatment plan should be developed per clinician's discretion after thorough counseling of the patient given the paucity of data.

Management of Incompletely Surgically Staged

In women with clinical stage II disease who did not undergo surgical staging, consideration could be given to surgical staging procedure, confirmation of distant metastases via biopsy, and/or imaging to assess extent of disease. In patients that undergo staging, adjuvant treatment would reflect treatment regimens previously described. If the patient is not a candidate for staging, then vaginal brachytherapy, possible para-aortic radiotherapy, and consideration of adjuvant chemotherapy depending on the grade of disease and extent of disease on imaging should be discussed. More recent data have suggested that patients with occult cervical involvement with negative lymph nodes may benefit from brachytherapy alone. The rate of pelvic recurrences has ranged from 0 % to 6 % [33, 35, 36].

High-Risk Histologic Subtypes

Serous and clear cell carcinomas represent 10 % and 4 % of endometrial carcinomas [37], respectively. In women with serous, clear cell, or carcinosarcoma (malignant mixed mesodermal tumor), a detailed work-up should be performed prior to surgical staging with attempt to remove all gross diseases [38]. CA125 assessment and imaging such as MR/CT or PET should be considered. Patients with serous and clear cell cancers present with stage III and IV disease 41 % and 33 % of the time, respectively.

Adjuvant Therapy for High-Risk Subtypes

For high-grade serous, clear cell, and carcinosarcoma histologic subtypes, NCCN guidelines recommend adjuvant treatment with taxane- and platinum-based chemotherapy with or without tumor-directed radiation therapy for stage II disease.

GOG 99 evaluated patients with clinical stage I and II disease and serous and clear cell histologies. After surgical management, patients received radiation (3000 cGy) with a pelvic boost (1980 cGy). Over half of the treatment failures occurred within the radiated field, suggesting additional chemotherapy should be considered for sensitization of the tumors [39, 40].

Taxane- and platinum-based regimens remain the current standard of care for serous and clear cell histologies [41]. "Sandwich therapy" has been evaluated in a phase II trial in women with stage I–IV disease after resection to no gross residual disease. Following surgery, patients received paclitaxel (175 mg/m^2) and carboplatin (AUC 6–7) every 3 weeks for three cycles, followed by radiation, and another three cycles of chemotherapy. Progression-free and overall survival for patients with stage I and II disease was 65.5 ± 3.6 months and 76.5 ± 4.3 months, respectively. Probability of 3-year survival for patients with stage I and II disease was 84 % [42]. Consideration may be given to radiation therapy, but results are conflicting, and data suggest that chemotherapy with or without additional radiation is more effective than radiation alone.

Paclitaxel and ifosfamide are the recommended treatment regimen for patients with carcinosarcoma. In a study with 65 evaluable patients, including 23 % with stage II disease, women with completely resected stage I and II carcinosarcoma were treated with ifosfamide (1.5 g/m^2) and cisplatin (20 mg/m^2) followed by mesna (120 mg/m^2 then 1.5 g/m^2 over 24 h as a continuous infusion). Two-year progression-free survival and overall survival were 69 % and 82 %, respectively. Overall 5-year survival was 62 % [43]. A phase III trial of patients with stage III, IV, and recurrent carcinosarcoma showed a survival advantage of 13.5 months in the arm treated with combination ifosfamide and paclitaxel versus ifosfamide alone [44]. In a multi-institutional cohort study of 111 women with stage I (85 %) and II (15 %) carcinosarcoma, the majority of women (40 %) received no additional therapy, 26 % received chemotherapy, 20 % received radiation, and 14 % received combination chemotherapy and radiation. Adjuvant chemotherapy was associated with improved progression-free survival [45]. Consideration may also be given to carboplatin (AUC 6) and paclitaxel (175 mg/m^2) given results of a phase II trial that showed a response rate of 54 %, as this study included only stage III and IV patients [46].

GOG 150 has been the only randomized phase III prospective trial evaluating the role of adjuvant radiation in patients with carcinosarcoma. After optimal surgical cytoreduction, patients received adjuvant radiotherapy (30 Gy of external beam radiation to the pelvis with a pelvic boost for a cumulative dose to 50 Gy) or chemotherapy (three cycles of cisplatin and ifosfamide). Women in the chemotherapy arm had a 32.8 % lower estimated death rate ($p = 0.042$) [47]. The most recent update of this study occurred after 63 months; the 5-year survival was 35 % versus 45 % for those receiving radiation and chemotherapy, respectively [48]. For stage II disease, the breakdown for the radiation versus chemotherapy arms was 11 out of 105 (10.5 %) versus 15 out of 101 (14.9 %) [47]. Overall, the data for radiation after diagnosis of carcinosarcoma remain mixed. Retrospective data, however,

suggest that adjuvant chemotherapy and radiation may offer women with stage II disease longer overall survival [49–51].

Adjuvant Chemotherapy

The role of chemotherapy has been evaluated in several randomized trials in women with stage II disease. In a 2006 study by Maggi et al., 345 patients with stage IC grade 3, stage II grade 3 disease with greater than 50 % myometrial invasion, and stage III disease were randomized to receive chemotherapy with adjuvant cisplatin (50 mg/m^2), doxorubicin (45 mg/m^2), and cyclophosphamide (600 mg/m^2) for five cycles every 28 days or external radiation therapy (45–50 Gy 5 days per week). The 3-, 5-, and 7-year overall survivals were 78 %, 69 %, and 62 % for the women who were in the radiation group and 76 %, 66 %, and 62 % in the chemotherapy arm. The 3-, 5-, and 7-year progression-free survivals were 69 %, 63 %, and 56 % and 68 %, 63 %, and 60 %, respectively. No differences in overall survival were seen in either arm [52].

The Japanese GOG published their findings of 385 intermediate- and high-risk endometrial cancer patients with stage IC to IIIC endometrial carcinoma with greater than 50 % myometrial invasion. Women were randomized to receive adjuvant pelvic radiation therapy (at least 40 Gy) or chemotherapy (cyclophosphamide at 333 mg/m^2, doxorubicin at 40 mg/m^2, and cisplatin at 50 mg/m^2 every 4 weeks for three or more cycles). They found no statistically significant difference in overall or progression-free survival. In a separate analysis of 120 patients with high- to intermediate-risk factors (defined as stage IC in patients, age greater than 70 years old, or with grade 3 endometrioid adenocarcinoma or stage II or IIIA). Patients in the chemotherapy arm had a statistically significant longer progression-free survival (83.8 % vs. 66.2 %; $p=0.024$) and longer overall survival (89.7 % vs. 73.6 %; $p=0.006$) [53].

A Finnish study randomized 156 women with stage IA–B grade 3 or stage IC–IIIA grade 1–3 disease to radiation alone (divided into two courses of 28 Gy each separated by 3 weeks) or radiation with three cycles of chemotherapy (cisplatin at 50 mg/m^2, epirubicin at 60 mg/m^2, and cyclophosphamide at 500 mg/m^2). The first cycle of chemotherapy was administered 1–2 weeks after cytoreduction, the second was given during a break in radiation, and the final cycle was given 2 weeks following completion of the last radiation course. Again, there was no difference in overall survival, but the chemotherapy and radiation arm demonstrated increased progression-free survival by 7 months ($p=0.134$) [54].

In another analysis, the results of two randomized studies were pooled (NSGO-EC-9501/EORTC-55991 and MaNGO ILIADE-III) and included 534 evaluable patients with stage I, II, and IIIA (positive cytology only) or IIIC (positive pelvic lymph nodes), patients at high risk for micrometastases, and serous, clear cell, or anaplastic histologies. Women received adjuvant pelvic radiation with or without brachytherapy and with or without chemotherapy. The regimens included four cycles of cisplatin (50 mg/m^2), doxorubicin (50 mg/m^2), or epirubicin (75 mg/m^2) prior to 2004 or paclitaxel (175 mg/m^2), epirubicin (60 mg/m^2), and carboplatin (AUC 5–6). No differences were detected in overall survival in either study when considered alone; however, there was a trend toward increased overall survival in the group that received sequential chemotherapy and radiotherapy. The combination of chemotherapy and radiation demonstrated a 36 % reduction in relapse risk or mortality (HR 0.64, CI 0.41–0.99, $p=0.04$) in the NSGO/EORTC study. The MaNGO study had a similar trend but was not statistically significant. The pooled analysis approached statistical significance in overall survival (HR 0.69, 95 % CI 0.46–1.03, $p=0.07$) [55].

GOG 0249 is a phase III study that addresses the still unanswered question regarding management of early stage endometrial cancer patients with high-risk features. The study population includes women with stage I disease with high intermediate-risk factors (defined as grade 2 or 3 disease, LVSI, and/or invasion of the outer half of the myometrium). If the woman is greater than or equal to 70, 50, or 18 years, then one, two, and three risk factors are required, respectively. Stage II patients with any histologic subtype are included with either occult or gross cervical involvement. Finally, women with either stage I

or II disease with serous or clear cell histologies that have disease confined to the uterus are included. Women receive pelvic radiation for 5–6 weeks (total of 25–28 fractions). Patients with stage II disease or stage I disease and a diagnosis of serous or clear cell histologies may receive one to two vaginal brachytherapy boosts. Patients in arm I receive conventional or intensity-modulated pelvic radiotherapy once daily, 5 days a week, for 5–6 weeks (total of 25–28 fractions) in the absence of disease progression or unacceptable toxicity. Patients with stage II disease or stage I disease with a confirmed diagnosis of clear cell and/or papillary serous histology may also undergo one or two intravaginal (i.e., vaginal cuff) brachytherapy boost treatments. Patients in arm II received vaginal cuff brachytherapy with three to five high-dose-rate brachytherapy treatments over 2 weeks or one to two low-dose-rate brachytherapy treatments over 1–2 days. Within 3 weeks of brachytherapy administration, patients receive intravenous paclitaxel and carboplatin on day 1 with repeat administration every 3 weeks for up to three cycles [56].

PORTEC-3 is an ongoing multicenter, prospective trial randomizing women with high-risk stage IB to III endometrial cancer to two arms. In the treatment arm, women receive external beam radiation (5 days per week for 6 weeks) with concurrent cisplatin (two cycles during radiation at 3-week intervals), and patients with cervical involvement receive an additional brachytherapy boost. Three weeks later, women receive carboplatin and paclitaxel every 3 weeks for up to four cycles in the absence of disease progression. In the control arm, patients receive external beam radiation and vaginal brachytherapy if cervical involvement is present [57]. This trial along with GOG 0249 will help delineate which women fall into high-risk categories and should receive more aggressive adjuvant chemoradiation while avoiding toxicities in those who will not benefit.

Sarcomas

Women with uterine sarcoma typically present with abnormal uterine bleeding, pelvic masses, abnormal cervical cytology, and/or ascites. These tumors are frequently diagnosed as incidental findings on final pathology after surgery for a suspected benign condition such as leiomyoma. Patients with known extrauterine disease or symptoms suspicious of metastatic disease should have preoperative imaging including MR, PET-CT, or CT of the chest, abdomen, and pelvis. Because of the aggressive natures of these histologies, even suspected early stage disease warrants imaging and CA125. If disease is known to be limited to the uterus and the patient is a surgical candidate, the surgeon should perform a hysterectomy, bilateral salpingo-oophorectomy, and cytoreduction. FIGO staging of leiomyosarcomas and endometrial stromal sarcomas classifies stage II disease as tumor that extends beyond the uterus but within the pelvis; IIA involves the adnexa and IIB involves other pelvic tissues [58]. Medically inoperable patients may receive pelvic radiation and chemotherapy or chemotherapy alone.

After a careful review of imaging with experienced radiologists, surgery should be recommended based on the patient's symptoms, extent of disease outside of the uterus, and the surgeon's best prediction about his or her ability to resect the disease completely and safely.

Patients with stage II endometrial stromal sarcoma (defined here as having low-grade cytologic features on final pathology) may be managed with observation if all disease is removed with cytoreduction, and lymph node metastasis or ovarian preservation has not been shown to affect overall survival in this group of patients [59]. A 2009 study of 1010 women with endometrial stromal sarcoma from the National Cancer Institute's Surveillance, Epidemiology, and End Results Program evaluated outcomes of patients treated with surgery alone and surgery with adjuvant radiation. With a median follow-up of 54 months, radiation was not found to correlate with improved survival for any stage. Five-year overall survival was 72.2 % and 83.2 % for patients treated with surgery plus radiation or observation only, respectively [60]. For stage II patients, postoperative therapy is recommended with hormonal therapy with or without radiation. Hormonal agents that may be considered included megestrol, medroxyprogesterone, aromatase

inhibitors, and gonadotropin-releasing hormone analogues [61, 62]. Adjuvant radiation remains controversial given the lack of effect on survival but may reduce local recurrence rates with reports of 5-year actuarial survival rates of 63.4–76 % in those patients that received postoperative radiation [63, 64].

Patients with stage II undifferentiated high-grade endometrial sarcomas and uterine leiomyosarcomas should be offered adjuvant chemotherapy with or without tumor-directed radiation. A phase III trial evaluated the role of radiation for stage I and II uterine sarcomas in 224 patients with leiomyosarcomas, carcinosarcomas, and endometrial stromal sarcomas. Patients were randomized to undergo observation or receive pelvic radiation (51 Gy in 28 fractions over 5 weeks). A reduction was seen in local relapse in patients who received radiation, but there was no improvement in overall survival when compared to the observation group [65].

In a recent study by Ricci et al., 108 patients with stage I and II high-grade leiomyosarcoma were evaluated (13 % had stage II disease); 31.5 %, 32.4 %, and 39 % received no adjuvant treatment, radiation, and chemotherapy, respectively. Recurrence rates were not statistically significant based on treatment, but the radiation arm had a statistically significant higher rate of recurrence (95.2 %; $p = 0.012$). Recurrences that had been treated previously with chemotherapy had a high rate of successful treatment ($p = 0.031$) [66]. For those patients who have residual disease after surgery or distant metastatic disease at the time of initial diagnosis, chemotherapy and tumor-directed radiation should be considered. GOG 277 is a randomized phase III trial currently enrolling patients with high-risk leiomyosarcoma into two arms: a chemotherapy arm with gemcitabine and docetaxel up to four cycles followed by doxorubicin in patients without evidence of disease or observation [67]. The preferred chemotherapy regimen for uterine leiomyosarcoma is gemcitabine and docetaxel [68]. Other regimens include doxorubicin/ifosfamide, doxorubicin/dacarbazine, gemcitabine/dacarbazine, and gemcitabine/vinorelbine [19]. Single-agent options include dacarbazine, doxorubicin, epirubicin, gemcitabine, ifosfamide, liposomal doxorubicin, pazopanib, temozolomide, vinorelbine, and docetaxel [19].

Recurrence

Posttreatment surveillance should begin after a patient has concluded primary treatment. Patients with stage I and II disease have a recurrence rate of about 15 %, but the majority of these (up to 70 %) will be symptomatic and occur within 3 years of diagnosis [19]. Treatment for recurrence should be based upon the site of recurrence and prior therapy.

Summary and Conclusions

Stage II endometrial carcinoma invades the cervical stroma but does not extend beyond the uterus. Surgical management remains the primary treatment modality with the goal of removing all gross diseases. Adjuvant therapy should be tailored after complete pathologic evaluation. Controversies exist about the role of adjuvant radiation given the paucity of data to support improved overall survival. Patients whose tumors are at high risk for recurrence (serous, clear cell, carcinosarcoma, high-grade endometrial sarcoma, and leiomyosarcoma) should receive adjuvant chemotherapy with or without tumor-directed radiation.

Key Points

1. Stage II endometrial carcinoma includes any grade tumor that invades the cervical stroma, but does not extend beyond the uterus. Involvement of the endocervical glands should not be upstaged and is considered to be stage I disease.
2. Prior to definite surgical management, a detailed history and physical examination must be performed to rule out extrauterine disease including endometrial and/or cervical biopsies to confirm histological subtype if unknown.

3. Surgical staging may be performed by a variety of surgical approaches with the goal of surgery to remove all tumors to no gross residual disease.
4. In a patient who has undergone surgical staging, adjuvant therapy depends on intraoperative findings and thorough pathologic assessment of submitted tissue. Radiation therapy remains a mainstay of adjuvant therapy in the stage II endometrial cancer patient, but controversies exist given the lack of data to support improved overall survival. Each patient should be counseled on the risk of recurrence, ability to salvage their recurrence in the event of a recurrence, risk of side effects, and impact on progression-free and overall survival.
5. In patients with unresectable stage II disease, upfront radiation may be administered with or without chemotherapy.
6. Radical hysterectomy, bilateral salpingo-oophorectomy, and surgical staging should be reserved for patients in whom a simple hysterectomy would cut through the primary tumor.
7. For high-grade serous, clear cell, and carcinosarcoma histologic subtypes, adjuvant treatment with taxane- and platinum-based chemotherapy should be administered with or without tumor-directed radiation therapy for stage II disease.
8. Several ongoing studies have been designed to answer the questions that remain regarding optimal treatment of women with early stage disease and high-risk features.
9. Patients with stage II endometrial stromal sarcoma (and low-grade cytologic features) may be observed after cytoreduction to no gross residual disease. Lymph node metastasis or ovarian preservation has not been shown to affect the overall survival. Hormonal therapy is recommended postoperatively.
10. Patients with stage II undifferentiated high-grade endometrial sarcoma or uterine leiomyosarcoma should be offered adjuvant chemotherapy with or without tumor-directed radiation.

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Posttreatment Surveillance in Endometrial Cancer

26

Bindiya Gupta and Shalini Rajaram

Introduction

Endometrial cancer is the most common genital tract malignancy in the Western world with 44,000 new cases and 8000 deaths due to endometrial cancer in the United States alone annually [1]. Its incidence in India is on the rise mainly because of changes in lifestyle and obesity. In a recent study, the incidence of endometrial cancer was 2.8–4.3/100,000 women per year in various cities in India [2]. Most of the endometrial cancers are diagnosed at an early stage, as a result of which 5-year survival rates are up to 95 % in stage I disease with an overall survival of 83 % [3, 4]. Recurrence develops in 10–20 % of women in early stage and in 40–60 % of women in stages III and IV [5, 6].

Routine surveillance is aimed to detect recurrence early and institute treatment with the goal of favorable outcomes. In addition, follow-up also helps to diagnose treatment complications and provide psychological support for the patient. Most of the endometrial cancer recurrences, mostly vaginal cuff, occur within 3 years of diagnosis of primary tumor and 50–80 % of them are symptomatic [7–9]. The surveillance guidelines are more intensive for the first 5 years of posttreatment.

Guidelines for follow-up vary in different parts of the world and lack uniformity and prospective studies. There is a lack of evidence of clear benefit of follow-up protocols [10]. The National Comprehensive Cancer Network (NCCN) and American College of Obstetricians and Gynecologists recommend 3–6 monthly visits for the first 2 years, and then every 6 months or annually [11, 12]. The European Society for Medical Oncology (ESMO) recommends 3–4 monthly visits in the first 3 years, 6 monthly visits in the next 2 years, and then annually [10].

At each visit, a detailed history and physical examination should be done. Patients should be asked of any symptoms suggestive of local metastasis like vaginal bleeding, urinary complaints, changes in bowel habits, and abdominal and/or pelvic pain. Systemic symptoms like loss of appetite, lethargy, and weight loss should be ruled out. Signs and symptoms of distant recurrence like cough, headaches, hemoptysis, and back and other bony pains should be noted as up to 70 % of distant recurrences may be symptomatic [9, 13]. Hence, patient education about signs and symptoms of recurrence is integral to surveillance.

Physical examination alone detects 35–68 % of all recurrences and 80 % in presence of symptoms

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[14]. A detailed physical examination includes general physical examination for pallor, icterus, pedal edema, and lymph nodes and breast examination. A thorough abdominal and pelvic examination including per speculum and rectovaginal examination should be conducted at each visit.

Role of Imaging

Symptomatic patients with new onset pelvic and abdominal symptoms, with worsening of previous symptoms, or with a positive finding on physical examination should be subjected to ultrasound or computed tomography (CT) scan. Ultrasound may detect 4–30 % of local recurrences alone which is similar to physical examination. Various studies have concluded that survival of patients with disease detected on CT scan was similar to those diagnosed on clinical examination [15, 16]. Hence, there is no role of routine ultrasound or CT scan in asymptomatic patients. In certain centers, chest radiographs have been advocated for detection of asymptomatic recurrences every 6 months or annually because of low cost [14].

Similar to other malignancies, endometrial carcinoma has increased rate of glycolysis, which makes it a suitable target for ^{18}F-FDG PET imaging [17]. The advantage of PET is that it overcomes the limitations of MRI or CT since functional changes precede anatomical changes. PET-CT is an accurate method for detection and localization of recurrent lesions and has an overall sensitivity and specificity of 94 % [18]. Larger, prospective studies are needed to determine its exact role in routine surveillance and cost effectiveness [14].

Role of CA-125

CA-125 levels should not be used routinely and in low-risk patients, but is useful in follow-up for patients with advanced disease, elevated pretreatment CA-125 levels, high-grade lesions, and serous histology and should be done at each visit [19].

Role of Vaginal Cytology

The NCCN guidelines recommend vaginal cytology every 6 months for 2 years and annually thereafter [11]. In contrast, the Society of Gynecologic Oncology (SGO) does not support the routine use of cytology for detection of recurrence [14]. According to them, the detection rate of vault recurrence in asymptomatic patients ranges from 0 % to 7 % while it detects 25 % of all recurrences in symptomatic patients [20–22]. Hence, inclusion of vaginal cytology at each visit is not cost-effective [23].

A uniform consensus on the advantage of history and physical examination in high detection rates for recurrence is present in all guidelines. Intensive follow-up using these methods may provide psychological reassurance to some patients. However, evidence-based uniform guidelines still need to be developed for posttreatment surveillance, and the use of these methods must be balanced against limited health-care resources.

Conclusions

To conclude, uniform protocols for follow-up in endometrial cancer are yet to be developed. History and physical examination is the mainstay of surveillance and imaging is only for symptomatic patients. The role of vaginal cytology is still debatable, and CA-125 may be used for follow-up in high-risk patients.

Key Points

1. Follow-up is recommended every 3–6 months for the first 2 years, every 6 months in the next 2 years, and then annually.
2. A detailed history and physical examination is done at each visit. Vaginal cytology is recommended every 6 months for 2 years and then annually.
3. Annual chest X-ray is recommended, but routine imaging (ultrasound/CT/MRI) should only be done in symptomatic patients.
4. CA-125 is recommended in patients with advanced disease, elevated pretreatment CA-125 levels, high-grade lesions, and serous histology.

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Part IV

Advanced Stage and Recurrent Endometrial Cancer

Surgery for Advanced Endometrial Cancer

27

Shalini Rajaram and Monisha Gupta

Introduction

Endometrial cancer is a gynecological malignancy that generally has a good prognosis, largely because of the fact that approximately 75 % of women present with stage I disease [1, 2]. For early-stage disease, surgery alone or in combination with adjuvant therapy is considered optimal therapy [2].

In approximately 10–15 % of all new cases of endometrial cancer, disease is found outside the uterus. These cases account for more than 50 % of all uterine cancer-related deaths, with survival rates as low as 5–15 % [2, 3]. Due to rarity of such cases, no randomized controlled trials currently provide insight on the best treatment options.

Based on the clinical, histological, and molecular features, endometrial cancers have been classified into type I and type II tumors. Type I (endometrioid) cancers are more common (85 %), tend to be found in younger women, usually present in early stage with minimal myometrial invasion, and, thus, have good survival outcome [3]. They usually exhibit a well-differentiated histology.

Type II tumors account for a smaller percentage of endometrial cancers, tend to occur in older population, and are mostly present in advanced stage III/IV. Serous, clear cell, carcinosarcoma, and perhaps grade 3 tumors fit in to the type II category. These non-endometrioid cancers exhibit more aggressive behavior and account for large number of deaths due to endometrial cancer and hence mandate aggressive surgical management and adjuvant chemoradiation [4–10].

Pattern of Spread

Endometrial cancer spreads initially by direct infiltration into the myometrium and to the cervix and adnexa [11]. Lymph node involvement adds substantially to the morbidity associated with endometrial cancer and is one of the most important prognostic factors. Hematogenous spread to the lung and liver occurs late in the course of disease [11].

Due to high risk of occult lymph node metastasis, these cancers are treated by complete surgical staging including systematic pelvic and paraaortic nodal dissection. When type 2 endometrial cancers present in advanced stages, surgical cytoreduction is the most important component of treatment followed by adjuvant chemotherapy [4–10]. Serous cancers in view of their tendency to spread intraperitoneally like epithelial ovarian cancers also need omentectomy in addition

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to full surgical staging [4]. Carcinosarcomas are also aggressive endometrial tumors and managed by surgery followed by chemotherapy and radiotherapy [6].

Metastatic Work-Up

Because endometrial cancer is surgically staged, a preoperative assessment for disease spread is usually not indicated; however, under special circumstances, a preoperative metastatic work-up may be clinically relevant. The exceptions are when the patient is a poor surgical candidate or is symptomatic for extrapelvic disease or in cases of type II endometrial cancer, wherein the rate of extrapelvic metastasis is higher [2, 3].

Commonly used imaging modalities include computed tomography (CT) scan and magnetic resonance imaging (MRI) scan. Both have comparable accuracy in detecting lymph node metastasis, sensitivity ranging from 27 % to 66 % and specificity 73–99 % [2, 3]. However, to assess the depth of myometrial involvement and cervical stromal invasion, MRI is a better imaging modality. Literature has reported a sensitivity of 69–94 % and a specificity of 64–100 % of MRI for the assessment of myometrial invasion, respectively. The accuracy of MRI for detection of cervical stromal involvement reaches 92 % with sensitivity of 75–80 % and specificity of 94–96 % [12, 13]. Positron emission tomography integrated with CT (PET/CT scan) has higher sensitivity (50–70 %) and specificity (90–100 %) than CT/MRI in detecting lymph node involvement and distant metastasis [2, 3, 14]. However, PET/CT cannot be integrated into routine preoperative metastatic assessment for endometrial cancers, as it is not routinely available and is more expensive.

Multiple studies have evaluated the role of preoperative CA-125 as a marker for extrapelvic metastasis and have demonstrated a positive correlation between CA-125 concentrations and extrauterine disease, including lymph node metastasis. On the other hand, many studies have shown that either there is no correlation or a high false-positive rate, thus, raising a question about the usefulness of the test. Thus, again selective use of CA-125 in special situations, such as non-endometrioid high-risk pathologies that are associated with transperitoneal spread, may be helpful in the management of patients.

Management Principles

Clinical Stage II Endometrial Cancer

When both endometrium and cervix are clinically involved with adenocarcinoma, it will be difficult to differentiate between stage IB1 carcinoma cervix and stage II endometrial cancer. Histological assessment is usually not helpful; however, evaluation with immunohistochemistry markers can be done to make correct diagnosis.

Due to lack of well-designed randomized studies, the optimal mode of therapy for stage II EC cannot be stated, but current literature advocates primary surgery with type II radical hysterectomy with bilateral salpingo-oopherectomy and systematic pelvic lymphadenectomy with or without para-aortic lymphadenectomy. In stage II, lymphadenectomy is recommended to guide surgical staging and adjuvant therapy [2, 3] (for a detailed management of Stage II endometrial cancer, the reader is referred to Chap. 25)

Stage III/IVA Endometrial Cancers

The treatment paradigm for advanced FIGO stage III and IV endometrial carcinoma has shifted in the past few decades to a multimodality approach that includes surgery, chemotherapy, and radiation therapy, with cytoreduction being the most critical aspect. In cytoreductive surgery, the tumor is debulked along with hysterectomy, pelvic and para-aortic node dissection, and omentectomy. Multiple retrospective studies address the advantages of optimal cytoreductive surgery in patients with stage III and IV endometrial adenocarcinoma. Each study demonstrates a statistically significant progression-free and overall survival advantage when optimal cytoreduction was achieved [15, 16].

Support for initial maximal cytoreductive effort is provided by data showing that the extent of

residual disease among advanced-stage endometrial cancer appears to have a direct influence on survival. Theories explaining the possible advantages of cytoreduction of large-volume disease include improved performance status, decreased hypermetabolic tumor burden, improved vascular perfusion and drug delivery after resection of devitalized tissue, and decreased tumor volume. However, drug delivery after resection of devitalized tissue, and decreased tumor volume and concomitant mutation potential can lead to drug resistance. All cited studies report cytoreduction as an independent prognostic factor for overall survival. For those patients in whom the tumor was determined to be unresectable, the median survival was 2–8 months, regardless of further treatment with radiation and/or chemotherapy [15–17].

Stage IVB Endometrial Cancer

Endometrial cancer with distant metastasis at presentation is uncommon and outcomes of therapy are generally poor. Treatment of stage IVB disease must be individualized, and both location and extent of metastatic disease must be considered before making a decision for upfront surgery. There may be a role of cytoreductive surgery, although the evidence is limited to a small retrospective series from Baltimore on 65 patients with stage IVB disease. Optimal cytoreduction, defined as <1 cm of residual disease patients, was accomplished in 36 (55.4 %) patients, whereas 29 (44.6 %) patients underwent suboptimal surgery, with resulting significant benefit of 23 months in the optimally debulked women (34 vs. 11 months) in median survival between the groups ($p=0.0001$) [18]. Also, as per ESMO Guidelines 2013, for patients with stage IVB disease, palliative surgery could be considered in patients with a good performance status [2].

When surgery is not feasible due to medical contraindications (5–10 % of women), or because of unresectable disease, external radiation therapy with or without intracavitary brachytherapy to the uterus and vagina is suitable for individual clinical use [2, 3].

Role of Minimal Invasive Surgery in Management of Endometrial Cancer

Traditionally, surgical staging for endometrial cancer has been accomplished with open laparotomy. However, recent data advocates that laparoscopy should be embraced as the standard surgical approach for comprehensive surgical staging in women with endometrial cancer.

In the last two decades, multiple studies have demonstrated the feasibility of laparoscopic approach for surgical staging in endometrial cancer. And subsequently, laparoscopy has been compared with laparotomy in few randomized controlled trials. In Gynecology Oncology Group (GOG) Lap2 Trial, 2,616 women with clinical stage I to IIA were randomized in 2:1 fashion between laparoscopy and laparotomy for comprehensive staging in accordance with FIGO staging 1988. The proportion of participants randomly assigned to the laparotomy and laparoscopy arms found to have surgical stage II were identical at 6 % each. Similarly, the no. of women with advanced surgical stage (FIGO stage IIIA, IIIC, IVB) was not significantly different between the two arms (17 % vs. 17 %; $p=0.851$) [19].

Although operative time was longer for laparoscopy, the incidence of hospitalization of more than 2 days (52 % vs. 94 %; $P=0.0001$) and moderate-to-severe postoperative adverse events (14 % vs. 21 %; $P=0.0001$) were significantly lower in the laparoscopy arm as compared to the laparotomy arm. Laparoscopy patients reported higher scores on several quality-of-life measures over the 6-week recovery period compared to laparotomy patients. Also, the estimated overall 5-year survival for laparotomy and laparoscopy were almost identical at 89.8 %. Though GOG LAP2 failed to demonstrate the non-inferiority of laparoscopy compared to laparotomy with respect to recurrence, the overall recurrence rates were less than expected in both the arms, 11.4 % and 10.2 % respectively [19].

The rate of port-site metastasis after laparoscopic management of endometrial cancer has always been a concern; it is as low as <1 % in

early-stage endometrial cancer. Few studies in literature have suggested the possibility of port-site metastasis in women with disseminated intra-abdominal disease; however, the chances are very rare (1.18–1.2 %) and are considered the expression of an aggressive disease [20, 21]. Again, it emphasized the need for proper metastatic work-up before deciding the route of surgical management. Thus, port-site metastasis in patients with endometrial cancer cannot be used as an argument against laparoscopic management.

Role of Neoadjuvant Chemotherapy Followed by Debulking Surgery in Advanced Endometrial Cancer

It has already been demonstrated in multiple studies that the amount of residual disease after surgery for advanced endometrial cancer is an important prognostic factor both for median survival and progression-free interval [22, 23]. However, the rate of postoperative complications associated with primary debulking surgery for endometrial cancer (36–39 %) should be taken into consideration [24]. Neoadjuvant chemotherapy followed by debulking surgery has been administered as an alternative to primary debulking surgery for advanced ovarian cancer [24, 25]. The strategy of NACT enables to identify chemosensitive disease that is more likely to be benefitted by debulking surgery as compared to chemoresistant disease. Furthermore, due to reduced tumor burden, it permits a less morbid surgery and, thus, improves patient's quality of life due to fewer intraoperative and postoperative complications [24]. However, no randomized study has ever compared the role of NACT versus primary debulking surgery in advanced endometrial cancer [24].

Currently, patients with stage IV endometrial cancer receive either no surgery (systemic therapy) or primary debulking surgery [2, 3]. Table 27.1 presents an overview of multiple studies exploring the role of cytoreductive surgery (primary or interval) in patients with advanced endometrial cancer, and it can be clearly stated that both OS and PFS depend upon the amount of residual disease and women with no residual disease had a better outcome.

In addition, the rate of minor postoperative complications (wound infections, urinary tract infections, and deep vein thrombosis) and major life-threatening events (myocardial infarction, pulmonary embolism, small bowl obstruction) were 38 % and 13 % respectively with primary debulking surgery as compared to 13 % and 4 % respectively with interval debulking [22–24]. Thus, it can be concluded that use of NACT followed by debulking surgery is associated with a higher rate of optimal cytoreduction along with significant reduction in postoperative morbidity and better survival outcomes in advanced endometrial cancer with transperitoneal spread [24].

Table 27.1 Studies investigating the role of cytoreductive surgery in advanced endometrial cancer

Study	Stage	Histology	Surgery	Residual	%	PFS (months)	OS (months)
Bristow et al. [22]	IV	UPSC	PS	<1 cm >1 cm	52 48		
Memahzadeh et al. [33]	IIIC+IV	UPSC	PS	0 Macro	57 43	22 8	40 10
Thomas et al. [23]	IIIC+IV	UPSC	PS	0 <1 cm	37 60	9 6	51 14
Lee et al. [34]	IV	UPSC	NACT+IDS	0	100		
Prince et al. [35]	IIIC+IV	UPSC	NACT+IDS	0	100	11	17
Vandenput et al. [24]	IV	EEC+UPSC	NACT+IDS	<1 cm inoperable	80 13	13	23 12

PFS progression-free survival, *OS* overall survival, *UPSC* uterine papillary serous carcinoma, *EEC* endometrioid endometrial carcinoma, *PS* primary surgery, *NACT* neoadjuvant chemotherapy, *IDS* interval debulking surgery

Adjuvant Treatment

Radiation

The outcome of patients with isolated adnexal involvement (stage IIIA) is better than patients with isolated serosal involvement (stage IIIA), with a reported 5-year DFS of 70.9 % versus 41.5 % after treatment with pelvic radiation [26]. If pelvic lymph node involvement is present (stage IIIC1), postoperative pelvic radiation can yield a 50–60 % long-term survival in these patients; however, distant failure remains a problem [26, 27]. Furthermore, stage IIIC2 patients, by virtue of para-aortic node involvement, represent a particularly high-risk group with a higher rate of distant relapses. This has prompted many investigators to evaluate the role of whole abdominal radiation (WAR) and many chemotherapeutic drugs in advanced-stage endometrial cancers [26–28].

Chemoradiation

Multiple trials have compared chemotherapy to radiation therapy as well as to other chemotherapeutic regimens for adjuvant treatment in patients with advanced endometrial cancer.

Two randomized trials have compared radiation therapy to chemotherapeutic regimes: GOG 122 compared WAR therapy to doxorubicin/cisplatin regimen and a Japanese GOG 2033 compared whole pelvic radiation (WPR) therapy to CAP (cyclophosphamide/doxorubicin/cisplatin) [28, 29]. Both trials had shown an improved PFS and OS in chemotherapy arm, largely due to reduction in abdominal and other distant site of recurrence.

Subsequently, two randomized clinical trials (NSGO-EC-9501/EORTC-55991 and MaNGO ILIADE- III) were undertaken to clarify whether the sequential use of chemotherapy and radiotherapy improved PFS over radiation therapy alone in high-risk endometrial cancer patients (stage I–IIA, IIIC, any histology). The results of pooled analysis showed that the combined modality treatment was associated with 36 % reduction in the risk of relapse or death [hazard ratio (HR) 0.64, 95 % confidence interval (CI) 0.41–0.99; $P = 0.04$]. Cancer-specific survival was significantly different (HR 0.55, 95 % CI 0.35–0.88; $P = 0.01$) and favored the use of adjuvant chemotherapy in addition to radiotherapy [30].

Because of the safety and efficacy of carboplatin and paclitaxel in the management of other gynecologic malignancies, there is an interest in using this regimen as first-line treatment in patients with advanced endometrial cancer. A GOG 209, randomized trial was conducted to compare doxorubicin/cisplatin/paclitaxel (TAP) with carboplatin/paclitaxel (TC) in stage III, IV, and recurrent endometrial cancer. Interim analysis showed that TC was not inferior to TAP in terms of both PFS (13.5 vs. 13.3 months) and OS (40.3 vs. 36.5 months). Furthermore, the toxicity profile favored TC with less sensory neuropathy [31].

Management of Type II/Non-endometrioid Histology

Uterine Papillary Serous Carcinoma (UPSC) and Clear Cell Carcinoma

Uterine papillary serous carcinoma (UPSC) and clear cell carcinoma of uterus are biologically distinct entities. Although they represent around 20 % of endometrial cancers, they account for more than 50 % of relapses and death attributed to endometrial cancer. UPSC represents an aggressive histological subtype of endometrial cancer with 60–70 % of women presenting with disease extending outside the pelvis, with a poor 5-year survival of ~18–27 %. Similarly, clear cell carcinoma tends to occur in older women and in tamoxifen-treated breast cancer patients and is associated with higher rate of extrauterine spread [2–5].

Due to rarity of these high-risk histologies, treatment recommendations are largely based upon small, retrospective single and multi-institutional studies. Given their more aggressive behavior and pattern of recurrences, a multimodality treatment has been employed for these biologies. In one of the largest series of advanced-stage (IIIC-IV) UPSC, Rauh-Hain et al. showed that optimal cytoreduction, defined as <1 cm of

the largest residual tumor, is associated with significant improvement in median survival (39 vs. 12 months; $p=0.0001$) [32]. Similarly, Thomas et al. showed superior survival results in patients with stage III and IV clear cell carcinoma of uterus, who underwent an complete cytoreductive surgery as compared to patients with gross residual at the end of surgery [22, 23].

The role of adjuvant radiation therapy in the management of high-risk pathology, with a high propensity for distant failures or failures within the radiated field, remains elusive. Similar to endometrioid histology, platinum-based adjuvant chemotherapy in a doublet or triplet format in combination with paclitaxel and/or doxorubicin should be considered in women presenting with extrauterine disease [4, 5, 7, 22, 23].

Carcinosarcoma (CS)

Uterine carcinosarcoma (CS) is another rare but aggressive histology with 50 % patients presenting with disease extending outside uterus. Only few prospective trials have evaluated the optimal therapeutic strategy for uterine CS independently from other uterine sarcomas; therefore, disease-specific surgical management for advanced-stage uterine CS remains unclear. In a retrospective series by Tanner and Leitao [6] of 44 patients with advanced-stage CS of uterus, complete gross resection was associated with median OS of 52.3 months versus 8.6 months in patients with gross residual disease. Also, in patients who received adjuvant therapy (either chemotherapy or chemoradiation), OS was 30.1 months versus 4.7 months in patients who did not receive any adjuvant therapy. Thus, cytoreductive surgery with a goal of achieving complete gross resection, followed by adjuvant chemoradiation, can be suggested as optimal therapy for advanced-stage carcinosarcoma of uterus [2, 6].

Conclusion

Approximately 10–15 % of new cases of endometrial cancer present with extrauterine disease. Currently, there are no randomized trials for the best surgical management for advanced-stage endometrial cancers. Type II radical hysterectomy with bilateral salpingo-oopherectomy with systematic pelvic with or without para-aortic lymph node dissection has been considered the optimal surgical treatment for stage II endometrial cancer. For stage III and IVA disease, a multimodality approach with maximal effort at cytoreduction followed by adjuvant chemoradiation is recommended. Management of endometrial cancer with distant metastasis (stage IVB) should be individualized based upon the location and extent of disease and patient's performance status. NACT followed by debulking surgery for advanced-stage endometrial cancer could be a promising approach and needs to be evaluated further in randomized controlled trials. For advanced-stage non-endometrioid/type II endometrial cancers, optimal cytoreduction with maximal effort at complete gross resection followed by adjuvant chemoradiation should become the norm.

Key Points

1. Endometrial cancer usually carries a good prognosis as majority of the patients present in early stage confined to uterus; however, 10–15 % of new cases present with extrauterine disease and associated with poor survival outcomes.
2. Endometrial cancers have been divided into type I and type II cancers based upon clinical, histopathological, and molecular features. Type I cancers usually present in early stage and, thus, have good prognostic outcome, whereas type II/non-endometrioid cancers are more aggressive in behavior, accounting for more than 50 % of deaths due to endometrial cancer.
3. A preoperative metastatic work-up can be done when the patient is a poor surgical candidate or is symptomatic for extrapelvic disease or in cases of type II

endometrial cancers. Both CT and MRI exhibit similar efficacy for detection of extrapelvic metastasis and lymph node involvement. However, MRI is a better modality for depth of uterine invasion. Similarly, selective use of CA-125 levels for non-endometrioid histology can be of clinical utility to detect transperitoneal spread.

4. Although, there are no randomized prospective studies, current evidence advocates type II radical hysterectomy with bilateral salpingo-oopherectomy with systematic pelvic and para-aortic lymph node dissection for clinical stage II EC.
5. For advanced-stage III and IVA endometrial carcinoma, a multimodality approach with surgery, chemotherapy, and radiation therapy is recommended. Optimal cytoreduction involving tumor debulking with total abdominal hysterectomy and bilateral salpingo-oopherectomy and pelvic and para-aortic lymph node dissection with omentectomy is associated with improved survival.
6. Individualized management of EC with distant metastasis (stage IVB), based upon location and extent of metastatic disease, should be adopted. There may be a role of cytoreductive surgery in patients with good performance status.
7. There is emerging level I evidence that laparoscopy should be considered as new standard surgical approach for comprehensive surgical staging in endometrial cancers; however, the possibility of port-site metastasis should be kept in mind in women with disseminated intra-abdominal disease.
8. Multiple studies have shown that NACT followed by debulking surgery in advanced endometrial cancer is associated with higher rate of optimal cytoreduction and a significant lower rate of postoperative morbidity; however, randomized controlled trials comparing the two strategies are needed.
9. There is robust evidence in the literature regarding optimal adjuvant therapy after cytoreductive surgery for advanced EC, and it recommends the use of adjuvant chemotherapy in addition to radiation therapy. Due to better toxicity profile, a combination of carboplatin and paclitaxel is the favored regimen.
10. For type II/non-endometrioid tumors, cytoreductive surgery with a goal of achieving complete gross resection, followed by adjuvant chemoradiation, has been suggested; however, due to rarity of these tumors, no randomized trial has ever evaluated optimal therapeutic strategies for these tumors.

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Systemic Treatment of Advanced Endometrial Carcinoma

28

Arun Warrier

Introduction

Endometrial cancer has shown a rising trend over the past 30 years. The incidence has gone up by 21 % since 2008, and the death rate has increased by more than 100 % over the past two decades [1]. Adoption of a sedentary lifestyle with a rising proportion of obesity in the population has been postulated as a major reason. In adipose cells, aromatization of androstenedione to estrogen occurs. Although there is strong data correlating hyperestrogenism and low-grade endometrial cancers, recently link with higher-grade/stage tumors also has been reported [2]. As the median age of endometrial cancer is 63 years, aging population with an increase in average life span also contributes to rise in incidence. Racial disparity as evidenced by higher mortality rates and poor response to treatment in African American when compared to Caucasian women has remained unexplained despite genetic profiling and matching for stage/grade of cancer [3]. In early-stage disease which comprises almost 85 % of case, advancements in surgical techniques as well as staging, focused/limited radiation, and incorporation of structured chemotherapy have dramatically improved outcomes. In developed countries, stage 3 comprises 12 % and stage 4 less than 5 % of endometrial cancers [4]. Depending on the histology, there is wide variation in response to systemic treatment. The more common endometrioid histology has good prognosis compared to serous and clear cell histology. Systemic management encompasses chemotherapy, hormone manipulation, and molecularly targeted agents. In high-grade tumors with a rapid growth pattern and visceral metastases, chemotherapy is preferred. With the advent of molecular profiling, cancer signaling pathway mutations in endometrial carcinoma have been understood. Various agents to target these have been developed, and many are still in clinical trials.

Chemotherapy

Chemotherapy has been used in the management of endometrial carcinomas for the last 40 years. In the 1970s, cisplatin and cyclophosphamide were the favored drugs, and adriamycin was added in the 1980s. This was followed by the era of taxanes. Various other single-agent drugs like ifosfamide, methotrexate, vincristine, and liposomal doxorubicin have also been used. The response rates for single agent in chemotherapy-naive patients are given in Table 28.1 [5].

In order to improve the response rates, combination chemotherapy was introduced. Initially two drug combinations and later three drug combinations were used (Table 28.2).

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Table 28.1 Response rates to single-agent therapy [5]

Drug	Dose	Response rate (%)
Cisplatin	50–100 mg/m^2 every 3 weekly	18–27
Doxorubicin	50–60 mg/m^2 every 3 weekly	22–32
Paclitaxel	175–250 mg/m^2 every 3 weekly	36

Table 28.2 Response rates to combination chemotherapy

Combination	Number of patients	CR + PR%	Ref
Cyclophosphamide + doxorubicin	26	31	[6]
Doxorubicin + cisplatin	30	60	[7]
Cyclophosphamide + doxorubicin + cisplatin	87	45	[8]
Paclitaxel + doxorubicin + cisplatin	133	57	[9]
Paclitaxel + carboplatin	**1300**	51	[10]

GOG 122 trial results were published in 2006, and this compared whole-abdominal irradiation (WAI) versus doxorubicin and cisplatin (AP) chemotherapy in advanced endometrial carcinoma [9]. At 5 years, adjusting for stage, 55 % of AP patients were predicted to be alive compared with 42 % of WAI patients. Significant side effects of AP therapy are hematologic, which includes grade 3/4 neutropenia (55 %) and non-hematologic, namely, grade 3/4 alopecia (72 %) and nausea/vomiting (36 %). In the **GOG 177** trial, addition of paclitaxel improved objective response (57 % vs. 34 %; $P<0.01$), PFS (median, 8.3 vs. 5.3 months; $P<0.01$), and OS (median, 15.3 vs. 12.3 months; $P=0.037$) [11]. Use of growth factor support ensured that febrile neutropenia was just 3 % in the TAP arm (doxorubicin, cisplatin, and paclitaxel) compared to AP (cisplatin + doxorubicin). Neurologic toxicity was worse for those receiving TAP, with 12 % grade 3 and 27 % grade 2 peripheral neuropathy, compared with 1 % and 4 %, respectively, in those receiving AP. As endometrial carcinoma is a disease of the elderly with multiple comorbidities, intensification of chemotherapy led to an increased but tolerable rise in toxicities. From a chemotherapy perspective, cisplatin is highly emetic, and drug delivery requires close monitoring of hydration to prevent complications. As carboplatin was being substituted in many other solid malignancies, the same approach was tested in **GOG 209**. In chemotherapy, naive women with stage III, IV, or recurrent disease doxorubicin, cisplatin, and paclitaxel (TAP) were compared with carboplatin and paclitaxel (TC). In this non-inferiority trial, the PFS (median PFS of TAP vs. TC: 13.5 vs. 13.3 months) and OS (40.3 vs. 36.5 months) were similar. The toxicity profile favored TC with less sensory neuropathy (sensory neuropathy >grade 1: 26 % vs. 19 %, $p<0.01$) [10] in TC regimen; chemo schedule is as carboplatin AUC = 6 mg/mL/min IV + paclitaxel 175 mg/m^2 IV repeated every 3 weeks. TAP schedule is as doxorubicin [45 mg/m^2 on day 1], cisplatin 50 mg/m^2 on day 1 plus paclitaxel 160 mg/m^2 over 3 h on day 2 every 3 weeks with growth factor support.

In a recurrent setting, selective proliferation of chemoresistant cells occurs. Tumor cells may develop resistance to paclitaxel by overexpression of the multidrug-resistance gene (MDR-1), which encodes P-glycoprotein (P-gp), an efflux pump that prevents accumulation of a variety of natural product-based chemotherapeutic agents. Five-year survival rate for patients with advanced/recurrent measurable disease is <10 %, and for those with stage III disease, it is typically around 50–60 %. As use of chemotherapy is increasing in the adjuvant setting, dose-limiting toxicities like cardiotoxicity with doxorubicin and sensory neuropathy with paclitaxel have to be taken into consideration. In a GOG analysis of approximately 1200 patients with recurrent disease, factors independently associated with longer survival included white/Hispanic race, better performance status, stage III disease, no prior radiation therapy, and endometrioid tumor histology. The best response rates with chemotherapy in a recurrent setting were in the range of 9–13 % [12]. In a Phase 2 clinical trial, epothilone B analogue ixabepilone 40 mg/m^2 as a 3-h infusion on day 1 of a 21-day cycle was recently reported to have a 12 % response rate in an extensively pretreated population [13].

Targeted Therapy

In endometrial cancer, there is a subset of hormonally sensitive disease. In high-grade, extensive, and recurrent tumors, chemotherapy has limited, short-lasting benefit. Genetic basis of carcinogenesis is a multistep process progressing through initiation, promotion, and invasion. Mutations in genes like K ras, P 53, and PTEN have been described in endometrial carcinoma. In endometrial cancer, the mutation of genes associated with cancer initiation varies with clinical characteristics (type I or II), tissue differentiation, and histological type (Table 28.3) [14]. Mutations accumulate when DNA repair mechanisms are defective. hMSH2 and hMLH1 alterations in endometrial carcinomas are associated with Lynch syndrome. Epigenetic changes like hypermethylation of the hMLH1 promoter reduces the ability to repair mismatches during DNA replication, leading to mutations of phosphatase and tensin homolog (PTEN) and subsequent generation of endometrioid adenocarcinoma [15]. As this is a stepwise progression, there is scope of intervention at any of these steps to arrest cancer growth.

NCCN guidelines have recommended the use of two molecules, temsirolimus and bevacizumab, which are discussed in detail. Trials are ongoing for multiple other drugs, in combination and sequentially, but they have not come to the level of recommendation [14]. Although there are a large number of studies about the molecular alterations in endometrial carcinomas, the clinically relevant ones with druggable targets and their response rates are given in Table 28.4

Table 28.3 Genetic mutations in endometrioid and non-endometrioid cancers

Alteration	Endometrioid (%)	Non-endometrioid (%)
PTEN mutation	30–50	0–11
PIK3CA mutation	30–40	20
KRAS mutation	10–30	0–10
EGFR overexpression	46	34
HER-2 overexpression	3–10	32
p53 mutation	20	90
Microsatellite instability	15–25	0–5

Table 28.4 Targeted therapies and response rates in endometrial cancer

Drug	Response rate (%)
Angiogenesis inhibitors	
Bevacizumab	13.5
Aflibercept	6.8
Thalidomide	12.5
EGFR inhibitors	
Gefitinib	3.4
Erlotinib	4.3
HER2 neu inhibitors	
Trastuzumab	0.0
mTOR inhibitors	
Temsirolimus	26.0
Ridaforolimus	28.9 (CBR)

Temsirolimus

PI3K/AKT pathway plays a central role in cell survival, growth, and avoidance of apoptosis. Stimulation of the PI3K/AKT pathway occurs through the activity of receptors including epidermal growth factor receptor (EGFR), insulin-like growth factor I receptor (IGFIR), etc. Constitutive activation of the PI3K/AKT pathway in endometrial cancer occurs most commonly through loss of PTEN (phosphatase and tensin homolog, a tumor suppressor gene). The mammalian target of rapamycin (mTOR), a serine/threonine kinase, is a critical downstream target of the PI3K/AKT pathway (Fig. 28.1). mTOR upregulation through AKT leads to subsequent activation of the protein S6 kinase (pS6K) which regulates protein translation and cell cycle progression [16].

In a Phase 2 study of temsirolimus, dramatic variations in the response rates for chemo-naive patients (14 % partial response (PR) and 69 % stable disease (SD)) when compared to post-chemo patients (4 % PR and 28 % SD) were seen [17]. In view of this, GOG has included temsirolimus combined with carboplatin and paclitaxel as a treatment arm in an ongoing three-arm trial exploring combination therapies in advanced

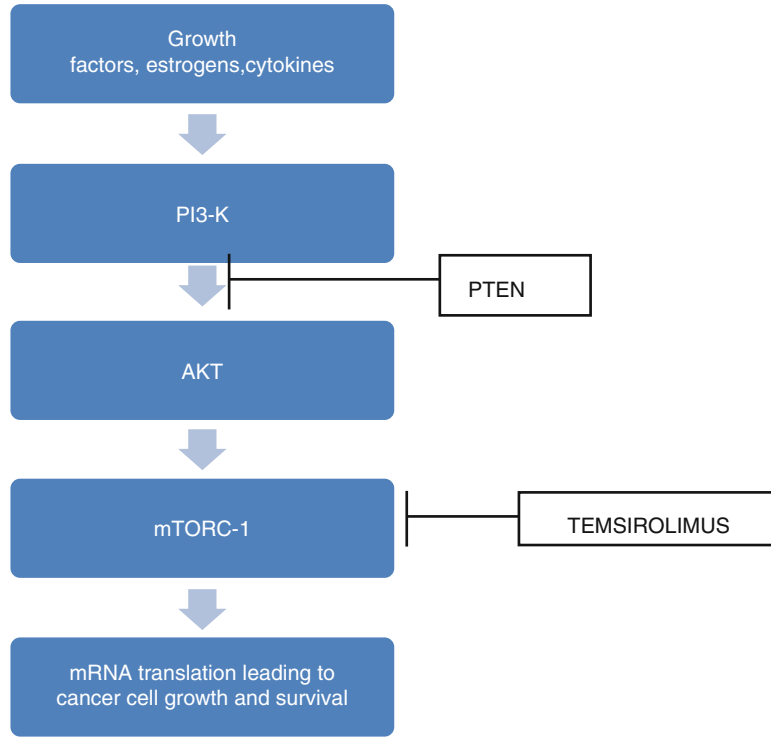

Fig. 28.1 A simplified representation of relevant pathway in endometrial carcinoma. Tumor suppressor action of PTEN by inhibiting PI3-K to AKT and the site of action of temsirolimus on the mTOR complex is depicted

endometrial cancer. Oral mTOR inhibitor, everolimus, is being studied in combination with letrozole.

Bevacizumab

Angiogenesis is a key factor in tumorigenesis that allows for the supply of nutrients, oxygen, and growth factors to the tumor and promotes tumor dissemination and metastasis. Proangiogenic factors such as vascular endothelial growth factor (VEGF) are found in tumors, resulting in an increased unregulated division and growth of the endothelial cells. Overexpression of VEGF is associated with poor prognostic factors in endometrial cancer such as deep myometrial invasion and lymph node metastasis [18]. The results with thalidomide, sunitinib, and sorafenib were not encouraging. In a GOG trial, patients progressing after chemotherapy were assigned to bevacizumab 15 mg/kg once in 3 weeks. Median PFS and overall survival times were 4.2 and 10.5 months, respectively. 40 % of patients were progression free for at least 6 months [19]. An important finding from this study was the relationship of high-circulating VEGF-A levels with poor outcome.

Other Agents

Metformin

Risk for endometrial cancer is increased by hyperinsulinemia. In obesity, there is excessive insulin secretion to counteract hyperglycemia, which can stimulate cancer cell proliferation through action on insulin-like growth factor-1(IGF-1). Metformin improves insulin resistance and decreases the blood insulin concentration, and therefore the efficacy of these drugs for prevention of cancer has been evaluated. Metformin administered with medroxyprogesterone acetate (MPA) antagonizes IGF-2 and enhances PR expression, providing an effective combination therapy [20].

Histone Deacetylase (HDAC) Inhibitors

HDAC inhibitors enhance transcription of tumor suppressor genes, arrest the cell cycle, and induce apoptosis. They are targeted drugs that inhibit the growth of cancer cells. The major HDACs which have shown a response in endometrial cancer are trichostatin A, n-butyrate, apicidin, and valproic acid.

Hormonal Treatment

Hormonal therapy is effective in endometrioid histology only. In advanced-stage disease, when patients cannot tolerate systemic chemotherapy due to age or comorbidities, hormonal therapy has a useful role. Over the past 40 years, there has been a series of clinical trials based on the biochemical and histopathological profile of endometrial carcinoma. NCCN recommends the use of either of progestational agents or tamoxifen or aromatase inhibitors for hormonal treatment.

Progestins

Hormonal sensitivity of endometrium leads to continuous tissue proliferation and breakdown during menstrual cycle. The chances of DNA mutation are thus increased. The effect on progestins is within the glandular epithelium of the endometrium to act as an antagonist to estrogen-mediated cell proliferation [21]. Progestin is also involved in cell cycle regulation through cyclin-dependent kinase (Cdk). Effect of progestins is more in low-grade tumors and varies from 15 % to 25 %. Among patients with histologic grade 1, 2, and 3 tumors, the percentage who responded to MPA was 37 %, 23 %, and 9 %, respectively. Other factors associated with improved response are long DFS (exceeding 2 or 3 years) and positive estrogen or progesterone receptor status. Even PR-negative tumors show response to treatment by unknown mechanism. The recommended dose of oral progestin for metastatic endometrial cancer given in the form of megestrol acetate is 200 mg/day. Thigpen et al. in GOG 81 study compared MPA 1000 mg/day to 200 mg/day and concluded that a higher dose reduces the response rates and progression-free survival [22]. Progestins are classified into first- to fourth-generation agents. Typical first-, second-, third-, and fourth-generation progestins used clinically include norethisterone, levonorgestrel, desogestrel, and dienogest, respectively. Dienogest is of particular interest as the mechanism of action is proposed to be different from other progestins [23]. Studies are ongoing to specify the optimal dosage and duration of these newer compounds. With the development of newer agents, progestational activity is increased, and androgenic side effects like acne, hirsutism, obesity, increased libido, and virilism are minimized.

Tamoxifen

When used for treatment of carcinoma breast, tamoxifen increases the chance of endometrial cancer. Measurement of endometrial thickness is required during treatment with tamoxifen. However, tamoxifen can augment the amount of progesterone receptors, thus improving response rates in endometrial carcinoma [24]. As a single agent, responses of 10–22 % were seen, with low-grade tumors having the maximum benefit, similar to progestins. GOG conducted a trial with MPA at 160 mg/day for 3 weeks alternating with tamoxifen at 40 mg/day for 3 weeks. This showed some improvement in response rate (27 %), but similar PFS, OS, and side effect profile when compared to single-agent progestins [25]. The dosage and sequencing of tamoxifen and MPA have been different in various trials.

Other Agents

Aromatase inhibitors like anastrozole and letrozole have been studied. With letrozole, although the total number of evaluable patients was low, 39 % had stable disease for a median duration of 6.7 months [26]. In the year 2000, a study with arzoxifene (a nonsteroidal SERM) reported response rates between 25 % and 31 %, with an

acceptable toxicity profile. The patient populations enrolled onto these trials were selected for low-grade disease and the presence of progesterone receptor. An ongoing GOG trial is investigating the activity of fulvestrant, a pure ER antagonist that induces degradation of the ER in patients with recurrent/metastatic endometrial carcinoma. In a GOG study, GnRH analogue, goserelin acetate showed an overall response rate of 12.5 % and a median progression-free survival of 1.9 month [27].

Conclusions

Advanced endometrial carcinoma is a heterogeneous disease. In low-grade, endometrioid tumors, hormonal agents can be used. This is of particular benefit in the elderly with comorbidities and chemoresistant disease. Fourth-generation progestins like dienogest and sequencing of tamoxifen with progestational agents are the future in this area. Chemotherapeutic agents as single agents or in combination have shown improvements in response rates and progression-free survival. Cumulative toxicities and chemoresistance are reasons for concern. Over the years, the benefit of chemotherapy has plateaued out. The understanding of signaling cascade in endometrial cancer has helped in the development of targeted agents. PTEN pathway and mTOR inhibitors are the most promising ones. As in other solid tumors, antiangiogenic agents have also shown benefit in a refractory setting. Multitude of available options makes the selection and sequencing of agents a challenge in systemic treatment of advanced endometrial cancer.

Key Points

1. Treatment decisions in advanced endometrial carcinoma are based on histological subtype and grade of tumor.
2. Low-grade endometrioid tumors respond to hormonal therapy.
3. In chemo-naive patients, single or combination chemotherapy improves progression-free survival and overall survival.
4. Response rate for second-line chemotherapy is low, approximately 10 %.
5. Peripheral neuropathy, nephropathy, and cardiac toxicity are dose limiting in the elderly population with multiple comorbidities.
6. mTOR inhibitors like temsirolimus are effective as a single agent. In clinical trials, combination of mTOR inhibitors and chemotherapy is being tested.
7. Bevacizumab may be considered for patients who have progressed on prior cytotoxic chemotherapy (NCCN guidelines).
8. Sequential administration of available options will ensure optimal patient outcome.

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29 Therapeutic Strategies in Recurrent and Metastatic Endometrial Cancer

Lalit Kumar

Introduction

Endometrial cancer (EC) is primarily a disease of menopausal and postmenopausal women. As many as 45 % of all endometrial cancer patients are diagnosed in the elderly, aged 65 years and older [1]. Incidence of endometrial cancer varies from 19.2 to 22.3/100,000/year in developed countries to 5.8 in urban India and to 0.8 per 100,000 women/year in rural India [2]. In India, the incidence is gradually on the rise because of changing lifestyle, westernized food habits, and increased longevity [2]. A number of risk factors are associated with development of endometrial cancer. These include chronic estrogenic stimulation, early menarche, late menopause, nulliparity, and anovulation. Patients with diabetes mellitus, gall bladder disease, hypertension, and prior pelvic radiation are at higher risk [3, 4].

Histopathologically, EC is divided in two major subtypes: (i) endometrioid subtype (called type I) accounts for about 87 % of cases and papillary serous type and clear cell type (called type II) account for the rest (Table 29.1). Uterine serous carcinoma (type II) is a clinically aggressive disease that has an early predilection for deep myometrial invasion, lymph-vascular space invasion, and intra-abdominal, as well as distant, spread. Immunohistochemically, the tumor cells of type II are strongly and diffusely positive for p53, p16, and mib-1. Estrogen receptor and progesterone receptor are usually negative or weakly patchy positive. WT-1 nuclear staining can be seen in a subset of the tumor but is not a reliable marker for distinguishing from an ovarian primary serous carcinoma. Compared to type I, patients with type II disease have a higher relapse rate and inferior 5-year survival [3–6]. Table 29.2 describes molecular characteristics of type I and II endometrial cancer.

Standard Treatment

Standard treatment almost universally begins with a total hysterectomy (via any of a number of approaches—abdominal, vaginal, or minimally invasive) and removal of the remaining adnexal structures. Comprehensive staging, including pelvic and para-aortic lymph node assessment, is crucial in guiding postoperative adjuvant treatment (Table 29.3). EC spreads beyond the uterus by infiltrating directly through the myometrium, extending into the cervix or metastasizing, most often to the pelvic nodes and less frequently to the para-aortic nodes [3, 4].

Adjuvant postoperative treatment recommendations in advanced stage disease are widely disparate and an area of active research. However,

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Table 29.1 Endometrial cancer: pathological types [4, 5]

Characteristic	Type I	Type II
Chronic estrogenic stimulation	Present (hormone dependent)	Absent (not hormone dependent)
Growth	Slow growing	Rapid
Precursor lesion	Atypical hyperplasia	Endometrial intraepithelial carcinoma
Age at initial diagnosis	Pre-/perimenopausal	Postmenopausal
Built	Obese	Thin built
Histology	Endometrioid	Serous, clear cell
Grade	Low	High
Depth of invasion	Usually superficial	Often deep
ER, PR	>90 %	0–31 %
5-year survival rates FIGO stage I/II/ III/IV	85–90 %/70 %/ 40–50 %/15–20 %	60 %/50 %/ 20 %/5–10 %

Table 29.2 Molecular characteristics of endometrial carcinoma (Adapted from Ref. [3, 5, 6])

Molecular aberration	Type I	Type II	Aberrant pathway
PTEN (loss of function through deletion or mutation)	50–80 %	10–11 %	PI3K/AKT/mTOR pathway
P53 mutations	5–10 %	80–90 %	Tumor suppressor gene
HER-2/neu (overexpression)	3–10 %	32–43 %	Cell surface receptor
P16 inactivation	10 %	40 %	Cyclin D/CDK4-CDK6/RB
EGFR expression	46 %	34 %	Cell surface receptor
Ploidy	67 % diploid	45 % diploid	Aneuploid associated with poor prognosis
		55 % aneuploid	
K-ras (mutational activation)	13–26 %	0–10 %	Ras-Raf-Mek-Erk pathway
E-cadherin (loss or non expression)	10–20 %	62–87 %	Wnt/-catenin./LEF-1 pathway
Catenin CTNNB1 (gain of function mutation)	25–38 %	Rare	Wnt/-catenin./LEF-1 pathway
HIF1a overexpression	25 %	80 %	Gene transcription nuclear protein
EpCAM overexpression	Unknown	96 %	Transmembrane protein

Table 29.3 Guidelines for treatment of endometrial cancer: type I (Adapted from Ref. [4])

Stage	Recommendation
Stage IA, grade I–II	Total abdominal hysterectomy, bilateral salpingo-oophorectomy, lymph node sampling
Stage IA, grade III, IB, stage II	Total abdominal hysterectomy, bilateral salpingo-oophorectomy followed by pelvic radiation
Stage III A, Gr I–II	Total abdominal hysterectomy, bilateral salpingo-oophorectomy followed by pelvic radiation
Stage III A, high grade, III B,C	Total abdominal hysterectomy, bilateral salpingo-oophorectomy followed by chemotherapy and pelvic radiation
Stage IV	Systemic therapy: chemotherapy or progestins

assuming an adequate performance status, virtually all women with advanced stage disease (stage III and IV) will be recommended for chemotherapy, external beam pelvic radiotherapy with or without an extended para-aortic field, or some combination of both modalities. These treatments are

geared at improving disease-free and overall survival in a population in whom overall survival remains disappointing—as low as 20 % in stage IV disease [7]. The role of surgical lymphadenectomy has been continuously debated since the FIGO staging criteria were adopted. Specifically, identifying which patients benefit from lymphadenectomy represents a unique challenge [4].

Type II EC-serous and clear cell carcinoma is biologically similar to high-grade serous carcinoma of ovary with high propensity for upper abdomen relapse. Currently, there is lack of prospective, randomized trials for type II EC. From available literature, there is suggestion that surgical staging should be performed even in the setting of minimally invasive/noninvasive disease. For all patients of type II EC-serous papillary or clear cell histology, chemotherapy should be included in both early stage and advanced disease. The role of radiation in combination is unclear and is currently being investigated in GOG 249 and GOG 258 protocols [8]. Currently, paclitaxel- and carboplatin-based protocol (similar to epithelial ovarian cancer) is being used [4–6].

Treatment of Recurrent and Metastatic Disease

Local Recurrence

Disease usually recurs within the first 3 years following initial treatment. After the diagnosis of the recurrence, a complete evaluation (including imaging) for assessment of the disease extent is important. Surgery is considered only in solitary/isolated recurrences (e.g., single lung metastasis) and in cases where it is hoped it will improve the patient's symptoms and quality of life.

Pelvic recurrences are most commonly found at the vaginal vault. Selected patients with vaginal recurrence who have not received radiation earlier can be treated with radiation with complete response rate of 40–81 %. If the remaining tumor after pelvic RT is <3–5 mm, intracavitary brachytherapy can be used. Otherwise, interstitial brachytherapy can be considered if available. Small central pelvic recurrence within a radiation field can be treated with pelvic exenteration [4–6] (Fig. 29.1).

Metastatic or Disseminated Disease

Patients with low-grade disease with estrogen receptor (ER) and progesterone receptor (PR) positive EC tend to respond to hormonal therapy as well as chemotherapy. Hormonal therapy may be preferred in patients with poor performance status and/or medical comorbidities. Cytotoxic chemotherapy is preferred in patients with high-grade EC [3–5].

Hormone Therapy

Hormone therapy is effective in type I endometrial cancer (those with endometrioid histology); ER/PR status in metastatic disease predicts response to hormone therapy. Progestational agents that have been used in treatment of recurrent/metastatic disease include hydroxylprogesterone, medroxyprogesterone, and megestrol. These agents produce a partial or complete response rate of 20–29 %. Long-term exposure to progestins leads to downregulation of ligand-dependent activation of PR and may lead to loss of response within the endometrium. In a Gynecology Oncology Group (GOG) study, 61 patients with advanced or recurrent uterine cancer were treated with a combination of megestrol and tamoxifen (antiestrogen). This strategy was based on hypothesis that intermittent exposure to progestins would permit tamoxifen to induce progesterone receptor and thus enhance effect of progestin therapy. The complete response rate was 21 %, and 5.4 % had a partial response. The average survival was 14 months. Toxicity was moderate and there were no treatment-related deaths. Of those who responded, 50 % sustained this response for an average of 20 months. It was noted that, overall, younger women had better responses to the treatment than older women [4, 5].

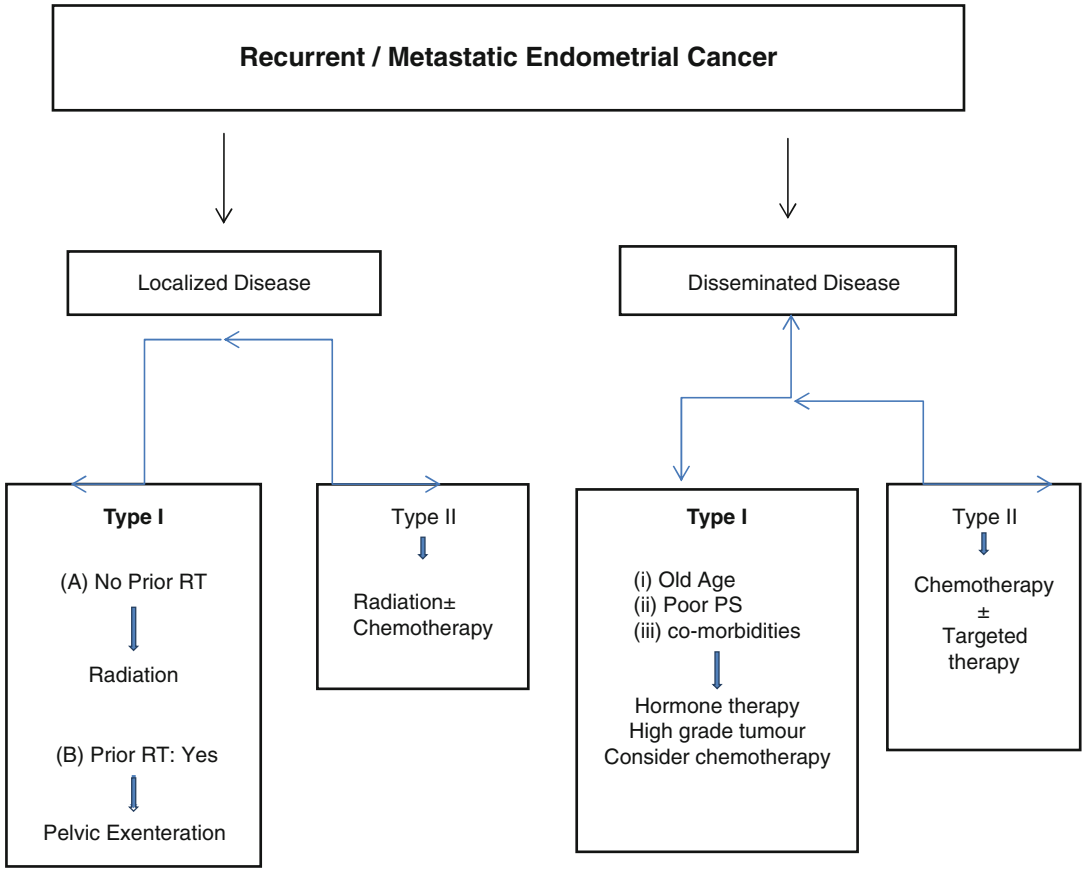

Fig. 29.1 Algorithm for the management of recurrent/metastatic Endometrial cancer

Chemotherapy

Doxorubicin, epirubicin, platinum (cisplatin, carboplatin), and taxanes (paclitaxel, docetaxel) are active agents and have been used both as a single agent and in combination (Table 29.4). Patients who have received adjuvant platinum-based chemotherapy earlier can be retreated with platinum-based salvage chemotherapy; those with platinum-free interval of ≥12 months have better response rates and overall survival [9]. Recently, in a randomized GOG study, standard doxorubicin and cisplatinum treatment regimen was compared to doxorubicin and paclitaxel in 314 women with advanced or recurrent EC. Paclitaxel was given with G-CSF to hasten recovery of blood counts. Side effects were similar between both treatments. The response rate following doxorubicin and cisplatin was 40 %, and 15 % of these were complete responses. The response rate following doxorubicin and paclitaxel was 43 %, and 17 % of these were complete responses. There is suggestion that addition of megestrol acetate to paclitaxel and

Table 29.4 Chemotherapy in metastatic/recurrent endometrial cancer (Adapted from Ref. [4, 5])

Drug	Dose	Response rate (%)
Doxorubicin	50–60 mg/m^2	17–37
Epirubicin	80 mg/m^2	26
Cisplatin	50–100 mg/m^2	17–42
Carboplatin	360–400 mg/m^2	24–33
Paclitaxel	Various	20–36
Docetaxel	35 mg/m^2	21
Ifosfamide	5 G/m^2 q 3 weeks	12–25
Etoposide (VP-16)	50 mg/day × 21 days q 4 weeks	14

carboplatin chemotherapy may improve outcome [8, 10]. Two large randomized studies (EORTC 55872 and GOG-107) have compared doxorubicin and cisplatin (AP) with doxorubicin and found that the combination gave better response rates, but no significant differences in survival. Mainly on the superior response rates, the combination of doxorubicin and cisplatin has been used as a standard treatment in endometrial cancer [8]. Other combinations with or without taxanes are being studied.

Vale et al. in a Cochrane Review included trials accruing women with advanced/recurrent/metastatic EC (not amenable to potentially curative surgery or radical RT) who were suitable for cytotoxic chemotherapy. Meta-analysis has shown that progression-free survival was significantly improved (HR = 0.80; 95 % CI 0.71–0.90; P = 0.004), but there was only a trend towards improved overall survival (HR = 0.90; 95 % CI 0.80–1.03). Addition of paclitaxel to combination chemotherapy was at the expense of increased toxicity [I, A] [11].

In GOG-122 study, 400 patients with FIGO stage III or IV endometrial carcinoma of any histology (including serous and clear cell carcinomas) were randomized. The study compared chemotherapy with whole abdominal RT of 30 Gy in 20 fractions with an additional 15 Gy pelvic boost. Eligibility required TAH and BSO, surgical staging, tumor resection, and no single site of residual tumor greater than 2 cm. Nodal sampling was optional. Chemotherapy consisted of doxorubicin (60 mg/m^2) and cisplatin (50 mg/m^2) every 3 weeks for seven cycles, followed by one cycle of cisplatin. Both overall survival and progression-free survival were significantly better for patients treated in the chemotherapy arm [8].

Targeted Therapy

Type I and II endometrial cancers are not only different morphologically but also differ at molecular (genotypic) level. Improved understanding of molecular biology of endometrial cancer and identification of potential pathways has led to the development of targeted therapies (Table 29.2). Currently, a number of these are under active investigations (Table 29.5). HER2/neu, which is targeted by the anti-HER2 monoclonal antibody trastuzumab (i.e., Herceptin), may represent the first of a series of novel diagnostic and therapeutic markers. Currently, a multi-institutional randomized phase II trial is enrolling patients in the USA (ClinicalTrials identifier: NCT01367002). The primary objective of this phase II study is to evaluate whether the addition of trastuzumab to paclitaxel and carboplatin chemotherapy improves progression-free survival when compared to paclitaxel and carboplatin alone in stages III–IV and recurrent serous endometrial cancer patients overexpressing erbB2 at 3+ levels by IHC or positive by FISH. The results of this trial will be very helpful in determining whether there is a role for trastuzumab in the management of this disease [10]. Results from phase II trials for other molecules are given in Table 29.5.

Table 29.5 Targeted therapy in endometrial cancer

Drug	Response rate (CR + PR, %)	Author (Reference)
Antiangiogenesis agents		
Bevacizumab	13.5	Aghajanian et al. [12]
Aflibercept	6.8	Coleman et al. [13]
Sunitinib	18.1	Castonguay et al. [14]
Sorafenib	5.0	Nimeiri et al. [15]
EGFR inhibitors		
Gefitinib	3.4	Leslie et al. [16]
Erlotinib	12.5	Oza et al. [17]
Her-2-neu inhibitors		
Trastuzumab	0	Fleming et al. [18]
mTOR inhibitors		
Temsirolimus	22.0	Fleming et al. [19]
Everolimus	5.0	Ray-coquard et al. [20]
Ridaforolimus	11 %	Colombo et al. [21]
	8.8 %	Tsoref et al. [22]

Conclusions

The prognosis of women with recurrent and metastatic endometrial cancer is poor. Patients with localized recurrence benefit with radiation. Surgery can be considered in eligible patients with isolated metastasis. Patients with endometrioid histology and those with

low-grade disease are likely to be estrogen and progesterone receptor positive and are candidates for hormonal therapy. Those with serous or clear cell histology or high-grade disease can be considered for systemic chemotherapy on the lines of serous ovarian cancer. Recent understanding of molecular biology has led to the option of targeted therapy. Currently, a number of molecules are under investigations with initial promising results.

Key Points

1. Type I endometrial cancer (endometrioid subtype) accounts for about 87 % of cases. Papillary serous type and clear cell type (called type II) account for the remaining 13–15 % of cases.
2. Endometrioid subtype is estrogen dependent, while p53 mutation is the major molecular aberration in type II cancers (serous).
3. Biology and outcome of type II endometrial cancer are similar to that of high-grade serous ovarian cancer.
4. Surgery is a preferable option for solitary or isolated recurrence. Patients with disseminated or metastatic disease benefit with chemotherapy.
5. For patients having type I endometrial cancer with metastatic disease, hormonal therapy with medroxyprogesterone is a reasonable option.
6. Paclitaxel, carboplatin, and adriamycin are the most active chemotherapeutic drugs.
7. A number of targeted agents (antiangiogenesis, mTOR inhibitors) have shown promising results in phase II trials.

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Part V

Uterine Sarcomas

Uterine Sarcomas: Risk Factors, Clinical Presentation, Diagnosis, and Staging

30

Monisha Gupta and Shalini Rajaram

Introduction

Mesenchymal tumors of the uterine corpus are rare, accounting for approximately 7–8 % of all uterine cancers [1]. As per The American cancer society's estimates for cancer of uterine corpus in the USA for 2014, about 52,630 new cases of cancer of the uterine corpus will be diagnosed, but only about 1,600 (3 %) of these cases will be uterine sarcomas [1, 2]. In stark contrast, a registry from a tertiary centre in north India has shown that uterine sarcomas constitutes roughly 25 % of all uterine malignancies [3]. There has also been a rise in the incidence of uterine malignancies in the Indian subcontinent in the past decade [4].

They arise from dividing cell populations in the myometrium or connective tissue elements within the endometrium. Compared with the more common endometrial carcinomas, uterine sarcomas behave aggressively and are associated with a poorer prognosis; however, outcomes do vary significantly based upon specific histology [2].

Based upon the differentiation/growth pattern of the neoplastic cells and their presumed cell of origin, The World Health Organization and College of American Pathologists have published classification systems for uterine sarcomas (Table 30.1). It consists of two main groups:

Mesenchymal tumors: The pure mesenchymal tumors can be further classified into endometrial stromal sarcoma (ESS), leiomyosarcoma (LMS) – including the epithelioid and myxoid variants – and undifferentiated endometrial/uterine sarcoma (UUS) according to the cell of origin.

Mixed epithelial and mesenchymal tumors. Mixed tumors include carcinosarcoma and adenosarcoma, and are composed of a mixture of epithelial and mesenchymal components [1, 2, 5]

Historically, uterine carcinosarcoma was classified as a type of uterine sarcoma and was termed malignant mixed Müllerian tumor (MMMT) or mixed mesodermal sarcoma. However, these neoplasms are now classified as carcinomas since they derive from a monoclonal neoplastic cell, which has more characteristics of epithelial than stromal neoplasms. In addition, the epidemiology, risk factors, and clinical behavior associated with carcinosarcoma suggest a closer relationship

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Table 30.1 WHO classification of uterine sarcomas

Mesenchymal tumors	Mixed epithelial and mesenchymal tumors
Endometrial stromal and related tumors	Carcinosarcoma
Endometrial stromal sarcoma, low grade	Adenosarcoma
Endometrial stromal nodule	Carcinofibroma
Undifferentiated stromal sarcoma	Adenofibroma
Smooth muscle tumors	Adenomyoma
Leiomyosarcoma	Atypical polypoid variant
Epithelioid variant	
Myxoid variant	
Smooth muscle tumor of uncertain malignant potential	
Leiomyoma, not otherwise specified	
Histologic variant	
Mitotically active variant	
Cellular variant	
Hemorrhagic cellular variant	

to endometrial carcinoma than to sarcoma [6–8]. Despite this, and probably because it behaves more aggressively than the ordinary endometrial carcinoma, carcinosarcoma is still included in most retrospective studies of uterine sarcomas, as well as in WHO 2003 classification [1].

ESSs have traditionally been divided into low-grade and high-grade tumors. However, as high-grade ESS often lack evidence of endometrial stromal cell differentiation and are clinically more aggressive, it has been proposed that they should be classified as undifferentiated endometrial or uterine sarcoma. Thus, ESS are by definition now considered all "low-grade" sarcomas and undifferentiated sarcoma is now the preferred terminology for all "high-grade" ESS [1, 5, 6]

Epidemiology

Histopathological criteria for uterine sarcomas have greatly evolved over the last few years. As per a large series with 127 cases including carcinosarcomas, the most common uterine sarcoma were leiomyosarcoma and carcinosarcoma [9] (Fig. 30.1). However, leiomyosarcomas and endometrial stromal sarcomas accounts for 66–23 %, respectively, of all uterine sarcomas after excluding carcinosarcomas, with all of the other subtypes being exceedingly rare. According to most recent and largest series ($n=419$) in Norway on uterine sarcomas from 1970 to 2000 using 2003 WHO classification by Abeler and

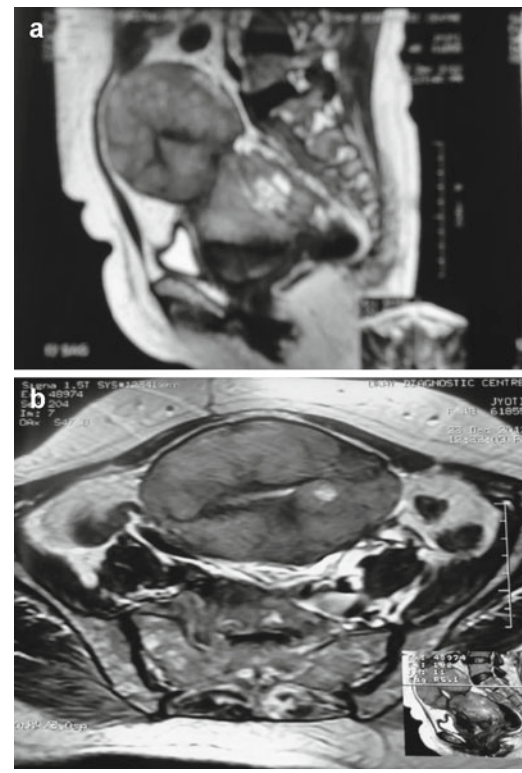

Fig. 30.1 A 60-year-old woman with carcinosarcoma. (**a**), Sagittal and (**b**), coronal T2-weighted MR image of pelvis shows heterogeneous endometrial mass with areas of necrosis

colleagues (excluding carcinosarcomas), 62 % were leiomyosarcomas, 20 % were ESSs, and 18 % were rare subtypes including undifferentiated sarcomas (6 %), adenosarcomas (5.5 %), sarcoma, not otherwise specified (NOS) (4.5 %), rhabdomyosarcoma (<!%), giant cell sarcoma (<!%), and perivascular epithelioid cell tumor (PEComa; <1 %) [10].

According to a published series, the median ages reported ranges from 48 to 57 years for leiomyosarcoma, 57 to 67 years for carcinosarcomas, 42 to 51 years for ESSs, and 58 to 66 years for adenosarcomas [5]. In a review of 208 patients with leiomyosarcomas from the Mayo clinic, only 41 % were postmenopausal [11]. Thus, many patients with carcinosarcoma are postmenopausal at the time of diagnosis, whereas patients with leiomyosarcoma, ESS, or undifferentiated sarcoma may be pre- or postmenopausal at the time of diagnosis. This would have potential implications in terms of fertility for these patients.

Genetic factors have been suggested to play a role, as incidence is twice as high among black women compared to white women. This race-specific incidence pattern is reversed in endometrial carcinoma, in which the incidence among white women is three times higher than that among black women [5, 12]. In a series by Zelmanowicz et al., women with carcinosarcoma are more likely to be of African American descent than those with endometrial adenosarcomas (among 453 patients and controls, 28 % versus 4 %, $p=0.001$) [8]. Then, Brooks et al. reported that the age adjusted incidence of uterine sarcomas in African American women was twice that of controls. The age-adjusted incidences of leiomyosarcomas for black and white women, respectively, were 1.5 and 0.9 per 100,000. Similarly, those for carcinosarcoma in black and white women, respectively, were 4.3 and 1.7 per 100,000 [13].

Etiology and Risk Factors

The development of the basic understanding of uterine sarcoma has been slow. The majority of cases are felt to be sporadic, with no specific etiology, and most have complex karyotypes [14]. However, specific chromosomal translocations have been identified in an increasing number of uterine sarcomas, resulting in fusion genes that are constitutive and involve activation of transcription factors [5, 15].

Genetics of Uterine Sarcomas

ESS has specific somatic mutations that have been discovered by cytogenetic studies namely, fluorescence in situ hybridization (FISH) and polymerase chain reaction (PCR) analyses. In the database of chromosome aberrations in cancer by Mitelman, the cytogenetic features **t** (7;17) (P15;q11), **t** (6;7) (P21, P15), and **t** (6,10) (P21;P11), and molecular genetic features (JAZF1/ SUZ 12), (JAZ F1/PH F1), and (EPC1/ PH F1 fusion gene) of ESS, are recorded [16].

Undifferentiated endometrial sarcomas lack these JAFZ1 based rearrangements but instead appear to frequently harbor the YWHAE-FAM22A/B genetic fusion and is considered to be specific for these tumors [16].

LMP2-deficient mice are reportedly prone to spontaneous development of uterine LMS and histopathological experiments demonstrated a high correlation between a loss of LMP2 and malignancy of uterine tumors developing in myometrium. Recent reports have also shown a loss in the IFN-γ-inducible expression of LMP2 in a LMS culture cell line. Also, histopathological examinations with IFN-γ-deficient mice revealed that the IFN-γ pathway is especially required for LMP2 expression in normal myometrium. Therefore, organ-specific LMP2 functions might be one of the factors involved in sarcogenesis of uterine leiomyosarcomas [17].

Cowden and colleagues analyzed carcinosarcomas for the presence of somatic mutations. The rate of mutations identified for each gene analyzed was PIK3CA (56 %), KRAS (44 %), TP53 (33 %), and CTNNB1 (6 %). Tp53 mutation was the only mutational event that retained an independent association with survival. Also, the Akt/b-catenin pathway and alteration in Rb expression have been suggested to be involved in the development of carcinosarcomas [18].

Prior Radiation Therapy

Although prior exposure to pelvic radiotherapy is considered a risk factor primarily for carcinosarcoma and undifferentiated sarcoma, this is rarely an etiological factor for leiomyosarcoma or STUMP.

In a large series from Mayo clinic of 208 leiomyosarcoma cases, only 1 woman (0.6 %) was exposed to prior pelvic radiation [11]. MD Anderson Cancer Center described 41 cases of STUMP and found that none of them had a history of prior radiation exposure [19]. Christopherson et al. described 2 cases among 33 patients with leiomyosarcoma who had a history of pelvic radiation [20].

On the other hand, Norris at al described in his series that 29 % of carcinosarcoma (9 of 31 patients) had received pelvic radiotherapy 7–26 years prior to diagnosis [21]. Among 1,208 patients of uterine malignancies reported by Meredith et al. in 1986, 30 patients (2.4 %) had received prior radiation and 5 (17 %) among them developed carcinosarcoma, for a crude association of 11 %. It has been concluded that postradiation carcinosarcoma occur at a younger age than those arising de novo; however, latency to diagnosis of malignancy is shorter in older age group [22].

Pothuri et al. compared clinicopathological characteristics of 23 cases of uterine malignancies occurring after prior radiation therapy to 527 cases of uterine cancers arising de novo [23]. Carcinosarcomas and undifferentiated sarcomas accounted for 9 (39 %) of the 23 radiation associated malignancies compared to only 33 (8 %) of sporadic cases. They also suggested that radiation induced malignancy tend to have worse outcome, possibly due to lack of early symptomatology.

Exposure to Hormones and Tamoxifen

An association between exposure to hormonal agents, including tamoxifen, and increased risk of uterine sarcomas has been suggested.

As per the data from Finish Cancer registry, uterine sarcomas occurred in 76 out of the 243,857 women who were identified as having used estradiol-progestin therapy for more than 6 months [24]. The ever use of estradiol-progestin therapy was associated with 60 % elevation in the risk for any uterine sarcoma, mostly for leiomyosarcoma (standardized incidence ratio [SIR], 1.8; 95 % CI, 1.3–2.4), but not for endometrial stromal sarcoma (SIR, 1.4; 95 % CI, 0.9–2.1). Also, this elevated risk was only noted in women who had used estradiol-progestin therapy for 5 years or more. However, despite a possible increased risk, the overall absolute risk of uterine sarcomas is still exceedingly low.

Recently, similar to endometrial adenocarcinoma, a possible association between tamoxifen use among breast cancer patients and increased risk for uterine sarcomas, particularly carcinosarcomas, has been reported and is significant with more than 4 years of tamoxifen use. In a study by Hoogendoorn et al. [25], among patients diagnosed with uterine cancer, carcinosarcomas accounted for a larger proportion of cases in those who had received prior tamoxifen therapy compared to those who had not (15 % vs. 4 %, respectively).

Hereditary Predisposition

Hereditary predisposition to certain uterine sarcomas has also been suggested but still remains to be clearly elucidated. As per Danish Hereditary Nonpolyposis Colorectal Cancer (HNPCC)-register, sarcomas of various sites represented 1 % ($n = 14$) of 164 HNPCC families with disease predisposing mutations [26]. Three of these 14 sarcomas were uterine: one was a carcinosarcoma in a 44-year-old with loss of MSH2 and MSH6 expression in the sarcoma, other was also a carcinosarcoma in a 55-year-old with loss of MSH6 expression and the third was leiomyosarcoma in a 44-year-old with loss of MSH2 and MSH6 expression. The overall risk of uterine sarcoma is still low in these hereditary syndromes.

Clinical Presentation and Diagnosis

The most common presenting symptom of uterine sarcomas is abnormal uterine bleeding (pre- or postmenopausal bleeding), and is nearly

Table 30.2 Presenting symptoms in women with uterine sarcomas (% of cases describing that symptom) [1, 5, 7]

Symptom	ESS (%)	CS (%)	LMS (%)	AS (%)
Asymptomatic	10–15	5–10	10–14	10–15
Abnormal vaginal bleeding	65–70	65–70	50–55	60–62
Abdominopelvic mass	10–15	1–15	45–50	–
Abdominopelvic pain	15–20	8–10	20–25	18–22
Uterine enlargement	60–65	–	–	–
Uterine cavity lesion	18–20	–	–	–
Vaginal discharge	1–5	–	–	–
Abdominal distension	–	–	–	1–2

universal in those with carcinosarcoma, but may occur in as few as 40 % of those with leiomyosarcomas [1, 5, 6]. (Table 30.2).

Carcinosarcomas usually occur in an older age group; most patients being postmenopausal. The frankly malignant variants grow rapidly and at physical examination, 50–95 % of patients have enlargement of the uterus with 50 % of patients having protrusion of a polypoidal lesion through the endocervical canal. In advanced cases, presentation maybe similar to that of ovarian cancer with pleural effusion, ascites, and adnexal masses. Uterine curettage usually detects malignant tissue in the uterus, as it is a lesion that arises in the endometrium (unlike true uterine sarcoma that often does not have an endometrial component).

Uterine enlargement and a presumptive diagnosis of uterine leiomyomas, leiomyomas are nearly universal findings in patients with leiomyosarcoma. They usually present in women above 40 years of age and majority of these tumors arise de novo, with less than 5 % arising from malignant transformation of an existing leiomyoma. Occasionally, the presentation may be that of hemoperitoneum due to tumor rupture, extrauterine extension, or metastases such as persistent cough, back pain, and ascites [27] Berchuck et al. reported that in 14 patients with leiomyosarcomas undergoing dilatation and curettage, a prehysterectomy diagnosis was made in only 8 (31 %).

Endometrial stromal sarcoma usually presents between 40 and 55 years of age. Again, the most common presenting symptom is abnormal uterine bleeding with some women presenting with pelvic pain and/or dysmenorrhea but as many as 25 % of them may be asymptomatic. In a report by Memorial Sloan-Kettering Cancer Center, endometrial stromal sarcoma was diagnosed as an incidental finding in 42 % of cases [28]. Some cases have been reported in women with ovarian polycystic disease, after estrogen use, or tamoxifen therapy. At presentation, extrauterine pelvic extension, most commonly involving the ovary, is found in up to one-third of patients. Thus, when evaluating an ovarian tumor microscopically consistent with an endometrial stromal tumor, it is important to exclude a prior history of uterine endometrial stromal tumor and to suggest inspection of the uterus, as the latter are far more common.

Preoperative endometrial assessment with either office Pipelle or dilation and curettage (D&C) under anesthesia are limited in the evaluation and correct diagnosis of uterine sarcomas; however, it is the investigation of choice in women who presents with abnormal uterine bleeding. Diagnosis of carcinosarcoma is usually confirmed, or at least suggested, at the time of endometrial assessment, but leiomyosarcomas are rarely diagnosed before hysterectomy. In a series by Bansal et al. [29], invasive tumor was diagnosed in 86 % cases of uterine sarcomas on preoperative endometrial sampling and 64 % out of them had correct histology as compared with final histopathology. However, 70 % of cases in his series were carcinosarcomas with only four leiomyosarcomas, two endometrial sarcomas, and eight other sarcomas diagnosed on final histology. Diagnosis of carcinosarcoma may be missed because endometrial biopsy/curettage does not adequately sample both the epithelial and stromal components of the tumor; however, appropriate preoperative referral is usually made because of the presence of a malignancy, and staging is accomplished at the time of hysterectomy. Conversely, most leiomyosarcomas are diagnosed after hysterectomy at the time of histological review of the surgical specimen. This has been highlighted in a GOG study reported by Major et al. [30] where fewer patients with leiomyosarcoma were referred to a higher centre than

those with carcinosarcoma (301 carcinosarcomas, 59 leiomyosarcomas, and 93 endometrial stromal sarcomas).

Imaging Perspective

Based on imaging findings, the preoperative diagnosis of uterine sarcomas and the distinction among the various histologic subtypes is challenging.

MRI is usually a preferred modality for assessing carcinosarcoma because of its improved ability to characterize the depth of the lesion, delineate local extrauterine spread of disease as well as assessing for the presence of necrosis and hemorrhage (please see chapter on "Imaging"). The tumor generally appears as areas of heterogeneous high intensity on T2-weighted magnetic resonance (MR) images and low intensity on T1-weighted images (Fig. 30.1). CT is preferred for staging and assessment of distant metastases and nodal involvement.

The appearance of leiomyosarcoma is variable on MRI and no preoperative imaging can reliably differentiate between leiomyoma and leiomyosarcoma. They usually appear as large heterogeneously enhancing uterine masses, with central T2 hyperintensity indicative of necrosis. Role of CT scan has been limited to identifying extrauterine disease, including local spread and metastasis. There is low incidence of adnexal or pelvic lymph node involvement. The most common site of metastasis is the lungs followed by liver and other abdominal sites, thus CT chest is usually indicated for evaluation.

ESS appears as a polypoidal lesion with low T1 signal and heterogeneously increased T2 signal . Because of its tendency for lymphatic and vascular invasion, ESS may show a "bag of worms" appearance, especially in cases of high grade tumors.

Tumor Markers

There is no reliable tumor marker for diagnosis of uterine sarcomas. Serum CA-125 is seen to be increased in 17–33 % of leiomyosarcomas, ESSs, and carcinosarcomas [9]. However, it should not be used routinely in the evaluation and diagnosis of these tumors. Recently, serum lactate dehydrogenase has been found to be an interesting addition to imaging in the evaluation of uterine leiomyosarcomas. In a series by Goto et al. [31], combining serum LDH and dynamic MRI has been found to have accuracy of 99.3 % in predicting uterine leiomyosarcomas. These results are impressive and may be of help in evaluating women with presumed benign leiomyoma.

Staging and Nodal Involvement

Uterine sarcomas were traditionally staged according to the 1988 FIGO staging system for carcinomas of the corpus uteri, even though their biologic behavior differs significantly from that of endometrial carcinoma [32]. In contrast to endometrial adenocarcinoma which is often associated with lymphatic dissemination and carries a relatively favorable prognosis especially at early stage, uterine sarcomas exhibits a propensity for hematogenous dissemination and is associated with high local and distant recurrence rates [1, 5, 6, 15, 32].

Recently, two large series comparing the merits of the 1988 FIGO and AJCC soft tissue sarcoma staging systems for use in uterine sarcomas were published. Both studies concluded that neither the old FIGO nor the AJCC staging systems were ideal to stage uterine sarcomas [32]. The old FIGO system was developed primarily for staging of endometrial carcinomas and takes in account parameters such as myometrial invasion, cervical involvement, and positive peritoneal washings that may not be relevant to the biologic behavior of sarcomas. The majority of uterine sarcomas are confined to the uterine corpus at the time of diagnosis and are therefore regarded as FIGO stage I. However many of these patients have high recurrence and mortality rates and it is difficult to predict the behavior of these tumors based solely on FIGO stage [32, 33, 34]. The AJCC staging system was developed primarily for staging soft tissue sarcoma of the extremities and includes parameters like tumor size, location (superficial versus deep), and grade, which may

Table 30.3 FIGO staging for uterine sarcomas (2009) [1]

Stage	Definition
1. Leiomyosarcomas and endometrial stromal sarcomas[a]	
I	Tumor limited to uterus
IA	Less than or equal to 5 cm
IB	More than 5 cm
II	Tumor extends beyond the uterus, within the pelvis
IIA	Adnexal involvement
IIB	Involvement of other pelvic tissues
III	Tumor invades abdominal tissues (not just protruding into the abdomen)
IIIA	One site
IIIB	More than one site
IIIC	Metastasis to pelvic and/or para-aortic lymph nodes
IV	
IVA	Tumor invades bladder and/or rectum
IVB	Distant metastasis
2. Adenosarcomas	
I	Tumor limited to uterus
IA	Tumor limited to endometrium/endocervix with no invasion
IB	Less than or equal to half myometrial invasion
IC	More than half myometrial invasion
II	Tumor extends beyond the uterus, within the pelvis
IIA	Adnexal involvement
IIB	Tumor extends to extrauterine pelvic tissue
III	Tumor invades abdominal tissues (not just protruding into the abdomen)
IIIA	One site
IIIB	More than one site
IIIC	Metastasis to pelvic and/or para-aortic lymph nodes
IV	
IVA	Tumor invades bladder and/or rectum
IVB	Distant metastasis
3. Carcinosarcomas	
Carcinosarcomas should be staged as carcinomas of the endometrium	

[a]Note: Simultaneous endometrial stromal sarcomas of the uterine corpus and ovary/pelvis in association with ovarian/pelvic endometriosis should be classified as independent primary tumors

not be useful in the stratification of uterine sarcomas into clinically meaningful subgroups. Since all uterine sarcomas are considered "deep," and most are confined to the uterus at initial diagnosis and are usually of high grade, most tumors would be stage III using the AJCC system. Another disadvantage of the AJCC system is its failure to take into account local invasion or regional extension at the time of surgery.

Recently, a new FIGO staging system (2009) has been proposed for uterine sarcomas including LMS, ESS, and adenosarcoma (Table 30.3) [35, 36]. Carcinosarcomas are to be staged using the system for endometrial carcinomas. Unlike the 1988 staging system, this new FIGO staging system has replaced myometrial invasion and cervical involvement with tumor size. Several studies have provided evidence to support the rationale of adopting this new parameter. In a study of 819 cases of leiomyosarcomas gathered from the SEER database, Garg and co-workers reported a significant decrease in the 5-year survival of stage I patients with tumor size >5 cm compared to those with tumor size ≤5 cm, supporting the

use of 5 cm as a cutoff for tumor size for the purpose of risk stratification in the new FIGO staging system [35]. In contrast to the AJCC soft tissue sarcoma staging system, the new FIGO staging system for uterine sarcomas also does not consider tumor grade [36].

Whereas carcinosarcomas, like endometrial adenocarcinomas, commonly metastasize to pelvic or para-aortic lymph nodes, leiomyosarcomas rarely spread to nodal sites. In the GOG study reported by Silverberg et al. [37] on 203 stages I and II carcinosarcomas, nodal metastases were detected in 34 cases (16.7 %). Nearly all subjects had lymphatic or vascular involvement in the myometrium. Doss et al. [2] confirmed that pelvic lymph nodes were the most common site of metastasis in carcinosarcomas, and others have confirmed a rate of nodal spread in clinically localized disease between 13.2 % and 31.0 %.

In another GOG Study by Major et al., lymph node metastases were identified in only 3.5 % of patients with clinically localized leiomyosarcomas at the time of surgical staging [30]. In the recent Mayo Clinic series [11], 4 of 36 (11 %) patients had nodal spread, but only 1 of these (2.6 %) had isolated nodal metastases. Data from three series indicate that lymph nodes were histologically positive only if clinically enlarged or associated with obvious intra-abdominal spread. Thus, the need for lymph node dissection in patients with leiomyosarcomas remains unsubstantiated.

Among patients with Müllerian adenosarcomas who underwent surgical staging including lymph node sampling [38], 20 % were found to have spread outside the uterus to involve lymph nodes, vagina, parametrium, ovary, and malignant peritoneal washings. Similar yields are reported for endometrial stromal sarcomas.

Prognostic Factors by Tumor Type

Leiomyosarcoma

LMS is defined as a malignant neoplasm composed of cells with smooth muscle differentiation. These tumors frequently exhibit marked cellular atypia, high mitotic index (MI), and tumor cell necrosis (TCN). Lack of residual tumor following primary surgery is the main prognostic factor for patients with LMS. Five-year crude survival was 51 % for patients with stage I LMS, 25 % for those with stage II LMS, and 32 % for all patients combined. All LMS patients with distant metastasis died within 5 years [10, 39]. Tumor size was the second most important independent prognostic factor for survival. When the tumor diameter was less than 5 cm, the overall survival was 86 %, compared to 18 % when the tumor diameter was larger than 10 cm [39]. MI above 10 mitosis per 10 HpF in LMS conferred an increase in hazard ratio (HR) of about 2.5-fold.

Endometrial Stromal Sarcoma

ESS is by definition a hormone-sensitive low-grade tumor with indolent growth, composed of cells resembling those of proliferative phase endometrial stroma. There is little cellular atypia, mitosis, or myometrial and vascular space infiltration. TCN may occur in rare cases. Nordal et al. [40] showed that tumor-free resection margins after primary surgery were the main prognostic factor for ESS. Patients with stage I ESS had a 5-year and 10-year crude survival of 84 % and 77 %. The values were 62 % and 49 % for those with stage II ESS, and the 5-year crude survival of all patients was 69 %. After tumor-free resection margins, the most important prognostic factors were grade of malignancy, tumor diameter, and menopausal status. When the tumor diameter increased from 5 cm to more than 10 cm, the 5-year cancer-related survival decreased from 89 % to 33 %. In the recent population-based study in Norway by Abeler et al. [10] 83 ESS cases were found in which prognosis was clearly related to MI and TCN. The 5 and 10-year crude survival was 88 % and 84 %, and 57 % and 25 % for patients with a MI 5 and 10, respectively. Patients with no TCN had a highly significantly better 5-year crude survival than patients with TCN, 96 % versus 69 % ($p = 0.002$).

Undifferentiated Stromal Sarcoma

UUS is defined as a high-grade malignant tumor of mesenchymal origin that bears no resemblance to endometrial stroma and shows no evidence of smooth muscle or any other differentiation. These tumors frequently display pleomorphic cells with a high MI [10]. Patients with stage I UUS had a 5-year crude survival of 57 %; for all stages combined this figure was 37 %, and all patients with higher than stage I died within 5 years. Abeler et al. [10] showed that vascular invasion was the only statistically significant factor in the prognosis of UUS, with a 5-year crude survival of 83 % and 17 % in the absence and presence of vascular invasion, respectively ($p=0.02$). Localized recurrences and distant metastases were also associated with high mortality.

Uterine Morcellation

Morcellation of the uterus, either for removal of the specimen during minimal invasive procedures, myomectomy for fertility preservation, or supracervical hysterectomy is a common occurrence. It is usually not done in patients with carcinosarcoma as majority of them are older and a diagnosis is often made preoperatively. However, it is not unusual that leiomyosarcoma and endometrial stromal sarcoma is incidentally diagnosed after some form of uterine morcellation or less than total hysterectomy. Studies have shown that morcellation of uterine leiomyosarcoma is associated with a worsened outcome. In a series by Perri et al., the hazard ratios (HR) for recurrence and survival for TAH compared to other type of resection (myomectomy, morcellation, or supra-cervical hysterectomy) were 0.39 and 0.36, thus, signifying a higher recurrence rate and a lower overall survival (OS) [41]. Park et al. reported in their series a 5-year disease free survival of 40 % in women who underwent morcellation as compared to 65 % in controls ($p=0.04$). Similarly, the 5-year OS was 46 % after morcellation compared to 73 % in those not morcellated ($p=0.04$). Thus, morcellation is not reasonable in patients with highly suspicious MRI findings, as well as in postmenopausal women with enlarging uterine masses [42].

Molecular Biology

The current staging systems for sarcomas rely on anatomic, clinical, and pathologic criteria that have not been constantly associated with outcome. Thus, this limits their prognostic capabilities and addresses the need for a better molecular understanding that may possibly provide greater prognostication.

In a report by Leitao and colleagues, estrogen (ER) and progesterone (PR) receptor expression was associated with outcome in leiomyosarcoma, where disease was limited to uterus; however, in cases with extrauterine spread, involving cervical involvement, ER/PR expression was not prognostic. Sub-typing hormone receptor may provide even better further improved prognostication.

Fox [43] reviewed the value of DNA-ploidy in uterine sarcoma and reported contradictory results. Kildal et al. recently examined the prognostic value of DNA-ploidy in 354 uterine sarcomas in Norway between 1970 and 2000, and concluded that DNA-ploidy might be useful as a prognostic factor in patients with LMS and adenosarcoma [44]. Evaluation of p16, Ki-67, and Bcl-2 has been used in LMS, adenosarcoma, and UUS to predict outcome [44]. However, none have shown any prognostic independence. Nordal et al. [43] studied the prognostic role of p53 protein accumulation (p53) in ESS and LMS using a monoclonal p53 antibody. Nuclear p53 was found in 27 % of ESS and in 38 % of LMS. A significant correlation was found between p53 and malignancy grade, MI, and DNA-ploidy, but not with FIGO stage. Amant et al. studied ErbB-2 (HER-2/neu) gene alterations in LMS, ESS, and adenosarcoma. They used the FISH technique, and 10 LMS, 21 ESS, 10 UUS, and 4 adenosarcomas were evaluated. The results showed absence of ErbB-2 overexpression in LMS, ESS, and adenosarcoma, whereas the ErbB-2 gene might have a biological role in UUS.

Conclusion

Uterine sarcomas are rare tumors and as compared to the more common endometrial carcinoma, they behave aggressively and have poor prognosis. In 2003, WHO classified uterine

sarcomas into pure mesenchymal tumors and mixed epithelial-mesenchymal tumors. Leiomyosarcomas and carcinosarcomas are most common uterine sarcomas, followed by endometrial stromal sarcomas. Patients with carcinosarcoma are usually postmenopausal, whereas, those with leiomyosarcoma and endometrial stromal sarcoma may be pre- or postmenopausal. Prior exposure to radiation is definitely a risk factor for carcinosarcoma and undifferentiated sarcoma. Also, an association between hormone use, including tamoxifen, and increased risk for sarcoma has been reported, although the absolute risk is very low. Recent advances in molecular biology has revealed the role of various genetic mutations in the pathogenesis of uterine sarcomas. Sarcomas usually presents with abnormal uterine bleeding; however, uterine enlargement and presumptive diagnosis of uterine leiomyoma is nearly universal in leiomyosarcoma and endometrial stromal sarcoma. Endometrial biopsy is usually the first investigation of choice; however, its role in definitive diagnosis is limited. Based on imaging findings, the preoperative diagnosis of uterine sarcomas and the distinction among the various histologic subtypes is challenging. The new FIGO staging system (2009) has been proposed for uterine sarcomas including LMS, ESS, and adenosarcoma. Various prognostic factors including tumor size, mitotic index, coagulative necrosis, and DNA ploidy have been described and it differs with each tumor subtype.

Key points

1. Uterine sarcomas arise from dividing cell population in myometrium or connective tissue elements within the endometrium. They account for 7–8 % of all uterine cancers.
2. In 2003, WHO published a classification system for uterine sarcomas, consisting of pure mesenchymal tumors and mixed epithelial-mesenchymal tumors.
3. MMMT/carcinosarcomas are now classified as uterine carcinomas, since they derive from a monoclonal neoplastic cell, which has more characteristics of epithelial than stromal neoplasms. Similarly, ESSs are by definition now considered all “low-grade” and undifferentiated sarcoma is now the preferred terminology for all “high-grade” ESSs.
4. The most common uterine sarcomas are leiomyosarcomas and carcinosarcoma; however, among pure mesenchymal tumors, leiomyosarcomas followed by endometrial stromal sarcomas are commonest.
5. Patients with carcinosarcomas are usually postmenopausal and mostly presents with abnormal uterine bleeding. Leiomyosarcomas and ESS can present both in pre- and postmenopausal age group and a finding of enlarging uterine mass is universally present.
6. Prior exposure to pelvic radiation is a risk factor for carcinosarcoma. Similarly, prolong use of hormonal agents have been found to increase the risk for leiomyosarcoma. Recently, the role genetic mutations have been elicited in the pathogenesis of each subtype of uterine sarcomas.
7. Preoperative endometrial assessment has a limited role in diagnosis of uterine sarcomas. MRI is a preferred modality for initial evaluation of uterine sarcomas and CT is more accurate for staging and nodal assessment.
8. The FIGO staging system (2009) is currently used for staging of uterine sarcomas, including LMS, ESS, and adenosarcomas. Carcinosarcomas are to be staged using the 2009 FIGO staging system for endometrial carcinomas.
9. Stage is the primary prognostic factor for all uterine sarcomas. Various other factors including tumor size, resection margins, mitotic index, and presence of

necrosis have been described for each subtype. Recent development in molecular biology have given new insights for better prognostication of uterine sarcomas.

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Surgical Management of Uterine Sarcoma

31

Amita Maheshwari

Introduction

Uterine sarcomas are rare malignant tumors of mesenchymal origin and account for 3–8 % of all uterine cancers [1, 2]. They are heterogeneous tumors of diverse histological types. The three most common subtypes are carcinosarcoma (CS) also known as malignant mixed Mullerian tumor (MMMT), leiomyosarcoma (LMS), and endometrial stromal sarcoma (ESS). Although recently carcinosarcoma has been reclassified as a dedifferentiated or metaplastic form of endometrial carcinoma [3], it is still included in most studies on uterine sarcomas. The important pure mesenchymal malignant tumors of the uterus are leiomyosarcoma (LMS) and endometrial stromal sarcoma (ESS). Uterine sarcomas are in general the most malignant group of uterine tumors and differ from endometrial cancers with respect to diagnosis, clinical behavior, pattern of spread, and management.

The rarity of uterine sarcomas and their pathologic diversity have made them difficult to study in large numbers. The published literature reflects this particularly with regard to treatment guidelines. However, surgery is the primary and the only curative modality of treatment for all uterine sarcomas.

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Presurgical Work-Up and Staging

A detailed description of preoperative work-up and FIGO staging is given in a previous chapter. With the exception of carcinosarcoma that is generally diagnosed on endometrial biopsy, the preoperative diagnosis of uterine sarcoma is often difficult. Many imaging modalities, including Doppler ultrasound, computed tomography, magnetic resonance imaging, and positron emission tomography, have been evaluated for preoperative distinction between a sarcoma and benign uterine pathology; however, none has been found to be reliable. Therefore, a preoperative referral to oncology center is rare. This fact was highlighted in our series of 108 women also; 81 women (75 %) had primary surgery by a non-oncologist before presenting to our center (unpublished data).

Surgical Management

As the various histological types differ in their clinical behavior and metastatic patterns, surgical management also varies. Therefore, it will be discussed separately for each subtype.

Leiomyosarcoma

Leiomyosarcoma (LMS) is the most common pure uterine mesenchymal malignancy and accounts

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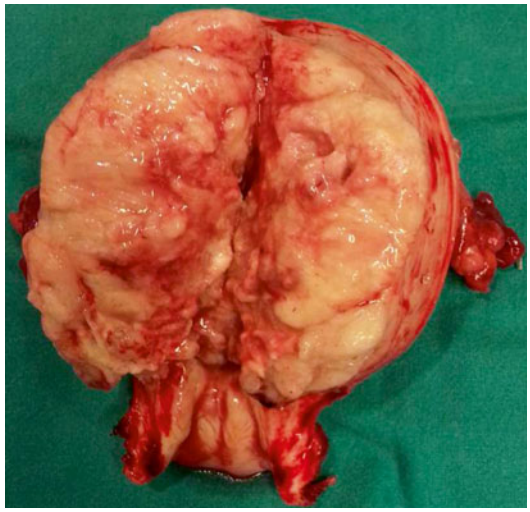

Fig. 31.1 Uterine leiomyosarcoma. Multi-lobulated grey-white tumor with areas of hemorrhage and microcysts

for 42–60 % of all uterine sarcomas (Fig. 31.1) [4]. It commonly affects peri- or postmenopausal women with median age at diagnosis around 52 years [5]. The common presenting symptoms are abnormal vaginal bleeding, lower abdominal mass, or abdominal pain. The clinical profile of LMS overlaps with more common benign leiomyoma, and in many women, the diagnosis of sarcoma comes as a surprise after hysterectomy or myomectomy for presumed leiomyoma.

Simple hysterectomy with or without bilateral salpingo-oophorectomy is the mainstay of surgical management of uterine LMS. Ovaries can be preserved in a young patient with early-stage LMS. The risk of occult ovarian metastasis in early-stage disease is very low, reported to be less than 4 % [6–9]. Ovarian metastasis is generally associated with other extrauterine diseases [8]. A routine oophorectomy has not shown to provide survival advantage or reduce the risk of recurrence [5, 10–13]. Kapp et al. [5] in a Surveillance, Epidemiology, and End Results (SEER) study found no difference in disease-specific survival based on oophorectomy in women younger than 50 years and stage I or II disease. Similarly, in the study by Gadducci et al. [12] that included 126 women with uterine LMS all treated surgically, there was no difference in relapse rates among stage I women younger than 50 years who had ovarian tissue preserved compared to those who had bilateral salpingo-oophorectomy (relapse rates: 23.8 % vs. 33.3; p value = not significant). On the contrary, some retrospective studies have reported an adverse impact of oophorectomy on survival. Garg et al. [14] in a SEER data base analysis of 819 women with LMS showed that on multivariate analysis performance of salpingo-oophorectomy was a poor prognostic factor ($p = 0.02$) along with other factors, i.e., age, tumor size, and tumor grade. In a study of 208 women of LMS from Mayo Clinic, Giuntoli et al. [11] reported that oophorectomy, high grade, and advanced stage were associated with significantly worse DSS (disease-specific survival). So the current literature suggests that grossly normal ovaries can be conserved in a young patient with early-stage LMS without any detrimental effect on survival. Likewise, when the diagnosis of LMS is made after simple hysterectomy, a re-surgery for removal of the normal adnexa is not indicated.

Another controversial issue is the role of pelvic and para-aortic lymphadenectomy in early-stage LMS. Like soft tissue sarcomas at other sites, hematogenous spread is the primary route of metastasis for uterine LMS. Spread to retroperitoneal lymph nodes is infrequent and almost always associated with advanced disease. The risk of lymph nodal metastasis in early-stage disease is less than 3 %. Table 31.1 summarizes important studies that looked at the incidence of lymph-node metastasis in LMS [5, 7, 9, 11–13, 15–19]. Moreover, no therapeutic benefit has been reported from routine lymphadenectomy in women with early disease and clinically normal lymph nodes. Kapp et al. [5] retrospectively analyzed 1,396 women of uterine LMS; out of 348 women (24.9 %) who underwent lymphadenectomy, 23 (6.6 %) had lymph-node metastasis. All women with positive lymph nodes had advanced disease; 70 % were stage IV. The 5-year disease-specific survival was 64.2 % for women who had negative lymph nodes and 26 % with positive lymph nodes. The 5-year disease-specific survival rates were 75.8 %, 60.1 %, 44.9 %, and 28.7 % for stage I, stage II, stage III, and stage IV,

Table 31.1 The incidence of lymph-node metastasis in women with uterine leiomyosarcoma

Authors (year)	Total number, N	Lymph-node dissection or sampling, N (%)	Overall lymph-node metastasis, N (%)	Early stage, N	Occult lymph node metastasis, N (%)
Major et al. [7]	59	57 (96.6 %)	2 (3.5 %)	57	2 (3.5)
Goff et al. [15]	21	15 (71.42)	4 (26.7 %)	9	0
Gadducci et al. [12]	126	7 (5.55)	2 (29 %)	4	0
Ayhan et al. [16]	63	34 (53.9 %)	3 (8.8 %)	27	1 (3.7)
Leitao et al. [9]	37	37 (100)	3 (8.1 %)	27	0
Giuntoli et al. [11]	208	36 (17.3)	4 (11 %)	NR	NR
Wu et al. [13]	51	21 (41.2 %)	0	12	0
Park et al. [17]	46	11 (23.9 %)	0	NR	NR
Kapp et al. [5]	1,396	348 (24.9 %)	23 (6.6 %)	NR	NR
Koivisto-Korander et al. [18]	39	15 (38.5 %)	0	NR	NR
Hoellen et al. [19]	14	5 (35.7 %)	0	NR	NR
Total	2,060	586 (28.4 %)	41 (6.9 %)	136	3 (2.2 %)

NR = not reported

respectively ($P<0.001$). Lymphadenectomy did not show any impact on survival in this study. A subset analysis of early-stage disease ($n=1,079$) revealed no significant difference in 3-year DSS in women who had lymphadenectomy ($n=291$) compared to those who did not ($n=788$) (69.7 versus 69.8 %, respectively; $p=0.90$). In the Mayo Clinic study [11], lymphadenectomy was performed in 36 out of 208 women; 19 women had both pelvic and para-aortic lymph-node dissection. Four out of 36 (11 %) had positive lymph nodes. Extrauterine disease was present in three of four women with lymph-node involvement emphasizing that lymph-node involvement is generally associated with advanced disease. In another retrospective analysis of 37 women of uterine LMS who underwent lymphadenectomy, none of the women with stage I or II disease had positive nodes and all three women (8.1 %) with nodal metastases had clinically suspicious nodes [9]. Authors also suggested that even in women with gross extrauterine disease, the benefit of removing microscopically involved nodes is limited as most of these women have poor prognosis and die of distant metastasis. Therefore, the current evidence is not in favor of routine retroperitoneal lymph-node dissection in uterine LMS, and this procedure should be undertaken only if lymph nodes are grossly enlarged or in advanced disease as part of cytoreductive surgery.

Approximately 20 % of LMS women will have advanced disease at presentation. Management of these women should be individualized. Surgical cytoreduction should be considered in select cases with good performance status and in whom complete resection of tumor with acceptable morbidity seems to be feasible. The survival of women with complete tumor resection has shown to be better compared to those who had incomplete resection [20]. Lung is the most frequent site of hematogenous spread in uterine LMS. Resection of isolated or limited number of lung metastasis has shown to have a survival benefit and should be considered in appropriately selected women [21, 22].

Management of women diagnosed after surgery for benign lesion can be challenging. If the initial surgery was a myomectomy, a complete hysterectomy is recommended. However, if the initial surgery was a total hysterectomy and postoperative imaging study does not suggest residual disease, a re-surgery is not indicated. Management of women of LMS diagnosed after laparoscopic morcellation of presumed leiomyoma will be discussed later.

Endometrial Stromal Sarcoma

Endometrial stromal sarcoma (ESS) accounts for approximately 15–20 % of all uterine sarcomas in Western literature [23, 24]. Although endometrial stromal malignancies have been classified into low-grade endometrial stromal sarcoma and undifferentiated endometrial sarcoma (UES) [25], the term "endometrial stromal sarcoma" generally refers to low-grade tumor that is typically hormone sensitive with an indolent growth and good outcome. The mean age at presentation ranges from 40 to 55 years, and many women are premenopausal at diagnosis. Abnormal vaginal bleeding is the most common presenting symptom [26]. Like uterine LMS, a preoperative diagnosis of ESS is rare, available only in less than 25 % cases [27], and many women undergo initial surgery for presumed leiomyoma or adenomyosis (Fig. 31.2).

A total hysterectomy is the mainstay of surgical management of low-grade ESS. Role of salpingo-oophorectomy in a young patient with early-stage disease is controversial. The risk of ovarian metastasis in early disease and with grossly normal ovaries is extremely low. Dos Santos et al. [28] reported a study of 94 cases of low-grade ESS. Out of 87 women who underwent salpingo-oophorectomy, 11 (13 %) had adnexal metastasis; all had gross adnexal tumor and disease at other pelvic extrauterine sites. Despite low risk of ovarian metastasis, conventionally bilateral salpingo-oophorectomy has been recommended as part of initial surgery because of the hormone-sensitive nature of the tumor and the potential increased risk of recurrence when ovaries were retained [29, 30]. Subsequently many authors challenged this dogma and showed that leaving ovaries in situ does not adversely affect oncological outcome in premenopausal women with early-stage, low-grade ESS [24, 31–35]. However, many recently published large retrospective studies showed adverse impact of ovarian preservation on recurrence-free survival. The study from by Bai et al. [36] included 153 women of low-grade ESS; 44 (28.8 %) had ovaries preserved at initial surgery. On multivariate analysis, ovarian preservation was found to be an independent risk factor for relapse ($p=0.0001$); however, there was no impact on overall survival ($p=0.0810$). In another study from Korea, Yoon et al. [37] evaluated 114 women of low-grade ESS. In this study also ovarian preservation was found to be an independent predictor for poorer recurrence-free survival (HR, 6.5; 95 % CI, 1.23–34.19; $P=0.027$). Feng et al. [38] in a study of 57 women of early-stage low-grade ESS showed much higher recurrence rate with ovary-preserving primary surgery compared to those without (75 % vs. 2 %; $P<0.0001$). Although the role of oophorectomy in a young patient with early-stage ESS remains controversial, the current evidence suggests that ovarian conservation increases the risk of recurrence without impacting overall survival as most recurrences can be salvaged by surgery and hormonal treatment. Therefore, ovarian preservation should be done only after appropriate counseling.

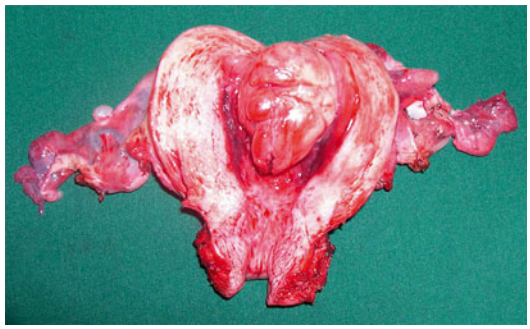

Fig. 31.2 Low-grade ESS. On gross exam. seen as solitary, polypoidal mass projecting into the uterine cavity

The role of routine lymphadenectomy is another controversial issue in surgical management of low-grade ESS. Table 31.2 summarizes important studies that looked at the incidence of lymph-node metastasis [15–17, 24, 28, 29, 32–34, 36, 38–43]. The overall incidence of lymph-node metastasis varies from 0 % to 37 %. The incidence of lymph-node metastasis is low in early stage (ranges from 0 % to 16 %) and is associated with other evidences of extrauterine disease or gross nodal enlargement. Many studies have reported no survival benefit from systematic lymphadenectomy in low-grade ESS [36, 38]. Therefore, a routine retroperitoneal lymph-node dissection is not recommended with apparently early-stage

Table 31.2 The incidence of lymph-node metastasis in women with uterine ESS

Authors (year)	Total women, N	Lymph-node dissection or sampling, N (%)	Overall lymph-node metastasis, N (%)	Early stage, N	Occult lymph node metastasis, N (%)
Goff et al. [15]	10	7 (70 %)	0 (0 %)	5	0 (0 %)
Gadducci et al. [39]	26	2 (7.7 %)	0 (0 %)	2	0 (0 %)
Ayhan et al. [16]	8	4(50 %)	0 (0 %)	2	0 (0 %)
Riopel et al. [40]	15	8 (53.3 %)	3 (37 %)	6	1 (16 %)
Reich et al. [41]	64	9 (14 %)	3 (33 %)	NR	NR
Li et al. [32]	36	12 (33.3 %)	0 (0 %)	12	0 (0 %)
Amant et al. [33]	31	6 (19.3 %)	1 (16 %)	NR	NR
Leath et al. [42]	72	23 (31.9 %)	2 (9 %)	NR	NR
Li et al. [29]	37	1 (2.7 %)	0 (0 %)	NR	NR
Park et al. [17]	37	17 (45.9 %)	2 (11.8 %)	NR	NR
Shah et al. [34]	383	100 (26.1 %)	7 (7 %)	63	3 (5 %)
Chan et al. [24]	831	282 (33.9 %)	28 (9.9 %)	NR	NR
Signorelli et al. [43]	64	19 (29.7 %)	3 (16 %)	16	1 (5 %)
Dos Santos et al. [28]	94	36 (38.3 %)	7 (19.4 %)	20	2 (10 %)
Feng et al. [38]	57	36 (63.1 %)	0	36	0
Bai et al. [36]	153	46 (30.1)	1 (2.2 %)	NR	NR
Total	1,918	608 (31.7 %)	57 (9.4 %)	162	7 (4.3 %)

NR = not reported

disease without extrauterine disease or gross lymph-node involvement. Lymphadenectomy should be considered only in cases with advanced disease or when nodes are enlarged on preoperative imaging or on intraoperative assessment. However, even in these cases, there is no consensus on the extent of lymphadenectomy, whether to debulk enlarged lymph nodes only or to do a complete pelvic and para-aortic lymphadenectomy. Other staging procedures, i.e., peritoneal biopsies, peritoneal cytology, and omentectomy, are not recommended for early-stage ESS.

Nearly 20 % women of low-grade ESS will have advanced disease at diagnosis. Although the benefit of cytoreductive surgery in these cases has not been systematically evaluated, surgery is generally recommended because of the indolent nature of the disease and the efficacy of adjuvant hormonal therapy. The extent of surgery should be individualized with the aim to achieve a complete tumor resection with minimal morbidity. Bilateral ovaries should always be removed at the time of surgery for advanced disease.

Uterus Preservation in Low-Grade ESS

Rarely, low-grade ESS may occur in a young nulliparous woman who might be keen to conserve her reproductive potential. Many cases of uterine-sparing surgery and subsequent successful pregnancies have been reported in the literature [36, 44–46]. Dong et al. [44] recently reported a case of early-stage low-grade ESS in a 25-year-old woman, treated with fertility-preserving tumor resection with uterine reconstruction followed by high-dose progesterone (medroxyprogesterone, 250 mg daily) for 1 year. Subsequently, she had spontaneous conception and delivered a healthy baby at term. Bai et al. [36] reported 19 women of low-grade ESS who underwent myomectomy. Among these, 8 women had spontaneous pregnancy.

Although uterine-sparing surgery is feasible in selected women with low-grade ESS, this approach should be considered experimental and offered only after appropriate counseling. The

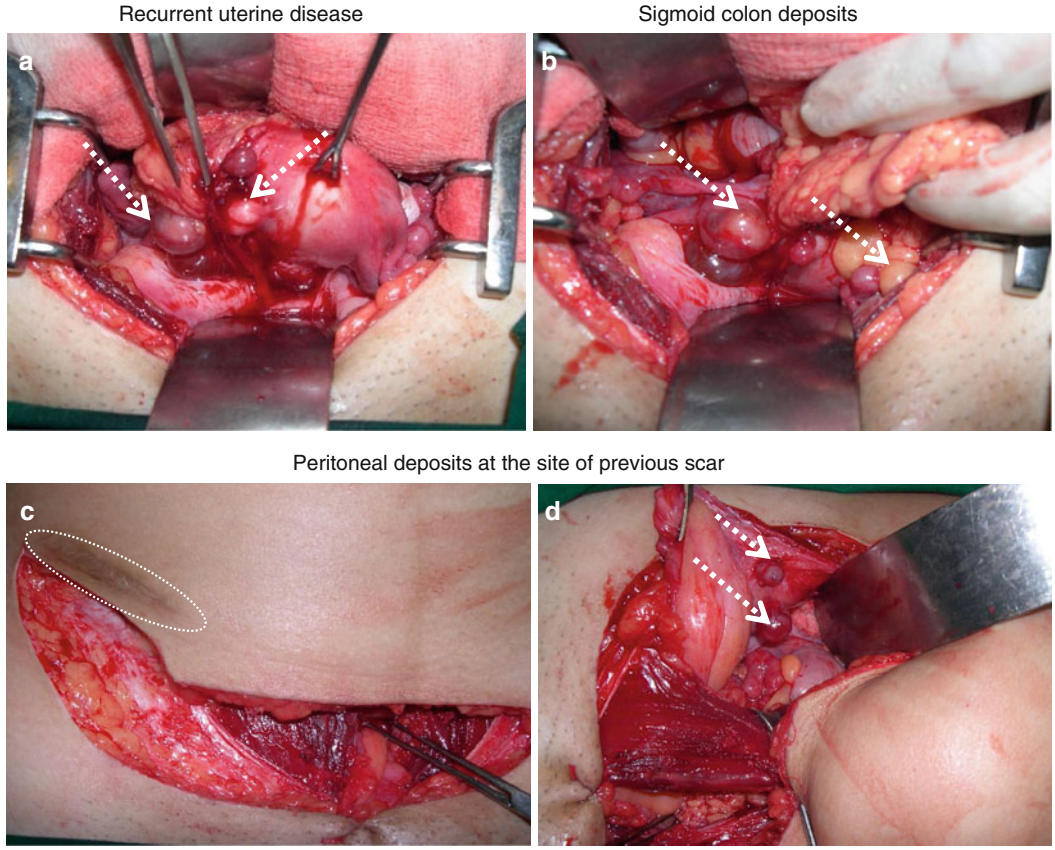

Fig. 31.3 Recurrent ESS: disease at multiple sites in a 24-year lady after initial uterine preservation surgery

risk of relapse is higher with conservative surgery (Fig. 31.3). In the study by Bai et al. [36], myomectomy was found to be an independent risk factor for relapse. The recurrence rate was 78.9 % (15/19) in the myometrial resection group and 25.4 % (34/134) in the hysterectomy group ($p = 0.0075$), although OS was not affected ($P = 0.8845$) as most recurrences could be salvaged. There is also a potential risk of tumor regrowth during pregnancy due to alteration in the hormonal milieu. Koskas et al. [47] reported a case of low-grade ESS treated with conservative surgery which developed disseminated peritoneal recurrence following delivery of a healthy baby. Recently Morimoto et al. [48] reported a fatal case of ESS 10 years after fertility-sparing surgery. Therefore, myomectomy should only be offered to young women with a strong desire for fertility, after obtaining informed consent. Hysterectomy is recommended after the completion of childbearing. The long-term follow-up is mandatory as late recurrences are known in low-grade ESS. The median time of recurrence is 65 months for stage I disease [49].

Undifferentiated endometrial sarcoma (UES) is uncommon but aggressive tumor with poor prognosis. Local recurrence and distant metastasis occur early in the course of disease (within 6 months) and is associated with high mortality. Surgery is the primary treatment modality although adjuvant radiation therapy and chemotherapy are frequently used. UES do not express hormone receptors and hence do not respond to antiestrogenic treatment.

Uterine Sarcoma and Morcellation

Globally, minimal access surgery has become the standard for the surgical management of uterine leiomyoma. Intracorporeal morcellation of a large myoma for removal of the specimen is a

common practice in minimal access surgery. However, one of the most dreaded complications of morcellation of presumed uterine leiomyoma is unexpected sarcoma and its inadvertent dissemination in the peritoneal cavity. In the past, it was estimated that between 1 in 500 and 1 in 1,000 surgical specimens for presumed leiomyoma would reveal leiomyosarcoma on final histopathology [50, 51]. However, a recent report from the Food and Drug Administration (FDA) has estimated much higher risk for occult uterine cancer in women with symptomatic fibroids who are referred for surgery, about one in 350 [52]. With dramatic increase in the use of minimal access surgery and morcellator in recent years, there is a potential threat of increase in the number of cases of uterine sarcoma undergoing inadvertent morcellation. Unfortunately, preoperative diagnosis of uterine sarcoma is rare, and majority undergo initial surgery for presumed benign lesion.

Many studies have demonstrated that intraperitoneal morcellation of undiagnosed uterine sarcoma is associated with an increased risk of tumor recurrence and poorer disease-free and overall survivals [53–56]. This is most likely secondary to uncontrolled dissemination of tumor fragments in the peritoneal cavity [54, 57–59]. Residues of benign and malignant uterine tissue have shown to have biological potential for neovascularization and intraperitoneal growth.

Park et al. [55] reported 56 consecutive women with stages I and II uterine LMS treated between 1989 and 2010 at South Korean tertiary care center, 25 with and 31 without tumor morcellation. In this series, tumor morcellation was found to be an independent prognostic factor for survival. The 5-year survival was 46 % in women who had morcellation versus 73 % when uteri were removed intact ($p=0.04$). Morcellation was also associated with higher incidence of peritoneal sarcomatosis and vaginal vault recurrence (44 % with vs. 12.9 % without morcellation, $P=0.032$). Recently, a study by George et al. [57] revealed detrimental effects of morcellation in women with uterine LMS. They reported a series of 58 consecutive women of uterine LMS treated from 2007 to 2012. Nineteen women had intraperitoneal morcellation while 39 underwent total abdominal hysterectomy without tumor disruption. Intraperitoneal morcellation was associated with a significantly increased risk of abdominopelvic recurrences ($P=0.001$) and with shorter recurrence-free survival (10.8 months vs. 39.6 months; $P=0.002$). A multivariate-adjusted model showed three times increased risk of recurrence associated with morcellation (hazard ratio, 3.18; 95 % confidence interval, 1.5–6.8; $P=0.003$). The OS rate at 36 months was 64 % in the morcellation group and 73 % in the TAH group. Similarly, inadvertent morcellation of low-grade ESS has shown to increase the risk of abdominopelvic recurrence and adversely affect the disease-free survival [60].

Due to many reports on adverse patient outcome after inadvertent morcellation of uterine sarcoma in recent times, the safety of morcellator in minimal access surgery has fallen in disrepute. On April 17, 2014, the Food and Drug Administration (FDA) released a safety communication to discourage the use of laparoscopic power morcellation in hysterectomy and myomectomy stating that the "Procedure poses risk of spreading undetected cancerous tissue in women with unsuspected cancer" [52]. As a result, several medical centers in the United States have banned morcellation. It is recommended that the risks and benefits of laparoscopic surgery in the management of uterine myomas should be discussed with women as part of the informed consent procedure before surgery.

In order to avoid tissue dispersion, some surgeons recommend performing tumor morcellation inside of an insufflated bag within the peritoneal cavity, though there are no studies to prove safety of bags. Furthermore, use of large bags can obscure the surgeon's vision and has potential to increase the risk of visceral injury. Management of women with inadvertently morcellated uterine sarcoma poses a great clinical dilemma. Although there are no clear guidelines in the literature on this issue, a reoperation for completion surgery and staging is recommended because a significant proportion of women will have residual disease and will be upstaged. The information obtained at surgical staging is also useful in tailoring the adjuvant

treatment. Women with extrauterine disease detected at immediate re-exploration have inferior survival compared to women with early-stage LMS. Einstein et al. [59] reported the outcome of women with uterine malignancy that were inadvertently morcellated or diagnosed after a supracervical hysterectomy. Thirteen out of seventeen women with uterine malignancy were surgically restaged; four of these women had undergone tumor morcellation during initial surgery. Two women (15 %) were upstaged after surgical re-exploration and both women had LMS. Oduyebo et al. [61] showed similar results in a recent study. Eleven women with early-stage LMS and STUMP who were initially treated with laparoscopic morcellation and underwent immediate surgical re-exploration were analyzed. A significant percent of women, 28.5 % and 25 % with LMS and STUMP, respectively, were found to have disseminated intraperitoneal disease and were upstaged. The authors recommended that at least the following steps should be undertaken at re-exploration: removal of the uterus and/or cervix (if not removed at initial surgery), multiple peritoneal biopsies including from the port sites, and omentectomy (or omental biopsy).

Carcinosarcoma

The clinical behavior including pattern of metastasis of CS is like that of high-grade uterine carcinoma; therefore, these tumors are treated on similar lines. FIGO staging system for uterine carcinoma is used to stage CS also. These tumors commonly occur in postmenopausal women in the sixth and seventh decade of life. Postmenopausal bleeding or discharge is the most common presenting symptoms. A significant number of women are diagnosed preoperatively on endometrial biopsy and undergo planned primary surgery at an oncology center.

CS has an aggressive behavior with substantial risk for metastasis. Nearly 50 % of women with clinically early disease will have extrauterine spread at surgery [62–64]. Common sites for metastasis include adnexa, retroperitoneal lymph nodes, omentum, and peritoneal surfaces. Therefore, a comprehensive surgical staging including collection of peritoneal washings, pelvic and para-aortic lymphadenectomy, omentectomy, multiple peritoneal biopsies along with a type I hysterectomy, and bilateral salpingo-oophorectomy is the standard of surgical management for early-stage CS. On gross examination of the uterus, CS usually appears as a polypoidal mass with areas of hemorrhage and necrosis projecting into the uterine cavity (Fig. 31.4). Radical hysterectomy is advocated in cases with cervical or parametrial involvement [65]. The risk of ovarian metastasis in apparently early-stage CS varies from 12 % to 23 %; therefore, bilateral adnexa should always be removed even in young women [7, 64, 66]. CS also has a higher propensity for retroperitoneal lymph nodal spread compared to other sarcomas. The overall incidence of lymph-node metastasis ranges from 14 % to 38 % [62, 63, 67, 68], and a systematic pelvic and para-aortic lymph-node dissection is recommended. Removing only enlarged nodes have the risk of missing microscopic metastasis. The extent of lymph-node dissection should include both pelvic and para-aortic lymph nodes because nearly 50 % of women with pelvic lymph-node metastasis will also have para-aortic node involvement and in about 7 % para-aortic nodal involvement will be present without pelvic node involvement [7, 69]. Many retrospective studies have evaluated the impact of lymphadenectomy on the survival in early-stage carcinosarcoma. In a retrospective study of 690 women of CS, Garg et al. showed lymphadenectomy $p<0.001$ to be an independent predictor of survival [70].

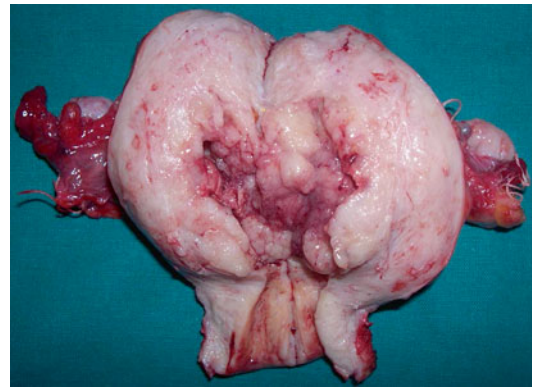

Fig. 31.4 Carcinosarcoma. Polypoid, multilobulated grey-white tumor projecting into the endometrial cavity

A SEER data base analysis [68] reported a median survival of 54 months in women who underwent lymphadenectomy compared to 25 months in those who did not (5-year overall survival rates of 49 % and 34 %, respectively). It is possible that removal of occult lymph-node metastasis may improve therapeutic efficacy of adjuvant treatment and therefore prognosis. Although lymph-node dissection helps in accurate staging of the disease, provides prognostic information, and helps in tailoring the adjuvant treatment, its therapeutic value is controversial. There is lack of level I evidence about the impact of systematic lymphadenectomy on the survival in early-stage CS. Further research is warranted on this issue.

Positive peritoneal cytology has been reported in more than one fourth of women with early disease and shown to be associated with poor prognosis [7, 63, 66, 70, 71].

Women with gross extrauterine disease should undergo surgical debulking with the aim to achieve optimal cytoreduction whenever feasible.

Surgery for Recurrent Disease

Uterine sarcomas have aggressive clinical behavior and a high tendency to relapse even in early stages of disease. Most recurrences occur within the first 2 years. LMS have a higher propensity for hematogenous spread; lung is the favored site. The overall relapse rate is nearly 60 % and 42 % of relapses occur outside the pelvis [72]. On the other hand, ESS has more indolent course with long latency. The relapse rate ranges from 36 % to 56 %, and the median time to recurrence in stage I disease is 65 months. The major sites for recurrence are the pelvis, abdominal cavity (Fig. 31.5), and lung [49].

The treatment options for recurrent disease include surgery, chemotherapy, hormonal therapy, radiation therapy, or a combination. Due to rarity of uterine sarcomas, there is lack of randomized trials evaluating the optimal management strategy for these women. The most available evidence is from retrospective studies on heterogeneous patient population.

Surgery plays an important role in the management of selected women with localized disease limited to a single or a few lesions. Although the favorable clinico-pathologic factors for secondary cytoreduction have not been well established; longer disease-free interval, localized disease, and complete resection have shown to significantly improve the survival after secondary cytoreductive surgery. Giuntoli et al. [73] in a retrospective study of 128 women of recurrent uterine LMS reported that longer time to recurrence, localized recurrence, and complete debulking at recurrence were significantly associated with prolonged survival. When survival of women who underwent surgery was compared with those who had chemotherapy and/or radiation therapy, both disease-specific

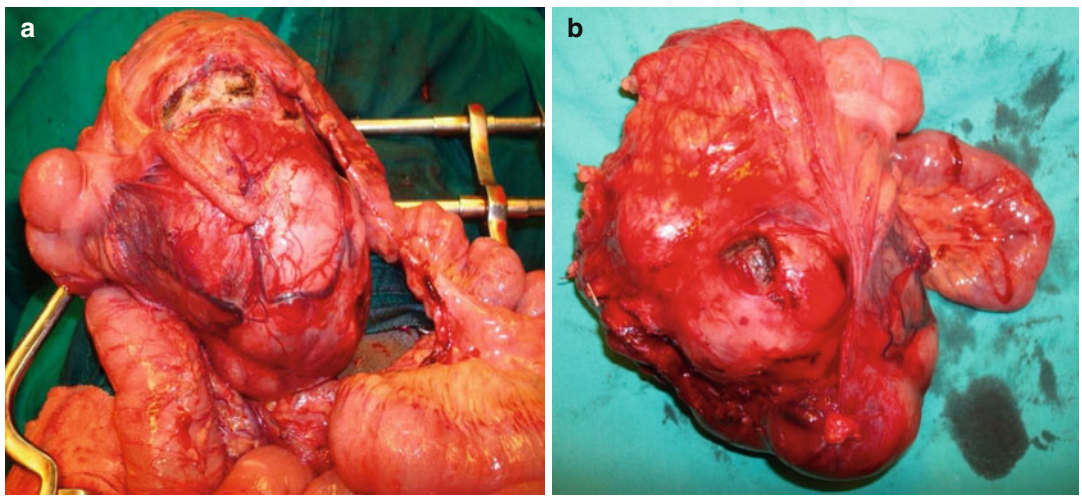

Fig. 31.5 Intra abdominal recurrence in a case of low grade ESS, treated by secondary cytoreductive surgery

and overall survivals were significantly better in the surgery group, with a mean overall survival from the time of recurrence of 2.0 versus 1.1 years in surgery versus nonsurgical groups, respectively. Leitao et al. [22] reported a retrospective study of 41 women with recurrent LMS who underwent surgical resection for both pelvic and pulmonary diseases. In univariate analysis, time to first recurrence and optimal resection were significant prognostic factors for overall survival. Many other studies have also shown that a complete surgical resection of recurrent disease is associated with improved survival in women with recurrent uterine sarcoma [74]. Women with isolated or limited lung metastases are good candidates for surgical resection regardless of histological type. A retrospective study from the Memorial Sloan Kettering Cancer Center on 45 women of uterine sarcoma who underwent pulmonary metastasectomy reported 5- and 10-year survival rates of 43 % and 35 %, respectively [21]. Although there is no level I evidence in favor of surgery for recurrent disease, it should be considered in select cases after appropriate preoperative assessment and risk stratification.

Conclusions

Surgery is the main and the only curative modality of treatment for uterine sarcomas. As various histological subtypes have different clinical behavior and metastatic patterns, surgical management also varies. A preoperative diagnosis of ESS and LMS is rare, and a large majority of women undergo initial surgery for presumed leiomyoma. Utmost care and judgment should be executed while treating "benign" uterine masses with laparoscopic morcellation. Ovaries can be preserved in a young patient with early-stage LMS without adverse effect on survival. In women with low-grade ESS, ovarian conservation has shown to increase the risk of recurrence without affecting the overall survival. The role of systematic lymphadenectomy in LMS and ESS remains controversial. CS should be treated like high-grade uterine carcinoma.

Key Points

1. Uterine sarcomas include a heterogeneous group of rare tumors that have an aggressive clinical behavior and a poor prognosis.
2. A total abdominal hysterectomy with or without bilateral salpingo-oophorectomy is the treatment for LMS. Grossly normal ovaries can be preserved in young women with early-stage LMS.
3. A total abdominal hysterectomy with bilateral salpingo-oophorectomy is the standard treatment for low-grade ESS. Ovarian preservation is associated with increased risk of recurrence without affecting overall survival. Therefore, ovarian preservation is possible in a young patient after appropriate counseling.
4. Lymphadenectomy is not indicated for early-stage ESS and LMS and should be done only if nodes are enlarged.
5. Intraperitoneal morcellation/rupture of undiagnosed uterine sarcoma is associated with an increased risk of tumor recurrence and adversely affects survival.
6. Carcinosarcoma should be treated like high-grade carcinoma with a comprehensive surgical staging.
7. Treatment of women with advanced disease should be individualized, and cytoreductive surgery should be offered if optimal debulking is achievable.
8. Selected cases of recurrent/metastatic sarcoma may benefit from secondary cytoreductive surgery.

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Role of Radiation Therapy in Uterine Sarcoma

32

Reena Engineer

Introduction

Uterine sarcomas are relatively rare tumors with a dismal survival rate of 30–40 %. Fifty percent of women present in FIGO stage I [1]. Most of the tumors spread hematogenously, resulting in an extremely poor prognosis in advanced stages. Even in the early stages (FIGO stage I–II), 35 % of patients fail locally and 65 % fail in distant sites [2, 3]. Radiotherapy to pelvis is given usually as an adjuvant therapy with an aim to decrease local recurrence.

Role of Radiotherapy as per Histological Subtypes

The three histological subtypes are mainly carcinosarcoma, leiomyosarcoma (LMS), and endometrial stromal sarcoma (ESS). Uterine carcinosarcomas, also known as malignant mixed mesodermal tumors (MMT) or malignant mixed Mullerian tumors (MMMT), have both malignant epithelial and malignant mesenchymal components. Of the three histologies, uterine carcinosarcomas are the most common followed by leiomyosarcomas and then endometrial stromal sarcomas [4]. In recent years, carcinosarcoma has been reclassified and moved from the uterine sarcoma group to endometrial carcinomas of high-risk type [5]. Though the benefits of postoperative radiotherapy and chemotherapy are still under debate, the role of radiotherapy is more defined in carcinosarcoma compared to LMS and ESS [1, 6–9].

Uterine Carcinosarcoma

In literature, there are many retrospective studies with contradicting results and inferences regarding the efficacy of adjuvant radiotherapy in improving local control rates and its impact on overall survival. The two large SEER (Survey, Epidemiology, and End Results) cancer registries showed lack of overall survival benefit in stage I–III carcinosarcoma, and the one by Smith et al. showed an overall survival benefit in stage IV disease [10, 11].

Uterine sarcomas usually metastasize hematogenously early in their course, leading to a lack of survival benefit by pelvic radiotherapy. Sampath et al. reported a study of 3,650 women from USA and concluded that adjuvant radiotherapy does not have overall survival benefit but confers a 53 % reduction in the risk of locoregional failure at 5 years. The 5-year actuarial locoregional failure-free survival was 90 % vs. 80 % ($P<0.05$), in favor of adjuvant radiotherapy [12].

Sorbe et al. reported a large population-based study of 322 patients of primary uterine

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carcinosarcomas. Prophylactic pelvic irradiation and/or chemotherapy was used postoperatively in large majority of patients. Radiotherapy (external beam therapy followed by brachytherapy) was given in 204 cases (63 %). The locoregional recurrence rate in stage I–II tumors was lower (though not statistically significant) in patients who received adjuvant radiotherapy compared to surgery alone (8 % vs. 19 %; $p=0.103$). Addition of radiotherapy plus chemotherapy resulted in a superior overall and recurrence-free survival compared with patients treated with chemotherapy alone or no adjuvant therapy ($p=0.000001$). This effect on survival was evident across all stages, stages I–II ($p=0.032$) and stages III–IV ($p=0.000001$) [13].

In the Gynecological Oncology Group study by Major et al., it was seen that addition of pelvic radiotherapy to surgery (at the discretion of treating physician) was associated with lower local failure rate, 17 % (43 out of 182) compared with surgery alone 24 % (20 out of 119) but with higher distant failures [2].

Whole abdominal radiation also does not seem to be effective in controlling pelvic failures or improving overall survival as seen in phase III randomized trial by GOG [14]. This could be because of lower doses of radiotherapy used in this study, i.e., 30 Gy compared to 45–50 Gy which is routinely used.

The recently reported EORTC-GCG is a landmark phase III trial addressing the utility of adjuvant pelvic RT for all subtypes of uterine sarcomas. All the 224 patients underwent total abdominal hysterectomy and bilateral salpingo-oophorectomy and washings, but nodal sampling was optional. They were randomized to pelvic RT of 50.4 or observation. There was statistically significant reduction in local failure in patients who received adjuvant radiotherapy (14 vs. 24; $p=0.004$) but no improvement in overall or progression-free survival [15]. This benefit was limited to patients with histology of carcinosarcomas but not in leiomyosarcomas. Besides this, many other studies also report a better local control with the use of adjuvant radiotherapy [16]. Recent Cochrane meta-analysis published in 2013 evaluated the effectiveness and safety of adjuvant radiotherapy in the management of uterine carcinosarcoma. It included five randomized controlled trials and radiotherapy to the abdomen were not associated with improved survival [17].

Uterine Leiomyosarcoma

These are rare but challenging tumors with a poor prognosis. They occur most commonly around or shortly after the menopause. Like carcinosarcomas, they also have a high metastatic potential. In a retrospective study of 208 patients, Giuntoli et al. reported a significantly better local control ($p=0.011$) and a trend ($P=0.056$) for improved cause-specific survival in the patients who underwent adjuvant pelvic radiotherapy [18]. Another retrospective study of 147 patients by Madhavi et al. reported a better local control with adjuvant RT (18 % vs. 49 %; $P=0.02$). The 5-year survival receiving adjuvant radiotherapy was significantly superior to those who did not receive radiotherapy (70 % vs. 35 %), but this survival advantage was lost at the extended follow-up at 90 months.

A large population-based study by Garg et al. of 819 women collected from SEER database did not report any survival advantage with RT though there were more advanced tumors in the RT group [19, 20].

The retrospective study by Sampath et al. also showed that patients receiving adjuvant RT had significantly reduced local failure (2 % vs. 16 %, $p<0.05$) [12]. But in the EORTC trial, patients with LMS histology who received RT had significantly higher rates of distant metastasis (54 % vs. 33 %); therefore, authors concluded that RT should not be given in this group of patients [15]. This could be due to RT leading to a better local control in the pelvis with the distant metastasis being more evident. Therefore, for uterine leiomyosarcomas, RT should be reserved for select cases till future trials give level I evidence.

Endometrial Stromal Sarcoma

ESS is a rare malignant tumor of the uterus, and most of the information on the use of adjuvant radiotherapy is based on a small series or case

reports. Hormone therapy, radiotherapy, and surgical excision of the metastasis are recommended for recurrences.

Tumor grade is the most important factor predicting outcome. High-grade tumors have a propensity for distant metastasis leading to a poorer survival, but in most studies, the outcomes with the use of RT have not been reported as per the grade of tumor. Adjuvant radiotherapy does not improve overall survival though in many non-randomized series it is reported to result in a better local control [21]. In a retrospective analysis of 376 women with ESS, Sampath et al. observed a lower recurrence rate in patients receiving adjuvant RT compared to surgery alone (8 % vs. 2 %; $P<0.05$) though it was not reported according to the grades [12]. In a retrospective series of 106 patients by Leath et al., there were more local failures in the patients with high-grade ESS compared to low grade justifying the use of adjuvant RT for the high-grade tumors [22]. In the absence of any concrete evidence regarding the use of adjuvant RT, it should be individualized. NCCN (National Comprehensive Cancer Network) consensus recommends observation for early stage, low-grade tumors, whereas RT can be given for more advanced disease [23].

Conclusion

Due to the rarity of these tumors, the role of adjuvant radiotherapy is limited by only two randomized control trials. Though there is no evident benefit in improving overall survival, it results in better local control. Adjuvant radiotherapy is definitely indicated in early-stage carcinosarcomas; however, for leiomyosarcomas and endometrial stromal sarcomas, it is recommended for high-grade tumors to achieve better local control.

Key Points

1. Adjuvant pelvic radiotherapy is indicated in early-stage carcinosarcoma (level 1 evidence).
2. Adjuvant pelvic radiotherapy leads to better local control but no improvement in overall survival in uterine leiomyosarcoma.
3. For endometrial stromal sarcoma, there is no direct evidence supporting the use of pelvic radiotherapy. Hence, the use of radiotherapy should be individualized and can be considered for high-grade tumors.

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33 Role of Systemic Therapy in the Management of Uterine Sarcomas

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Introduction

Uterine sarcomas are a heterogenous group of rare neoplasms with varied histologies, clinical behaviors, and chemosensitivities [1]. The broad terminology of uterine sarcomas encompasses leiomyosarcoma [LMS], carcinosarcoma, endometrial stromal sarcoma (ESS), and undifferentiated sarcomas [2, 3]. Uterine sarcomas generally have an aggressive clinical behavior, with a tendency for local recurrence and distant spread. Most distant relapses of uterine sarcomas involve the lung and upper abdomen, while brain metastases are less common [4–6]. However, the metastatic potential is very wide and distant lesions can be found in any part of the body. Despite high risk of recurrence, the role of adjuvant therapy in uterine sarcoma is still controversial. A phase III randomized trial comparing adjuvant chemotherapy (ACT) to a no-chemotherapy control group is needed to give a final verdict to the management strategy.

The management of patients with advanced uterine sarcoma involves those with localized and those with disseminated disease. Surgery is the mainstay for treatment of early-stage disease. Selected patients with single or oligo-metastatic disease also benefit from surgical resection. However, in a large majority of patients, recurrent/metastatic disease requires integrated multimodality therapy. There is no single curative option currently available, except surgery for lung metastases and hormone therapy with or without debulking surgery for recurrent low-grade ESS. Patients should be encouraged to enter clinical trials in pursuit of new active drugs for these rare aggressive malignancies [7].

Prognostic Factors in Uterine Sarcoma

Due to rarity and heterogeneity of uterine sarcomas, prognostic factors have not been well defined, and there is no consensus on the risk stratification. However, few important prognostic factors appear clinically significant as evident from the literature. Disease stage is the most important prognostic factor in leiomyosarcoma with 5-year overall survival (OS) ranging from 50 % to 75 % in stage I to less than 10 % in stage IV disease (Table 33.1) [4, 8–11]. Advanced age at diagnosis has also been found to be a poor prognostic factor. De Angelo [12] has shown that there is 2.073 times increased risk of progression, and Wu et al. [13] found 11.07 times increased risk of death in women aged 50 years and above. Mitotic count was found to be a significant

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Table 33.1 Stage as prognostic factor in uterine leiomyosarcoma

Study	Stage	Number	Clinical outcome
Kapp et al. [8]	I	951	5-year DSS: 76 %
	II	43	5-year DSS: 60 %
	III	99	5-year DSS: 45 %
	IV	303	5-year DSS: 29 %
Blom et al. [9]	I–II	29	5-year OS: 52 %
	III–IV	20	5-year OS: 0 %
Gadducci et al. [4]	I–II	90	5-year DFS: 54 %
	III	16	5-year DFS: 6 %
	IV	20	5-year DFS: 0 %
Mayerhofer [10]	I	49	5-year OS: 75 %
	II	5	5-year OS: 14 %
	III–IV	17	5-year OS: 0 %
Salazar et al. [11]	I	113	5-year OS: 53 %
	II–IV	50	5-year OS: 8 %

DSS disease-specific survival, *OS* overall survival, *DFS* disease-free survival

Table 33.2 Mitotic count as prognostic factor

Authors	Mitotic count	Recurrence rate
Major et al. [14]	<10	No recurrence
	10–20	3-year recurrence rate: 61 %
	>20	3-year recurrence rate: 79 %
Wu et al. [13]	<15	RR = 3.22
	>15	RR = 3.38
Gadducci et al. [4]	<10	5-year DFS: 80 %
	10–19	5-year DFS: 48 %
	>20	5-year DFS: 20 %
Blom et al. [9]	<10	RR = 1
	11–20	RR = 1.9
	>20	RR = 2.5

RR recurrence risk, *DFS* disease-free survival

prognostic factor in some studies [4, 9, 13, 14] (Table 33.2). Tumor grade had mixed results in prognostic relevance in different studies. In two of the studies by Kapp [8] and Blom [9], it was found to be an independent prognostic factor. However, the Gynecologic Oncology Group (GOG) study failed to find statistical relevance of tumor grade [14]. Vascular space involvement was found to be a poor prognostic factor associated with short metastasis-free interval in the study by Pelmus et al. and in another study by Mayerhofer [10]. Progesterone receptor [PR] positivity is associated with diagnostic and prognostic relevance. There have been many retrospective reviews that have shown a good prognostic outcome in patients who are PR positive compared to those who are PR negative [15]. Further, there are many prognostic factors at molecular level which are the focus of active research and evaluation including KI67, p53, p16, bcl2, Twist oncogene, etc. [16].

This review provides an overview of consensus and controversies on the role of chemotherapy and targeted therapy, in adjuvant and metastatic setting in patients with uterine sarcomas based on the existing evidence.

Role of Chemotherapy/Targeted Treatment in Uterine Leiomyosarcoma [LMS]

Chemotherapy for Advanced/Metastatic LMS

For advanced/metastatic LMS, doxorubicin, ifosfamide, gemcitabine, trabectedin, and docetaxel have shown activity. Landmark studies addressing the role of chemotherapy in uterine sarcoma are summarized in Table 33.3.

Single-agent doxorubicin was compared with a combination of doxorubicin and DTIC in a phase III trial in patients with various sarcomas including uterine LMS and carcinosarcoma. The overall response rate of 25 % was achieved in patients of uterine LMS treated with doxorubicin, and there was no further improvement with the addition of DTIC [17]. In another phase III trial, the addition of cyclophosphamide to doxorubicin did not improve outcomes in 104 women with uterine sarcomas [18]. Ifosfamide has shown single-agent activity in phase II trial, with a response rate of 6/32 (17.2 %) [19], while in combination with doxorubicin, an objective response of 30 % in LMS was achieved [20]. Liposomal doxorubicin, in a prospective phase II trial, achieved a 16 % response in first-line setting [21]. Gemcitabine studied in a second-line setting in a phase II trial achieved objective response in 20 % of women [22]. Gemcitabine, delivered as a fixed dose rate infusion, in combination with docetaxel, achieved objective

Table 33.3 Chemotherapy in advanced uterine leiomyosarcoma

Chemotherapeutic agent	Treatment schedule	Patient setting	Response	Reference
Doxorubicin				
Single agent	Doxorubicin 60 mg/m^2 every 3 weeks	First line in stage III uterine sarcoma	7/28 (25 %)	Omura [17]
Combination	Doxorubicin + DTIC	First line in stage III sarcoma	16/66 [24.25]	Omura [17]
	Doxorubicin + cyclophosphamide	First line in advanced uterine sarcoma	Doxo = 19 % Doxo + cyclo = 19 %	Muss [18]
Ifosfamide single agent	Ifosfamide 1.5 g/m^2 for 5 days	First line in phase II	6 PR 6/35 (17 %)	Sutton [19]
Ifosfamide in combination with adriamycin	Ifosfamide 5 g/m^2 plus doxorubicin 50 mg/m^2	Phase II, uterine leiomyosarcoma	10/33 (30.3 %)	Sutton [20]
Liposomal doxorubicin	Liposomal doxorubicin 50 mg/m^2	Phase II, uterine leiomyosarcoma	5/32 (16 %)	Sutton [21]
Gemcitabine Single agent	Gemcitabine 1,000 mg/m^2 for days 1, 8, and 15	Phase II, uterine leiomyosarcoma	9/42 (20 %)	Look et al. [22]
Gemcitabine + docetaxel	Gemcitabine 900 mg/m^2 over 90 min for days 1 and 8 plus docetaxel 100 mg/m^2 on day 8 (25 % lower doses if prior pelvic radiation)	Phase II, uterine leiomyosarcoma or non-uterine leiomyosarcoma	18/34 (53 %)	Hensley [23]
	Gemcitabine 900 mg/m^2 over 90 min for days 1 and 8 plus docetaxel 100 mg/m^2 on day 8	Phase II, uterine leiomyosarcoma	First line: 15/42 (36 %) Second line: 13/48 (27 %)	Hensley [14, 24]
Trabectedin	Trabectedin 1.5 mg/m^2 intravenous over 24 h	Phase II, soft-tissue sarcoma	6/35 (17 %)	Garcia-Carbonero [25]

response in 53 % of heavily pretreated women of LMS with uterine and non-uterine primary. However, the combination was found to be more toxic than doxorubicin alone [23]. In two other phase II studies, objective response of 36 % was seen in women on first-line therapy with this combination [24], while response was 27 % in women on second-line treatment [14].

Role of Trabectedin

Trabectedin is a marine alkaloid isolated from the Caribbean tunicate *Ecteinascidia turbinata*; it has covalent interaction with the minor groove of the DNA double helix and with adjacent nuclear proteins. The compound's chemical interactions trigger a cascade of events that interfere with several transcription factors, DNA-binding proteins, and DNA repair pathways. Trabectedin also causes modulation of the production of cytokines and chemokines by tumor and normal cells, suggesting that the antitumor activity could also be attributed to changes in the tumor microenvironment. Trabectedin has been approved for soft-tissue sarcomas in Europe, based on objective response rates ranging from 4 % to 17 % in phase II trials. Another retrospective analysis of 56 women with uterine LMS reported a response rate of 20 %. In a study of trabectedin for advanced liposarcoma or LMS, the objective response rate was 5.6 % with the 24-h infusion schedule and 1.6 % with the weekly schedule. However, to date, there is insufficient evidence to support or refute the use of trabectedin in these patients [25–30].

Chemotherapy for Adjuvant Treatment of Completely Resected LMS

The risk of disease recurrence is about 50–70 % even in completely resected patients [31, 32]. No prospective, randomized trial has shown a survival benefit from adjuvant therapy. The standard approach in completely resected, uterus-limited LMS is only observation. The current evidence for adjuvant therapy in surgically resected LMS is weak and is summarized in Table 33.4. A randomized phase III trial comparing doxorubicin with observation in women with uterine LMS or carcinosarcoma was conducted by the GOG [33]. In the subgroup of LMS, recurrence rate was 44 % with doxorubicin and 61 % with observation alone. Another retrospective analysis of 18 women with uterine sarcomas compared adjuvant doxorubicin, cisplatin, and pelvic radiation, with pelvic radiation alone [34]. The chemotherapy-radiation group had a recurrence rate of 38 %, with 72 % among women who had only radiation. Another prospective study in women with completely resected uterine LMS of all stages was conducted. They were treated with four cycles of adjuvant fixed dose rate gemcitabine plus docetaxel, and the median progression-free survival (PFS) exceeded 3 years, and 59 % were

Table 33.4 Adjuvant chemotherapy in uterine leiomyosarcoma

Chemotherapeutic agent	Study setting	Response	Reference
Doxorubicin/ Observationobservation	GOG RCT phase III Uterine leiomyosarcoma/ carcinosarcoma	Recurrence rate: Doxo: 44 % Observation: 61 % [Statistically NS]	Omura [33]
Doxorubicin + cisplatin + RT	Retrospective case control study Uterine sarcoma in 18 women	RT alone: 72 % RT + chemo: 38 %	Pautier [34]
Gemcitabine + docetaxel	Prospective leiomyosarcomas in all stages	Median PFS > 3 years Progression-free at 2 years: 59 %	Hensley [35]
Gemcitabine + docetaxel 4# + doxorubicin 4#	47 women with uterus-limited leiomyosarcoma	Progression-free at 2 years: 78 % Median PFS: 39 months	Hensley [35]

progression-free at 2 years. In another study in a group of 47 women, treated with four cycles of fixed dose rate gemcitabine plus docetaxel, followed by four cycles of doxorubicin, 78 % of women remained progression-free at 2 years, and median PFS was 39.3 months [35].

Role of Targeted Treatment in Uterine Leiomyosarcomas

The potential targets that have been identified for therapy in LMS and in ESS are summarized in Table 33.5. Targeted agents of estrogen and progesterone receptors (ER and PR) like medroxyprogesterone, aromatase inhibitors (AI), and mifepristone are successful for treating patients with uterine LMS with indolent growth as studies have revealed ER/PR positivity of up to 18–80 % in various series. The studies are summarized in Table 33.5.

Potential Targeted Therapies

The important signal transduction pathways implicated in uterine sarcomas include insulin-like growth factor (IGF) receptor-AKT-mTOR, PI3K-AKT pathway [36], negative regulator PTEN [37], and many others. PI3K, AKT, and mTOR inhibitors are currently being investigated in clinical trials. Deforolimus, an mTOR inhibitor, is currently being tested in the SUCCEED phase III trial [38]. COX-2 inhibitors [39] like sulindac and celecoxib are also in the pipeline. Acrogranin [40], a pluripotent growth factor that mediates cell-cycle progression and cell motility, is highly expressed in uterine LMS and correlates with poor prognosis and high histological grades. WT1 [41, 42] is yet another potential target meriting immunotherapy.

To conclude, at present, the standard of care in women with completely resected, uterus-limited leiomyosarcoma remains an observation.

Table 33.5 Targeted therapy in uterine LMS and ESS

Targeted therapy in uterine LMS				
Targeted agent	Target	Response	Response duration	Reference
Mifepristone	Progesterone receptor	PR	3 years	Koivisto [43]
Medroxyprogesterone	Progesterone receptor	PR	3.75 years	Uchida [54]
Anastrozole	Estrogen receptor	PR	1 year	Hardman [55]
Letrozole	Estrogen receptor	PR	5 months	O'Cearbhail [56]

Targeted therapy in uterine ESS			
Targeted agent	Response	Duration of response	Reference
Progestins			
MPA	CR	9–50 months	Pink [57], Brons [59], Baggish [58]
	PR	12–90 months	Brons [59], Gloor [60], Keen [61]
Aromatase inhibitor [letrozole]			
	PR	3–37 months	Pink [57], Leunen [62]
GnRH analogue [triptorelin]			
	PR	12 months	Burke [63]

Potential targets for immunohistochemistry		
Target	Uterine LMS	ESS
PDGFR-alpha	60–70 %	87 %
PDGFR-beta	7–100 %	0–100 %
C-KIT	0–100 %	0–100 %
Estrogen receptor	18–85 %	40–100 %
Progesterone receptor	18–80 %	60–100 %
GnRH receptor	100 %	76 %
Androgen receptor	40 %	36 %
WT1	76 %	45–93 %

Table 33.6 Systemic therapy options in carcinosarcoma

Chemotherapy in advanced carcinosarcoma			
Chemotherapeutic option	Patient setting	Response rate	Reference
Cisplatin	First line	19 %	Thigpen [43]
	Second line	18 %	Thigpen [38]
Ifosfamide	First line	32 %	
	Second line, post-platinum	18 %	Sutton [44]
Ifosfamide + cisplatin	Phase III, first line	54 % response but six deaths [no OS benefit]	Sutton [45]
Paclitaxel	Second line	18 %	Curtin [46]
Paclitaxel + ifosfamide	Phase III, first line	45 %	Homesley [47]
Paclitaxel + carboplatin	First line	54 %	Powell [48]
Topotecan	Second line	10 %	Miller [51]
Gemcitabine + docetaxel wkly	Second line	8 %	Miller [52]
Etoposide	Second line	7 %	Slayton [53]

Adjuvant chemotherapy in carcinosarcoma of the uterus			
Chemotherapy option	Setting	Response	Reference
Whole abdominal radiation/3# of ifosfamide plus cisplatin	GOG randomized phase III study: adjuvant therapy for completely resected stage I, stage II, stage III, or stage IV uterine carcinosarcoma	Risk reduction in death = 29 %	Wolfson [49]
Paclitaxel + carboplatin	Retrospective analysis		Makker [64]
Ifosfamide + paclitaxel/ paclitaxel + carboplatin	GOG phase III RCT	Ongoing	

Role of Chemotherapy/Targeted Treatment in Uterine Carcinosarcoma

Chemotherapy for Advanced Carcinosarcoma

Active chemotherapy agents for uterine carcinosarcomas have been identified from various phase II trials and are summarized in Table 33.6. Cisplatin [32] achieves response rate of 19 % as first-line treatment and 18 % as second-line treatment [43]. Ifosfamide is another effective agent that achieves responses of 32 % in first-line management [38] and in 18 % of women who were treated prior with platinum [44]. The efficacy of ifosfamide plus cisplatin combination was compared with that of ifosfamide monotherapy in a phase III trial. Although higher response rates were seen in the combination arm (54 % vs. 36 %), this was associated with six deaths, and hence, no difference was found in OS [45]. Paclitaxel monotherapy achieves response rate of 18 % as second-line treatment [46]. A phase III trial that compared the combination of paclitaxel plus ifosfamide with ifosfamide alone and achieved 45 % response rates with improved OS, thus establishing paclitaxel-ifosfamide as a reasonable first-line treatment for advanced uterine carcinosarcoma. Paclitaxel plus carboplatin has also achieved objective response rates of 54 % in women with advanced carcinosarcoma [48] making it a very attractive treatment option.

Chemotherapy for Completely Resected Carcinosarcoma

In a randomized phase III study to assess the role of adjuvant therapy for completely resected uterine carcinosarcoma of all stages, whole abdominal RT was compared with three cycles of ifosfamide with cisplatin. The estimated 5-year recurrence rate was 58 % in RT arm and

52 % in the chemotherapy arm. Adjusting for stage and age, the recurrence rate was 21 % lower for chemotherapy patients (hazard ratio = 0.789, 95 % confidence interval [CI]: 0.530–1.176, $p = 0.245$). The estimated death rate was 29 % lower among the chemotherapy patients (hazard ratio = 0.712, 95 % CI: 0.484–1.048, $p = 0.085$). This study [49] highlighted the role of adjuvant chemotherapy in uterine carcinosarcoma. Another retrospective analysis highlights role of paclitaxel with carboplatin as an effective option for adjuvant therapy in carcinosarcoma. At present, GOG is conducting a phase III study [GOG-261] on completely resected carcinosarcoma comparing ifosfamide with paclitaxel versus paclitaxel plus carboplatin [50]. The study had started its enrollment in August 2009 and is expected to have its primary completion by November 2015 with an estimated enrollment of 603 patients. The primary end point of this study has been OS and secondary end points being PFS, adverse events, and quality of life assessment. The study is now ongoing but not recruiting further patients.

Role of Targeted Treatment in Uterine ESS

PR is the most significant potential target for hormonal treatment. There are multiple case reports of patients responding to various progestational agents, namely, medroxyprogesterone, megestrol, and hydroxyprogesterone acetate. At least 25 cases of ESS have been reported in 16 studies, with a response rate of 76 % (19 of 25). Another potential target is estrogen, and aromatase inhibitors like letrozole have been shown to reduce estrogen concentrations by inhibiting estrogen synthesis in both tumor tissue and peripheral sites, therefore preventing proliferation of the tumor and translating to a clinical response in eight of nine patients [88 %]. GnRH analogues resulted in partial remission in a single case. WT1 is a potential target for immunotherapy. WT1, located on chromosome 11p13, has a role in several hematological and solid malignancies by an overexpression of its protein in these tumors. Because WT1 is highly immunogenic and restricted to tumor cells, it is an attractive target for immunotherapy.

High-grade Undifferentiated Uterine Sarcoma

No prospective studies on the role of chemotherapy for advanced metastatic disease in undifferentiated sarcomas are available. Hence, patients are encouraged to participate in clinical trials to try and answer this question.

Uterine Sarcomas with a Limited Role for Chemotherapy

ESS and adenosarcomas without sarcomatous overgrowth are low-grade malignancies with an indolent clinical course. In this rare subset, chemotherapy is usually not effective.

Conclusion

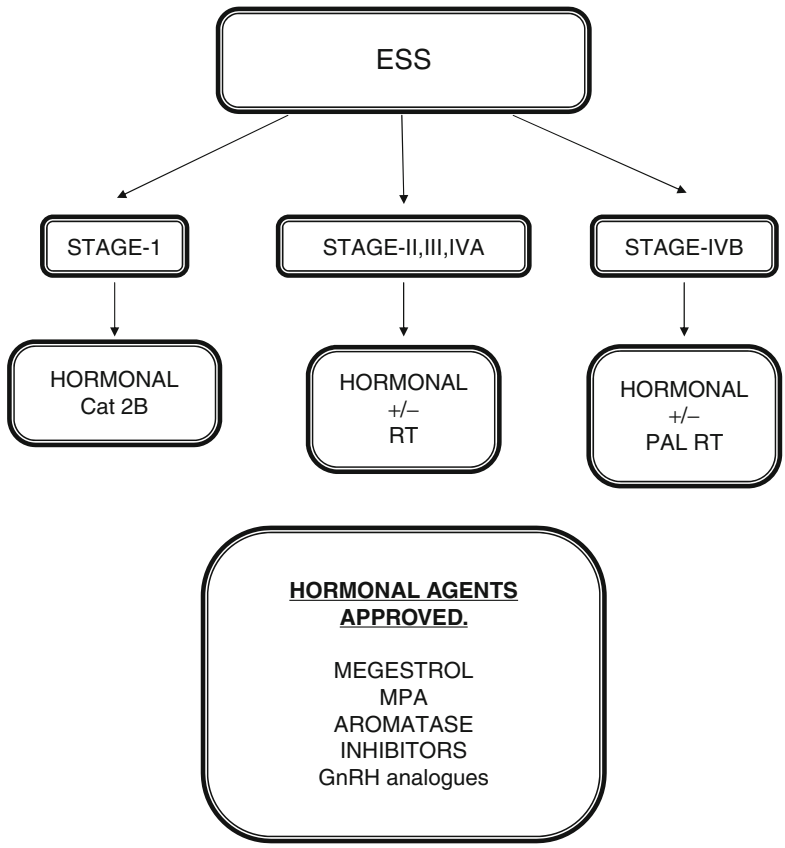
There is a high risk of recurrence after resection of uterus-limited disease, but no adjuvant therapy (i.e., radiotherapy, chemotherapy, or hormonal targeted) has shown to prolong overall survival. The role of adjuvant chemotherapy in completely resected, uterus-limited leiomyosarcoma should be addressed in a prospective phase III trial with a no-chemotherapy control arm in order to determine whether chemotherapy can improve survival.

The treatment of recurrent/metastatic disease should be personalized and individualized, requiring multimodality approach to therapy, balancing the benefit with adverse effects and quality of life of patients. No curative therapeutic option is currently available today. Patients should be strongly encouraged to enter clinical trials. Overall survival of patients of uterine sarcomas has shown no improvement in survival despite recent advances in chemotherapy regimes. The answer lies in deciphering molecular biology and drivers at the genetic level to develop novel and effective targeted agents.

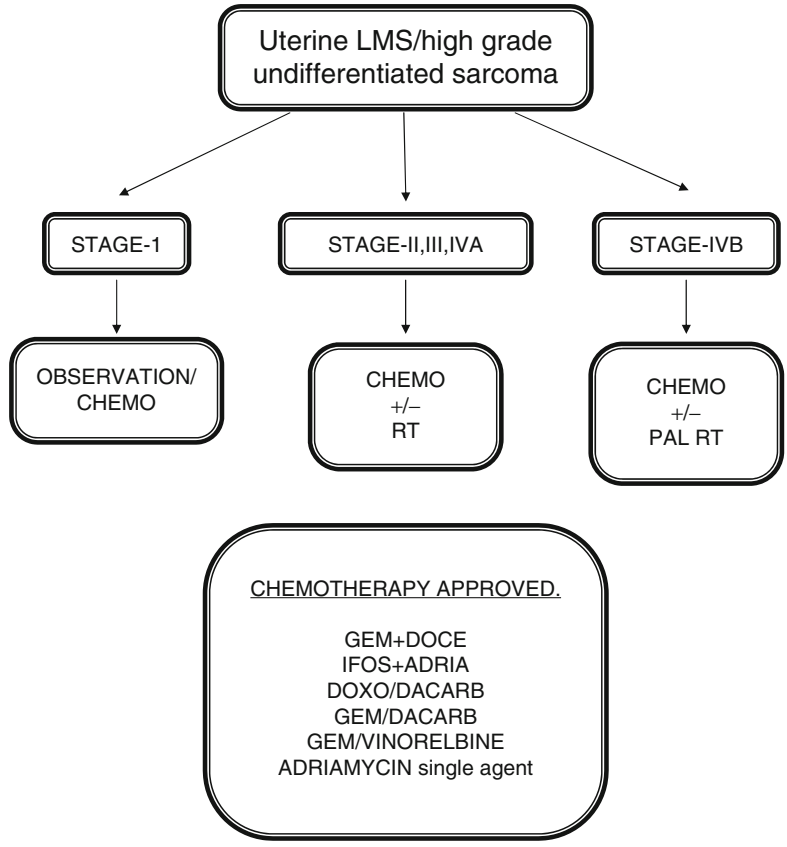
Key Points

1. Uterine sarcomas are a heterogenous group of rare neoplasms with varied histologies, clinical behaviors, and chemosensitivities.
2. There is no consensus on the risk stratification and/or no well-defined prognostic factors. However, stage, age, grade, mitotic count, and molecular markers have emerged to be of prognostic relevance.
3. Despite, the high recurrence rate, the standard approach in completely resected, uterus-limited LMS is only an observation, as no adjuvant therapy has shown survival benefit.
4. For advanced/metastatic LMS, doxorubicin, ifosfamide, gemcitabine, and docetaxel have shown activity. The role of trabectedin is controversial.
5. The treatment of recurrent/metastatic disease should be personalized, requiring multimodality approach balancing the benefit with adverse effects and quality of life of patients.
6. Patients should be strongly encouraged to enter clinical trials. The future lies in deciphering molecular biology and drivers at the genetic level and to develop novel and effective targeted agents that can be brought from the bench to the bedside.

ESS Management Algorithm



LMS Management Algorithm



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Surveillance of Uterine Sarcomas

34

Neha Kumar and Shalini Rajaram

Introduction

Uterine sarcomas are uncommon tumors which constitute 3 % of all uterine malignancies [1]. They are aggressive tumors with a tendency for local and distant spread and hence have a guarded prognosis. They include leiomyosarcomas (LMS), endometrial stromal tumors (ESS), undifferentiated uterine sarcomas (UUS), and pure heterologous sarcomas. Mixed epithelial and mesenchymal tumors are adenosarcomas and carcinosarcomas.

Leiomyosarcomas constitute 1 % of all uterine malignancies – 60 % presenting in early stage limited to the uterus. The relapse rate for stage I and II disease is up to 70 % which commonly occurs as distant metastasis in liver and lungs due to hematogenous spread [2, 3]. Survival rates are about 50 % for stage I–II disease, whereas dismal results have been reported in advanced stage disease [4]. Endometrial stromal sarcomas account for 0.2–1 % of uterine cancers and present at a younger age (mean 42–58 years) [5]. They have an indolent clinical course, but about 37–60 % of women eventually have disease recurrence, most commonly in the pelvis and abdomen and less frequently in the lungs and vagina. They generally recur after about 10–20 years, and 15–25 % of patients die of the disease. Five- and ten-year survival rates for stage I tumors are 84–100 % and 77–89 %, respectively [6]. Endometrial stromal sarcomas are hormonally sensitive and express estrogen receptor in 70 % and progesterone receptor in about 95 % of the cases [7].

Prognostic Factors

Tumor stage is the strongest prognostic factor for all uterine sarcomas with 5-year survival of about 50–55 % for stage I and 8–12 % for more advanced stages [6]. When adjusted for stage, the prognosis of leiomyosarcoma is poorer than that of carcinosarcoma, but no survival difference is found between leiomyosarcoma and undifferentiated endometrial sarcoma. The prognosis of stage I leiomyosarcoma is also associated with the mitotic index (MI) and tumor size and of stage I endometrial stromal sarcoma with MI and tumor cell necrosis (TCN) [8]. Age, tumor grade, vascular space invasion, and p53, p16, and Ki-67 overexpression have been found to be prognostic variables in leiomyosarcoma in some studies [9–11], while DNA diploidy, S Phase fraction (SPF) less than 10 %, and progesterone receptor positivity

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seem to be associated with better outcomes [10, 12]. In endometrial stromal sarcomas, tumor-free resection margins were found to be the most important prognostic factor ($P<0.001$) on a multivariate analysis, followed by tumor grade ($P=0.002$), tumor diameter ($P=0.019$), and menopausal status ($P=0.019$) [13]. In carcinosarcomas, the role of pathological variables like cell type, lymph-node status, grade of epithelial component, grade and mitotic count of sarcomatous component, depth of myometrial invasion, lymph-vascular space involvement, and peritoneal cytology has been debated [2, 14]. Carcinosarcomas containing serous and clear cell carcinomas and heterologous components have been associated with poorer prognosis and survival rates [2, 15, 16]. Elevated postoperative serum CA-125 is also an independent prognostic factor for poor survival (HR 9.85; $P<0.001$) [17] in these tumors. Tumor extent, vascular invasion, and nuclear uniformity are important prognostic variables for undifferentiated endometrial sarcomas [18, 19]. The prognosis of adenosarcoma is usually favorable, with features like extrauterine spread, deep myometrial invasion, and sarcomatous overgrowth (presence of pure sarcoma in more than 25 % of the tumor) associated with an increased risk of recurrence [4].

Surveillance

Total hysterectomy with bilateral salpingo-oophorectomy is the mainstay of treatment for uterine sarcomas. The ovaries can be preserved in premenopausal women with stage I leiomyosarcomas and endometrial stromal sarcomas. Routine lymphadenectomy is not necessary unless enlarged lymph nodes are present. The status of tumor-free resection margins at primary surgery is important for survival, and adjuvant therapy includes chemotherapy, radiotherapy, and hormone therapy (for ESS). Carcinosarcomas of the uterus should undergo full surgical staging including peritoneal washings, total hysterectomy with bilateral salpingo-oophorectomy, bilateral pelvic and para-aortic node dissection, and omental biopsy (or omentectomy) with excision of all gross disease. Adjuvant treatment includes radiotherapy depending on operative findings and chemotherapy.

The surveillance for uterine sarcomas after the completion of primary treatment includes a complete physical exam every 3 months for the first 2 years, every 6 months for the next 3 years, and then yearly thereafter. Patients should be educated about symptoms like lower abdominal or pelvic pain, pressure symptoms, vaginal bleeding, or unexplained cough and instructed to report immediately in case such symptoms should arise. The National Comprehensive Cancer Network (NCCN) guidelines advise a chest X-ray and a CT scan every 6–12 months for the first 5 years. A CT scan, an MRI, or other appropriate imaging should be advised in case of clinically suspicious signs or symptoms [20]. The recurrence could be restricted to the vagina (negative chest and abdomino-pelvic CT), isolated to the pelvis, or present as disseminated disease. A local vaginal recurrence can be treated with radiotherapy if the patient has not received radiation before. In case of prior pelvic radiation, treatment options include surgical exploration and resection, chemotherapy, hormone therapy (ESS), or re-radiation. For isolated metastasis in the pelvis, surgical resection can be tried if the disease is resectable followed by chemotherapy or hormone therapy. In cases of disseminated disease or unresectable isolated metastasis, chemotherapy, hormone therapy, and palliative radiotherapy are the treatment options.

Conclusion

Uterine sarcomas are rare but aggressive tumors with a tendency for local and distant spread. They usually have an unfavorable clinical outcome, except endometrial stromal sarcomas and adenosarcomas. Since these tumors have high rates of recurrence, a regular follow-up is crucial. Surveillance involves regular physical exams, chest X-ray, and CT scans to diagnose recurrences early and manage them timely with appropriate treatment.

Key Points

1. Tumor stage is the strongest prognostic factor for all uterine sarcomas.
2. Total hysterectomy with bilateral salpingo-oophorectomy is the treatment for uterine sarcomas. The ovaries can be preserved in premenopausal women with stage I leiomyosarcomas and endometrial stromal sarcomas. Routine lymphadenectomy is not necessary unless enlarged lymph nodes are present.
3. Carcinosarcomas should undergo full surgical staging including peritoneal washings, total hysterectomy with bilateral salpingo-oophorectomy, bilateral pelvic and para-aortic node dissection, and omental biopsy (or omentectomy) with excision of all gross disease.
4. The surveillance for uterine sarcomas involves a physical exam every 3 months for the first 2 years, every 6 months for the next 3 years, and then yearly thereafter. The NCCN guidelines advise a chest X-ray and a CT scan every 6–12 months for the first 5 years.
5. A CT Scan, an MRI, or other appropriate imaging should be advised in case of clinically suspicious signs or symptoms like lower abdominal or pelvic pain, pressure symptoms, vaginal bleeding, or unexplained cough.

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Part VI

Special Case Scenarios

Metabolic Syndrome and Endometrial Cancer

35

K. Chandramohan and P.M. Arun

Introduction

Metabolic syndrome (MetS) is a group of interrelated disorders, which increase the risk of cardiovascular disease and type 2 diabetes mellitus and is considered a worldwide epidemic by the International Diabetic Federation [1]. The components of MetS are dyslipidemia [characterized by an abnormal lipid profile such as high level triglyceride (TG) and low high density lipoprotein (HDL)], high arterial blood pressure, abnormal glucose metabolism, central adiposity, and insulin resistance. Recently other abnormalities such as chronic pro-inflammatory and pro-thrombotic states, fatty liver, and sleep apnea have been added to the syndrome [2]. Reaven first suggested the concept of "Syndrome X," which was later renamed as MetS [3]. Various definitions are put forth by different international organizations like World Health Organization, the European Group for study of Insulin Resistance (EGIR), National Cholesterol Education Programme Treatment Panel (III) (NCEP–APT III), American Association of Clinical Endocrinology (AACE) etc. (Table 35.1). In the Indian scenario, Indian Diabetes Risk Score (IDRS) – which has simple clinical information like age, waist circumference, family history of diabetes, and physical activity – is useful to diagnose metabolic syndrome [4] (Table 35.2). IDRS ≥60 predicts MetS. In a simplified criteria, metabolic syndrome should be suspected whenever waist circumference divided by height is more than 0.5 [5].

Insulin resistance syndrome (Syndrome X), described by Reaven, has insulin resistance as the main component and later the obesity part was added. The metabolic syndrome is given by ICD(10) code of E88.81 [6]. Prevalence of metabolic syndrome in nondiabetic population in European countries is 15 % (modified definition by WHO) [7] and in USA is 23 % of population (National Cholesterol Education Program/Adult Treatment Panel III criteria) [8].

The first definition of MetS was made by WHO in 1998 as the presence of insulin resistance and some of its components – impaired glucose tolerance (IGT) or diabetes mellitus type 2 – along with at least two of the following parameters: raised blood pressure, hypertriglyceridemia (and or reduced HDL cholesterol), central obesity, and microalbuminuria [9].

The basic defect in metabolic syndrome is now recognized as insulin resistance. The metabolic syndrome usually begins with central adiposity and subsequent increased B cell function leading to hyperglycemia [10, 11]. Hypertension develops as a result of the effect of insulin on sympathetic

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Table 35.1 Definitions of the metabolic syndrome

	NCEP-ATPIII [75]	Modified WHO [9]	EGIR [76]	AACE [77]	IDF [1]	Simplified definition of metabolic syndrome [78]
Mandatory	…	Insulin resistance[a] >75th percentile glucose ≥110 mg/dL; 2 h glucose ≥140 mg/dL	Insulin resistance[a] (or fasting insulin) in >75th percentile	"High risk for insulin resistance" or BMI >25 kg/m^2 or waist ≥102 cm (men) or ≥88 cm (women)[b]	Ethnic based waist: European: ≥94 cm (men) or ≥80 cm (women); Asian: ≥90 cm (men) or ≥80 cm (women)	Index of central obesity[c] (ICO) ≥.50
No. of factors	≥3	≥2	≥2	≥2	≥2	None
Glucose	≥110 mg/dL		≥110 mg/dL	≥110 mg/dL; 2 h glucose ≥140≥100 mg/dL	≥100 mg/dL; or previously diagnosed Type 2 DM	
HDL cholesterol	<40 mg/dL (men) <50 mg/dL (women) or on medications	<35 mg/dL (men) <39 mg/dL (women)	<39 mg/dL	<40 mg/dL (1.03 mmol) (men) <50 mg/dL (1.29 mmol) (women)	<40 mg/dL (1.03 mmol) (men) <50 mg/dL (1.29 mmol) (women) or on medications	
		And/or	**And/or**			
Triglycerides	≥150 mg/dL or on medications (1.7 mmol/l)	≥150 mg/dL (1.7 mmol/l)	≥150 mg/dL (1.7 mmol/l)	≥150 mg/dL (1.7 mmol/l)	≥150 mg/dL or on medications (1.7 mmol/l)	
Obesity	Waist ≥ 102 cm (men) ≥88 cm (women)	Waist/hip ratio >0.9 (men); >0.85 (women); or BMI ≥30 kg/m^2	Waist ≥94 cm (men) ≥80 cm (women)			
Hypertension	≥130/85 mm Hg or on medications	≥140/90 mm Hg	≥140/90 mm Hg	≥130/85 mm Hg	135/85 mm Hg or on medications	
Other:		Microalbuminuria[d]: albumin excretion > 20 mcg/min Or albumin/creatinine ratio ≥ 30 μgm/mg				

[a]Insulin resistance was calculated by the homeostasis model assessment of insulin resistance (HOMA-IR). The upper quartile was in individuals with HOMA-IR values >3.87
[b]In this study, BMI and waist circumference cut-points were used to define individuals at "high risk for insulin resistance"
[c]Waist size divided by height
[d]Microalbuminuria was not used in the definition of the metabolic syndrome in this study as it was not assessed in C

Table 35.2 Indian diabetes risk score [4]

Parameter	Score
Age	
<35	0
35–49	20
≥50	30
Abdominal obesity	
Waist <80 cm (female), 90 cm (male)	0
Waist 80–89 cm (female), 90–99 cm (male)	10
Waist ≥90 cm (female), ≥100 cm (male)	20
Physical activity	
Exercise (regular) + strenuous work	0
Exercise (regular) or strenuous work	20
No exercise + sedentary	30
Family history	
No family history	0
Either parent	10
Both parents	20

nervous system and on sodium metabolism, but the effect of other hormones like angiotensinogen, resistin, and leptin secreted from adipose tissue also contribute to hypertension. Insulin resistance causes significant changes in endothelial wall including abnormal nitric oxide (NO) metabolism and reduced PK/Akt signaling. Insulin resistance also causes structural and genetic damage to endothelial cell, so hypertension is caused by reduced vasodilatation and endothelial damage. Several studies have shown that apart from genetic predisposition, changes in lifestyle such as working shift duties, increased stress, sleep deprivation, and light exposure lead to metabolic syndrome [12].

In 2005, International Diabetes Foundation (IDF) detected abdominal obesity as a prerequisite for diagnosing MetS [13]. In 2008, the WCEP: ATP III included waist circumference, blood lipids, blood pressure, and fasting glucose in definition of MetS [14]. ATP III definition and IDF depend on waist circumferences while WHO definition depend on insulin resistance. Another issue in generalizing obesity in various populations is lack of uniform criteria in definition of obesity across various ethnic populations, which is addressed in IDF criteria.

Obesity is now an epidemic all across the world [15, 16]; when measured with NCEP–ATP III criteria, the prevalence of metabolic syndrome increased by 5 % during last 15 years. The increase is more evident in developing nations where food habits are changing from traditional to western culture [17].

Metabolic Syndrome and Cancer

Metabolic syndrome is associated with a number of cancers. The most commonly associated cancers are colorectal, endometrial, breast, and prostate [18]. Among gynecologic cancers, carcinoma endometrium has a strong association with MetS. It has been estimated that in the year 2012, cancers of the corpus uteri accounted for 319,605 new cases. This accounted for 4.8 % of the total cancers among women with an age standardized rate (ASR) of 8.3 per 100,000 women. There were an estimated 76,160 deaths due to endometrial cancers among women globally during 2012 [19]. The ASR for mortality due to endometrial cancer was 1.8 per 100,000 women accounting for 2.1 % of the total cancer deaths among women [1].

In a case control study done by Rosato et al. where 454 women with incident endometrial carcinoma and 798 controls were included, the multivariate odds ratio (OR) for development of endometrial carcinoma was 2.18 for type II diabetes, 1.77 for hypertension, 1.2 for hyperlipidemia, and 1.62–2.23 for various grades of central obesity. MetS is associated with odds ratio for endometrial cancer ranging between 1.67 and 2.77 when waist circumference was used and 8.40 when BMI was used to define MetS [20]. World Cancer Research fund defined obesity as a predisposing factor for endometrial carcinoma on the basis of evidence from large number of studies [21].

In a meta-analysis done in 2013, where the six studies were selected, metabolic syndrome was associated with increased risk of endometrial cancer (RR 1.89, 95 % CI 1.34–2.67, $p < .001$). When each factor contributing to metabolic syndrome was analyzed, the relative risk was 2.21 ($P < .001$) for higher body mass index or waist circumference, 1.81 ($p = 0.044$) for hyperglycemia, 1.81 ($p = 0.014$) for high blood pressure, and 1.17 ($p < 0.001$) for high triglyceride levels [22].

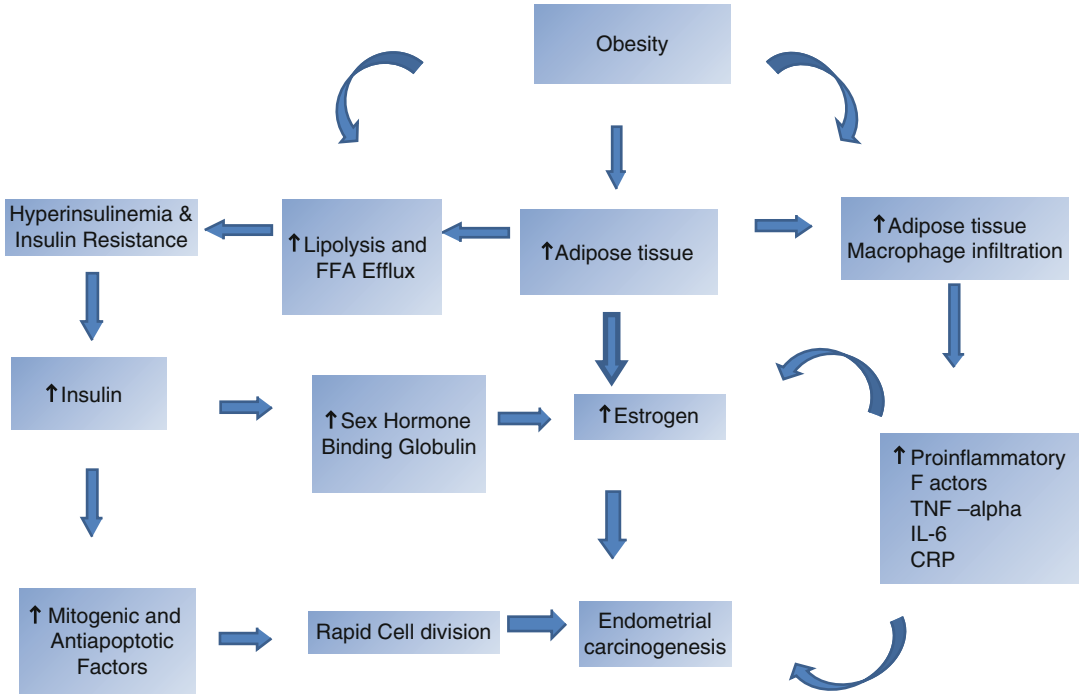

Fig. 35.1 Carcinogenesis in metabolic syndrome

Another study done in Austria, Norway, and Sweden, which was a part of Metabolic Syndrome and Cancer project (Me-Can), showed the relative risk of endometrial cancer in metabolic syndrome to be 1.37 (95 % CI 1.28–1.46) [23].

Metabolic syndrome is associated with various other gynecological cancers as well. In Me-Can study the association between "MetS" and rare gynecologic cancer was explored [24]. The rare cancers included those of vulva, vagina, and other rare sites. The hazard ratio of developing these cancers were 2.08 (95, CI 1.29–3.37) when mean BMI was 29.7 kg/m^2 when compared with women with mean BMI 20.8 kg/m^2. This was statistically significant. For vaginal cancers HR was 2 (0.62–6.90) (p value = 0.027), but vulvar cancers and other cancers (cancer occurring in ligaments and otherwise not specified cancers) showed nonsignificant association.

Various components of metabolic syndrome and its relation to endometrial cancer will be discussed.

Obesity

From several studies it is evident that the key factor in endometrial carcinogenesis in MetS is obesity [20, 25]. Endometrial cancer risk in obesity is thought to be mediated through increased availability of serum estrogens and insulin resistance [26] (Fig. 35.1).

In a Norwegian study involving 222 patients, there was a strong relationship between BMI and endometrial cancer ($p < .0001$). The adjusted relative risk (RA) was 0.53 (95 % confidence interval CI .19–1.47) for BMI <20 kg/m^2, 4.28 (95 % CI 2.58–7.09) when BMI was 35–39 kg/m^{2}and 6.36 (95 % CI 3.08–13.16) for BMI ≥40 kg/m^2 [27].

Type I endometrial cancer, which is estrogen-dependent, is associated with obesity [28]. In a study involving one million Norwegian women, overweight and obese women had relative risk of 1.36 (95 % CI 1.29–1.44) and 2.51 (95 % CI 2.53–2.66), respectively, for endometrial carcinoma [29]. In a similar study done in Sweden among postmenopausal women aged 50. 74 years,

overweight women (BMI 28–29.98) had 50 % increase in risk of endometrial carcinoma when compared to lean women (BMI <22.5 kg/m^2). In the same study obese women (BMI 30–33.99) had three times risk, and markedly obese women (BMI ≥34) had six times increase risk of endometrial carcinoma [30].

According to a review study done in Europe, excess body mass accounts for 5 % of cancers in Europe, and endometrial cancers are caused by obesity in 39 % of women [31]. In a meta-analysis, overall risk ratio (RR) of endometrial cancer in a linear model increases 1.6 (95 % CI 1.52–1.68) for every 5 kg/m^2 increase in BMI [32]. Weight gain in young adulthood increases the risk of endometrial cancer but weight gain in middle life does not increase the risk of endometrial cancer [33].

If the basic mechanism of endometrial carcinogenesis is considered, it is well understood that exposure to high level of estrogen plays a significant role [34]. Obesity exposes the women to higher levels of estrogen produced in adipose tissues and is now considered an etiologic factor for endometrial carcinoma [35]. Obesity also leads to insulin resistance and hyperinsulinemia [35]. Increased insulin causes carcinogenesis through mitogenic and antiapoptotic properties [36, 37]. Similarly insulin reduces serum sex hormone binding globulin and increases bioavailability of estradiol. Obesity also causes increased adipose tissue infiltration by macrophages, which secretes many proinflammatory mediators which include TNF-alpha, interleukin-6(IL-6), and C-reactive protein (CRP). These mediators cause increased invasion, progression, and metastasis [38, 39]. Increase in obesity, especially in developing nations like India, is definitely a cause for increase in incidence of endometrial carcinoma (Fig. 35.1).

Among the individual components of metabolic syndrome, obesity is the strongest risk factor for endometrial carcinoma.

Diabetes

The Norwegian study showed that women with diabetes mellitus had three fold higher risk of endometrial cancer (RR 3.13 95 % CI 1.92–5.11) when compared with women without diabetes mellitus [27]. In a study from Sweden, OR of type I diabetes mellitus was 13.3 (3.1–56.4) when compared to 1.5 (95 % CI 1–2.1) in type II diabetes [30]. The mechanism of carcinogenesis in a diabetic patient is insulin resistance, increased inflammatory mediators, and other hormonal factors [35, 40–42]. Another factor leading to carcinogenesis is increased blood glucose level, which makes glucose available for rapid cell division [35, 40–42]. Yet another factor is upregulation of glucose transport-protein, reactive free radicals, and increased products of glycosylation [43–46].

In a case control study done in Italy, there was no increased risk in juvenile diabetes (insulin dependant), while there was increased risk of endometrial cancer in insulin independent diabetes mellitus with (OR 3.1 (95 % CI 2.3–4.2) in ≥40 years. Similarly the OR in obese women (BMI >25–24) was 3.6 compared to 3 in non-obese women (BMI <25) [47].

Insulin resistance is caused by increased circulating fatty acids mostly derived from adipose tissue. Insulin resistance leads to hyperinsulinemia which also leads to increased level of circulating insulin-like growth factors. This causes endometrial hyperplasia [48–51]. The mechanism by which endometrial cancer risk is increased in diabetes is via two pathways. In the first one, insulin stimulates adrenal glands in postmenopausal women to produce more ovarian testosterone which is metabolized to estrogen in adipose tissue [52–54]. As described earlier, insulin reduces serum level of circulating sex hormone binding globulin and thus leads to hyperestrogenemia [54, 55]. The second mechanism is reduction in insulin-like growth factor-binding protein (IGFBP) which increases IGF-1 which stimulates endometrium and causes endometrial hyperplasia and carcinogenesis [48, 49, 51, 56].

Hypertension

It has been thought that hypertension promotes inhibition of apoptosis [57]. Many studies have shown that hypertension increases the risk of

endometrial cancer [58]. In a case control study done at Italy, involving 3406 individuals, after adjusting all other variables, hypertension was associated with odds ratio of 1.6 (95 % CI 1.3 to 1.9) for endometrial cancer. In hypertension women with BMI ≥30 kg/m^2 the risk of endometrial cancer (OR) was 4.9 when compared with nonobese women with BMI <25 kg/m^2 [59]. The mechanism by which hypertension increases the endometrial cancer risk is poorly understood. It was postulated that hypertension may increase the risk of cancer by blocking apoptosis [57, 60]. Secondly, hypertension is usually associated with insulin resistance [20], hormonal imbalance, and obesity.

Hypertriglyceridemia

Increased triglycerides lead to increased oxidative stress, and elevated cytosolic triglycerides in nonadipose tissue leads to enhanced formation of free radicals. These two mechanisms are thought to contribute to carcinogenesis.

Strategies to Reduce Cancer Risk in Metabolic Syndrome

Two pronged strategies for reducing the risk of endometrial cancer in metabolic syndrome are by treating metabolic syndrome and screening for endometrial cancer in affected population.

The strategies to treat metabolic syndrome include dietary modification, exercise, and treating individual components of metabolic syndrome separately. The use of low fat diet which was fashionable in the last few decades has actually concluded the epidemic of metabolic syndrome [61]. The recommendations include a saturated fat intake of <7 % of energy intake, reduction of trans fatty acids to less than 1 % of energy intake, dietary cholesterol to less than 300 mg/dL, and a total 25–30 % of energy from fat [62]. Dietary modifications include reducing the intake of fried foods, sausages, potatoes, and increasing the intake of raw and salad vegetables [63], dairy products [64], antioxidants and food substances rich in antioxidants [8]. Similarly studies have shown that high fiber content [65] and Mediterranean food are [66] associated with a reduction in metabolic syndrome.

Various drugs have been tried in management of metabolic syndrome. The drugs used to treat metabolic syndrome are Rimonabant, Metformin, and Rosiglitazone. Rimonabant reduced metabolic syndrome in 30–33 % of patients [67–69]. Metformin, though not useful in treating metabolic syndrome [70] has shown to reduce cell proliferation in endometrial cell lines [71]. Treatment with metformin resulted in G1 phase arrest, induction of apoptosis and reduced hTeRT (human telomerase reverse transcriptase) expression. In a study, metformin reduced endometrial cancer cell proliferation, establishing its potential role in prevention of endometrial cancer in obesity and MetS. Similarly Rosiglitazone showed improvement in 30 % of women with metabolic syndrome [72]. Laparoscopic weight reduction surgery has shown reversal of metabolic syndrome in 80–96 % of women [73, 74].

Though there is no strong recommendation from any organization or body for screening for cancer in metabolic syndrome, it is recommended that there should be a strict observation of such a patient for development of cancer which includes colorectal, breast, and endometrial cancers (see chapter 4. on Prevention & Screening)

Regular and moderate intensity exercise programs significantly reduce the risk of metabolic syndrome and cancer risk. The probable mechanism of action includes its effect on hormonal mileu of the body and menstrual function. Exercise reduces blood insulin level and blood glucose, adiposity (and thus reduces estrogen level), and inflammation and brings about favorable adipokine metabolism [74]. Athletes and physically active women have late menarche, few ovulatory cycles, and low levels of estrogen and progesterone. All these factors reduce metabolic syndrome and cancer risk.

In short, metabolic syndrome is a disorder which has reached epidemic proportions and will increase the risk of cardiovascular diseases and cancer. But with lifestyle modification and surveillance for cancer, the risk of cancer and mortality from endometrial cancer can be reduced significantly.

Conclusions

Metabolic syndrome results in altered hormonal milieu in the body like increased estrogen hormone, hyper insulinism and insulin resistance which can promote carcinogenesis especially leading to carcinoma endometrium. Better awareness of the relationship between metabolic syndrome and cancer can help physicians advise women on reducing risk of cancer and also counsel regarding the role of screening for cancer in presence of metabolic syndrome. Metabolic syndrome can also be treated with drugs and life style modification.

Key Points

1. Metabolic syndrome is associated with increased incidence of endometrial cancers.
2. Proposed mechanisms include higher levels of estrogen secondary to obesity and hyperinsulinemia and insulin resistance seen in metabolic syndrome.
3. Patients with metabolic syndrome should be advised to attend regular cancer screening programmes in addition to taking measures to modify life style, which mainly includes low fat diet and increased physical exercise
4. Drugs like metformin are also useful in the treatment of Metabolic Syndrome.

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Management of Incompletely Staged Endometrial Cancer

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Shalini Rajaram and Neha Kumar

Introduction

Majority of endometrial cancers, about 80 %, are diagnosed in stages I and II. The 5-year survival rate of stage I cancers is 85–91 % [1]. The rate of pelvic and para-aortic lymph node metastases increases with the grade of endometrial lesion and the depth of myometrial invasion. Women with grades 1, 2, and 3 lesions have pelvic lymph node metastases in 3 %, 9 %, and 18 % cases, respectively, and para-aortic lymph node metastases in 2 %, 5 %, and 11 % cases, respectively. In lesions with no myometrial invasion, inner one-third invasion, middle one-third invasion, and outer one-third invasion, pelvic lymph node disease is found in 1 %, 5 %, 6 %, and 25 % cases, respectively, while the para-aortic disease is found in 1 %, 3 %, 1 %, and 17 % cases, respectively. The highest risk is found in women with grade 3 lesions and outer third myometrial invasion with pelvic lymph nodes involved in 34 % cases [2]. The presence of disease in the lower segment increases the risk of pelvic lymph node (16 %) and para-aortic lymph node (16 %) metastases as compared to when only fundal disease is present (8 % pelvic and 4 % para-aortic disease). The presence of lymphovascular invasion is also an important prognostic factor as it increases the incidence of pelvic and para-aortic lymph node metastases to 27 % and 19 %, respectively. Adnexal involvement is significantly associated with involved pelvic (32 %) and para-aortic (20 %) lymph nodes. Women with nodal disease have a poorer prognosis, with a 3–5-year survival rate of 50–75 %, and increased rates of nodal and distant recurrences than those without nodal disease (3–5-year survival rate of 80–95 %, with mostly vaginal cuff failures) [3].

Surgical Staging: Importance and Current Status

The management of endometrial cancer is surgical staging with total extra-fascial hysterectomy and bilateral salpingo-oophorectomy, collection of peritoneal washings, excision of suspicious or enlarged lymph nodes in pelvic and para-aortic regions, bilateral pelvic lymph node and para-aortic lymph node dissection in high-risk cases, and biopsy or excision of extrauterine lesions suspicious of tumor. Minimally invasive surgery has now been routinely adopted in the surgical staging of endometrial cancer. The margins of pelvic lymph node dissection are circumflex iliac vein distally, bifurcation of iliac vessels proximally,

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genitofemoral nerve laterally, and the superior vesical artery medially with the floor being the obturator nerve. Para-aortic lymph node evaluation – either removal of enlarged para-aortic lymph nodes or a complete dissection up to the renal vessels – is done for staging of select high-risk tumors like deeply invasive lesions, high-grade histology, and serous and clear-cell adenocarcinomas or when lymph nodes are visibly enlarged (determined preoperatively, intraoperatively, or on frozen section) [4]. However, only 10 % of women with lymph node metastases will have grossly enlarged nodes [2], and even in these women, direct palpation through the overlying peritoneum may not detect involved nodes. Removal of adnexa is essential as 5 % of endometrial cancers have metastatic disease to the ovaries and fallopian tubes.

Lymph node dissection provides accurate assessment of spread of disease (as compared to intraoperative palpation or imaging). Lymph node status is important for prognosis and helps decide which women need adjuvant therapy. The advantage of surgical staging is the ability to identify unrecognized disease in the nodes which will help tailor the adjuvant therapy. In a completely staged endometrial cancer, this also results in lesser use of radiation and substitution of vaginal cuff brachytherapy for pelvic radiation. The disadvantages associated with nodal dissection are that it requires surgical expertise, increases operative time, and may have complications like vascular injury and blood loss, ileus, genitofemoral nerve injury, lymphocyst formation, and lymphedema in 2–6 % cases [5].

The emphasis has recently shifted from routine pelvic and para-aortic lymphadenectomy to selection of women where lymphadenectomy may improve survival and avoiding it in low-risk cases to decrease morbidity. Previously, a full pelvic and para-aortic lymphadenectomy was advocated for all women, but now, a more selective and tailored lymphadenectomy is recommended by the National Comprehensive Cancer Network (NCCN) panel to avoid overtreatment [4]. Controversies exist whether the nodal dissection should be avoided, selective or routine; whether only biopsy of enlarged nodes should be done or a complete lymphadenectomy, should pelvic lymph node dissection be accompanied by para-aortic lymph node dissection and also, what should be the extent of para-aortic lymphadenectomy – up to the inferior mesenteric artery or the renal vessels.

Surgical staging with lymphadenectomy helps us in knowing accurately the extent of spread of endometrial disease. Without nodal information, physicians must rely on uterine factors to estimate the probability of nodal disease and the risk of pelvic failure, and this leads to increased use of postoperative radiation. Lymphadenectomy has also been reported as therapeutic in some trials. Kilgore and associates found that lymph node dissection resulted in better survival than no lymph node dissection plus postoperative radiation [6]. Havrilesky et al. reported that the 5-year survival rate in stage IIIC endometrial disease was 63 % in cases with microscopic metastatic lymph nodes, 50 % in women with grossly positive lymph nodes completely resected, and 43 % in those with unresected lymph nodes. In multivariable analyses, gross nodal disease not debulked (HR = 6.85, $p = 0.009$), serosal/adnexal involvement (HR = 2.24, $p = 0.036$), older age (HR = 1.09, $p < 0.001$), and >2 positive lymph nodes (HR = 3.12, $p = 0.007$) were associated with lower disease-specific survival [7]. The Survival effect of para-aortic lymphadenectomy in endometrial cancer (SEPAL) study from Japan showed that the survival was significantly better in women undergoing pelvic and para-aortic lymphadenectomy. This was true in those with intermediate- and high-risk factors but not in those with low-risk factors. Survival was also better in the group which had both pelvic and para-aortic lymphadenectomy compared to that with only pelvic lymphadenectomy [8]. A subset of women with stage IC, grade 3, with no lymph node dissection and treated with postoperative radiotherapy were followed up in the Post Operative Radiation Therapy in Endometrial Carcinoma (PORTEC) trial [9]. The 5-year survival rate for these women was 58 %, and 12 % had pelvic or vaginal failures despite radiation. This outcome was poorer than that reported in women with stage IIIC who had complete lymphadenectomy and then received radiation.

A study in the treatment of endometrial cancer, ASTEC, was a randomized trial where 1369

women were allotted to either hysterectomy with lymph node dissection (LND) or hysterectomy without lymph node dissection (no-LND) group [10]. After surgery, stage I–II cases were randomized to either observation or pelvic radiation therapy (grade 3, serous or clear-cell histology, >50 % myometrial invasion, cervical involvement). Nodal status did not affect the use of radiation therapy – even node-positive women were randomized to the observation arm. There was no difference in progression-free survival (HR=1) and overall survival (HR = 1.25, $p = 0.14$) in LND and no-LND groups. The LND group was associated with longer operating time, increased ileus, deep vein thrombosis, lymphocytes, and wound complications. The pitfalls of this study were that 8 % women in the LND group did not have a lymph node dissection, 12 % had <5 lymph nodes removed (median = 12), and para-aortic lymph node dissection was not done.

The second trial, comparing lymphadenectomy or not in the surgical staging of endometrial cancer, was the Italian CONSORT trial [11]. Five hundred and fourteen women were randomized to undergo hysterectomy with or without pelvic lymph node dissection. Cases with grade 1 tumors and less than 50 % myometrial invasion on intraoperative frozen section were excluded from the trial. In the no-LND group, 22 % of the cases had nodal dissections due to clinical suspicion. The para-aortic lymph nodes were removed at the discretion of the surgeon. In the LND group, the median number of lymph nodes removed was 26, and para-aortic lymph nodes were removed in 26 % cases. Node-positive disease was found in 13 % cases of the LND group and 3 % cases of the no-LND group, on histopathological analysis. Postoperative radiation was more common in the no-LND group (25 % vs. 17 %). The 5-year progression-free survival was 81 % in both groups, and 5-year overall survival rate was 90 % in the no-LND group and 86 % in the LND group.

The weaknesses of both the ASTEC and CONSORT trials were the absence of treatment in cases with positive nodes, limited power, poor quality or absence of para-aortic lymph node dissection and over-representation of low-risk women. However, these are the only trials which provide level I evidence for lymphadenectomy in endometrial cancer and suggest that its benefit may be modest and that removing negative nodes is unlikely to improve outcome.

Studies like ASTEC and CONSORT have indicated that in women who are at low risk for nodal metastasis, i.e., the grade 1 lesions on endometrial biopsy, lymphadenectomy can be avoided. However, a significant number of these seemingly low-risk women are found to have high-risk factors after full surgical staging, which have an impact on adjuvant therapy. Ben-Shachar and colleagues studied 181 women with grade 1 endometrial cancers (on endometrial biopsy) and found that 19 % had grade change on hysterectomy specimen, 11 % had extrauterine disease, 4 % had lymph node metastasis, and 26 % had high-risk uterine factors. Because of full surgical staging, 12 % of these women received adjuvant therapy, while 17 % who may have received some therapy did not, because of surgical findings [12]. As the grade of the endometrial lesion increases, the accuracy of intraoperative assessment of myometrial invasion by gross examination decreases. In one study, the depth of myometrial invasion was accurately determined by gross examination in 87 % cases of grade 1 lesions, 65 % of grade 2 lesions, and 31 % of grade 3 lesions [13]. Studies have also reported the inaccuracies of intraoperative frozen section in determining the grade and depth of myometrial invasion compared to final histopathology report. The depth of invasion correlated with the final report only in 67 % cases, while 28 % cases were upstaged [14].

In 2000, the Mayo group described a model that classified a group of endometrial cancers with low risk of nodal disease spread and high disease-free survival based on the frozen section evaluation of the uterus. These were the grade 1–2 endometrioid tumors with inner 50 % invasion and tumor size <2 cm [15]. Mariani followed up 422 women with endometrial carcinoma and found that 33 % of women with endometrioid tumors qualified as low risk, based on the Mayo model. Twenty-two percent of women outside the low-risk model had positive nodal spread at the time of lymphadenectomy [16].

Following nodal dissection, most women with node-negative disease will be classified as low risk and avoid pelvic radiation or receive vaginal brachytherapy instead of pelvic radiation. Randomized trials comparing radiotherapy to observation have failed to demonstrate survival advantage of radiation in women with stages I–II disease, and in the absence of nodal disease, no therapy is reasonable. Women with low-risk uterine factors and negative nodes have low risk of recurrence and death (2 % at 48 months) with or without adjuvant pelvic radiation [11, 17, 18]. GOG 99 was a randomized controlled trial conducted in women with surgically documented negative nodes and any amount of myometrial invasion, randomizing them into two groups – observation and pelvic radiation. A high-intermediate-risk (H-IR) group was identified depending upon the woman's age and number of risk factors (LVSI, grades 2–3 tumor and outer one-third myometrial invasion) which accounted for two-thirds of the recurrences. Women who did not have these H-IR features had low risk of recurrence (2.1–2.9 %), and these low-risk groups can avoid postoperative radiation without affecting overall outcome [17].

Endometrial Carcinoma Detected After Hysterectomy

In clinical practice, we often come across cases where endometrial carcinoma has been detected postoperatively on a hysterectomy specimen. These cases where only hysterectomy and bilateral salpingo-oophorectomy have been done, especially those with high-risk intrauterine features, are incompletely staged. One of the first steps in managing such women is a thorough histopathological review of the hysterectomy specimen to determine the grade and stage of the lesion and the high-risk intrauterine factors. The high-risk factors include age, positive lymphovascular space invasion, tumor size more than 2 cm, and lower uterine involvement. A radiological imaging, most often a Contrast enhanced computed tomography (CECT) scan of the chest abdomen, and pelvis or better still a PET-CECT, is advised to look for nodal and any other metastatic disease.

According to the NCCN guidelines, in stage IA grades 1–2 lesions with no myometrial invasion, it is safe to put women under close observation with 3 monthly evaluations for the first 2 years, 6 monthly for the next 3 years, and then yearly thereafter. Women with stage IA grades 1–2 lesions with <50 % myometrial invasion who do not show any nodal or metastatic disease on postoperative imaging can be put under close observation or undergo vaginal brachytherapy with or without external pelvic radiation. However, if the imaging is suspicious for nodal or metastatic disease, surgical restaging or a pathological confirmation of metastatic disease (via image-guided biopsy of the involved nodes or other suspicious regions) should be strongly considered. The surgical restaging should include peritoneal washings, excision of suspicious or enlarged pelvic nodes or a pelvic lymphadenectomy, para-aortic lymph node assessment in select cases, exploration of the abdomen and pelvis, and biopsy or excision of any visible disease. Surgical restaging can be done laparoscopically or via robotic surgery, where available. Not only does minimal access surgery score over open surgery due to lesser postoperative morbidities and shorter hospital stay, but it also avoids the trauma of a repeat laparotomy within a few weeks of previous surgery. After complete staging, the adjuvant therapy for such women is similar to those who had complete surgery in the first sitting. These women could either be observed closely or receive vaginal brachytherapy with or without pelvic radiotherapy depending upon the final stage, grade of the lesion, and presence or absence of adverse risk factors. In cases where women are not willing for surgical restaging, they must undergo pelvic radiation and vaginal brachytherapy with extended field radiation in select cases.

In women with incompletely staged stage IA grade 3, stage IB, and stage II lesions, if the radiological imaging is positive for metastasis, surgical restaging should be considered and then adjuvant treatment given according to the final histopathology and stage after restaging. If, however, the imaging is negative, further treatment consists of pelvic radiation with vaginal brachytherapy with or without extended field radiation

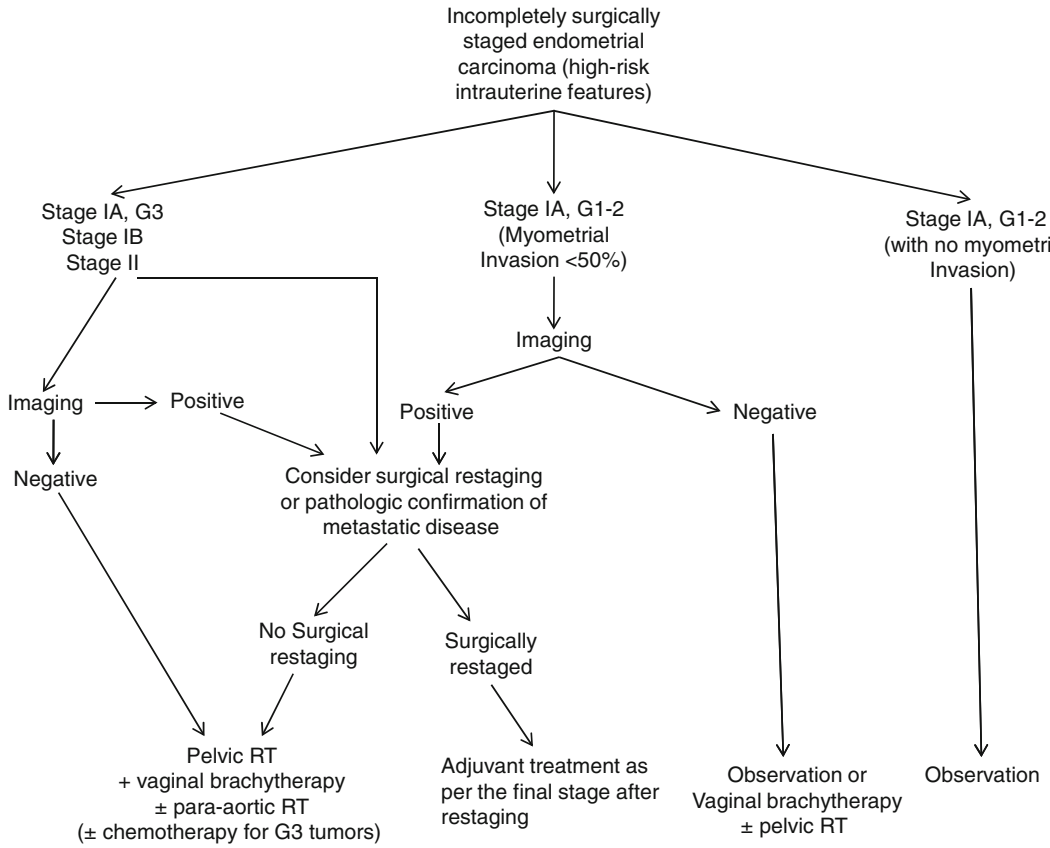

Fig. 36.1 Management of incompletely staged endometrial carcinoma (Adapted from the NCCN guidelines [4])

to cover the para-aortic lymph nodes [4]. Figure 36.1 adapted from the NCCN guidelines depicts the algorithm for management of a case of incompletely staged endometrial cancer.

Women with incompletely staged clear-cell or papillary serous carcinomas of the endometrium should undergo restaging with peritoneal cytology, excision of enlarged pelvic and para-aortic lymph nodes, omental biopsy or omentectomy, biopsies from peritoneal surfaces, and removal of any gross disease. This should be followed by chemotherapy with or without tumor directed radiotherapy. In women who have only undergone hysterectomy, where endometrial carcinoma was diagnosed on postoperative histopathology, it is indeed advisable to go for restaging to remove both the adnexa which may be involved in 5 % cases, as well as remove any suspicious pelvic and para-aortic lymph nodes and other disease in the same sitting. Adjuvant treatment then follows the algorithms for completely staged endometrial cancer depending upon the stage and risk factors.

Conclusions

Surgical staging in endometrial cancer enables appropriate tailoring of adjuvant treatment modalities that benefit high-risk women only. Previously, a full pelvic and para-aortic lymphadenectomy was recommended for staging of endometrial cancer. However, early stage cancers with well- or moderately differentiated histology may not benefit from lymphadenectomy. Hence, the recent NCCN guidelines recommend a selective and tailored lymphadenectomy to benefit high-risk cases and avoid overtreatment in low-risk cases.

Even in the United States, only 30–40 % cases are completely staged [19], the rates of lymphadenectomy understandably higher with gynecologic oncologists than general

gynecologists. Management of incompletely staged cases should include a histopathological review to determine the uterine risk factors, radiological imaging, and then appropriate adjuvant treatment according to the findings. Many of these women will require restaging to address the lymph nodes, and laparoscopic and robotic surgery is increasingly being used for the same, providing the advantages of minimally invasive surgery and the same overall survival rates as those with laparotomy.

Key Points

1. Eighty percent of endometrial cancers are diagnosed in stages I and II. The rate of pelvic and para-aortic lymph node metastases increases with the grade of endometrial lesion and the depth of myometrial invasion.
2. Women with nodal disease have a 3 to 5 year survival rate of 50–75 % with increased rates of nodal and distant recurrences compared to 80–95 % survival rate in those without nodal disease who mostly present with vaginal cuff relapses.
3. The management of endometrial cancer is surgical staging – total extra-fascial hysterectomy and bilateral salpingo-oophorectomy, collection of peritoneal washings, excision of suspicious or enlarged lymph nodes in pelvic and para-aortic regions (bilateral pelvic lymph node dissection and para-aortic lymph node dissection in high-risk cases like deeply invasive lesions, high-grade histology, and serous and clear-cell adenocarcinomas), and biopsy or excision of extrauterine lesions suspicious of tumor.
4. Previously, a full pelvic and para-aortic lymphadenectomy was recommended for all women, but now, a more selective and tailored lymphadenectomy is recommended by the National Comprehensive Cancer Network (NCCN) panel to avoid overtreatment.
5. Women with low-risk uterine factors and negative nodes have low risk of recurrence and death with or without adjuvant pelvic radiation.
6. In women with incompletely staged endometrial cancer, a histopathological review of the hysterectomy specimen is essential to determine the grade and stage of the lesion and high-risk intrauterine factors like positive lymphovascular space invasion, tumor size more than 2 cm, and lower uterine involvement. A radiological imaging – CECT scan of the chest, abdomen, and pelvis or a PET-CT – is advised to look for nodal and any other metastatic disease.
7. Depending upon the grade and stage of the endometrial lesion and findings on postoperative imaging, women with incompletely staged disease may be put on observation or undergo surgical restaging (and then adjuvant treatment according to the final histopathology and stage after restaging) or pelvic radiation. Surgical restaging can be done laparoscopically or via robotic surgery, where available.

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Synchronous Cancers of the Ovary and Endometrium

37

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Introduction

Synchronous cancers in the ovary and endometrium are a special clinical scenario in which primary cancers occur simultaneously in the endometrium and ovary. Synchronous cancers although rare form 1–2 % of gynecological cancers. When cancers occur simultaneously in the ovary and endometrium, they can either be synchronous or metastatic cancers because endometrial cancers are known to spread to ovaries and vice versa. It is very important to distinguish these two entities because the treatment and prognosis are different for each entity. Synchronous cancers occurring at two sites present in early stages and have good survival outcomes. Metastatic cancers are of advanced stage and the prognosis is poor. They can usually be distinguished from their clinical presentation and pathological features. Pathologists diagnose synchronous cancers using the criteria including endometrial cancer with superficial or no myometrial infiltration, early-stage and low-grade tumors, dissimilar grades, or dissimilar tumor histology between the endometrial and ovarian cancers [1]. Apart from clinicopathologic features molecular testing is also useful in difficult cases. There is scanty literature about this special clinical condition, and the available evidence comprises more of case series.

Incidence and Risk Factors

Endometrial and ovarian cancers coexist in approximately 5 % of patients with endometrial cancer and 10 % of cases of ovarian cancer [2]. Synchronous cancers are usually seen in younger premenopausal women usually associated with obesity and nulliparity. They usually have early-stage disease and hence have better prognosis than those with metastatic disease. In endometrial cancer patients less than 45 years, the incidence of synchronous ovarian cancer is higher [3–5]. The median age reported in various series ranges from 41 to 52 years, about a decade younger than median ages for development of endometrial or ovarian cancer alone. Walsh et al. reported a high rate of coexisting malignancy of 25 % in a study of 102 patients of less than 45 years with endometrial carcinoma. Women who are 9–22 kg above their ideal body weight have a threefold increased risk for developing endometrial cancer, and women more than 22 kg above their ideal body weight have a ninefold increased risk [6]. Obese women have excess peripheral conversion of androstenedione to estrone in adipose tissue. This hyperestrogenic state results in

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endometrial proliferation which may lead to development of endometrial cancer. Other conditions which produce hyperestrogenic state like polycystic ovarian disease, chronic anovulation, unopposed estrogen replacement therapy, and estrogen-producing ovarian tumors also increase their risk of endometrial cancer and synchronous ovarian cancers. Eifel et al. similarly found that 50 % of the women in their study with synchronous endometrioid tumors were nulliparous [7]. Herrinton et al. found that women with synchronous endometrial and ovarian cancers had a lower than expected mean parity compared with women with only one of these cancers [8].

Family history of Lynch II syndrome (hereditary nonpolyposis colorectal cancer) is also associated with synchronous endometrial and ovarian cancers. HNPCC is an autosomal dominant familial cancer risk syndrome that occurs due to a germ line mutation in one of several mismatch repair genes and is associated with an increased risk of colorectal, endometrial, and ovarian cancer. The diagnosis of HNPCC is made when the following three Amsterdam criteria are met: [1] at least three relatives with histologically verified HNPCC-related cancers (colorectal, endometrial, ovarian, gastric, hepatobiliary, small bowel, or transitional cell cancer of the renal pelvis or ureter), one of them a first-degree relative of the other two (familial adenomatous polyposis excluded), [2] at least two successive generations affected, and [3] in one of the individuals, the diagnosis of cancer is made before the age of 50 [9].

Pathogenesis

There are many postulations on the simultaneous occurrence of two cancers at two anatomical locations. One of the theories suggests that when tissues of same embryonic origin are subjected to hormonal exposure or to carcinogens, they develop synchronous malignancies [10]. The presence of estrogen receptors in these tissues indicate a hormonal field effect which could lead to the development of simultaneous cancers in the endometrium and ovary. Eifel et al. also suggested that the response of the uterine corpus, fallopian tubes, and ovarian epithelium as a morphologic unit could explain the development of synchronous endometrioid tumors in different components of the Müllerian system [5]. The theory of a secondary Müllerian system says that the epithelium of cervix, uterus, fallopian tubes, ovaries, and peritoneal surface have shared molecular receptors responding to carcinogenic stimulus leading to the development of multiple primary malignancies synchronously [8]. They further describe that the hypothesis provides an explanation for synchronous malignancies of similar histology. The epithelial linings of the endometrium, ovaries, and peritoneum have molecular receptors (the so-called secondary Müllerian system) responding to the same carcinogenic stimulus and therefore development of synchronous primary tumors [11–13]. However, this can only explain synchronous tumors of similar histology and not dissimilar types. Future studies are needed to further evaluate the role of estrogen in these synchronous endometrioid cancers of the endometrium and ovary.

Differentiating Synchronous from Metastatic Cancers

It is very important to differentiate synchronous tumors from metastatic tumors. Synchronous tumors involving the ovary and endometrium are both early-stage cancers, have favorable outcome, and do not mandate aggressive adjuvant treatment. On the other hand, metastatic tumors are of advanced stage and need aggressive postoperative treatment in the form of radiotherapy or chemotherapy.

About 5 % of women with endometrial adenocarcinoma of endometrioid type have synchronous ovarian carcinoma. It is usually possible for the pathologists to distinguish between synchronous and metastatic cancers. If the pathological examination of the uterus shows low-grade endometrial cancers confined to the endometrium or with superficial myometrial infiltration and no lymphovascular infiltration, the coexisting adnexal tumor is most probably synchronous cancer. In the presence of high-grade endometrial

tumor and lymphovascular invasion, the ovarian mass is usually metastatic disease. If pathological examination of ovaries shows features of borderline or low-grade cancer with associated endometriosis, this indicates synchronous cancer. Metastatic ovarian cancers are usually bilateral with multinodular pattern, vascular invasion, and tubal lumen involvement.

The first attempt to distinguish synchronous cancers from metastatic cancers was by Ulbright and Roth in 1985 [14]. They used pathological features like similar histology, grade, myometrial infiltration, vascular involvement, and tubal lumen involvement. This was later on modified by Scully et al. including clinical and pathological features which are now accepted by pathologists to differentiate synchronous from metastatic cancers.

Clinicopathologic Criteria to Diagnose Synchronous Tumors (Scully et al. [1])

1. Histologic dissimilarity of the tumors
2. No or only superficial myometrial invasion of endometrial tumor
3. No vascular space invasion of endometrial tumor
4. Atypical endometrial hyperplasia additionally present
5. Absence of other evidence of spread of endometrial tumor
6. Ovarian tumor unilateral (80–90 % of cases)
7. Ovarian tumor located in parenchyma
8. No vascular space invasion, surface implants, or predominant hilar location in ovary
9. Absence of other evidence of spread of ovarian tumor
10. Ovarian endometriosis present
11. Different ploidies of DNA indices, if aneuploid, of the tumors
12. Dissimilar molecular genetic or karyotypic abnormalities in the tumors

Metastatic cancer in the ovary from a primary in the endometrium will be histologically similar. The primary tumor will show features of advanced endometrial cancer like large tumor size, deep myometrial infiltration, presence of vascular and lymphatic infiltration, and lymph node metastasis. The ovarian metastases are usually bilateral, present in the ovarian hilum with vascular involvement. The tumors will also be karyotypically similar.

Molecular Studies

Although histopathology can differentiate synchronous from metastatic cancers in the large majority, there remain some cases in which the pathologist cannot accurately distinguish the two entities. In such situations molecular studies can complement histopathology. Various molecular methods of analysis have been developed which includes DNA flow cytometry, loss of heterozygosity on chromosome, X chromosome inactivation, PTEN/MMAC1, beta-catenin, and microsatellite instability to help in the differentiation of the two entities. Microsatellite instability (MSI) is a very useful tool in diagnosing synchronous cancers. Microsatellite instability is a variation in the size of microsatellite sequences in the tumor DNA compared with the matching normal DNA. MSI is caused by an underlying defect in the mismatch repair (MMR) system. In a study of 90 cases of simultaneous endometrial and ovarian cancers, it was found that histology alone provided a diagnosis in only 61 % of cases, whereas the combination of histology and molecular diagnosis based on LOH at 22 loci and MSI was able to categorize 98 % of cases [15].

β-Catenin mutation is more common in synchronous cancers than in metastatic cancers. β-Catenin is involved in cell adhesions and signal transduction, binding to the DNA to activate transcription. Deregulation of the β-catenin complex can lead to the development of several malignancies including ovarian and endometrial cancers [16–18]. Jiang et al. showed that endometriosis and endometrioid carcinoma have common genetic events such as loss of heterozygosity at the same loci involving the same allele and have the same pattern of X chromosome inactivation [19].

Clinical Presentation and Treatment

Patients present with signs and symptoms similar to endometrial and ovarian cancers. The most common symptom is irregular, heavy bleeding followed by abdominal distention and mass abdomen. Synchronous endometrial and ovarian cancers are often misdiagnosed as advanced endometrial or ovarian cancers and are overtreated. But pathological examination usually shows both endometrial and ovarian cancers are confined to their organ of origin and do not need such aggressive treatment. Due to a few number of patients and scanty literature, it is difficult to formulate treatment recommendations for synchronous cancers.

The cancers both in the endometrium and ovary usually present in early stage and hence benefit with surgical management. The standard surgical procedure is surgical staging with total abdominal hysterectomy with bilateral salpingo-oophorectomy with pelvic and para-aortic lymph node dissection and omentectomy. Depending on the risk factors, patients are treated with adjuvant chemotherapy and radiotherapy. Adjuvant treatment for ovarian cancers is usually platinum-based chemotherapy; a combination of carboplatin and paclitaxel for six courses is usually given. Endometrial cancers depending on the risk factors like deep myometrial infiltration and poorly differentiated histology benefit from adjuvant pelvic radiotherapy.

The possibility of synchronous ovarian cancer should be borne in mind in a young patient with early endometrial cancer who desires fertility preservation. These patients should ideally be assessed by CT or laparoscopy to rule out synchronous or metastatic cancers in the ovary before starting hormonal treatment. Premenopausal patients with early endometrial cancer desiring ovarian preservation should also undergo careful preoperative and intraoperative assessment of adnexa as there is a possibility of synchronous cancer in the ovary. But the available literature on ovarian preservation in early endometrial cancer does not show an increased rate of ovarian metastasis [5, 20–22].

Posttreatment survival rates are better with synchronous cancers compared to endometrial cancers with ovarian metastasis [23]. Eifel et al. found that patients with endometrioid cancers at both sites had a better overall prognosis when compared to patients with stage II ovarian disease or stage III endometrial cancer. The GOG study by Ramus et al. found that 74 patients with simultaneously detected endometrial and ovarian cancers had an overall good prognosis with a 5-year survival of 85.9 % and 10-year survival of 80.3 % [15]. Although almost one-third had metastases at operation, only 15 % of the entire study population suffered a recurrence within 5 years of diagnosis. The majority of their tumors were well differentiated and of endometrioid cell type. The presence of pelvic or abdominal metastases, as well as tumor grade, predicted an increased likelihood of recurrence. When tumor is localized to the uterus and ovary, the prognosis was excellent.

Conclusions

Synchronous cancer of the ovary and endometrium is a distinct clinical entity, the diagnosis of which is a challenge not just to the clinician but also to the pathologist. These cancers are often misdiagnosed as FIGO stage III of endometrial cancer or FIGO stage II ovarian cancer. It is more common in obese nulliparous young females. Apart from clinicopathologic features molecular studies including immunohistochemistry, DNA flow cytometry, and gene mutation analysis are useful in diagnosing these cancers. Synchronous cancers have better survival outcome compared to metastatic cancers.

Key Points

1. Synchronous cancers of the ovary and endometrium are rare conditions when primary cancers coexist in the ovary and endometrium.
2. Unlike metastatic cancers they present in early stages with low-grade disease and have good survival outcome.
3. Clinicopathologic features and molecular markers are useful in the diagnosis of synchronous cancers.

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38 Smooth Muscle Tumors of Uncertain Malignant Potential of Uterine Origin

Neetha Sreedharan and K. Chitrathara

Introduction

Smooth muscle tumors of uncertain malignant potential or otherwise known as "STUMP" is a rare group of smooth muscle tumors intermediate between leiomyomas and leiomyosarcomas (LMS) [1] . The term "STUMP" was first used by Kempson in 1973 [2]. It was the work of Taylor and Norris which established the importance of mitotic figures in evaluating smooth muscle tumors of the uterus a half century ago [2], but it soon became evident that some uterine smooth muscle neoplasms with relatively low mitotic indices (5–10 mitotic figures [mf] per 10 high-power fields [hpf]) were capable of behaving in a clinically aggressive manner and that not all tumors with a mitotic index greater than 10 mf/10 hpf were clinically malignant. The term *smooth muscle tumor of uncertain malignant potential* was created for the 5–9 mitotic index group to reflect the uncertainty about the true failure rate in this group [3–7]. WHO defines STUMP as a smooth muscle tumor that cannot be diagnosed reliably as benign or malignant on the basis of generally applied criteria [8].

Clinical Features

Literature does not add much to clinical presentation. Most patients belong to the premenopausal group with a mean age of around 45 years. Mode of presentation is similar to that of fibroids. Joseph et al. [9] in their review of 18 cases stratified the clinical presentation and indication for initial surgery as follows: pelvic mass in 50 % (9/18), findings consistent with uterine fibroids in 33.3 % (6/18), and menorrhagia in 16.7 % (3/18).

Imaging

None of the current imaging modalities reliably differentiates STUMP from either leiomyoma or leiomyosarcoma. Generally STUMP shows homogeneously low signal on T2 weighted images which may also occur in leiomyoma. STUMP and leimyosarcoma share a number of common MR imaging features such as areas of heterogeneous high T2 signal intensity [10].

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Pathology

The pathology of STUMP has been dealt with in detail in the chapter on pathology of uterine sarcomas. The histopathologic differentiation of STUMP from leiomyoma and leiomyosarcomas is quite challenging. It mainly depends on histologic criteria such as coagulative tumor cell necrosis (CTCN), nuclear atypia and mitotic activity.

Kempson et al. use this term when there is uncertainty about the evaluation of one or more of the histologic features used to assign cases to the benign, atypical, or malignant groups. Examples include minimally atypical smooth muscle neoplasms with a low mitotic index but over which there is uncertainty about the histologic type (i.e., standard versus myxoid or standard versus epithelioid), the combination of standard smooth muscle differentiation, marked diffuse severe atypia, low mitotic index, and uncertainty about whether coagulative tumor cell necrosis is present, and moderate to severe atypia in the face of uncertain mitotic index because possible mitotic figures may be degenerating nuclei mimicking mitotic figures.

According to WHO, the term STUMP should be used sparingly and is reserved for smooth muscle neoplasms whose appearance is ambiguous for some reason, and the relevant diagnostic possibilities differ in their clinical implications. Examples include cases in which the subtype of smooth muscle differentiation is in doubt, i.e. standard smooth muscle, epithelioid or myxoid, and application of the competing classification rules would lead to different clinical predictions. On other occasions the assessment of a diagnostic feature, e.g. the type of necrosis or the interpretation of mitotic figures, is ambiguous, and the competing alternative interpretations would lead to different clinical prediction [8].

Deodhar et al. [1] concluded in a review of STUMP and atypical leiomyoma conducted in Tata Memorial Hospital that critical evaluation of coagulative tumor cell necrosis (CTCN) is crucial and that individual tumor cell necrosis should be mentioned. It may probably be a part of infarction type necrosis, none the less, but should prompt further sampling. They also opined that correlation of histology with imaging is mandatory, especially if necrosis is not seen on biopsy and is seen on imaging.

Immunohistochemistry

Even though an attempt to triage problematic smooth muscle tumors using IHC has been attempted in numerous small series, a universal recommendation cannot be made at present with the available data. The most widely studied markers are p16, p21, p53, and Ki 67. A significant difference in staining intensity for Ki-67 between leiomyosarcoma and STUMP has been reported [9, 11]. Other investigators have suggested that STUMP tumors that express p16 and p53 may have a greater propensity to recur [12]. The question of the value of immunohistochemistry in diagnosis, characterization, and clinical stratification should be looked at with cost-benefit analyses.

Diagnosis and Treatment

STUMP diagnosis is made on hysterectomy or on myomectomy specimen. Outcome appeared to be equally good for women who initially underwent myomectomy or hysterectomy as their initial treatment. A diagnosis of STUMP does not warrant reoperation and hysterectomy which provides the options of fertility preservation in women diagnosed with this disease [13]. However these data must be interpreted with caution since data evaluating more conservative treatment options for STUMP are quite limited. This is evident from the case series of Guntuppalli et al. [14] where all women who underwent myomectomy were subsequently treated with hysterectomy within 6 months of their initial surgery.

Role of Adjuvant Treatment

The diagnosis of STUMP per se rules out any sarcomatous change, hence there is no role for

any adjuvant treatment. According to Joseph et al. [9] patients with a diagnosis of STUMP should be expectantly managed because of the low likelihood of sarcomatous transformation. There is lack of evidence supporting adjuvant treatments in improving long-term outcome. Recurrences are usually amenable to surgical resection.

Metastasis

STUMP uterine tumors generally do not metastasize. But recently few cases of distant metastasis in which the primary histopathological diagnosis was STUMP has been reported [15, 16]

Kostopoulos et al. [15] reported a rare case of STUMP with pulmonary metastases. A 51-year-old nulliparous woman was admitted with progressive dyspnea on exertion. Chest X-ray and chest computed tomography (CT) confirmed the presence of bilateral pulmonary nodules. The patient underwent video-assisted thoracoscopy and guided lung biopsies. Histopathology and immunohistochemical examination of the specimens confirmed it as a metastatic malignant smooth muscle cell neoplasm of uterine origin. Past medical history revealed that she had undergone total abdominal hysterectomy 3 years back for menorrhagia with a histopathology report of STUMP. Extensive sampling had then been done to exclude the possibility of leiomyosarcoma. The absence of necrosis and atypical mitosis made pathologists consider that the tumor belonged to the so-called "gray zone" or STUMP. Therefore, no adjuvant treatment was given and close follow-up was decided.

The possibilities in the above case are either the initial neoplasm could have been a leiomyosarcoma or the metastatic lung focuses were derived from malignant transformation of benign uterine metastasizing leiomyomas. However, all clinical, histopathological, and immunohistochemical indications were in favor of a diagnosis of "STUMP." Hence the authors concluded that the diagnosis and clinical course of STUMP are not totally and clearly known, and metastasis, especially pulmonary with pleural effusion, even though rare confers a poor prognosis [15].

Shapiro et al. in 2004 [16] reported a case of STUMP metastasizing to humerus. The primary was without coagulative tumor cell necrosis and so a diagnosis of STUMP was made, but the metastatic lesion was a high-grade leiomyosarcoma consistent with uterine origin.

Philip et al. [17] in their review on uterine smooth muscle tumors other than the ordinary leiomyomas and leiomyosarcoma opined that it would be more useful to clinically classify them as either tumors with or without recurrent and/or metastatic potential.

Recurrence

Vigilant close long-term follow up is a must for all those with a diagnosis of STUMP as recurrences are reported even though very rare. It can recur years after hysterectomy and recurrence rate is generally around 7 %. In a series by Ip et al. [12], after a mean follow-up of 80.8 months, 2 of 16 tumors recurred. The type of initial surgery usually does not influence recurrence. Available evidence gives similar rates of recurrence for myomectomy and hysterectomy.

Conclusions

There exists a very small group of smooth muscle neoplasms of the uterus for which the designation uncertain malignant potential is still warranted, at least until additional experience is accumulated and a better estimate of the potential clinical behavior for these lesions can be obtained**.** Making the diagnosis of STUMP is crucial and challenging and should be done only after thorough and meticulous histopathological examination to exclude all the possibilities of LMS. Critical evaluation of coagulative tumor cell necrosis and correlation with imaging is essential before the diagnosis is made.

Key Points

1. STUMPS are uncommon smooth muscle tumors intermediate between leiomyoma and leiomyosarcomas and the term should be restricted to those tumors where in the subtype of smooth muscle cell differentiation is in doubt.
2. A reliable imaging modality and also a specific IHC panel is yet to evolve.
3. A clinical classification of STUMP into two different entities as those with or without recurrence/metastatic potential may not be possible until more research is done in this field.
4. When a diagnosis of STUMP is made it warrants a close, long-term surveillance.

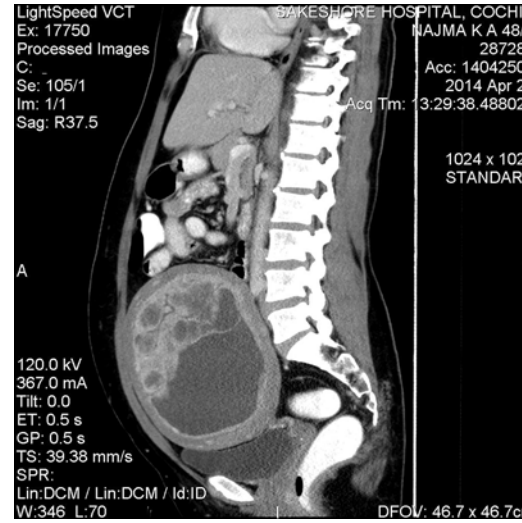

Fig. 38.1 CT scan showing enlarged uterus with cystic spaces and thinned out myometrium

Case Summary: STUMP (Contributed by Dr. K. Chitrathara)

A 48-year-old homemaker, P2, L2 presented with irregular, heavy menstrual bleeding of one and a half years duration and was on hemostatic agents and progestins. Recent use of Norethisterone for 3 months did not relieve her symptoms. She had no comorbidities.

On abdominal examination the uterus was of 24 weeks gravid uterus size. Per speculum showed a healthy cervix with bleeding from the os and clots in the vagina. Per vaginal examination confirmed abdominal findings and uterine mass appeared mobile. Systemic examination was within normal limits.

CT scan of abdomen and pelvis revealed thinned out uterine wall with irregularly enhancing soft tissue with large necrotic component and cystic areas and increase in vascularity of the uterus (Fig. 38.1). Mild hydronephrosis was present, probably due to extrinsic compression.

A differential diagnosis of uterine sarcoma/endometrial malignancy was made on imaging. CA125 and LDH were within normal limits. Ultrasound guided Trucut biopsy was taken and reported as smooth muscle neoplasm with no significant mitosis on histopathology. Peroperatively uterus was large, soft to firm in consistency with normal tubes and ovaries. Total hysterectomy with bilateral salphingo-oopherectomy was done. The specimen was sent for frozen section and reported as smooth muscle neoplasm with degenerative changes. Malignancy was excluded.

Final histopathology report with immunohistochemistry was consistent with STUMP.

Macroscopic description: Uterus 26×19 cm. Sectioning showed an intramural mass of 18×13 cms. Endometrium was mildly thickened.

Microscopy: Spindle cell neoplasm with occasional mitosis without pleomorphism or necrosis, with infiltrating margins (Figs. 38.2 and 38.3)

Immunohistochemistry: KI 67showed no proliferative activity.

P53: Occasional cells showed positivity.

Bcl2 was positive.

Chest CT was done postoperatively and was within normal limits. Patient is on close follow up and 12 months following surgery she has no evidence of recurrent disease.

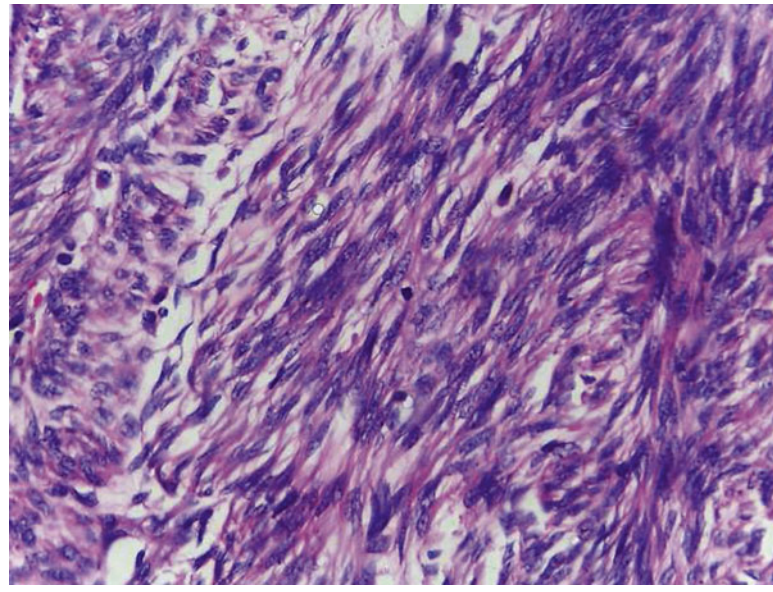

Fig. 38.2 Cellular tumor area with a mitotic figures

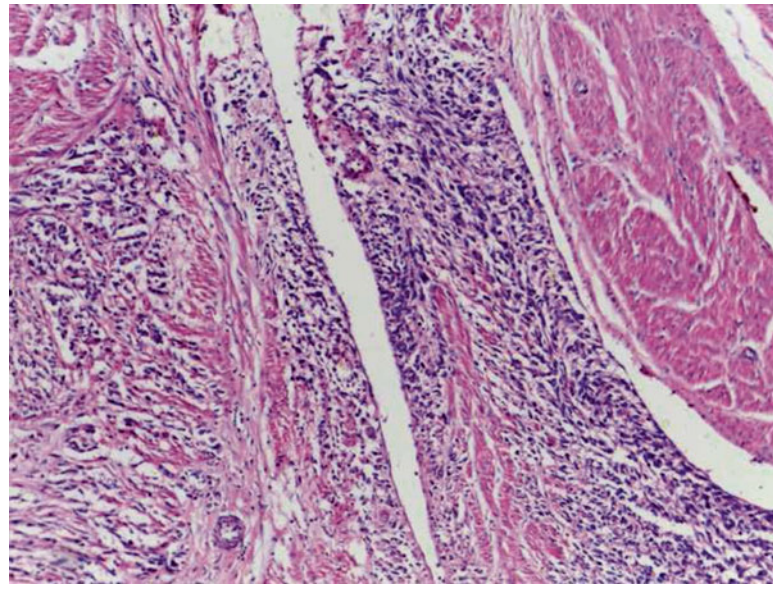

Fig. 38.3 Infiltrative margins

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39 Endometrial Cancers in Young Women: Conservative Management and Fertility Preserving Options

Bindiya Gupta and Shalini Rajaram

Introduction

Endometrial cancer is the most common gynecologic malignancy in the western world, and according to the latest SEER statistics, the number of new cases of endometrial cancer was 24.6 per 100,000 women per year. In USA, approximately 2.7 % have a lifetime risk of developing endometrial cancer [1]. Although, it is predominantly seen in postmenopausal women, it is increasingly diagnosed in women <40 years. Around 1.6 % cases occur between 20 and 34 year age and 6 % between 35 and 44 years of age according to the SEER statistics [1]. A woman under the age of 40 has a 1 in 1423 risk of developing endometrial cancer [2].

However, younger patients have excellent prognosis as they usually have type 1 endometrial cancer. These are usually well differentiated, low grade, endometrioid adenocarcinoma that are estrogen dependent and have an indolent course. These are generally associated with precursor lesions like atypia and hyperplasia and have estrogen, progesterone, and androgen receptor positivity. On immunohistochemical staining, positive stain is also seen for the phosphatase and tensin homolog (PTEN) gene (50–80 %) and microsatellite instability (20–45 %) [3].

Risk factors of endometrial cancer in women <45 years include nulliparity, chronic anovulation like polycystic ovarian syndrome, diabetes, obesity, and genetic predisposition. A high Body Mass Index (BMI) >35 has a two to four-fold increase risk of endometrial cancer [4]. Women with hereditary non-polyposis colorectal cancer (HNPCC) which is an autosomal dominant disorder caused by mutations in a family of DNA mismatch repair genes have a 40–60 % risk of endometrial cancer [4].

Oncologic Risks

This includes persistence of disease outside the uterus in stage I cancers and coexistence of a synchronous malignant ovarian tumor. The former may be seen in up to 22 % and depends on the grade of disease and depth of myometrial invasion [5]. Synchronous ovarian malignancy is seen 5–25 % young patients with endometrial cancer [6, 7]. Navarria I, et al. stated that the incidence of ovarian malignancy was 14 % in patients <45 years, while it was 2 % in older women [8].

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Selection Criteria for Conservative Management [9, 10]

The following factors should be considered in women offered conservative management.

Patient Profile

Women diagnosed with endometrial cancer should be under 40 years with a desire to preserve fertility and with a plan to achieve pregnancy soon after tumor regression. Age is a critical criteria because fertility declines with increasing age.

Tumor Histology and Stage of Disease

Only well differentiated adenocarcinoma on expert histopathological review should be managed conservatively. Well-differentiated adenocarcinoma can be diagnosed when one of the three essential criteria are met, including a confluent gland pattern, an extensive papillary pattern, and a desmoplastic stroma [11].

There should be minimal or no myometrial invasion, no extension to the cervix, pelvic and paraaortic lymphadenopathy, or adnexal involvement on magnetic resonance imaging (MRI). In case of suspicion of synchronous or metastatic adnexal involvement on MRI, a diagnostic laparoscopy should be done. Estrogen progesterone receptor status is determined in metastatic endometrial cancer to assess response to hormonal therapy. Hence, it is logical to do the same in cases selected for fertility preserving treatment although no reports are available.

Others

Evidence is also limited to recommend conservative management in women with HNPCC. They should be referred to the genetic clinic for counseling and risk evaluation and genetic testing. For conservative management the woman should be compliant and agree to all follow up protocols and visits. There should be no contraindication to high dose oral progestogens and patient should be able to tolerate high doses. Although there is no document to address the absolute contraindications, the guide for progestin-only oral contraceptives can be used a reference. Category 3 or 4 contraindications are given in Table 39.1.

Table 39.1 Contraindications to progestogen therapy in endometrial cancer

History of current breast cancer
Liver disease (i.e., severe cirrhosis) or liver tumors (hepatocellular adenoma or hepatoma)
Use of medications (i.e., phenytoin, carbamazepine, barbiturates, primidone, topiramate, oxcarbazepine, or rifampicin)

Counseling

Women should be counseled that medical treatment is not the definitive treatment modality and lacks good scientific evidence [9]. She should be willing to accept the definitive treatment after pregnancy in the form of hysterectomy and bilateral salpingo-oophorectomy as the recurrence rates are high after discontinuation of medical treatment. Extensive counseling about conservative management includes the success and relapse rates, risk of metastasis, and side effects of hormones. The patient should be advised to be compliant with follow-up protocols, need for repeated sampling of endometrium and consequent risk of Asherman's syndrome [9]. The woman should be encouraged to opt for assisted reproductive techniques soon after remission to achieve pregnancy as soon as possible. Patients with Lynch syndrome or HNPCC or autosomal dominant cancer syndromes (like Cowden syndrome) should be referred for genetic counseling so that the woman and her relatives can be given education and information on prevention strategies and any intervention instituted. Counseling sessions should be teamwork of gynecologists, oncologists, infertility specialists, and psychosocial experts and should involve the woman's family with a carefully written down plan, before initiation of treatment. The economic burden and feasibility should be included in the decision-making process.

Pretreatment Evaluation

Endometrial sampling using office based techniques (Vabra aspirator, Pipelle, and Karman cannula) have a sensitivity of 68–92 % and a false positive rate of 10 % [12]. However, some studies have shown that samples using dilatation and curettage or fractional curettage are less likely to change on expert review as compared to office sampling specimens [13]. Addition of hysteroscopy to sampling has the advantage of visually guided biopsies and identification and removal of focal lesions with a sensitivity and specificity of 80–98 % and 92–96 % respectively [14, 15].

Imaging plays an important role in evaluating the stage of disease. Transvaginal ultrasound (TVS) helps in evaluation of endometrial thickness, lesions, myometrial invasion, and adnexal involvement but is limited by its inability to evaluate the pelvic and paraaortic nodes. Its efficacy is almost similar to magnetic resonance imaging (MRI).

Contrast enhanced MRI has a high diagnostic accuracy for detection of myometrial invasion and cervical extension, with 95 % sensitivity, 60–70 % specificity, and a total accuracy of 88–90 % [16, 17]. The sensitivity and specificity of detection of lymph node involvement is 72 % and 92 %, respectively [18]. Positron emission tomography using [18F]-fluoro-2-deoxy-D-glucose has a sensitivity ranging from 28.6 % to 60 % and a high specificity of up to 98 % in identifying pelvic and para-aortic lymph-node metastasis, but has a limited role in conservative management [19].

As ovarian malignancy can be missed in up to 9–14 % cases even on MRI, a diagnostic laparoscopy can be considered in suspected cases [9]. The latter also has the advantage of lymph node biopsy when suspected on imaging.

Treatment Modalities

Progestogens

Progestogens have been used for a long time for recurrent endometrial cancer and in women unfit for surgical management with variable response. Currently, progestins administered for endometrial carcinoma include medroxyprogesterone acetate (MPA), megestrol acetate (MA), levonorgestrel intrauterine system (LNG IUS), intramuscular 17-hydroxyprogesterone, and natural progesterone. MPA and MA are the most commonly used drugs for hormone therapy [20].

Mechanism of Action

The effect of progesterone is mediated by two receptors in the endometrium, namely α and β. The latter is more abundant in the endometrium and is more important in the management of endometrial cancer. Effect of progesterone on α receptor induces cell senescence, while its effect on the β receptor induces secretory differentiation and inhibits in vitro human endometrial cancer cell growth. Both isoforms promote apoptosis and induce cell-cycle inhibition [21].

Expression of progesterone may positively correlate with response to progestogen therapy and up to 72 % overall response was seen in women with progesterone-rich tumors, while only 12 % response was seen with progesterone-poor tumors [21]. Continuous use of exogenous progestogens also down regulates both estrogen receptors and progesterone receptors.

Dose, Duration, and Side Effects

The dose of medroxyprogesterone acetate used is 200–800 mg per day and megesterol acetate is 40–320 mg/day in various studies. No evidence based guidelines are available on dose and duration of therapy, and the recommended dose needs to be adjusted to the woman's tolerance and coexisting morbidities like hypertension, obesity, and diabetes. Usually response is seen within 12 weeks of starting oral progesterone therapy, but it may even take up to 9 months [22].

Side effects include liver dysfunction and venous thromboembolism. Less serious side effects of high dose progestins include headaches, tender breasts, nausea, dizziness, weight gain, acne, thrombosis, and hair growth on face and body [23].

Levonorgestrel Releasing Intrauterine System (LNG-IUS)

Experience with the use of LNG-IUS alone in the setting of endometrial cancer is still limited, and evidence is needed. In a small study of 12 women, who had a 36-month follow-up with LNGIUS treatment (65 μg/day (Progestasert®)), the endometrial biopsy results were negative in 75 % at 12 months, suggesting that LNG-IUS can be useful for treatment of Stage IA, Grade 1 endometrioid cancer in women at high risk for perioperative morbidity [24]. Various recent studies have also reported a success rate ranging from 40 % to 100 %, but more commonly used regimens are a combination of oral and intrauterine progestins [25–27]. Studies have also reported success of 50 % with a combination of LNG-IUS and gonadotropin releasing hormone analogue [28]. Aromatase inhibitors have also been used in combination with progestogens in research studies.

Till date, the recommendation is to use a combination of LNG-IUS and oral progestogens for treatment as only few studies are available to evaluate the sole use of LNG-IUS [27].

Hysteroscopic Resection Combined with Progestogen Therapy

In some cases with small discrete lesions, hysteroscopic resection of tumor and the underlying myometrium can be done, followed by progestogens. A three-step hysteroscopic resection has been described by Mazzon et al., with a pathological analysis at each step. First step consisted of removal of the tumor, second step is removal of the adjacent endometrium, and final step is removal of the myometrium underlying the tumor [29]. This was followed by administration of 160 mg of MA. However it is associated with theoretical risk of tumor dissemination, risk of intrauterine adhesions, and pregnancy complications related to resection and there is insufficient evidence to recommend it in routine practice.

Monitoring After Conservative Management

There is no well-defined protocol of follow up after conservative management, and it varies with different institutions. As the time of response to therapy is variable (4–60 weeks), with a median duration of 12 weeks, a repeat hysteroscopy and biopsy can be performed after 3–6 months. A transvaginal scan (TVS) and Pap smear should be performed every 3 months. Endometrial thickness less than 5 mm is suggestive of response [30]. MRI or laparoscopy can be performed six monthly to one yearly whenever indicated [10].

If no cancer detected at this point of time, treatment should be continued for three more months to consolidate the response [9]. In case of tumor progression or persistence of disease, patient should be counseled regarding hysterectomy, possibility of ovarian metastasis should be ruled out by MRI or laparoscopy and a repeat MRI can be done to revise staging. In case the patient still insists on conservative therapy, an endometrial sampling should be done after 3 months. Additionally, complications of hormone therapy like deep vein thrombosis should be ruled out. Consultation with specialists in reproductive medicine should be taken to achieve pregnancy soon after remission.

Response to Therapy

In a systematic metaanalysis, complete response rates were reported to be around 53 %; 25 % had initial response followed by recurrence within 24 months while 22 % failed to respond to hormone therapy [27]. In another recent meta-analysis of 34 observational studies, Gallos et al. reported that fertility sparing hormonal treatment was associated with a pooled regression rate of 76.2 %, relapse rate of 40.6 %, and live birth rate of 28 % [31].

The most common causes of failure to response are occult extrauterine or ovarian metastasis, lymph node involvement, and presence of synchronous ovarian tumor [9]. Lymph node

metastasis may be seen in 3 % cases with myometrial invasion >50 % [32].

Prognosis is good with a 5-year survival up to 95 % in stage I, low grade disease [1]. Positive estrogen and progesterone receptor and negative HER-2 receptor status indicates good prognosis.

Ovarian Preservation During Hysterectomy

Ovarian preservation and hysterectomy alone gives an option of oocyte retrieval with surrogacy for childbearing and is labeled as partial preservation of fertility [10]. Moreover it also helps delay menopause. However, it is associated with risks of missing out a synchronous ovarian malignancy or an occult metastatic disease in the ovaries. Up to 22 % of young women with stage I cancers may have extrauterine disease and a 5–25 % incidence of any stage synchronous ovarian malignancy, which is at least five times greater than women older than 45 years [6, 7]. Criterion for ovarian preservation is similar to that described in the section on "Counseling" and must be individualized after weighing risks and benefits .

In a study of 251 women, younger than 45 years, 75.3 % had FIGO Stage I disease, there was no statistically significant difference in overall survival and disease free survival in Stage I patients with or without BSO [33]. According to the data of the SEER study, 5-year survival was 98 % for patients with 1988 FIGO IA endometrial cancers, with or without ovarian preservation [34]. Among patients with 1988 FIGO IC (2009 FIGO IB) endometrial cancer, survival was 89 % in the oophorectomy group and 86 % with ovarian preservation which was not statistically significant.

Management of Infertility and Reproductive Outcomes

The most common cause of infertility is chronic anovulation, followed by endometriosis, Asherman's syndrome post treatment, and male factor infertility. All efforts should be made to achieve successful conception soon after histological remission is achieved which is usually by 16 weeks of therapy [30]. Assisted reproductive techniques (ART) must be offered especially to women with history of infertility. Ovulation induction with clomiphene citrate or human menopausal gonadotrophins can be given in patients with chronic anovulation. Intrauterine insemination (IUI) can be done in patients with coexistent male infertility. In case the patient fails to respond, in vitro fertilization (IVF) is recommended [20]. It has an added advantage of cryopreservation of embryos for future cycles. Failure to achieve pregnancy after ART may be due to an impaired endometrial response because of primary endometrial disease, repeated endometrial samplings, and thin endometrium due to high-dose progestin treatment [35].

Pregnancy rates are around 30–40 % following conservative management, out of them 40–50 % conceptions are following assisted reproductive techniques [36, 37]. In a systematic review by Tong et al. [20], out of 152 patients, 60 % had successful pregnancy with a live birth rate of 70 %. There was no increase in spontaneous abortions or ectopic pregnancy. Pregnancy rates were significantly higher after ART as compared to spontaneous conceptions (80.0 % vs. 43.2 %). In the ART group, 7.1 % conceived on ovulation induction, while conceptions after IUI and IVF were 21.4 % and 71.4 % respectively [20]. A recent study from Japan reported a high rate (7 %) of placenta accreta in these patients and 24 % relapse rate after delivery [38].

Treatment After Child Bearing

The decision to conserve the uterus after child birth is still controversial. Till now, evidence supports a complete surgery with hysterectomy and bilateral salpingo-oophorectomy once child bearing is complete [9]. Women who insist on conserving uterus should be counseled regarding the risk of recurrence and should be advised strict surveillance and an option of LNG-IUS [20].

Conclusions

Fertility preservation in younger women with endometrial cancer is associated with oncologic risks and therapeutic challenges. They should be carefully selected, extensively counseled and encouraged to go for assisted reproductive techniques soon after remission. Progestogens are the mainstay of treatment. Close surveillance should be done post therapy and genetic testing for hereditary syndromes should be offered to all younger women.

Key Points

1. Younger women usually have type 1 endometrial cancer, which is generally associated with precursor lesions and has excellent prognosis.
2. Conservative management should be offered to women less than 40 years of age with a desire to achieve pregnancy soon after tumor regression. Women with well differentiated adenocarcinoma on histopathology, disease limited to FIGO IA, and no contraindication to high dose oral progestogens are suitable for conservation management.
3. Pretreatment evaluation includes office hysteroscopy with endometrial sampling, transvaginal ultrasound, contrast enhanced MRI for detection of myometrial invasion, cervical extension, and lymph node metastasis. Positron emission tomography and diagnostic laparoscopy can be considered in suspected adnexal involvement.
4. Progestins are the treatment of choice for conservative management for endometrial carcinoma. The most commonly used are medroxyprogesterone acetate (200–800 mg per day) and megesterol acetate (40–320 mg/day).
5. LNG-IUS with oral progestogens or GnRH and hysteroscopic resection of tumor are other conservative management options available.
6. Women should try to conceive only after remission, usually with assisted reproductive techniques. Pregnancy rates are around 30–40 % following conservative management.
7. Ovarian preservation should be offered only after weighing risk and benefits. Hysterectomy with removal of ovaries is recommended after child bearing is complete.

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Hormone Therapy in Normal Postmenopausal Women and After Treatment for Endometrial Cancer

40

Nilanchali Singh, Shalini Rajaram, and Neerja Goel

We keep dreaming of a future, a future with a long and healthy life…
Not lived in the shadow of cancer but in healthy light….

-Patrick Swayze

Introduction

Endometrial carcinomas are common female genital tract tumors. About 20–25 % of women with endometrial carcinomas are diagnosed premenopausaly [1]. Hysterectomy and bilateral salpingo-oophorectomy is the obligatory operative therapy, which results in surgically induced menopause. The abrupt loss of estrogen gives rise to deficiency symptoms, mainly hot flushes, sleep disorders, and depressive mood, reducing quality of life. Hormone therapy (HT) has been used for decades to improve quality of life of menopausal women by reducing menopausal symptoms. Many health benefits were emphasized in earlier studies [2]; however randomized studies showed that associated risks outweigh benefits [3, 4]. The principal risks of HT, apart from pathologies like thromboembolic, cardiovascular, and gallbladder diseases, also include cancers [2]. Large studies evaluating the safety of HT, including the Women Health Initiative Study (WHI) and the Million Women Study, challenged the safety and raised concerns over HT usage including risk of various cancers, endometrial cancer being one of them [3, 4]. With this began the debate on the role of HT in women with endometrial cancer and risk of endometrial cancer in women on HT.

Recent evidence based on data accumulated from these studies have shown that, initiating HT near menopause in only symptomatic women is beneficial with proven benefit-risk ratio [5]. Endometrial carcinoma is listed as a contraindication to estrogen therapy and estrogen–progestin therapy in drug data information of hormone preparations. Nevertheless, for the past 25 years, more endometrial cancer patients are being treated with HT, following definitive therapy for endometrial cancers. This is limited to FIGO stage I, and rarely stage II, endometrial cancers. Since 80 % of all endometrial cancers are detected in early stages at the time of diagnosis, many women may have the option of HT. [1] This chapter will look at the evidence and risk of developing endometrial cancers while on HT and also when and how to prescribe HT in women treated for endometrial cancer.

Hormone Therapy in Postmenopausal Women Without Endometrial Cancer

Earlier, the decision surrounding hormone therapy (HT) mainly focused on whether to take estrogen or not, and if the addition of a progestogen was

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required. However the last 5 years has seen an evolution in the form of several new drugs and regimens for estrogen therapy in menopausal women.

Estrogen Doses of estrogen range from very low doses of oral estrogen (0.3 mg conjugated equine estrogen [CEE], 0.25 mg of 17β-estradiol), transdermal patches which deliver a minimum of 20 μg of 17 β-estradiol per day, or intranasal methods which deliver 100–400 μg of 17beta-estradiol, to the more commonly prescribed doses of 0.625 mg of CEE or 0.5 mg 17beta-estradiol.

Progestogen The decision to add a progestogen to the regimen of therapy is well accepted, particularly in a woman with an intact uterus; however, the focus now is on which progestogen least attenuates the lipid benefits obtained from estrogen therapy. Various forms including oral preparations of norethisterone, medroxyprogesterone, dydrogesterone, micronized progesterone, and LNG-intrauterine system have been used. The dose of progestin needs to be increased according to the dose of estrogen used for HT. In sequential therapy, progestin used comprises of medroxyprogesterone (10 mg), dydrogesterone (10 mg), and micronized progesterone (200 mg); whereas, in combined therapy, medroxyprogesterone (2.5 mg) and micronized progesterone (100 mg) are used.

Estrogens and Endometrial Cancer

Type I endometrial carcinoma is an estrogen dependent tumor, associated with estrogen dominance. The risk factors are adiposity, anovulation, early menarche, and late menopause. It is often preceded by hyperplastic endometrial changes.

Molecular Changes At the molecular level, mutation of the ras oncogene, depletion of the expression of tumor suppressor genes, and disturbances in the function of DNA repair genes play a central role [6]. Estrogens act as tumor promoters in type 1 carcinoma. Through mitogenic activity, they increase the potential development of endometrial hyperplasia, with chances of progressive transformation to carcinoma, which is mostly well-differentiated. Further mutations in p53-gene, loss of expression of estrogen, and progesterone receptors promote transformation to more aggressive and undifferentiated carcinoma with poorer prognosis.

Type II endometrial carcinoma is not associated with hyperestrogenism. It typically develops from the atrophic endometrium of postmenopausal women.

Mutation of the p53 gene seems to be important for development of these cancers.

Endometrial Sarcomas Low-grade stromal sarcomas have also found to be sensitive to estrogens. Notably, over 50 % were observed to be premenopausal, and the relapse rate, after bilateral oophorectomy and subsequent high-dose progestogen therapy, was greatly reduced. Accordingly, based on level II studies, tumors of this primary type are considered a contraindication to HT [7].

Role of Progestins in Hormone Therapy

The progestational agent in estrogen-progestin therapy (EPT) is provided to oppose proliferative effects of estrogen on the postmenopausal endometrium. Progestins are known to mediate renewal of the endometrial epithelium and reduce the concentration of estrogen receptors [8]. The *International Menopause Society, 2014,* published a *Practitioner's Toolkit for Managing the Menopause* in which it is recommended that progestogen be added for endometrial protection. In addition, treated endometrial carcinoma is not a contraindication for HT [9]. The provision of a daily progestin dose in continuous-combined EPT is thus expected to reduce the endometrial mitotic rate compared to what would be observed in the presence of sequential EPT (where progestin is given for fewer days per month) and unopposed estrogen therapy. If the progestin component in continuous-combined EPT truly is effective in opposing the proliferative effects of the estrogen component, it is plausible that users of continuous-combined EPT would experience no

increased risk of endometrial cancer compared to never users of hormone therapy.

Demerits of Progestins in Hormone Therapy

Sturdee et al. reported that for many years it has been perceived that hormone therapy for women with a uterus should include a progestin to prevent the proliferative effects of estrogen on the endometrium and endometrial cancer [10]. But, with reports from the Women's Health Initiative (WHI) and Million Women Study indicating that such regimens are associated with an increased risk of breast cancer, whereas unopposed estrogen may not increase this risk, or even reduce it, it is pertinent to reassess the merits of adding a progestin. In addition, the suggestion from the WHI that the effects of estrogen and progestins are a "class effect" are clearly inaccurate, as there is particular evidence from the French E3N cohort studies of differential effects of progestins, with progesterone and dydrogesterone additions showing no increase in risk of breast cancer [11]. The data are presented but an answer to the question remains unclear and dependent on the circumstances and views of each individual woman and her medical adviser.

Risk of Endometrial Cancer with Hormone Therapy

Estrogen-only HT substantially increases the risk of endometrial cancer in women. The use of cyclical progestogen for at least ten days per 28-day cycle eliminates this risk. The risk of developing endometrial cancer in women on HT is listed in Table 40.1.

According to the British Menopause Society report, 2013, unopposed estrogen therapy increases the incidence of endometrial cancer; this risk is largely avoided by the use of combined sequential estrogen/progestogen therapy [12]. Long-term use of cyclic sequential HT for more than 5 years may be associated with a small increase in risk of endometrial cancer. Continuous combined regimens are associated with a significantly lower risk of endometrial cancer than even untreated population.

Table 40.1 Risk of developing endometrial cancer in patients on HT [12]

Estrogen-only HT increases the risk in women with uterus
Continuous combined HT reduces the risk
Cyclic combined HT neither offers protection nor does it increase risk
Cyclic Sequential HT use for more than 5 years may slightly increase the risk
Tibolone has a controversial role as risk factor of carcinoma endometrium

Major Studies on This Issue

The Million Women Study found that HT containing estrogen alone increased the risk of endometrial cancer (compared to women who had never taken HT) [4]. Progestogens, however, counteract the adverse effect of estrogens. The effect of continuous combined preparations was a reduction in risk, while there was no significant risk (or protection) from use of cyclical preparations.

The *Women's Health Initiative* and the *Heart and Estrogen/Progestin Therapy* trials observed a reduced risk of endometrial cancer associated with use of continuous-combined EPT [5, 13]. Both trials were limited by small case numbers ($N=58$ and $N=10$, respectively) and a shorter duration of exposure than has been examined in most observational studies.

Brinton et al., in a recent review published in 2014, reported that numerous epidemiologic studies have shown substantial risk of endometrial cancers with use of unopposed estrogens, especially among thin women [14]. This risk, however, can be reduced if progestins are added to the therapy. The manner in which progestins are prescribed is a critical determinant of risk. Most studies show that women who have ever used progestins continuously (>25 days/months) are at somewhat reduced risk relative to nonusers (metaanalysis relative risk, RR, based on observational studies = 0.78, 95 confidence intervals, CI,

Table 40.2 Relative risk of endometrial cancer in patients on hormone therapy with or without progestogen in various studies

Studies	*Estrogen Therapy (ET)	Sequential Combined Estrogen/ Progestin Therapy (SCEPT)	Continuous Combined Estrogen Progestin Therapy (CCEPT)
Grady 1995 [22]	2.3 (2.1–2.5) 9.5 > 10 years	Cohort studies RR 0.2–0.9 Case control studies RR 0.9–2.0	–
Pike 1997 [16]	2.2 (1.9–2.5)	1.9 (1.3–2.7)	1.1 (0.8–1.4)
Weiderpass 1999 [18]	6.2 (3.1–12.6)	2.9 (1.8–4.6)	0.2 (0.1–0.8)
Personn 1999 [24]	4.2 (2.5–8.4)	1.4 (0.6–3.3)	–
Hill 2000 [23]	4.0 (3.1–5.1)	–	0.6 (0.3–1.3)

0.72–0.86). The reduced risk in greatest among heavy women. In contrast, women who have ever used progestins sequentially for <10 days each month are at increased risk, with metaanalysis results showing on overall RR of 1.76 (1.51–2.05); in contrast, progestins given for 10–24 days/month appear unrelated to risk (RR = 1.07, 0.92–1.24). These risks were based on varying patterns of usage, with little information available regarding how endometrial cancer risk is affected by duration of use, type, and/or dose of estrogen or progestin, or mode of administration. Effects may also vary by clinical characteristics (e.g., differences for type I vs. II tumors).

Another study reported that approximately 20 % of women given unopposed estrogen for 1 year develop endometrial hyperplasia [15].The relative risk of endometrial carcinoma is 2–3. This is dramatically reduced by the addition of progestogen to the regimen, but cyclical progestogen as part of a sequential HT regimen does not completely eliminate the risk of carcinoma. The prevalence of endometrial hyperplasia associated with sequential HT is 5.4 %, and that of atypical hyperplasia (endometrial intraepithelial neoplasia) is 0.7 %. Continuous combined HT is not associated with the development of hyperplasia or carcinoma, and may normalize the endometrium of women who have developed complex hyperplasia on sequential HT.

There are several other observational studies which have explored the possible association between use of continuous-combined EPT and endometrial cancer, with varying results. While several studies have reported either no increased risk or a modest decreased risk of endometrial cancer associated with use of continuous-combined EPT, three studies have reported an increased risk [16–21].

Risk of Endometrial Carcinoma and Type of Progestin Therapy

Grady et al. conducted a metaanalysis of 30 studies conducted after 1970 and reported that the protective effect is seen if progestogen is administered for a minimum of 10 days, or even better, i.e., 12–14 days (Evidence level II) [22]. However, increased risk has also been demonstrated with addition of monthly sequential progestogen (SCEPT), in contrast to CCEPT (Evidence level II) [23]. Indeed, the question of whether the risk with CCEPT is lower than with no treatment is to be investigated in further clinical trials, because, in the present studies, only a relatively small number of patients are represented. It is certain that with estrogen monotherapy, after metaanalysis of over 30 studies a two- to fourfold risk with short term and 10-fold relative risk with long-term therapy (10 years) is calculated (Evidence level II). The elevated risk also remains for at least 5 years after stopping estrogen therapy [24]. Table 40.2 depicts the relative risk (95 % confidence interval) of endometrial cancer in patients on hormone therapy with or without progestogen in various studies.

Hormone Therapy in Endometrial Cancer Survivors

Some women developing endometrial cancer have already gone through menopause. However, younger women with endometrial cancer, undergo premature menopause after surgical treatment. A recent study based on gynecologists' experience reported that although HRT is not actively recommended, HRT given posttherapy to endometrial cancer patients is considered acceptable [25].

For survivors of endometrial cancer, the concern is that endometrial cancer is an estrogen-linked cancer, and estrogen used in HT may increase the risk of endometrial cancer recurrence. Only limited research has been done on this HT risk. Guidelines on treating uterine cancers from the **National Comprehensive Cancer Network (NCCN)** state that studies have not conclusively proved that estrogen therapy causes a higher relapse rate (Table 40.3).

Global Consensus Statement on Menopausal Hormone Therapy, 2013, by International Menopause Society labels breast carcinoma survivors as a contraindication to hormone therapy but endometrial carcinoma survivors are not labeled as a contraindication [27].

The Hormone Therapy Position Statement of the North American Menopause Society gives its recommendations as stated in Table 40.4.

Table 40.3 The NCCN guidelines on estrogen therapy in endometrial cancer [26]

1. Any recommendation for HT should be on an individual basis
2. Patient counseling and consent is necessary
3. HT should be started 6–12 months after completing therapy
4. Other options to HT, like, a selective estrogen-receptor modulator, such as raloxifene, which does not appear to stimulate breast or uterine tissue should be explained to patient. (Unfortunately, raloxifene does not relieve hot flashes and vaginal dryness)

Table 40.4 Hormone therapy position statement of the North American menopause society [28]

1. Unopposed systemic estrogen therapy in menopausal women is associated with increased endometrial cancer risk
2. This risk is associated with dose and duration of estrogen therapy
3. This increased risk persists several years after discontinuation of estrogen therapy
4. In general, *HT is not recommended in women with a history of endometrial cancer*
5. Progestogen alone could be considered for the management of vasomotor symptoms but no long-term data are available

Hormone Therapy After Endometrial Carcinoma

According to the latest official statements of the North American Menopause Society (2012), the treatment of moderate to severe menopause symptoms (vasomotor symptoms and sleep disruption from vasomotor symptoms) remains the primary indication for systemic ET and EPT. In women who have been treated previously for endometrial cancer, these benefits must be weighed against the risk of stimulating tumor growth and recurrence. There is no available evidence based from randomized clinical trials. For a definite conclusion that HT after endometrial cancer is not deleterious, large randomized trials are required.

According to the ACOG committee opinion, in the absence of HT a well-differentiated neoplasm of endometrioid cell type with superficial invasion would entail an approximate 5 % risk of recurrent disease, and a moderately differentiated neoplasm with up to one-half myometrial invasion entails a 10–15 % risk [29].

The essential outcomes of some nonrandomized controlled studies are listed in Tables 40.5. All studies are retrospective, nonrandomized case–control studies (evidence level II). These studies produced no data showing that a higher risk exists with HT after treated endometrial carcinoma.

Table 40.5 Hormone therapy after endometrial cancer, FIGO stage I or II – case control studies

Studies	Number of cases/ control	ET/EPT in cases	Duration of HT	Recurrence cases/control
Creasman 1986 [30]	47/174	ET:CEE (47)	26 months	2 %/15 %
Lee 1990 [31]	44/99	EPT/CEE (15/29)	64 months	0 %/8 %
Chapman 1996 [32]	62/61	CCEPT/CEE(33/29)	39.5 months	3 %/10 %3
Suriano 2001 [33]	75/75	CCEPT/CEE(37/38)	83/63 months	1 %/15 %

Table 40.6 Various vaginal formulations of estrogen therapy

Formulation	Brand name	Dosing	Advantages	Disadvantages
Vaginal Cream Estradiol Conjugated equine estrogens Estriol succinate	Estrace Premarin Evalon	*Initial:* 2.0–4.0 g/d for 1–2 weeks *Maintenance:* 1.0 g/d Cyclic 0.5–2.0 g/d *Alternative:* 0.5 g twice weekly 0.5–3 mg/d	Less expensive	Difficult appropriate dose administration Poor patient compliance Messy and relative inconvenience Increased systemic absorption
Vaginal ring Estradiol Estradiol acetate	Estring Femring	Device containing 2 mg releases 7.5 mcg/day for 90 days Systemic-dose device containing 12.4 or 24.8 mg releases estradiol 0.05 or 0.10 mg/day for 90 days	Improved patient acceptability	Difficult insertion Dislodgement of the ring
Vaginal tablet Estradiol hemihydrate	Vagifem	*Initial:* 1 tablet/d for 2 weeks *Maintenance:* 1 tablet twice weekly (tablet containing 25.8 mcg of estradiol hemihydrate)	More consistent dose of estrogen, reduces potential for leakage Adherence to treatment	Because of twice-a-week dosing schedule, women may forget

Alternative Therapies

Since estrogen therapy may be associated with increased risks of endometrial carcinoma and safety profile of systemic estrogen therapy on endometrial carcinoma survivors is not known, alternative therapies have evolved. These therapies can be hormonal or nonhormonal.

Hormonal Therapies

Local Vaginal Estrogen Local low-dose estrogen can be applied as various formulations as mentioned in Table 40.6. It has advantages over systemic therapy as it does not have systemic side effects and more acceptable to many women. The vaginal formulations may revert atrophic changes, with limited systemic absorption.

Limited systemic exposure, lesser adverse effects compared with systemic therapy, and no requirement of concomitant progestin therapy are the advantages of local estrogen therapy.

Progestin Only Therapy

Progestogen therapy (PT) is justified for all forms of endometrial hyperplasia. According to observational studies (Evidence level II), even higher stages of endometrial carcinoma can be treated with moderate to high doses of progestin, in which case, nonaromatized gestagens, such

as MPA(100–500 mg) or megestrol acetate (40–120 mg), should be used. Menopausal complaints can also be alleviated by this therapy. However, gestagens in lower doses (5–10mgMPA; 20–40 mg megestrol acetate) may also be considered. There is experience of their efficacy, especially with hot flushes, in patients treated for breast cancer. However, PT is definitely inferior to estrogen replacement (ET or EPT), and clinical experience show that frequent treatment failures are seen. Significant improvement in menopausal symptoms with PT has been demonstrated, with a 60–90% reduction in hot flushes [34, 35]. Experience with low-dose gestagen therapy (PT) to treat hot flushes after endometrial cancer is limited. Trials with PT to treat climacteric symptoms are therefore justified.

Emerging Hormonal Treatment Options

Two other types of hormonal therapies are under investigation as alternatives to ET in patients with urogenital atrophy. These therapies include selective estrogen receptor modulators (SERMs) and dehydroepiandrosterone (DHEA). Both are not FDA-approved for use in vaginal atrophy.

Selective Estrogen Receptor Modulators

SERMs may be a useful therapeutic alternative to local ET in some women with urogenital atrophy. Evidence suggests that two upcoming SERMs, lasofoxifene and ospemifene, may be useful in treating vaginal atrophy, and reduce dyspareunia [36].

Role of Selective Estrogen Receptor Modulators (SERMs)

Tibolone has a controversial role as risk factor of carcinoma endometrium [37]. Some believe it does not increase the risk of either endometrial hyperplasia or endometrial cancer, whereas the Million Women Study reported increased risk of endometrial cancer with tibolone [4].

A recent study evaluated the role of various SERMs on endometrium [36]. SERM activity ranges from essentially neutral to agonist on the endometrium, depending on the individual SERM. Raloxifene, tamoxifen, lasofoxifene, ospemifene, and bazedoxifene demonstrated different degrees of endometrial tissue effects in preclinical and clinical studies. Bazedoxifene inhibits the effects of conjugated estrogens on the endometrium. These effects are attributable to tissue-specific estrogen receptor degradation, which effectively diminishes the molecular target of estrogen activity in the endometrium. Bazedoxifene has a favorable endometrial profile, with incidences of hyperplasia and bleeding/spotting similar to those of placebo. They concluded endometrial safety is a significant hurdle in the development of new hormone therapies for postmenopausal women. Preclinical and clinical findings suggest that bazedoxifene has an endometrial profile distinct from those of other SERMs.

Dehydroepiandrosterone

Recent studies have evaluated the effect of vaginal administration of DHEA in vaginal atrophy [38]. Treatment with intravaginal DHEA has been shown to increase vaginal maturation, decrease vaginal pH, and improve vaginal symptoms. The advantages are that endometrium is not stimulated.

Tissue Selective Estrogen Complexes (TSECs)

TSECs are a novel approach to providing relief of menopausal symptoms with adequate endometrial safety profile [39].They differentially modulate markers of proliferation and differentiation in endometrial cells. Combining an SERM with one or more estrogens to form a tissue selective estrogen complex (TSEC) can provide an improved blend of tissue-specific ER agonist and

antagonist effects. While both estrogens and SERMs affect the uterine endometrium, not all TSECs reverse the endometrial effects of estrogens preventing endometrial proliferation and hyperplasia. Their action in uterine cells is not completely understood. HOXA 10, leukemia inhibitory factor (LIF), progesterone receptor (PR), and EMX2 are genes known to regulate endometrial proliferation and differentiation. The expression of these genes was used to assess endometrial effects of SERMs and TSECs. The TSEC containing BZA uniquely decreased HOXA10 expression and increased EMX2 expression. The TSECs alter endometrial cell proliferation by selective modulation of estrogen responsive genes, maintaining the antiproliferative effects mediated by PR and inhibiting LIF. The differential effect of TSECs on endometrial gene expression suggests a mechanism by which they manifest differential effects on endometrial safety against the risk of estrogen-induced endometrial hyperplasia.

Nonhormonal Treatment Options

Lifestyle Modifications

Certain lifestyle modifications may improve the symptoms of vaginal atrophy. Smoking cessation, regular coital activity, avoidance of heavily scented and anti-itch products, and wearing loose-fitting cotton underwear may be useful. Women with recurrent UTIs also may benefit from the use of prophylactic antibiotics or regular consumption of cranberry juice (e.g., 200–750 mL daily). Bladder drill may be useful in urinary symptoms like frequency and urgency. Antimuscarinic agents may also be used for these symptoms. [45] these agents include Oxybutynin (5–30 mg/day), darifenacin (7.5–10 mg/day), and solifenecin (5–10 mg/day) etc.

Vaginal Lubricants

Water-soluble vaginal lubricants and moisturizers can be useful in relieving vaginal dryness, especially during intercourse. Lubricants may be water based, silicon based, or oil based. The effect is temporary. Vitamin E oil has also been found to be beneficial. Vaginal moisturizers are particularly useful in women with history of hormone dependent cancers [46].

Symptomatic Pharmacologic Therapy

The German Society of Senology recently recommends treatment with selective serotonin-reuptake inhibitors (SSRIs), such as venlafaxine or fluoxetine [40]. The tricyclic antidepressant opipramol is also effective; it has been used for years to treat menopausal complaints, and is particularly well tolerated. The antiepileptic gabapentin has also been shown to reduce hot flushes; this was only recently demonstrated in the first double-blind, placebo-controlled trial [41].Other nonhormonal alternatives are methyldopa, clonidine, veralipride (an antidopaminergic), lipophilic beta-blockers such as propranolol, tranquilizers, or related substances (such as belladonna and ginseng), and vitamin E. Currently, the most effective alternatives seem to be the SSRIs.

Phytoestrogens and Dietary Supplements

Use of various herbal compounds, such as phytoestrogens and dietary supplements, is of increasing. Although the risk of endometrial hyperplasia or carcinoma cannot be excluded with their use and reports are conflicting (evidence level II) [42, 43]. The compositions of the phyto-preparations, such as those from soya, isoflavonoids, red clover, Cimifuga extract, agnus castus and St John's wort, are complex, variable, and only partly known. The actions of the active ingredient have also been little investigated; phyto-preparations are socially well accepted, and, with longer treatment, satisfactory effects can be attained in some women, because of the high compliance of women in therapy with plant-based preparations. A recent study concluded that 3-year isoflavone soy protein supplementation has no effect on endometrial thickness or on

the rates of endometrial hyperplasia and cancer in postmenopausal women [43].

Customizing Treatment

Several safe and effective treatment options exist, including nonhormonal remedies, hormonal therapies, and lifestyle modifications. An umbrella treatment may not be useful for all menopausal women. Timely and careful assessment, as well as customizing treatment based on their individual needs, may facilitate successful outcome and enhance quality of Life. Vaginal lubricants and moisturizers may aid in sexual activity. Vaginal estrogens may somewhat reverse atrophic changes and aid in improving sexual performance. Evidence shows loss of testosterone affects libido in postmenopausal women, and testosterone coadministered with estrogen can improve libidinal functioning, enhance sexual desire, enjoyment, and frequency [44].

Reducing Cancer Risks of Hormone therapy

Optimization of diet and lifestyle should be incorporated into the routine management of all women with cancer having menopause, whether physiological or treatment related. Hormone therapy has proven risks pertaining to cancer. Table 40.7 shows few measures to reduce cancer risks of HT.

Table 40.7 Reducing the cancer risks of hormone therapy

If hormone therapy is desired for a woman, it should be provided in the lowest dose that is effective in alleviating her symptoms, and also for shortest possible duration. Other treatments for these symptoms and conditions should also be considered
Cancer screening for women on HT is mandatory. All women should be counseled to report any vaginal bleeding which can be a symptom of endometrial cancer
Women using vaginal cream, rings, or tablets containing only estrogen should also be under regular follow-up. In long-term therapy, the possible need for progestin therapy should be considered

Conclusions

Young women with endometrial cancer undergo premature menopause after surgical treatment. For survivors of endometrial cancer, the concern is that endometrial cancer is an estrogen-linked cancer, and estrogen used in HT therapy may increase the risk of endometrial cancer recurrence. Only limited research has been done on this risk. Guidelines on treating uterine cancers from the National Comprehensive Cancer Network state that studies have not conclusively proved that estrogen therapy causes a higher relapse rate. If hormone therapy is desired for a woman, it should be administered in the lowest effective dose and for shortest possible duration. Other treatment options should also be considered.

Key Points

1. Estrogen-only HT substantially increases the risk of endometrial cancer in women. The use of cyclical progestogen for at least ten days per 28-day cycle eliminates this risk.
2. Any recommendation for HT should be on an individual basis.
3. Patient counseling and consent is necessary.
4. HT may be started 6–12 months after completing therapy.
5. Other options to HT, like, a selective estrogen-receptor modulators, such as raloxifene, which does not appear to stimulate breast or uterine tissue may be offered to the woman.
6. Cancer screening for women on HT is mandatory. All women should be counseled to report any vaginal bleeding which may be a symptom of endometrial cancer.

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Effects of Tamoxifen and Other SERMs in the Endometrium and Follow-Up of Patients

41

S. Suchetha

Introduction

Hormone therapy remains an integral part of the treatment of hormone receptor-positive breast cancers. Tamoxifen, a selective estrogen receptor modulator, is the most common hormonal agent used in this scenario. Selective estrogen receptor modulators (SERMs) are competitive inhibitors of estrogen receptors which have an estrogen agonist and antagonist effect depending on target tissues. The antiestrogenic effect is by blocking the binding of estrogen to estrogen receptors.

The three SERMs are tamoxifen, raloxifene, and toremifene. The antagonist effect of tamoxifen is important with respect to breast cancer treatment. From 1970 onward tamoxifen has been used in the treatment of advanced breast cancer. When used as adjuvant treatment, it reduces the risk of recurrence, contralateral breast cancer, metastasis, and death in estrogen receptor-positive breast cancer patients. It is also used for prevention of both invasive and in situ carcinoma in women with high genetic risk. When used for 5 years, risk of recurrence is reduced during treatment and in the first decade. It also reduces breast cancer mortality for the first 15 years. Continuing tamoxifen for 10 years rather than 5 years produces a reduction in recurrence and mortality, particularly after year 10. This and previous reports suggest that 10 years of tamoxifen treatment can halve breast cancer mortality during the second decade after diagnosis [1]. In 1980 various reports have shown the association of tamoxifen to increased risk of endometrial cancer. This was proved by the National Surgical Adjuvant Breast and Bowel Project (NSABP) Breast Cancer Prevention Trial (BCPT) especially in postmenopausal women aged 50 years or more [2]. NSABP B14 trial randomly assigned 2843 breast cancer patients to tamoxifen or placebo for 5 years. The relative risk of endometrial cancer reported was 7.5 % in patients with tamoxifen. The use of tamoxifen for 5 years has shown to increase the incidence of thromboembolic events [3], and continuation for 5 more years still increases the side effects.

The new-generation SERMs being investigated for breast cancer treatment are idoxifene, droloxifene, GW-5638, arzoxifene, and EM-652. Raloxifene and arzoxifene are devoid of the estrogenic endometrial effect. EM-652 (Acolbifene) and GW5638 are antiestrogenic on both the uterus and breast and have minimum negative effect on endometrium (Table 41.1). But in ovariectomized rats they have shown estrogenic effect on serum cholesterol and bone with minimal antiestrogenic effect in endometrium [4, 5].

Many of the epidemiologic and genetic risks which predispose to breast cancer can also increase

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Table 41.1 Effects of various SERMs on the breast and uterus

SERM	Breast	Uterus
Tamoxifen	–	++
Raloxifene	–	–
Toremifene	–	+/–
Idoxifene	–	+/–
Droloxifene	–	+/–
GW 5638	–	+/–
Arzoxifene	–	–
EM-652	–	+/–

the risk of endometrial cancer, and the women taking tamoxifen for 5 years have two- to threefold increased risk for developing endometrial cancer than the age-matched population [6–8]. Use of 10 years would produce an additional risk of about 2 % by 15 years [3]. The cumulative risk and mortality from endometrial cancer also increase with 10 years of tamoxifen with an absolute mortality increase of 0.2 % [1]. The risk of endometrial cancer is greatly outweighed by the reduction in breast cancer mortality. Raloxifene, a second-generation SERM, seems to prevent invasive breast cancer but with only 76 % effect of tamoxifen in high-risk women and has few life-threatening side effects including endometrial cancer [9]. Cochrane database systematic review 2012 showed that toremifene and tamoxifen are equally effective in breast cancer treatment and safety profile of toremifene is not worse than tamoxifen.

Endometrial Abnormalities Associated with Tamoxifen

The estrogenic effect of tamoxifen on endometrium causes endometrial hyperplasia, polyp, endometrial cancer, and uterine sarcoma [10, 11]. Study by Cheng et al. found no significant endometrial abnormalities in premenopausal patient treated with tamoxifen whereas postmenopausal patients on tamoxifen had significant endometrial abnormalities [12].

The association between endometrial abnormalities and dose of tamoxifen had been addressed in several studies. The incidence of endometrial abnormalities in postmenopausal patients on tamoxifen is reported to be around

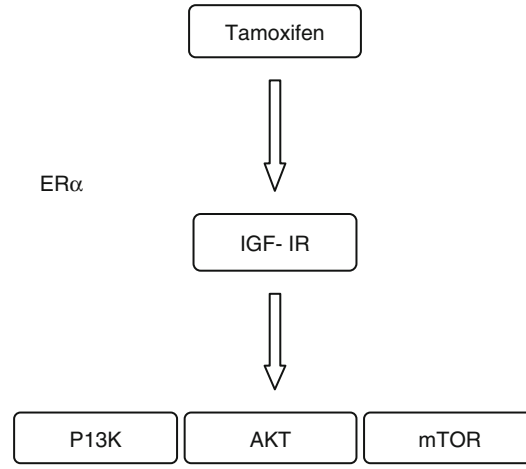

Fig. 41.1 Insulin-like growth factor signaling in endometrial carcinoma exposed to tamoxifen

40 %. Development of endometrial cancer is time and dose dependant. Prolonged tamoxifen intake more than 35 g seems to be associated with increased risk of endometrial cancer, and a substantial number is constituted by type II endometrial cancer. These are found to be p53 positive and ERα, PRα, and PR β negative [13]. Tamoxifen also has been proposed to interact with ERα in endometrium to induce insulin-like growth factor I (IGF-I) signaling via IGF-I R, thereby activating P13K/AKT/mToR pathway. This protein expression may lead on to development of targeted therapies in this group of patients [14].

The most common endometrial abnormality associated with tamoxifen is endometrial polyp (Fig. 41.1). These polyps are usually large and characterized by combination of cystically dilated glands, metaplasia, and stromal decidualization. The extensive stromal fibrosis causes difficulty in hysteroscopic resection. Malignant changes were seen in 3–7 % of these polyps. The reported incidence of endometrial hyperplasia in patients on tamoxifen is mainly from sonographic findings, and there is discordance between endometrial thickness and histopathology. Recurrent endometrial polyps are reported in association with tamoxifen exposure [15].

Histopathological review of endometrium in 700 patients who had 20 mg tamoxifen for mean of 4 years showed 4.7 % endometrial carcinoma, 8 % hyperplasia, 12.9 % polyps with atypical hyperplasia, and 23% benign polyp [16].

Tamoxifen may exert variable effects at different parts of endometrium. An individual patient can have atrophic, hyperplastic, and malignant areas in the endometrium. Even though office endometrial biopsy is the diagnostic tool for endometrial hyperplasia, false-negative rate may be high in tamoxifen patients because of heterogeneous changes in the endometrium. This leads to the argument for hysteroscopy or dilatation and curettage for these patients. Endometrial polyps associated with tamoxifen are usually translucent edematous, and more fibrotic with metaplastic changes of epithelial component. The incidence of endometrial pathology is higher in symptomatic patients than asymptomatic patients.

Most of the literature regarding side effects of tamoxifen is from Western countries. But there are limited data regarding safety and adverse effect profile in Indian population. Tamoxifen seems to have less carcinogenic potential in eastern Indian women. In a report from Chittaranjan National Cancer Institute, Kolkatta, none of the 3000 patients that received tamoxifen developed endometrial cancer [17]. A retrospective analysis of 65 breast cancer patients with tamoxifen with endometrial histology from Regional Cancer Centre, Thiruvananthapuram, showed 7 endometrial polyps, 5 atypical hyperplasias, 3 simple hyperplasias, and 8 endometrial malignancies including two carcinosarcomas (unpublished data). These patients were either symptomatic with abnormal vaginal bleeding or had sonography detected thickened endometrium. Of the 8 patients who had endometrial malignancy, 5 (62.5 %) patients had tamoxifen exposure of more than 48 months and seven were symptomatic with abnormal vaginal bleeding (unpublished data).

Gynecological Surveillance

Gynecologic surveillance in patients on tamoxifen still remains an area of concern among physicians in spite of various recommendations. Since the early 1990s various case series and reports have been published on the role of transvaginal ultrasound and endometrial sampling as screening to reduce the incidence of endometrial carcinoma. Two prospective randomized studies concluded that endometrial biopsy or transvaginal ultrasound is not warranted in patients on tamoxifen who are asymptomatic [18, 19]. The study by Barakat et al. [18] included 111 pre- and postmenopausal patients on tamoxifen with median age of 50 years. They underwent a total of 635 endometrial biopsies with an average of 5.8 per patient. 86 % of the samples were benign and 12 % were insufficient sampling which was considered as atrophic endometrium. Unnecessary surgical interventions and the costs associated are not justified when compared to the incidence or prognosis of tamoxifen-associated endometrial cancer.

The role of ultrasonography followed by endometrial biopsy in detecting tamoxifen-induced endometrial abnormalities has been examined in various studies. In a study by Kedar et al., ultrasonography was done in 111 asymptomatic patients who were randomized to receive 20 mg tamoxifen or placebo. The mean endometrial thickness was 9.1 and 4.8 mm, respectively. The incidence of premalignant and malignant changes was 16 %. The author concluded that endometrial thickness more than 8 mm was associated with 100 % positive predictive value for endometrial abnormalities [20]. In contrast Cohen et al. reported inadequate or normal endometrial tissue in 92 % patients on tamoxifen [21]. In the article by Gilber et al. [19], the role of transvaginal sonography (TVS) was evaluated in postmenopausal breast cancer patients. They also could not demonstrate TVS as a useful screening tool for asymptomatic patients. The poor correlation between ultrasonographic endometrial thickness and histology in asymptomatic patient is due to subepithelial stromal hypertrophy. In spite of thickened endometrium on ultrasonography, most women receiving tamoxifen have atrophic endometrium on biopsy. Hence there is no role for evaluation of endometrium by ultrasonography or endometrial biopsy in asymptomatic patients on tamoxifen.

Another imaging modality which may be used is sonohysterography. Sonohysterography has got improved sensitivity over ultrasonography in detecting endometrial abnormalities whenever evaluation is necessary [22]. It is useful in detecting endometrial polyp which is very common among these patients.

Detection of high-risk group by pretreatment evaluation of endometrium has been tested in some studies. There was an 18-fold increase in risk for developing atypical hyperplasia in patients who had pretreatment lesion. Another study by Cheng et al. showed 67 % of symptomatic patients had pathologic finding with 19 % having premalignant or malignant changes. Hence they recommend aggressive evaluation of symptomatic patients [12]. Office endometrial biopsy is the procedure of choice. But if report is negative, hysteroscopy and biopsy should be done to exclude any pathology.

Recommendations for Endometrial Evaluation

There is no evidence-based recommendation for endometrial evaluation in patients taking tamoxifen. According to ACOG (American College of Association), there is no increased risk for endometrial cancer in premenopausal patients taking tamoxifen, and hence they do not need extra gynecological evaluation apart from routine care. Annual gynecological examination is needed for postmenopausal patients. Postmenopausal patients should be monitored for symptoms. Patients should be educated to report to gynecologists whenever they develop symptoms like bleeding or abnormal vaginal discharge. Such patients should be investigated for any endometrial abnormalities. If the patient develops atypical endometrial hyperplasia, the continuation of tamoxifen should be reviewed. Hysterectomy should be done in case of further continuation of tamoxifen.

Key Points

1. Hormone therapy remains as an integral part of treatment in the hormone receptor-positive breast cancer.
2. Tamoxifen, a selective estrogen receptor modulator, is the most common drug used as adjuvant treatment and in metastatic disease.
3. The risk of endometrial cancer in women taking tamoxifen for 5 years is two to threefold than the age-matched population.
4. Risk of endometrial cancer is increased in postmenopausal patients on tamoxifen, not in premenopausal group with tamoxifen exposure.
5. The risk of endometrial cancer is greatly outweighed by the reduction in breast cancer mortality.
6. Symptomatic patients need to be investigated for endometrial abnormalities.

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Part VII

Palliative Care

Palliative Care and End of Life Options for Patients with Endometrial Cancer

42

Angelique Wong and Suresh Reddy

Introduction

Palliative care is an approach that improves the quality of life of patients and their families facing the problem associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial, and spiritual [1]. As such, palliative care is a complex specialty that emphasizes the need to provide early, effective symptom management to patients with serious illnesses and can be implemented and integrated at any point in the disease trajectory, not just at the end of life.

For patients with advanced disease, pain is intense, frequent, and debilitating. For instance, pain affects 70–90 % of patients with advanced cancer [2]. However, Fisch [3] reports pain is undertreated in the majority of those cases, especially among minorities. It is important to recognize that pain is rarely an isolated problem. Patients with advanced illness typically suffer from multiple concurrent symptoms, which include depression, anxiety, delirium, dyspnea, and fatigue [4].

Pain associated with gynecologic cancer can be severe, may limit potentially curative treatment of the malignancy, and often impairs quality of life. Thus, palliative care can be of benefit to patients with gynecologic cancer.

Pain Syndromes in Gynecologic Cancers

The International Association for the Study of Pain has defined pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage." [5]. As such, pain is one of the most common complaints for which a patient seeks help from clinicians. Currently, 1.5 billion people worldwide suffer from chronic pain. In patients with advanced cancer, pain is the primary symptom affecting 80–90 % of patients [2]. In palliative medicine, pain can be severely debilitating and devastating and sometimes financially burdensome.

Spiritual Pain and Total Pain

Dame Cicely Saunders created the concept "total pain" to describe the all-encompassing nature of pain within a "whole-person" framework.

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This concept conveys how pain has multiple dimensions – the physical aspect, the social aspect, the psychological aspect, and the spiritual aspect – and how these aspects interact and affect all aspects to manifest as suffering. Spiritual pain exists in the form of religious conflict, existential distress, and even loss of personhood. Identifying and addressing each aspect of pain is essential in developing a proper pain regimen, as analgesic therapies are often insufficient.

Causes and Types of Pain

As in all types of cancer, pain can be attributed to one or several causes (Table 42.1).

Types of Pain

Pain can be separated into two categories by pathophysiology: nociceptive pain and neuropathic pain.

Table 42.1 Causes of pain

Disease related
Neuropathy secondary to uncontrolled diabetes mellitus
Tumor infiltration and nerve impingement
Gynecologic malignancy-specific pain syndromes
Lumbosacral plexopathy
Pelvic pain
Malignant psoas syndrome
Treatment related
Radiation-induced pain (e.g., proctitis, pain from fistulas, mucositis, esophagitis)
Postsurgical pain syndromes (e.g., following amputation, mastectomy, thoracotomy)
Post chemotherapy pain (e.g., chemotherapy-induced painful peripheral neuropathy, myalgia, and arthralgia)
Preexisting pain
Chronic and/or preexisting pain (e.g., fibromyalgia, low back pain, postherpetic neuralgia, osteoarthritis)
Psychosocial pain
Spiritual pain (e.g., pain deep within the soul)
Total pain (e.g., the suffering that encompasses all of a person's physical, psychological, social, spiritual, and practical struggles)

Nociceptive Pain

Somatic pain is often well localized, usually to the skin, bone, muscle, or other soft tissues. It is usually associated with tenderness or swelling and can be described as sharp, gnawing, and aching.

Visceral pain is vague and not well localized but may be referred to a distant structure. Visceral pain is caused by activation of pain receptors in the chest, abdomen, or pelvic areas via stretching, ischemia, inflammation, or invasion of an organ. Visceral pain is often described as deep, squeezing, aching, dull, or sickening.

Neuropathic Pain

Neuropathic pain is caused by damage or disease affecting any part of the nervous system, central or peripheral. Neuropathic pain has two components: an epicritic or sharp lancinating component and a protopathic or chronic burning component. As such, neuropathic pain is often described as burning, tingling, electrical, pinching, stabbing, sharp, shooting, or pins and needles.

Time Course of Pain

Another way to classify pain is by timing and duration. Pain can be either acute or chronic. Acute pain occurs after trauma via nociceptive activation at the site of tissue damage and typically lasts for hours to days while the injured tissue heals. Chronic pain exceeds the expected time frame for healing and is typically perpetuated by factors other than the cause of pain.

Assessing Pain

The first step in devising a therapy plan is to obtain a thorough pain history and perform a physical assessment in order to determine the proper pain syndrome and select the most appropriate analgesic agents. When standard pharmacologic therapies are ineffective or produce unacceptable,

unmanageable adverse effects, interventional techniques are warranted. Clinicians must be aware of common concurrent emotional and physical symptoms as well as management techniques and available resources.

In order to formulate an effective therapeutic strategy, the different dimensions of pain need to be assessed, including the etiology of pain, the quality and intensity of pain, how pain affects daily activities and function, and barriers to pain management. An astute clinician must differentiate between the different causes and types of pain using history and physical and other available tools, including nonverbal cues and body language, radiologic imaging, and various pain scales. Pain is a complex and subjective syndrome. There are many tools to measure pain, including visual analog scales, verbal digital scales, numerical rating scales, or more complex pain questionnaires [6]. Other tools include the Brief Pain Inventory, Wisconsin Brief Pain Questionnaire, the Wong-Baker Faces Scale, and the Edmonton Symptom Assessment System (Fig. 42.1).

Managing Pain

Once pain has been thoroughly assessed, relief can be obtained through use of available analgesic agents appropriate for that specific pain syndrome.

Pharmacological and Nonpharmacological Treatment Options

Given the complexity of pain as a syndrome, no one treatment may effectively treat pain. The delicate balance of achieving relief yet minimizing side effects must be successfully met. Careful patient selection and a thorough assessment of pain should precede the decision to initiate a trial of opioids and/or nonopioid analgesics.

Opioids and Nonopioids for Pain Management and Addressing Their Side Effects

Opioids are commonly used in the treatment of cancer pain as recommended by the World Health Organization analgesic ladder for cancer pain [7]. Opioids have been shown to be slightly more effective in relieving pain and improving function in patients with various forms of chronic non-cancer pain as compared to placebo in a meta-analysis of 41 randomized trials [8]. There are low-potency and high-potency opioids as listed in Table 42.2. Guidelines such as those put forth by the World Health Organization (WHO), the National Comprehensive Cancer Network (NCCN), and American Cancer Society (ACS) exist as a systematic approach to guide treatment tailored to the individual patient and pain syndrome. Please refer to Fig. 42.2 for the WHO model. The most commonly used short-acting opioids are morphine, hydromorphone, oxycodone, oxymorphone, and fentanyl. Common side effects of opioids as well as their management are listed in Table 42.3.

Fentanyl is unique in that it is semisynthetic and highly lipophilic; its rapid onset and relatively short duration of action make it a good choice for control of acute pain and breakthrough pain. Methadone is a completely synthetic opioid agonist and an N-methyl-D-aspartate (NMDA) antagonist with unique pharmacodynamics and pharmacokinetic properties that make it a potent weapon against pain unrelieved by other potent opioids.

Much controversy exists over the use of opioids as it is not without risk. Side effects of opioids can include hyperalgesia, constipation, nausea and vomiting, somnolence, and opioid-induced neurotoxicity such as myoclonus, delirium, and hallucinations. Even more controversy surrounds the use of methadone given the possibility of prolonged QTc intervals; however, there is limited evidence regarding the efficacy or safety between methadone and placebo, other opioids, or other analgesics. Some studies have shown no prolongation of QTc interval in patients taking methadone in the palliative care setting [9, 10].

Edmonton Symptom Assessment System:
Numerical Scale
Regional Palliative Care Program

Please circle the number that best describes:

No pain	0	1	2	3	4	5	6	7	8	9	10	Worst possible pain
Not tired	0	1	2	3	4	5	6	7	8	9	10	Worst possible tiredness
Not nauseated	0	1	2	3	4	5	6	7	8	9	10	Worst possible nausea
Not depressed	0	1	2	3	4	5	6	7	8	9	10	Worst possible depression
Not anxious	0	1	2	3	4	5	6	7	8	9	10	Worst possible anxiety
Not drowsy	0	1	2	3	4	5	6	7	8	9	10	Worst possible drowsiness
Best appetite	0	1	2	3	4	5	6	7	8	9	10	Worst possible appetite
Best feeling of wellbeing	0	1	2	3	4	5	6	7	8	9	10	Worst possible feeling of wellbeing
No shortness of breath	0	1	2	3	4	5	6	7	8	9	10	Worst possible shortness of breath
Other problem	0	1	2	3	4	5	6	7	8	9	10	

Patient's Name _____

Date _____ Time _____

Complete by *(check one)*
☐ Patient
☐ Caregiver
☐ Caregiver assisted

Fig. 42.1 Edmonton symptom assessment scale (ESAS) (Reproduced with permission from Elsayem A, Driver LC, Bruera E. The MD Anderson Palliative Care Handbook. Houston, TX: MD Anderson Cancer Center, 2002)

As such, caution must be used when deciding to use methadone, carefully weighing risks and benefits of the use of methadone in the palliative care setting. Methadone will be available in India in the future.

Nonopioids including acetaminophen, nonsteroidal anti-inflammatory medicines, and adjuvant therapies such as anticonvulsants, antidepressants, local and topical anesthetics, and corticosteroids have also been effective in pain relief. Nonopioids can be the primary treatment for mild pain or an adjuvant therapy to opioid therapy for moderate to severe pain [1]. Tables 42.4 and 42.5 list common adjuvant therapies

Interventional Procedures

In cases where standard analgesic therapies have proven refractory or in very specific cases where specific nerves have been injured, interventional procedures may offer some relief. Various types of peripheral nerve/plexus blocks such as intercostal nerve block, celiac plexus, hypogastric, ganglion impar block, or other interventional procedures such as vertebral augmentation, spinal cord stimulation, intrathecal drug delivery system, and radiofrequency ablation have been shown to be helpful (see Box 42.1). Neurosurgical procedures can offer yet another form of pain relief, including rhizotomy, chordotomy, myelotomy, and motor cortex stimulation [11]. Additionally, physical therapy in patients with musculoskeletal pain can enhance exercise tolerance and aid in rehabilitation and possibly restore function.

Table 42.2 Low-potency opioids and high-potency opioids

Low-potency opioids	High-potency opioids
Tramadol	Morphine
Codeine	Hydromorphone
	Oxycodone
	Oxymorphone
	Hydrocodone
	Fentanyl
	Methadone

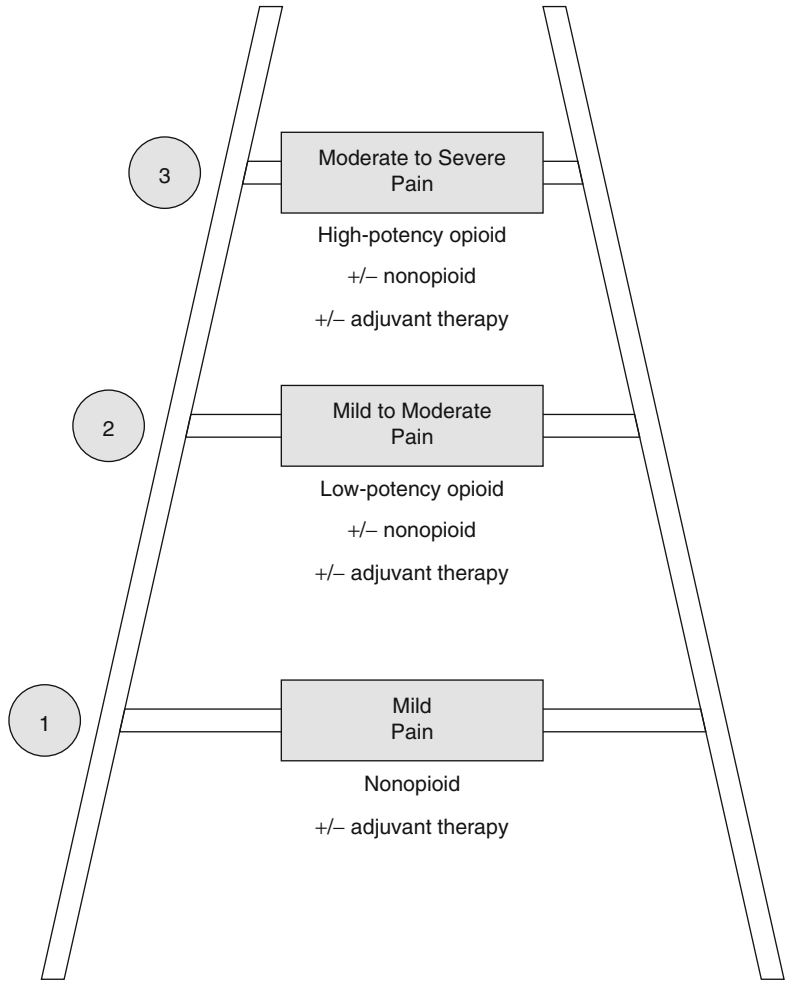

Fig. 42.2 World Health Organization (WHO) three-step ladder oral analgesic program for managing cancer pain

Table 42.3 Common side effects of opioids

Side effect	Cause	Management
Sedation	Most commonly excessive dosing	Downward titration of dose to level of analgesia Add an adjuvant If refractory, may consider stimulant (i.e., methylphenidate)
Tolerance	Reduction in effectiveness of central or peripheral opioid activity despite attempts at dose escalation	Reevaluate etiology of pain Rotation of opioids is usually necessary
Nausea and vomiting Compounded by decreased GI peristalsis in advanced malignancy secondary to circulating inflammatory cytokines and mediators	Direct effect of decreasing gastrointestinal motility Indirect effect of constipation	Metoclopramide works via multiple mechanisms centrally and peripherally to antagonize opioid effects at the central chemoreceptor trigger zone and the GI tract May also consider corticosteroids and neuroleptics such as haloperidol In special cases, diphenhydramine, serotonin antagonists, prochlorperazine, or neurokinin-1 antagonist may help
Constipation Watch for masquerading signs such as intractable nausea and vomiting, increased abdominal pain, delirium, anorexia, and/or overflow diarrhea	Directly caused by opioids	This may develop very slowly Thus, start a regular laxative regimen from the initiation and throughout the duration of opioid therapy Use a bowel stimulant (senna) and a softening agent (polyethylene glycol) For severe cases, osmotic laxatives and bowel lavages can be used Caution: Constipation may also be due to ileus, intestinal obstruction, or spinal cord compression. A simple abdominal x-ray may be helpful to delineate further etiology
Cognitive impairment Hallucinations may occur	Rule out other causes first before implicating opioids Sepsis, leptomeningeal disease, brain metastases, metabolic abnormalities, chemotherapy, antifungal therapy, radiation, hepatic encephalopathy, psychotropic medications	If opioid-induced cognitive impairment is suspected, the first step is to lower the dose, which can be diagnostic Do not add medications to treat agitation or other symptoms without this step May also rotate opioids If ineffective, add haloperidol or another neuroleptic
Urinary retention Relatively rare	More likely to occur in patients at extremes of ages or in conjunction with anticholinergic medications	Temporary catheterization Tolerance usually develops
Myoclonus	Dose-dependent phenomenon related to opioid metabolites, more often those of morphine and meperidine Results from central motor excitability Usually a sign that a patient's level of tolerance has been overwhelmed	Dose adjustment may stop symptom Sometimes, opioid rotation is required Temporary addition of benzodiazepine may be necessary

Table 42.3 (continued)

Side effect	Cause	Management
Respiratory depression Rare occurrence in patient on chronic opioid therapy	Can occur in accidental overdose Can be due to the addition of another sedative agent, such as benzodiazepines	If respiratory function is not significantly impaired, temporary discontinuation and restarting at a lower dose is recommended If severe respiratory compromise has occurred, give naloxone in 40 mcg increments until response occurs. Be wary of acute opioid withdrawal
Pruritus	Mechanism is not well understood Peripheral histamine release occurs Central action of mu-opioid receptors also contribute to phenomenon	H2 antagonists such as ranitidine may be beneficial However, centrally mediated pathways are more difficult to treat Opioid rotation may be necessary Naloxone reversal should be reserved for only severe cases

Table 42.4 Adjuvant therapies

Adjuvant	Use
Acetaminophen	Headache Musculoskeletal pain
Nonsteroidal anti-inflammatory drugs (NSAIDs) Ibuprofen Ketorolac	Musculoskeletal pain
COX-2 inhibitors Celecoxib	Musculoskeletal pain
Tricyclic antidepressants (TCAs) Nortriptyline Amitriptyline	Neuropathic pain syndromes
Anticonvulsants Gabapentin Carbamazepine Pregabalin Lamotrigine	Neuropathic pain syndromes Postherpetic neuralgia Phantom pain Nerve plexopathies (brachial, lumbosacral)
Lidocaine	Systemic administration can help with neuropathic pain and phantom pain with a predominance of central features
Ketamine	NMDA receptor antagonist usually used in cases of extreme opioid tolerance
Capsaicin	Topical cream form is used for neuropathic pain

Box 42.1: Useful Interventional Procedures

Nerve blocks

- Visceral blocks
  - Sympathetic blocks (i.e., celiac plexus/splanchnic block for abdominal visceral pain)
- Somatic blocks
  - Psoas compartment block
- Subarachnoid neurolytic block for extremity and thoracic wall pain

Spinal opioid therapy – for neuropathic or plexopathy pain

- Epidural opioids
- Intrathecal opioids
- Implantable programmable pumps

Neurosurgical procedures

- Rhizotomy (ablation of dorsal root fibers), more useful for perineal lesions
- Chordotomy (interruption of spinothalamic tracts) for intractable lower extremity pain
- Vertebroplasty (injection of cement into a vertebral body) for metastatic spinal pain involving one or two vertebrae
- Myelotomy (ablation of nociceptive fibers crossing to the opposite spinothalamic tracts) for intractable unilateral nociceptive pain

Table 42.5 Common side effects of opioids

Side effect	Cause	Management
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Table 42.5 (continued)

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Pruritus	Mechanism is not well understood Peripheral histamine release occurs Central action of mu-opioid receptors also contributes to phenomenon	H2 antagonists such as ranitidine may be beneficial However, centrally mediated pathways are more difficult to treat Opioid rotation may be necessary Naloxone reversal should be reserved for only severe cases

Alternative and Complementary Medicine

Complementary and alternative medicine measures should be considered for symptom management as per patients' preferences or when there are limited treatment options. Complementary and alternative measures for pain management include music therapy, massage therapy, healing touch, Reiki, acupuncture, and herbal remedies. Music therapy has been shown to reduce pain scores in hospitalized palliative care patients [12, 13]. The mind and body play an important role in pain management. In chronic pain, depression, anxiety, fear, and stress can amplify pain sensation. Techniques such as biofeedback, cognitive behavioral therapy, meditation, and relaxation techniques offer a mind-body approach to the control of pain [14].

Role of the Multidisciplinary Team

As pain is a complex syndrome, a multidisciplinary approach is vital to therapy. Distress caused by pain, both physical and spiritual, can only be addressed through a multidisciplinary approach that focuses on depression, anxiety, spirituality, and faith. By taking into account all these aspects, only then can a thorough assessment of pain and suffering be done. The multidisciplinary team includes members such as a counselor, psychologist, social worker, chaplain, physical therapist, occupational therapist, and pharmacist.

Other Non-Pain Symptoms in Palliative Care

Fatigue

Fatigue is the most common symptom in palliative care and can significantly affect quality of life of patients receiving palliative care. Fatigue has multiple etiologies and contributing factors, and, therefore, a thorough history and physical are crucial to identify any reversible cause before initiating pharmacologic therapies such as glucocorticoid and/or psychostimulants. There is limited data to support any one pharmacologic approach to fatigue [15]. Nonpharmacologic approaches such as moderate exercise, yoga, and cognitive behavioral therapy are beneficial as well.

Gastrointestinal Symptoms

Nausea With or Without Vomiting

Identifying and correcting any reversible underlying causes is the first step. Please refer to Table 42.6 for broad categories and examples.

Table 42.6 Common causes of nausea in palliative care

Toxic/metabolic	Disorders of the viscera	CNS causes
Drugs Chemotherapy Opioids NSAIDs Antibiotics SSRIs Substance abuse	**Obstruction** Small bowel Gastric outlet **Tumors of the GI tract and thorax**	**Increased intracranial pressure** Brain mass Hemorrhage
Metabolic Hypercalcemia Uremia Hyponatremia Liver failure	**Constipation**	**Vestibular** Labyrinthitis
	Gastroparesis	
	Inflammation/irritation NSAIDs Chemotherapy Abdominal infection Radiation	**Anxiety**

In patients with inoperable malignant bowel obstruction who are not candidates for a colonic stent and/or venting gastrostomy (in whom prokinetic agents are contraindicated), dexamethasone and haloperidol are the drugs of choice. In addition, medications that may decrease gut motility and the production of gastrointestinal secretions such as octreotide and glycopyrrolate may also help to further control nausea and vomiting [16].

Otherwise, in patients where a reversible cause cannot be identified and bowel obstruction is ruled out, metoclopramide is used empirically [17] and is helpful due to its central antiemetic and peripheral gastric emptying effects.

Constipation

If a reversible cause cannot be identified and modified, symptomatic treatment is appropriate. Senna, a peristaltic stimulant, may be started initially and titrated (maximum 70–100 mg/day) to daily soft bowel movements. Two studies [18, 19] were not able to demonstrate additional benefit when adding docusate with senna for the treatment of constipation. Other pharmacologic treatments include osmotic laxatives (lactulose, sorbitol, polyethylene glycol, magnesium hydroxide, magnesium citrate) and enemas (e.g., with soapsuds, mineral oil, or milk and molasses), and/or suppositories may be indicated for distal fecal impaction or if a patient has not had bowel movement for 3 days or more. Patients with refractory opioid-induced constipation may benefit from the use of methylnaltrexone, but it requires parenteral administration

Xerostomia

Dry mouth is a common symptom that can alter taste and made eating and swallowing difficult. Etiologies include radiotherapy, chemotherapy, dehydration, oral infections, and drugs (i.e., opioids, anxiolytics, and antihistamines). Frequent oral hygiene is the first step in treating xerostomia. Sipping and rinsing with cold water, sucking on ice chips, and chewing sugarless gum to increase salivation may provide comfort and relief. In severe cases, artificial saliva may be helpful.

Cachexia-Anorexia

Cachexia is a hypercatabolic state defined as accelerated loss of skeletal muscle in the context of a chronic inflammatory response. This can occur in the setting of cancer as well as chronic infection such as in acquired immunodeficiency syndrome (AIDS). Anorexia, defined as loss of appetite, is common among cancer patients as is weight loss; however, the profound weight loss that occurs in patients with cachexia cannot be entirely attributed to poor caloric intake. Patients with profound anorexia should be given permission to eat less with small, frequent, calorie-dense meals instead of two or three large meals with

emphasis on the pleasure of tasting food and the social aspect of partaking in meals with family.

Artificial nutrition and hydration may be helpful in a highly selected patient population, such as those with malignant bowel obstruction but with a prolonged life expectancy; however, the majority of patients in the terminal phase of advanced cancer experience reduced oral intake before death either due to lack of desire to eat or because they are unable to consume sufficient nutrients due to anorexia, nausea, vomiting, gastrointestinal obstruction, dysphagia, generalized weakness, or impaired cognition. For terminally ill patients, there is no evidence to support that artificial nutrition prolongs life or improves function [20].

Depression

Depression is the most common mental health problem in palliative medicine and is often misdiagnosed and undertreated. The first step is identifying any uncontrolled symptom and treating it, such as pain. Supportive psychotherapy should be started and may be sufficient in treating depression in cancer patients [21]. In advanced cancer patients, psychostimulants are preferred as they have a rapid onset of antidepressant action as compared to selective serotonin reuptake inhibitors (SSRIs) which may take weeks to be effective [22–26].

Delirium

Delirium is the most common neuropsychiatric complication in advanced cancer patients and can cause severe distress in patients, family members, and healthcare providers [27, 28]. Reversible causes should be identified such as infection/sepsis, brain tumor, opioid-induced neurotoxicity, cancer treatments (chemotherapy), psychotropic drugs, metabolic derangements (dehydration, hypercalcemia), and substance abuse/withdrawal. Haloperidol is the drug of choice, especially if hallucinations, delusions, and psychomotor agitation are present [29].

Dyspnea

In patients with advanced cancer and no underlying cardiopulmonary pathology, the sensation of dyspnea is likely due to increased ventilator demand (due to pleural effusion and/or lung metastases), impaired mechanical ventilation (due to muscle weakness and fatigue from cachexia), or both. Dyspnea is defined solely by the patient, as objective measures such as oxygen saturation and respiratory rate may not correlate to the patient's perception of dyspnea. Systemic opioids, corticosteroids, and sometimes anxiolytics are helpful in treating breathlessness [30]. Breathing training as well as relaxation techniques and cool air blowing are also effective treatments. Hypoxemic patients may benefit from oxygen supplementation [31].

Insomnia

Sleep disturbance is a common problem among advanced cancer patients. About 70 % of palliative care patients suffer from insomnia-related symptoms [32].

Addressing symptoms that could be contributing to insomnia (such as pain) is first line, and removing stimulating agents such as corticosteroids may be helpful. Nonpharmacologic interventions are then warranted such as addressing environmental factors, lifestyle modifications, and increasing physical activity during the day to establish a healthy sleep-wake cycle. Patients with advanced illness may be particularly sensitive to pharmacologic sleep aids and their side effects; thus, these should be used at the lowest effective dose and with caution.

Lymphedema

Lymphedema can be caused by cancer treatment (surgery, radiotherapy), venous obstruction, hypoalbuminemia, decreased mobility, fluid retention, and medications such as corticosteroids and can cause distress among cancer patients due to distress, discomfort, and decreased range of motion and mobility.

In patients with refractory lymphedema in the palliative care setting, few data offer guidance regarding management which includes manual lymphatic draining, compression therapy, exercise, complete decongestive therapy, and simple elevation of extremity and good skin care. A systematic review [33] concluded that specific therapeutic interventions were rated in the category of "effectiveness not well established."

Disease-Driven Symptoms in Endometrial Cancer

Endometrial cancer may recur regionally within the pelvis or in distant sites, including the lung, bone, liver, and brain. Complications from pelvic or intra-abdominal disease progression are managed according to the general principles outlined for all gynecologic malignancies. Recurrence in other sites warrants symptom-driven intervention.

Bone Metastases

The incidence of bone metastases in endometrial cancer is <1 % [34]. Bone metastasis can cause severe pain, compromise the spinal column or nerve roots, lead to fracture, and contribute to hypercalcemia. Focal external beam radiation directed at metastasis can prevent and alleviate impending spinal or nerve root injury [35]. Fractures or impending fractures of the femur require orthopedic surgical fixation to stabilize the weight-bearing structure followed by postoperative radiotherapy. Pain can also be managed with use of bisphosphonates [36].

Hypercalcemia

Hypercalcemia may occur with bone metastases or as a paraneoplastic phenomenon. Common symptoms of hypercalcemia include fatigue, delirium, obtundation, anorexia, pain, polyuria, polydipsia, dehydration, constipation, nausea, and vomiting. Cardiac dysrhythmias and cardiac arrest and coma may result. Symptoms are often reversed with treatment of hypercalcemia, which includes restoring volume, increasing calcium excretion, and inhibiting osteoclastic release of calcium. Intravenous hydration is the first step. Administering bisphosphonates and calcitonin inhibits osteoclastic activity. Bisphosphonates are commonly used because of their ease of administration, relatively long duration of action, and effectiveness throughout multiple treatments.

Hepatic Metastases

Liver metastases are usually asymptomatic and are frequently discovered after other metastatic sites have become manifest. There is a potential role for systemic chemotherapy for pulmonary or hepatic spread of disease, but response rates are generally low. Hepatic metastases can cause pain when the liver becomes enlarged, causing liver capsule distention. Analgesics, regional nerve block, and whole-liver radiotherapy can offer relief.

End of Life Care

The abovementioned symptoms occur more frequently and at more distressing levels in the weeks or months before death. A palliative care specialist can help manage these symptoms to help alleviate distress in patients and their family members to improve quality of life.

The Last Hours of Life

In the last hours of life, cognition and physical function suffer a great decline. Patients and families are often unaware of signs and symptoms of impending death. Clinicians should explain this expected decline before these changes occur to prevent excessive distress. Increased airway secretions may worsen dyspnea and cause coughing

spells. In the last stages of life, gurgling and crackling sounds due to excessive secretions may cause distress to family members. Clinicians should explain this phenomenon and reassure the family members as well as use techniques such repositioning and sometimes pharmacologic interventions like anticholinergics.

For patients at the end of life where symptoms are intractable despite standard treatment, palliative sedation may be considered as a last resort to alleviate severe symptoms. Palliative sedation is most commonly used for agitated delirium and must be cautiously used in a closely monitored setting.

Physical Signs of Impending Death

Hui et al. [37] identified five highly specific signs associated with death within 3 days among cancer patients in a prospective multi-institutional study in which the presence or absence of 10 physical signs was documented every 12 h from admission to death or discharge for 357 patients with advanced cancer who were admitted to two palliative care units. These signs included pulselessness of the radial artery, respiration with mandibular movement, decreased urine output, Cheyne-Stokes breathing, and death rattle. However, sensitivity was limited; these signs were present in fewer than 27 % of the patients who died.

Conclusion

Palliative care can help relieve pain and suffering in patients with endometrial cancer and especially in those whose disease has progressed or recurred or those who are nearing the end of life. Palliative care can also help to support family members of patients with life-threatening illness as patients proceed along the disease trajectory. Physician and philosopher Albert Schweitzer once said, "We must all die. But if I can save him from days of torture, that is what I feel is my great and ever new privilege. Pain is a more terrible lord of mankind than even death itself."

Key Points

1. Palliative care should be integrated early in the disease trajectory to aggressively control symptoms.
2. Palliative care can be introduced when the goal of treatment is no longer curative.
3. Pain is the most distressing symptom feared by patients and families.
4. Pain should be thoroughly assessed as it is multifactorial and multidimensional, including not only a physical/nociceptive aspect but also psychological, spiritual, and social aspects.
5. The mainstay of cancer-related pain management is opioids.
6. Open and regular communication between patients/families and healthcare professionals at the end of life is crucial to achieve adequate symptom control.
7. Family conferences can often facilitate communication between patients and their caregivers.
8. Healthcare professionals should explain the expected changes in cognition and physical function that occur at the end of life before they occur in order to alleviate distress and prevent panic.
9. Effective treatment will successfully alleviate the majority of symptoms affecting terminally ill patients.
10. End of life care is best done in the patient's home setting.
11. A cost-effective, hands-on, low-tech approach in the home setting is preferred for patients at the end of life.

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