Ranu Patni
Editor

Current Concepts in Endometrial Cancer

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This book is dedicated to all my patients who have provided me the incentive to write about the dilemmas in managing endometrial carcinoma. Dr. Sushila Kothari, my maternal aunt, deserves a special mention as she braved this disease very positively for almost twelve years after having been diagnosed in stage IV.

Preface

Of all gynecological malignancies, endometrial carcinoma is the most consistent in presentation, easy to diagnose and has a largely favorable outcome. At the same time, it has had a turbulent evolutionary journey and the most varied management protocols across institutions and individuals. Editing a book on this challenging topic has been a very satisfying experience.

This book is a genuine venture to provide a comprehensive coverage of the "Cinderella" of gynecological cancers, i.e., endometrial carcinoma. All ten chapters in this book are written by well-known specialists having vast experience in the fields of gynecologic oncology, gynecology, pathology, etc. The experience of the authors reflects in their writing. Basics as well as current facts and evidence-based practices have been incorporated in each chapter. There is a full chapter on "minimally invasive surgery" which is fast becoming the preferred mode of treatment of this disease.

The initial chapter will take the reader through a brief account of evolving concepts over time and gives an overview of the subject. The next few chapters will focus on epidemiology, prevention, pathophysiology, and diagnostic workup. The following chapters will deal with stagewise management of this malignancy and delineate the role of minimally invasive surgery. Lastly, one chapter is dedicated to future perspectives including surgical advancements, targeted therapies, and other developments in the offing. Each chapter carries a summary in the beginning to give the reader an idea of the content to follow. Illustrations add interest and color to the text.

I sincerely hope that this book will benefit medical undergraduates, postgraduates, and students as well as practitioners of gynecologic oncology thereby contributing to successful management and better outcomes in patients suffering from endometrial carcinoma.

I wish to acknowledge and thank all the authors for their contribution to this book without which this project would not have been possible. I extend special thanks and gratitude to Dr. Hemant Tongaonkar for his consistent encouragement and to Dr. Somashekhar for his helpful advice time and again. I am also thankful to Mr. Ramcharan for drawing the illustrations for my chapter in the book. Last but not the least, I heartily acknowledge the unconditional support provided by my family especially my husband, Dr. Rajeev, and my children, Prannay and Pallavi, in this venture.

Jaipur, India — Ranu Patni

About the Editor

Dr. Ranu Patni is a prominent gynecologic oncologist with more than 15 years of experience in "gynecologic oncology." After postgraduate work in obstetrics and gynecology, her quest for clinical, surgical, and academic excellence led her to constantly upgrade her skills through trainings from reputed international and national institutions, including King George V Hospital (Sydney, Australia) and Tata Memorial Hospital (Mumbai). She has been a pioneer in establishing the concept of "gynecologic oncology" and "menopausal medicine" in the state of Rajasthan, India.

Her surgical skills are backed not only by a large number of gynecological cancer surgeries including those on many challenging endometrial cancer patients but also by very competitive long-term results. She is well known for her age-appropriate approach to individual patients and routinely adopts evidence-based fertility preservation techniques and hormonal conservation measures.

She also has a keen interest in research and dissemination of knowledge among the medical fraternity as well as the public. She has organized and participated in numerous national and international conferences/workshops, contributed chapters to books of national repute, published papers in national and international journals, and edited and peer-reviewed papers for prominent journals, is an active member of many academic societies, and has been a principal investigator in large multicentric clinical trials on "postmenopausal osteoporosis."

A unique feature of Dr. Patni's career is her passion for public health education. Over the past 20 years, she has repeatedly engaged in efforts to educate the public, especially women, about the preventive and therapeutic aspects of various health issues.

Contents

Endometrial Carcinoma: Evolution and Overview

1

Ranu Patni

The uterus with its lining, i.e., the endometrium, is a very expressive organ. It manifests its suffering through a variety of symptoms pertaining to benign as well as malignant diseases. Pathophysiological behavior of the uterus and endometrium can be aptly described as follows:

> With life in it, it grows.
> With death in it, it throws.
> But, when it weeps
> It shows, it shows, it shows!

This book focuses on one of the most dreaded maladies of the uterus originating from the endometrium, i.e., the endometrial carcinoma. This chapter will give, the reader, an overview about endometrial carcinoma with the aim of creating a will to read on in order to gain maximum possible knowledge about this condition.

According to Seibold and Wolf (1973), reproductive cancers were rare in nonhuman primates. They reported one ovarian adenocarcinoma, no endometrial carcinoma, and no breast cancers in 1065 nonhuman primate necropsies [1]. Currently, it is the fourth most common cancer in women worldwide. According to the current Surveillance, Epidemiology, and End Results (SEER) fact sheets released in April 2016 based on data review from 1975 to 2013, the number of estimated new detected cases of endometrial carcinoma in 2016 is 60,050. This constitutes 3.6 % of all new cancer cases. Similarly, the number of estimated deaths due to endometrial carcinoma in 2016 is 10,470 which is 1.8 % of all cancer deaths. Median age at diagnosis is 62 years and the median age of death is 70 years as per SEER database. Five-year survival based on statistics from the year 2006 to year 2012 is 81.7 %. The 5-year relative survival has been more or less constant over the last three or four decades

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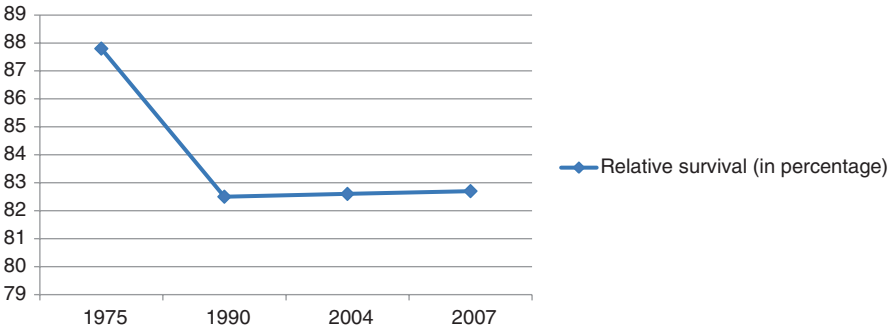

Graph 1.1 Five-year relative survival trend in endometrial carcinoma based on SEER database

Table 1.1 Number of cases and number of deaths per 100,000 persons by race/ethnicity: endometrial carcinoma based on SEER database

Race/ethnicity	Number of cases	Number of deaths
All races	25.4	4.5
White	26.0	4.1
Black	24.6	7.9
Asian/Pacific Islander	20.3	2.9
American Indian/Alaska Native	21.3	3.6
Hispanic	21.4	3.6
Non-Hispanic	25.9	4.5

(Graph 1.1). SEER database, 2016, also reiterates the old fact that the number of new cases per 100,000 persons is higher in white race (26.0) compared to black race (24.6) or Asians/Pacific Islanders (20.3) and American Indians/Alaska Natives (21.3). However, the number of deaths per 100,000 is higher in black race (7.9) compared to white race (4.1), Asians/Pacific Islanders (2.9), and American Indians/Alaska Natives (3.6) (Table 1.1). A small study comparing African-American and Caucasian patients found no clear differences in global gene expression profiles suggesting that environmental or social issues played a greater role in explaining disparity [2].

The Indian Council of Medical Research (ICMR) has published a 3-year report of population-based cancer registries (PBCRs) (2012–2014) from Bengaluru, India, in March 2016. On comparing the AARs (age-adjusted rates) per 100,000 persons, cancer of the corpus occupied the top three places in Chennai (6.0), Delhi (5.5), and Thiruvananthapuram districts (5.1). On analyzing the trends of endometrial carcinoma over time, PBCRs showed a significant increase in annual average of AARs for both three and five years in the metropolitan cities of Bengaluru, Chennai, Delhi and Mumbai.

Changing reproductive trends leading to prolonged estrogen exposure might be responsible for the increasing incidence of certain reproductive cancers in females. These include reduced age at menarche, delayed age at first pregnancy, less number of pregnancies, increased incidence of infertility, higher use of OCs/HRT, and

increased number of ovulations. However, it is not practical to divert current reproductive practices to those of our ancestors, e.g., early first birth, having more children, etc. At the same time, healthy lifestyle and dietary habits should be promoted. Evolutional and designed changes in microanatomical and hormonal milieu of human physiology need to proceed while debating their social desirability.

According to Henderson et al. (1982), women with endometrial carcinoma typically exhibit signs of high estrogen effect and higher plasma estrogen levels as compared to controls. The association of obesity with endometrial carcinoma supports this hypothesis called as "estrogen excess hypothesis" [1]. Endometrial glandular proliferation is inhibited by endogenous progesterone in premenopausal women. Endometrial proliferation is markedly reduced in premenopausal women receiving a synthetic progestin and in untreated postmenopausal women [3].

Women's Health Initiative (n = 16,608), a double-blind placebo-controlled trial, showed that after 5.6 years' median intervention and 13 years' median cumulative follow-up there were fewer endometrial carcinoma and statistically nonsignificant reduction in deaths from endometrial carcinoma in the combined hormone therapy compared with the placebo group [4].

A meta-analysis of 30 studies showed that the relative risk of ever users of unopposed estrogen therapy was 2.3 compared to nonusers, and it increased to 9.5 in users of 10 or more years [5].

The potential of anti-aromatase agents in management and the role of hormone receptors and immunohistochemical (IHC) markers in diagnosis as well as prognostication of endometrial carcinoma were also studied over a period of time.

Given the favorable responses to aromatase inhibitor therapy, as seen in women with endometrial carcinoma, these treatments may be of interest as preventive and adjunctive therapies for lesser proliferative lesions of the endometrium [6]. An overexpression of endometrial aromatase may underlie pathogenesis of endometrial polyps at least in a subset of cases [7].

Immunohistochemical analysis of endometrial carcinoma differentiating between various grades and histological types can be useful in identifying high-risk cases. Halperin et al found that the endometrioid G1–G2 cases showed increased immunoreactivity for ER, PR, and bcl-2 (85.7 %, 78.6 %, and 42.8 % respectively), and low expression of p53 (14.3 %) and HER-2/neu (14.3 %). In contrast, the serous papillary endometrial carcinoma cases showed immunonegativity for ER, PR, and bcl-2 and high immunoreactivity for p53 (81.8 %) and HER-2/neu (45.4 %). The endometrioid G3 cases demonstrated an intermediate immune profile characterized by immunonegativity for ER, PR, and HER-2/neu, low immunoreactivity for bcl-2 (7.1 %), and high expression of p53 (57.1 %) [8].

A review and meta-analysis report showed that in patients with endometrial carcinoma, higher level of ER and PR predicted favorable survival and increased level of HER2 was associated with poorer survival. All of the three hormone receptors had prognostic value for survival [9].

Precursor lesions like atypical endometrial hyperplasia (AEH) or endometrial intraepithelial carcinoma (EIC) frequently precede estrogen-related or serous endometrial carcinomas. However, prevalence of endometrial carcinoma is low (5 per

1000 women >45 years). Hence, standardized screening is not effective. At the same time, recognizing these precursor lesions and timely treatment will prevent these cancers. The American College of Obstetricians and Gynecologists (ACOG) and the Society of Gynecologic Oncology (SGO) do not recommend routine screening for uterine cancer. The American Cancer Society does recommend annual endometrial biopsies starting at age 35 for women known to have a risk for Lynch syndrome.

Timely assessment of symptomatic and high-risk patients is the key to correct diagnosis and management of endometrial carcinoma. When endometrial carcinoma was clinically staged (FIGO 1971), fractional dilatation and curettage was used to evaluate abnormal bleeding. This permitted the assessment of cervical tissue and endometrial tissue from all walls and surfaces of the uterus. Currently office endometrial biopsy has largely replaced D&C. The results of both methods correlate well and the accuracy to detect cancer is 91–99 % [10]. Hysteroscopy-guided biopsy is the standard practice used to evaluate abnormal uterine bleeding in many centers especially in postmenopausal women (Fig. 1.1). There is no substantial evidence to show that it improves the sensitivity to detect hyperplasia or cancers. Retrospective studies have suggested increased incidence of positive peritoneal cytology on hysterectomy after hysteroscopic evaluation. However, no prospective studies have been performed till date. Positive peritoneal cytology, independently, is not recognized as a stage-defining feature under the FIGO 2009 staging system [11].

There is very little role of preoperative imaging in patients with endometrial carcinoma, as surgery is essentially the same for stages 1, 2, and 3. Imaging studies have significant limitations in detecting nodal disease, which is microscopic in 90 %

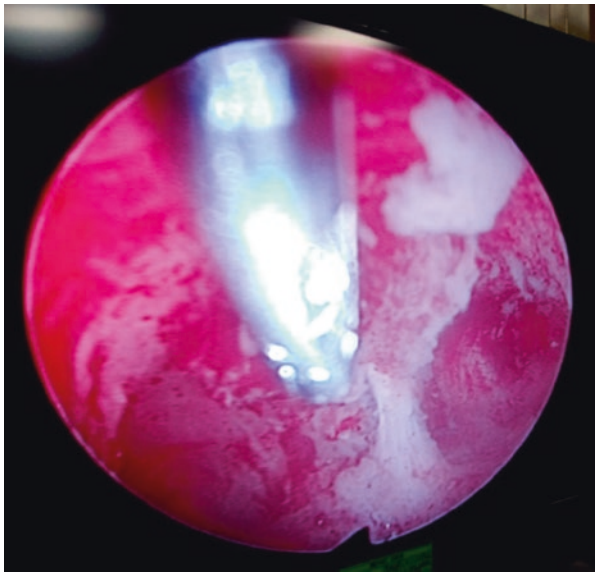

Fig. 1.1 Hysteroscopy-guided biopsy

of cases [12]. Imaging studies may be more helpful in assessing extrauterine spread in serous and clear cell carcinomas, in determining operability to some extent, and in counseling young women opting for fertility-conserving surgery. In a small prospective series by Signorelli et al., a high negative predictive value for FDG PET/CT (93 %) was shown in high-risk endometrial carcinoma patients [13]. The GOG 233 trial is an ongoing prospective assessment of PET/CT in patients with endometrial and cervical cancer. Biomarker, CA 125, may be used to predict the presence of extrauterine disease. Ideally, serum biomarkers should be tested in endometrial tissue.

The management of endometrial carcinoma has progressed from an era when pre- and postoperative radiotherapy was combined with simple hysterectomy to the present times of primary comprehensive surgical staging. The staging system given by FIGO has evolved over time from clinical staging in 1971 to surgico-pathological staging in 1988 and finally surgical staging in 2009 (Fig. 1.2). In the small number of patients in whom primary radiotherapy is given, clinical staging (FIGO 1971) is applied and noted. Standard surgical procedure includes obtaining peritoneal fluid

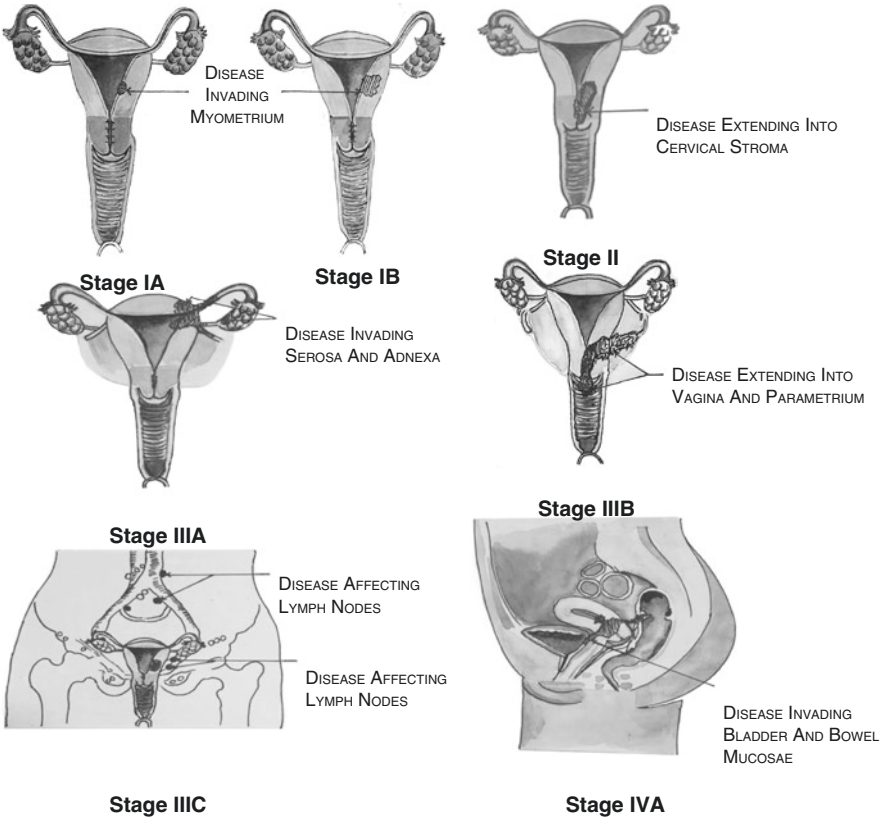

Fig. 1.2 Endometrial carcinoma: stages I to IV A

for cytology, exploring the abdomen and pelvis, biopsy/excision of suspicious extrauterine lesions, total hysterectomy with bilateral salpingo-oophorectomy, and retroperitoneal (pelvic and para-aortic) lymphadenectomy (Figs. 1.3 and 1.4). There is increasing trend of surgically reducing the disease to no residual volume like in ovarian cancer.

Minimally invasive surgery is fast becoming the standard practice especially in obese patients. In patients with severe medical comorbidity, advanced age, obesity, or inability to perform nodal dissection, vaginal hysterectomy with or without laparoscopic/robotic assistance may be done. Based on pathological features in final histopathology report, patients may be classified according to their risk of recurrence and adjuvant therapy offered to those at sufficient risk. Primary radiation

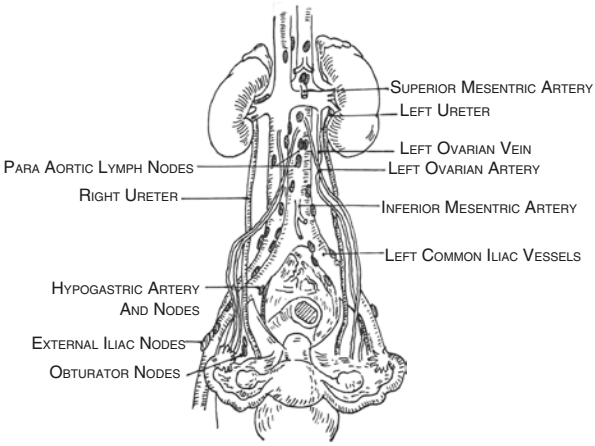

Fig. 1.3 Retroperitoneal lymph nodes

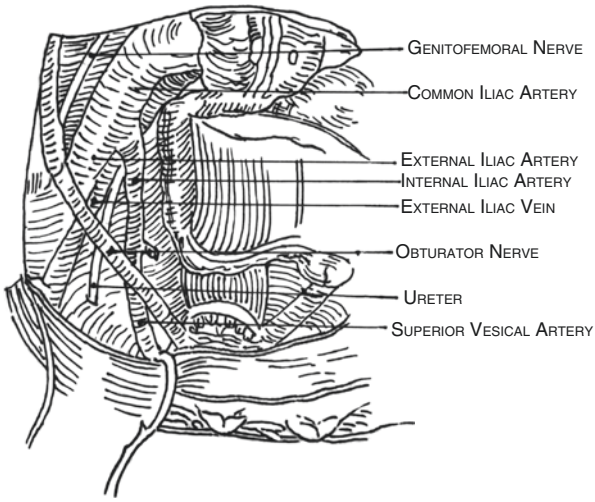

Fig. 1.4 Pelvic lymph node dissection

therapy or hormonal therapy may be used for patients not suitable for primary surgery. Progestational therapy is given in younger patients desiring fertility conservation. Radiotherapy, chemotherapy, or hormonal therapy may be given in disseminated or non-resectable disease [14].

It is indeed a challenge to identify patients who are likely to benefit from lymphadenectomy and from adjuvant therapies. Current trends suggest a less frequent use of pelvic radiation therapy or no use of any radiation [15]. The PORTEC study published in 2000 showed that postoperative radiotherapy in stage 1 endometrial carcinoma reduces locoregional recurrence but has no impact on overall survival. Radiotherapy increases treatment-related morbidity and is not indicated in patients with stage 1 endometrial carcinoma below 60 years and in patients with grade 2 tumors with superficial myometrial invasion [16]. In 2012, a Cochrane systematic review and meta-analysis published by Kong A et al. showed similar results with EBRT [17]. Continued efforts to minimize the morbidity associated with EBRT led to further research and modifications in the adjuvant radiotherapy protocol. The PORTEC 2 study showed that vaginal brachytherapy (VBT) is effective in ensuring vaginal control, with fewer gastrointestinal toxic effects than with EBRT, and VBT should be the adjuvant treatment of choice for patients with endometrial carcinoma of high-intermediate risk [18].

Also, there have been significant developments in chemotherapy in endometrial carcinoma. There is increasing use of combination chemotherapy in advanced and recurrent disease along with a promise of better outcomes in adjuvant setting. Pooled analysis of NSGO-EC-9501/EORTC 55991 and MaNGO ILIADE-III studies showed that addition of adjuvant chemotherapy to radiotherapy improves progression-free survival in operated endometrial carcinoma patients with no residual tumor and high-risk profile [19]. PORTEC 3 is an intergroup trial investigating survival improvement with adjuvant chemotherapy given during and after pelvic radiotherapy (CTRT) versus radiotherapy alone (RT) for women with high-risk endometrial carcinoma (HR-EC). Accrual was completed in December 2013. Toxicity and 2-year HRQL (health-related quality of life) results showed that CTRT for high-risk endometrial carcinoma causes significantly higher adverse events (AE) and symptom ratings and reduced HRQL during and after treatment as compared with RT, but with recovery over time, without differences in grade >/= 3AE at 2 years [20]. NCCN guidelines have updated treatment recommendations to assign a greater role to chemotherapy in primary (category 2B) as well as adjuvant setting. A section on sentinel lymph node mapping has also been included in these guidelines (NCCN guidelines version 2.2016).

The current challenge in management of endometrial carcinoma is to understand the tumor biology, utilize it to predict recurrence as well as survival, and exploit the genetic changes to define postoperative therapies with least toxicity. Targeted therapies based on molecular changes in patients with advanced or recurrent disease are currently under development in many clinical trials. These will help in individualizing therapy based on personal genotypic and phenotypic profile. P13K/AKT/

mTOR inhibitors, anti-HER-2/neu antibodies, biguanide (metformin), PARP inhibitors, etc. may hold promise in the future. It is also hoped that with evolution of understanding of molecular pathways, treatment based on histology may become available so as to provide better management and outcomes for poor prognosis endometrial carcinoma like serous carcinoma, clear cell carcinoma, and carcinosarcoma.

A Talhouk et al. have recently proposed a new system for classification of endometrial carcinoma based on molecular categories identified in The Cancer Genome Atlas (TCGA). This pragmatic molecular classification tool based on mismatch repair protein immunohistochemistry, POLE mutational analysis, and p53 IHC as a surrogate for "copy number" status can provide independent prognostic information beyond established risk factors [21].

With the background of the above evolutionary journey and overview, this book will further provide a detailed account of various aspects of endometrial carcinoma in its different chapters. "Uterine sarcoma" being a separate entity has not been covered in the text. Although "radiotherapy" and "chemotherapy" as treatment modalities have been described as appropriate, their detailed accounts are out of scope of this book.

I wish for a fruitful reading experience for the readers.

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Epidemiology and Prevention of Endometrial Carcinoma

2

Simmi Pokharna

Abstract

The objective of this chapter is to review the evidence related to the epidemiology of endometrial carcinoma and subsequent protective factors.

The majority of the cancers that occur in the body of uterus are endometrial cancers mostly adenocarcinomas. It is the fourth most common cancer in women, worldwide.

It is mainly a disease of high-income countries. Risk increases with transition from lower- to high-income economies and with age as majority of cases are diagnosed after menopause.

Obesity and physical inactivity are also important risk factors. As worldwide obesity epidemic shows no signs of abetting, as compared to other cancers, the relative risk of obesity-related deaths is highest in endometrial cancers.

Preventive strategies and early detection are required to reduce the burden of a disease whose incidence and mortality rates are on the rise.

As symptoms present at relatively early stages, it is generally diagnosed early and 5-year survival rate is high.

Endometrial cancer is the fourth most common cancer in women worldwide and the most common gynaecological malignancy in the United States. It accounts for 4–8 % of all cancers and is fourth after breast, colon and lung cancer [2]. It is estimated that a woman born in the United States in 2011 has a lifetime risk of 1 in 39 of developing endometrial carcinoma [1].

However, in India and Southeast Asia as a whole, the incidence and rates of endometrial carcinoma are lower. In developed countries, the incidence is 12.9 per

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100,000 women and mortality rate is 2.4 per 100,000. In developing countries the incidence is 5.9 per 100,000 with a mortality rate of 1.7 per 100,000 [19]. Lower rates in this part of the world may be explained by difference in the distribution of known risk factors amongst different races [2].

Worldwide, 290,000 women were diagnosed with endometrial carcinoma in 2008, accounting for nearly 5 % of all new cases of cancer in women [22]. The incidence has been increasing by 0.8 % each year since 1998 [3]. The reasons for this may be a result of a marked increase in the risk factors. Overall mortality and morbidity is low because normally the patients present at an earlier stage with abnormal uterine bleeding.

There are two types of endometrial carcinomas:

1. Type I, which are oestrogen dependent, low grade and endometrioid and account for 85 % of endometrial carcinomas and have better prognosis. These cancers are oestrogen driven and have hyperplastic endometrium.
2. Type II, which are oestrogen-independent, high-grade and serous or clear cell tumours with late-stage diagnosis and have poor prognosis [1]. These cancers are mostly related to ageing. Recent studies suggest that the two types of endometrial carcinomas share many common etiological factors. So type II tumours may not be completely oestrogen independent [5, 20].

Most of the *risk factors* of endometrial cancers are based on increased oestrogen exposure. Independent of this, there are certain clearly discernable demographic patterns which shall be elaborated further in this chapter (Table 2.1).

Table 2.1 Risk factors of endometrial carcinoma

Risk factors	Salient features
Age	Peak between 55 and 70 years
Race	More in White race and less in Indians and South Asians
Obesity	BMI >30 kg/m^2
Diet	High in fat and low in fibre
Diabetes mellitus	Increases the risk two- to threefold
Parity	More in nulliparous and infertile women
Hypertension	As common association with obesity and diabetes (corpus cancer syndrome)
Menstrual history	Early menarche, late menopause, long menstruation span
Hyperoestrogenic states	Oestrogen replacement therapy without progesterone, PCOS and oestrogen-producing tumours
Lynch syndrome	Inherited autosomal dominant disease
Use of tamoxifen	High index of suspicion is warranted in tamoxifen users
Family history	Family history of endometrial, ovarian and breast cancers
Molecular alterations	Mutation of the PTEN and p53 genes is a frequent event in endometrial cancers [1]

Endometrial cancers are *age dependent*. The risk of developing endometrial cancers increases with advancing age. The peak of occurrence is between 55 and 70 years of age and the average age is 61 years. More than 90 % of the patients are over the age of 50. Only 5 % or less develops before the age of 40 [3]. A woman under the age of 40 has 1 in 1423 chances of developing the disease but a woman older than 70 has a risk of 1 in 81 [9].

Race, as stated before, White women are more likely to be afflicted as compared to African, Asian, Hispanic, Chinese or Japanese women. In general, incidence is higher in North America, Australia and Europe than in South Asia, Central America and Africa. But once the women from other regions start living in the United States, the incidence of acquiring the disease increases as compared to those who choose to remain in the country of their origin. However, once the disease occurs, morbidity and mortality rates in Afro-American women are more than in White and Asian women [1].

Obese women have a higher risk of endometrial carcinomas. Nearly 70 % of the patients are obese women. With increase in BMI, the risk of getting the disease and concurrent morbidity and mortality also increase [17]. With a BMI of >30 kg/m2, the risk is 3 times and it becomes 4 times with BMI of >32 kg/m2. A BMI of >35 kg/m2 will increase the risk of developing endometrial carcinomas to 6 times as compared to a woman of BMI 23 kg/m2 [1, 12]. An abrupt increase in weight gain, especially during early adulthood, is also predictive of increased risk. Upper body obesity is also a risk factor independent of body weight. Both obesity and distribution of adipose tissue accumulated during adult life increase the risk of endometrial carcinoma substantially. In addition morbidly obese women have highest risk of cancer-related deaths [1, 17]. As compared to other cancers, the relative risk of obesity-related deaths is highest in endometrial cancers [6].

Obesity increases endogenous oestrogen by peripheral conversion of androstenedione to oestrogen by aromatase in adipose tissues. This increases the endometrial exposure to endogenous oestrogen and decreases serum sex-binding globulins, thereby leading to hyperoestrogenic state [1, 6].

A diet high in carbohydrates and high glycaemic index influences insulin secretion and insulin-like growth factors, which may exert relevant effects on obesity and diabetes mellitus. Both of these are important risk factors for endometrial carcinoma [7]. Food rich in fat and red meat significantly increases the risk [6].

Diabetes mellitus is an independent risk factor, and an increased incidence of type II diabetes mellitus is noted in patients of endometrial cancers since many years [1]. There is also a strong relationship between increased insulin resistance and endometrial cancer. An obese, diabetic menopausal woman has 2–3 times more risk of developing endometrial cancer [3].

Hypertension is often associated with obesity and hence also termed a risk factor [3]. The presence of a triad of obesity, diabetes and hypertension in a woman increases the risk of endometrial cancer and is commonly termed *corpus cancer syndrome*.

Parity has a positive association with the risk of development of endometrial cancer. Nulliparous women are 2–3 times more at risk than parous women. The

observed beneficial effects of pregnancies may be related to a strong exposure to progesterone during pregnancies [8]. Moreover, childbearing at an older age is associated with a lower risk. According to a study, women who give birth at age 40 or even more have 44 % less chances of disease when compared to women who had their last childbirth at age 25. The reduced risk persists for many years [4, 9].

Infertility, which may be a manifestation of nulliparity, has a three- to fivefold increase in the risk for disease as compared to fertile women although treatment for infertility may alter the woman's cancer risk [1].

Menstrual history also plays a role in risk development. The extremes of spectrum, i.e. early menarche (11–12 years) and late menopause (more than 50 years), have both been associated with increased risk [1]. The longer the menstruation span, the greater is the risk. The increase in menstruation span may be related to an accumulation of PTEN or p53 mutation [5].

Most of the risk factors are associated with *exposure to excessive oestrogen* (hyperoestrogenic states). The initial cases of endometrial carcinoma were reported relating to oestrogen replacement therapy (ERT) without concomitant progesterone. ERT increased the risk 4.5–8 times [3]. The risk which persisted for many years even after the treatment was stopped. In addition the risk increased with longer duration and higher dosages of oestrogen. A single year of unopposed oestrogen use increased the risk by 40 % of baseline [1].

Oestrogen-producing tumours were first reported by *Schroeder* in 1992 to be related to endometrial cancers. Since then, a large number of patients (6–12 %) with oestrogen-producing tumours have been found to have developed endometrial carcinoma [1].

Polycystic ovary syndrome is also related with risk of endometrial carcinoma. Elevated endogenous oestrogen levels along with certain comorbidities prevalent in PCOS like obesity, insulin resistance, type II diabetes mellitus and hypertension lead to an increase in the risk. Chronic anovulation leading to proliferative endometrial pathologies, polyps, hyperplasia and unopposed oestrogen exposure all cause an increase in the risk of development of endometrial carcinoma [11].

Hereditary nonpolyposis colorectal cancer (*HNPCC*) *or Lynch syndrome* is an inherited autosomal dominant disease in which women are at a risk of more than one primary cancer of colon, rectum, ovaries, small intestine, renal pelvis or endometrial cancer developing in their lifetime. Thirty-nine percent of these women may develop endometrial carcinoma by the age of 70 [1, 3].

A strong association has been found between endometrial cancer and BRCA mutation gene carriers. But it is difficult to differentiate whether there is an increased susceptibility on account of BRCA mutation or a consequence of *tamoxifen* usage in BRCA carriers with a history of breast carcinoma. Since 1985 multiple authors have confirmed the relation between endometrial carcinoma and the duration and use of tamoxifen. As the benefits of tamoxifen to breast cancer patients outweigh the risk of endometrial cancer, a high index of suspicion and close monitoring is warranted in tamoxifen users complaining of abnormal uterine bleeding [10].

Altered levels of hormones like prolactin and S.TSH may also play a role in risk of endometrial cancer by causing obesity and menstrual dysfunction [6].

Use of talc for pelvic hygiene is also associated with increase in risk of endometrial carcinoma [5, 19].

Karen Lu and Brian M. Slomovitz in Katz Gynaecology have defined the molecular alterations present in endometrial cancers. PTEN mutations are frequently seen in endometrioid endometrial carcinoma and have also been seen in complex endometrial hyperplasia. Microsatellite instability occurs in 25–30 % of all endometrial cancers and is the result of either germline mutations in DNA mismatch repair proteins (MLH1, MSH2 or MSH6) or more frequently from the somatic methylation of the MLH1 promoter. In contrast to endometrioid endometrial cancers, uterine papillary serous carcinomas have a high frequency of p53 mutations. HER-2/neu amplification is seen in 10–20 % of uterine papillary carcinomas and is likely associated with advanced age and poor prognosis of this histology [13].

Recent studies suggest that biomarkers like progesterone receptors, insulin-like growth factor I, retinaldehyde dehydrogenase type II, secreted frizzled-related protein 4 and anti-LeY monoclonal antibodies may be promising tumour markers. Adiponectin secreted by adipose cells is decreased in obesity and may be a marker for endometrial cancer. Leptin, another adipose-derived hormone, is also implicated in proliferation of the endometrium [6]. A five-panel biomarker (prolactin, GH, eotaxin, E-selectin and S.TSH) has also been used to diagnose the risk of endometrial cancer [6, 18].

HE-4 marker, a human epididymis-specific 4-disulphide core protein, a precursor of human epididymis protein, provides 46 % sensitivity for diagnosis and prognosis of endometrioid adenocarcinoma of endometrium in all stages of cancer and has a specificity of 95 %. Human serum amyloid apolipoprotein (SAA) is overexpressed and actively secreted by grade 3 endometrioid adenocarcinoma and serous papillary carcinoma of endometrium [21].

Endometrial carcinoma is a very common malignancy affecting a large number of women across the globe. An understanding of the epidemiology will aid not only in diagnosis but also in treatment and development of preventive regimens. Though endometrial cancer is less common in India and other developing countries, increase in longevity and changing lifestyles have increased the possibilities of rise in cases of endometrial cancers.

There are certain *protective factors* which can help in reducing the risk of endometrial cancers (Table 2.2):

(i) Weight loss remains the key to protection from endometrial carcinoma. It helps in reversal of hormonal imbalances and dysregulation of IGF/insulin pathway. The fact that so many diagnosed cancers of endometrium are associated with obesity leads us to hypothesize that a large portion of these cancers might be preventable by weight loss.

(ii) Prolonged use of oral contraceptive pills has long been known to decrease the risk of endometrial carcinoma by 40 % even up to 15 years after the discontinuation. This protection increases with the length of use. Four years of usage has been known to reduce the risk by 56 %, 8 years by 67 % and 12 years by 72 % [1, 3].

Table 2.2 Preventive factors in endometrial carcinoma

1	Weight reduction
2	Physical exercises
3	Oral contraceptive pills
4	Intrauterine devices
5	Good monitoring of diabetes mellitus
6	Metformin
7	Breastfeeding
8	Oestrogen with concomitant progesterone in hormone replacement therapy
9	High consumption of coffee, whole grains, vegetable and food rich in lutein and high fibre
10	Avoiding use of talc

(iii) Recent studies indicate that intrauterine devices may also be associated with decreasing the risk. The protective effect of IUD may be through the intense inflammatory response that leads to lysosomal and inflammatory actions, which may be responsible for early elimination of hyperplastic endometrium. Complete shedding of endometrium decreases hyperplasia and thereby reduces the risk of endometrial carcinoma [1, 5, 15, 16].

(iv) Hormonal IUDs help in reversal of endometrial hyperplasia and thus substantially reduce the incidence of this potentially preventable disease. Further studies are required for levonorgestrel-containing devices in obese patients [1, 15, 16].

(v) Active cigarette smoking has been found to have a beneficial effect in regard to the risk of developing endometrial cancer especially in postmenopausal women. This may be because of reduction in circulating oestrogens. Smoking causes reduction in body weight and induces early menopause. It is not seen in passive smokers. However, the protection is far outweighed by other health hazards associated with cigarette smoking and tobacco use [1, 6, 14, 18].

(vi) Metformin, an oral hypoglycaemic agent, lowers blood glucose by increasing its uptake. It seems to be a logical choice for prevention of endometrial cancer. Based on preclinical data, the Gynecologic Oncology Group is considering examination of metformin for the treatment of endometrial cancer [18].

(vii) Coffee also probably protects against endometrial cancer. Coffee drinking has been associated with higher sex hormone-binding globulin (SHBG), which reduces free oestradiol and stimulates synthesis of oestrogen metabolites, thus inhibiting oestrogen-mediated carcinogenesis. High coffee consumption has been associated with low levels of C-peptide and higher levels of adiponectin [22].

(viii) Encouragement of breastfeeding also has a preventive effect on the occurrence of endometrial cancers.

(ix) Judicious advice of HRT with concomitant progesterone weighs the risks of usage with non-usage. Progesterone as a differentiating factor may hold the key to the protective measures.

As the epidemiology and risk factors of occurrence of endometrial carcinomas are better known, mortality and morbidity relating to the disease may be significantly reduced by certain preventive measures.

Since endometrial carcinomas often present as postmenopausal bleeding or abnormal uterine bleeding, it is easier to diagnose in earlier stages as compared to other malignancies. It has been shown that 9 % of women in their early 50s with postmenopausal bleeding had endometrial carcinoma, while 60 % of women in their 80s with postmenopausal bleeding had endometrial cancers [7]. All women with postmenopausal bleeding and any patient with premenopausal abnormal uterine bleeding especially those with high risk (e.g. obese, diabetic, infertile) should undergo transvaginal ultrasound and thereafter endometrial biopsies. Fifty percent of the females may be diagnosed by routine Pap smear.

Women on tamoxifen should also undergo screening regularly by TVS and biopsy if needed. This evaluation is to be continued even after discontinuation of tamoxifen.

Endometrial biopsies have 99.6 % and 91 % detection rate in premenopausal and postmenopausal women, respectively. The specificity of endometrial biopsy is 98 % and sensitivity is 99 % [3].

All obese, diabetic postmenopausal women should be advised to maintain a healthy weight and do regular exercise for at least 30 min per day with an increase in routine physical activity. A sedentary lifestyle and physical inactivity have to be avoided.

There should be a controlled diet which is low in fats and high in fibre. Food with high glycaemic index is to be avoided. Coffee, whole grains, vegetables and food rich in lutein are inversely associated with cancer risk [6].

By lifestyle modification, improving technique of early detection and providing timely therapy, we can look forward to longer and healthier outcomes for possible patients and survivors. Risk assessment and proper clinical staging of disease are required for proper management.

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Premalignant Conditions of the Endometrium

3

Kusum Lata and Neerja Bhatla

Abstract

In developed countries, endometrial carcinoma is the most common female genital tract malignancy. It is showing an increasing trend in India as well. It is now recognized that a precursor lesion usually precedes it. The distinction between endometrial hyperplasia and true precancerous lesions is of utmost importance to provide appropriate intervention. At present, the endometrial intraepithelial neoplasia (EIN) classification best fits this requirement as compared to the more widely used four-class World Health Organization schema (1994), which does not distinguish between atypical hyperplasia and precancerous lesions.

The diagnosis of premalignant lesions is made by dilatation and curettage or endometrial suction curette, but the accuracy of both in diagnosing precancer and excluding concurrent carcinoma is unclear. Hysteroscopy with directed biopsy improves the sensitivity of diagnosis. Total hysterectomy for endometrial intraepithelial neoplasia allows definitive assessment of a possible concurrent carcinoma and effectively treats premalignant lesions. However, for women who wish to retain their childbearing potential, systemic or local progestin therapy has a role as an alternative to hysterectomy.

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Introduction

Globally, endometrial cancer is the fifth most common cancer in women, affecting 318,000 women every year [1]. While it is the most common female genital tract malignancy in the West, accounting for almost half of all new gynecologic cancers [2], in India, the incidence is low with an age-standardized incidence rate of 4.6 per 100,000 population [3].

Two main types of endometrial cancer are recognized: type 1 cancers that constitute 80–90 % of cases are estrogen-dependent endometrioid adenocarcinomas with good prognosis. On the other hand, type 2 tumors which are non-estrogen dependent are found to be more aggressive with poor prognosis carrying a high risk of relapse and metastasis.

The most common type of endometrial carcinoma is the endometrioid subtype (approximately 80–85 % of cases), which is preceded by a precursor lesion. Excess estrogenic stimulation of the endometrium, with consequent proliferative glandular epithelial changes, has been associated with both endometrioid endometrial carcinoma and its precursor lesions. Risk factors known to predispose to the development of endometrial carcinoma are obesity, unopposed estrogen therapy, diabetes mellitus, and nulliparity. Women most commonly present with abnormal uterine bleeding, whether in the form of menorrhagia, metrorrhagia, or postmenopausal bleeding, while some may present with abnormal Pap smear, i.e., atypical glandular cells or atypical endometrial cells, detected on routine Pap smear.

Endometrial Hyperplasia Classification Systems

Currently there are two systems of endometrial precancer classification: (1) the WHO 1994 schema and (2) the endometrial intraepithelial neoplasia (EIN) diagnostic schema developed by the International Endometrial Collaborative Group [2]. The WHO 1994 schema classifies histology based on glandular complexity and nuclear atypia into four categories of risk classification: (1) simple hyperplasia, (2) complex hyperplasia, (3) simple hyperplasia with atypia, and (4) complex hyperplasia with atypia. These categories, being descriptive in nature, make interpretation more subjective. Importantly, this classification does not provide specific management algorithms. Due to poor reproducibility of the WHO classification [3, 4], the EIN schema was introduced to improve clinical management.

There are three categories in EIN schema based on pathologic criteria [5, 6]: (1) benign (benign endometrial hyperplasia), (2) premalignant (endometrial intraepithelial neoplasia), and (3) malignant (endometrial adenocarcinoma, endometrioid type, well differentiated). Tables 3.1 and 3.2 show the diagnostic criteria and definitions of EIN, respectively. Using this classification, pathologists can classify the lesion more accurately, and clinicians can guide treatment appropriately. It has been shown to be a good prognostic tool in several retrospective studies and one prospective study [7–9], with better interobserver reproducibility than the WHO 1994 schema. Figures 3.1 and 3.2 are images of benign endometrial hyperplasia and endometrial intraepithelial neoplasia, respectively.

Table 3.1 Diagnostic criteria for endometrial intraepithelial neoplasia [6, 7]

Nomenclature	Topography	Functional category	Treatment
Benign endometrial hyperplasia	Diffuse	Prolonged estrogen effect	Hormonal therapy, symptomatic
Endometrial intraepithelial neoplasia	Focal progressing to diffuse	Precancerous	Hormonal therapy or surgery
Endometrial adenocarcinoma, endometrioid type, well differentiated	Focal progressing to diffuse	Malignant	Surgery, stage based

Table 3.2 Definitions of endometrial intraepithelial neoplasia criteria [6, 7]

Criteria	Comments
Architecture	Area of glands greater than stroma (volume percentage stroma less than 55 %)
Cytology	Cytology differs between architecturally crowded focus and background
Size greater than 1 mm	Maximum linear dimension exceeds 1 mm
Exclude mimics	Benign conditions with overlapping criteria (i.e., basalis, secretory, polyps, repair)
Exclude cancer	Carcinoma if maze-like glands, solid areas, or appreciable cribriform

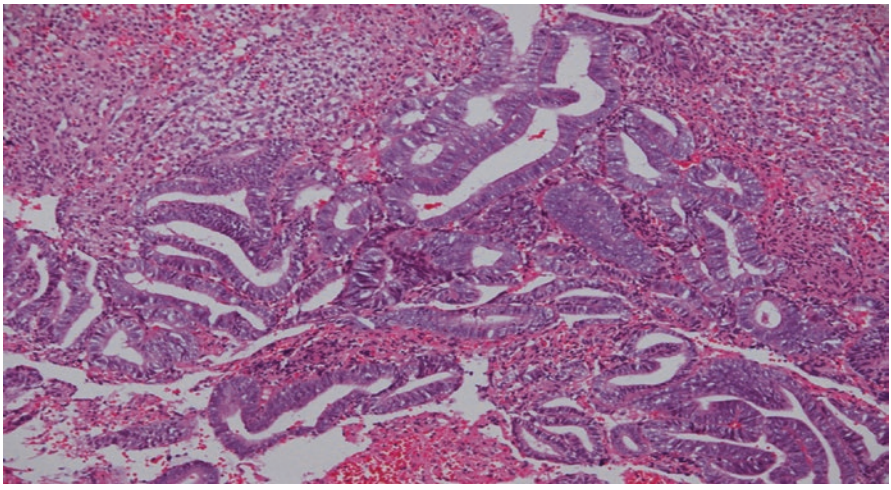

Fig. 3.1 Benign endometrial hyperplasia (Picture courtesy of Dr. Sandeep Mathur)

Precancer Diagnosis: Endometrial Sampling and Imaging

The management of patients with premalignant endometrial lesions requires accurate diagnosis of a precancer lesion and exclusion of coexisting carcinoma to prevent any under- or overtreatment. Ideally, it should be possible to make this diagnosis

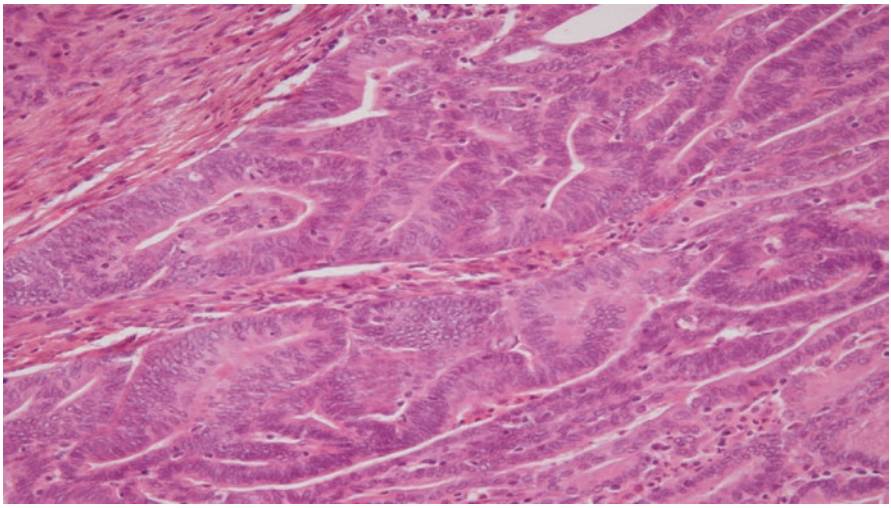

Fig. 3.2 Endometrial intraepithelial neoplasia (Picture courtesy of Dr. Sandeep Mathur)

preoperatively. However, it has been seen that in approximately 40 % of patients who had a diagnosis of endometrial intraepithelial neoplasia diagnosis by endometrial suction curette, the diagnosis changed to carcinoma after hysterectomy [8, 10], making exclusion of concurrent carcinoma a challenge.

Both dilatation and curettage (D&C) and endometrial suction curette have pitfalls in diagnosing precancer and excluding concurrent carcinoma. Both have sampling limitations: approximately 60 % of D&C specimens sample less than one half of the uterine cavity [11]. For women undergoing hysterectomy as a definitive management for premalignant lesions, the technique of sampling does not matter as much since hysterectomy eliminates the risk of failure to diagnose an endometrial cancer. Dilation and curettage and endometrial suction curette sampling devices have been reported to yield equal rates of cancer detection in patients with abnormal uterine bleeding [12]. The more accurate diagnosis of uterine lesions is made by hysteroscopy with directed biopsy as it helps in visual assessment of the background epithelium also [13–15]. It gives the best opportunity to confirm the diagnosis of a true premalignant endometrial lesion and exclude an associated endometrial carcinoma. Currently available diagnostic methods provide very little amount of endometrial tissue making cancer risk assessment less feasible. So it has been suggested that the assessment of sample adequacy should be included in the diagnostic scheme as is done for cervical cytology specimens.

In women with postmenopausal bleeding, transvaginal ultrasonography (TVS) is the most common employed imaging modality due to high specificity in excluding carcinoma. Endometrial sampling is not recommended if endometrial thickness is found to be 4 mm or less because of the very low risk of uterine malignancy in these patients [16]. An endometrial thickness greater than 4 mm in a patient with postmenopausal bleeding requires additional evaluation (such as sonohysterography,

office hysteroscopy, or endometrial biopsy) to adequately visualize endometrial thickness. The significance of an endometrial thickness greater than 4 mm in an asymptomatic, postmenopausal patient has not been established, and this finding need not routinely trigger evaluation [16].

Unlike postmenopausal women, the role of TVS is limited in premenopausal women as endometrial thickness is not static during different phases of the menstrual cycle and may overlap with women having carcinoma.

The role of tumor markers for endometrial carcinoma is not well established. An inexpensive, sensitive, and specific serum test, which would be the most attractive approach to screen women for endometrial cancer, has still not been discovered. Raised serum CA 125 usually signifies an advanced disease and a poor prognosis but has limited role in monitoring treatment response. The serum markers CA 19-9, CA 15-3, and CA 72-4 and CEA levels are raised in endometrial cancer patients in 22–24 %, 24–32 %, 22–32 %, and 14–22 % of cases, respectively [17]. It has been seen that only a combination of CA 125 and CA 19-9 has a role in posttreatment surveillance due to high sensitivity (83.3 %) for detection of recurrence, with only 12.8 % of false-positive cases [17]. Tumor markers should be used in conjunction with other modalities, such as ultrasound and high-resolution MRI to attain high specificity.

Management of Endometrial Intraepithelial Neoplasia

Management of a newly diagnosed case of endometrial intraepithelial neoplasia has the following main objectives: (1) to exclude a concurrent adenocarcinoma, (2) to minimize the risk of delayed discovery of an occult carcinoma, and (3) to prevent progression to endometrial cancer.

Nonsurgical Management Options

Nonsurgical management is advised to patients (1) whose clinical, radiological, and pathological assessment suggests endometrial hyperplasia without any evidence of malignancy and (2) who desire future fertility (3) or patients with sufficient medical comorbidities precluding surgical management.

Presently nonsurgical management options include hormonal therapy and endometrial ablation. Endometrial ablation using thermal or electrical cautery devices has been employed for non-precancerous endometrial lesions, but it is not recommended for the treatment of atypical endometrial hyperplasia (AEH)/endometrial intraepithelial neoplasia (EIN). The completeness of ablation cannot be guaranteed via any method, and subsequent adhesions may make the cavity less accessible for follow-up surveillance.

Several studies have evaluated the use of hormonal treatment to induce regression of hyperplasia. Progestins are widely used with acceptable toxicity profile. Progesterone counteracts the mitogenic effects of estrogens and induces

secretory differentiation [22]. Treatment with progestins may be an option for any patient who wants to retain childbearing, any patient with a hyperplastic or precancerous lesion who desires uterine preservation, and most elderly patients with medical comorbidities having diagnosis of endometrial intraepithelial neoplasia, a low-grade malignancy, or both. Although the efficacy of progesterone is well recognized, the exact dose and duration has not been specified till date [23–25]. Neither has the frequency been determined whether treatment should be cyclic or continuous. The appropriate length of follow-up after treatment also is still debatable.

Table 3.3 shows commonly used progestin regimes. Medroxyprogesterone acetate and megestrol acetate, with different doses and schedules, are the most common progestin therapies used in the clinical setting. Regression of hyperplasia (simple, complex, and atypical) has been observed in 80–90 % of individuals receiving medroxyprogesterone acetate (10 mg daily for 12–14 days per month) or micronized progesterone in vaginal cream (100 mg for 12–14 days per month) when treated for 3 months as shown in Table 3.3 [26–28]. Long-term systemic medical treatment to prevent reappearance of endometrial intraepithelial neoplasia requires awareness of concomitant adverse effects. Edema, gastrointestinal disturbances, and thromboembolic events are infrequent with these treatments, thereby making medical management a suitable therapeutic option for patients for whom surgical management is not desired. However, if endometrial intraepithelial neoplasia is present, there is a higher incidence of failure of medical management and subsequent development of cancer [29].

The levonorgestrel-releasing intrauterine system (levonorgestrel IUS) is another preferred option in these cases. The greatest advantage is a onetime insertion and the IUS is effective for a period of 5–7 years. Local-acting progesterone has an effect on the endometrium that is several times stronger than that exerted by systemic products and has a decreased systemic effect. A systematic review and meta-analysis found a pooled regression rate of 69 % (95 % confidence interval, 58–83) in 14 studies ($n = 189$) of women with atypical hyperplasia treated with oral progestins [30].

Follow-up and surveillance is important and is done by serial endometrial sampling every 3–6 months, but the appropriate frequency has not yet been determined.

Table 3.3 Hormonal treatment for endometrial intraepithelial neoplasia

Hormonal agent	Dosage and length
Medroxyprogesterone acetate	10–20 mg/day, or cyclic 12–14 days per month
Depot medroxyprogesterone	150 mg intramuscularly, every 3 months
Micronized vaginal progesterone	100–200 mg/day or cyclic 12–14 days per month
Megestrol acetate	40–200 mg/day
Levonorgestrel intrauterine system	52 mg in a steroid reservoir over 5 years

Modified from Trimble et al. [31]

Surgical Assessment and Management Options

In a woman who does not desire future fertility, total hysterectomy is the most preferred treatment option as it fulfills all the three objectives stated above. It gives a definitive diagnosis of possible concurrent carcinoma and effectively treats premalignant lesions. Hysterectomy can be performed via abdominal, vaginal, or minimally invasive procedures with or without bilateral salpingo-oophorectomy. Supracervical hysterectomy, morcellation, and endometrial ablation should not be performed for treatment of endometrial intraepithelial neoplasia because of concerns about underlying carcinoma [17]. Removal of the cervix and lower uterine segment along with the uterine corpus permits staging of any incidentally discovered cancer and reduces the risk of leaving behind residual disease. The possible need for additional surgery to complete surgical staging in case a carcinoma is identified should be explained to the patient clearly.

Intraoperatively, management may be altered based on intraoperative assessment and pathologic review. The specimen should be examined for gross evidence of a tumor or myoinvasion, which may require frozen section. This can help guide decisions about the need for comprehensive surgical staging, but the diagnostic accuracy of frozen section should be kept in mind as it varies from institution to institution. The correlation between frozen section and final pathology for histology, grade, and depth of myometrial invasion has been reported to be as high as 97.5 %, 88 %, and 98.2 %, respectively [18]. Furthermore, high-risk disease is detected more efficiently in frozen section compared with low-risk disease [19].

Comprehensive surgical staging with pelvic and para-aortic lymph node dissection at the time of hysterectomy for endometrial intraepithelial neoplasia is not recommended as it may result in overtreatment and increased surgical risk for a vast majority of patients. The risk of a concurrent high-risk uterine carcinoma with features like high-grade tumor, deep invasion, or lymphovascular space invasion, in women with a biopsy diagnosis of endometrial intraepithelial neoplasia, is approximately 10 % [10, 20].

Vaginal hysterectomy may be performed if the need for comprehensive surgical staging is excluded completely, as this is not feasible with a vaginal approach. Bilateral salpingo-oophorectomy is not absolutely required, especially in premenopausal women, and, in fact, removal of both ovaries in premenopausal or perimenopausal women without a confirmed gynecologic malignancy may increase overall morbidity and mortality [21].

As far as prevention is concerned, a healthy lifestyle, including adequate physical activity, daily exercise, healthy diet, and control of weight and blood sugar levels, is essential. Because endometrial intraepithelial neoplasia is often an antecedent of endometrial cancer, clinicians may counsel patients about weight loss or bariatric surgery to reduce the risk of progression/recurrence as obesity is one of the major risk factors for endometrial cancer.

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Pathophysiology of Endometrial Carcinoma

4

Arpita Jindal

Abstract

Endometrial adenocarcinoma may be preceded by endometrial hyperplasia.

Oestrogen has been associated with increased endometrial hyperplasia and adenocarcinoma.

It is divided into two classes, type I and type II, each with different pathophysiology, genetic alterations and prognosis.

Histologically endometrioid morphology accounts for 75–80 % of cases.

In addition to tumour type, the tumour grade and surgical stage influence the prognosis.

Immunohistochemistry is useful in the diagnosis of endometrial carcinomas only in some specific situations.

Premalignant Lesions of the Endometrium

Endometrial Hyperplasia

Endometrial hyperplasia is a term which denotes a proliferative lesion of the endometrium with architectural complexity and cytologic atypia (Fig. 4.1). This process is usually diffuse but it can occur focally. The most widely used WHO classification is a four-tier system which takes into consideration the atypia and the architecture [1]. Recent studies have shown that the cytologic atypia rather than the complex architecture determines the risk of progression. Atypical hyperplasia has a 40 % risk

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as compared to non-atypical/simple hyperplasia which has only 10 % chances of progression [2]. The most acceptable classification of endometrial hyperplasia is given in Table 4.1.

Pathophysiology

Oestrogen replacement therapy has been shown to have a strong association with the development of endometrial carcinoma, and the factors which decrease the exposure of the endometrium to oestrogen have decreased the risk of endometrial carcinoma including the addition of progestin to oestrogen replacement therapy [4, 5]. Atypical endometrial hyperplasia has been associated with a number of genetic alterations including mutation in the *PTEN* tumour suppressor gene and *KRAS* oncogene and microsatellite instability [6]. These are the most common genetic alterations in endometrioid carcinoma, which support atypical hyperplasia as a precursor lesion.

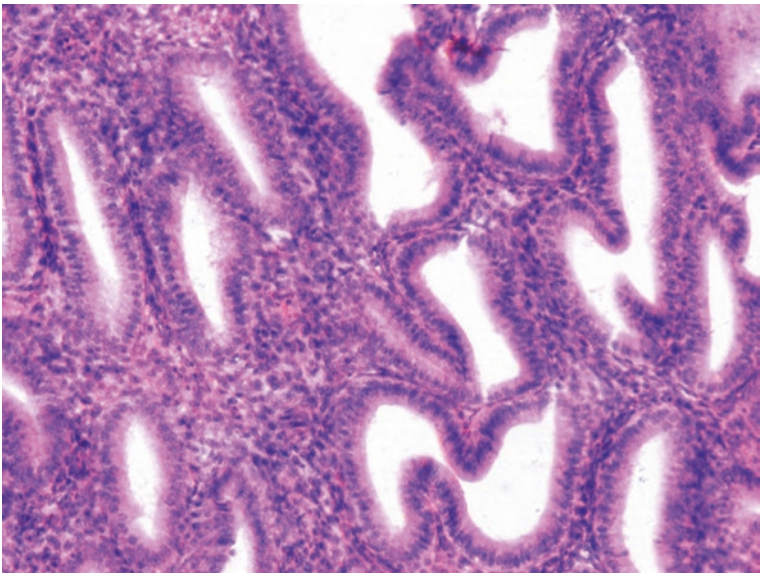

Fig. 4.1 Endometrium – simple hyperplasia

Table 4.1 World Health Organization classification of endometrial hyperplasia [3]

Hyperplasia(typical)
Simple hyperplasia without atypia
Complex hyperplasia without atypia
Atypical hyperplasia
Simple atypical hyperplasia
Complex atypical hyperplasia

Endometrial carcinoma

Definition

Endometrial carcinoma is a malignant epithelial tumour, arising in the endometrium with glandular differentiation, but it may have variable morphology.

Pathophysiology of Endometrial Carcinoma

A number of studies have demonstrated the association of oestrogen with the development of endometrial carcinoma. Exogenous oestrogen without progesterone has been associated with increased adenocarcinoma. The excess risk can be significantly reduced by the concomitant administration of progestins [4, 5]. There has been a conflicting data on the risk of endometrial cancer with the use of tamoxifen [7]. Obesity has been a well-defined risk factor too, due to increased availability of oestrogen as a result of aromatization of androgens in the adipose tissue [8]. Prolonged exposure to oestrogen due to chronic anovulation in nullipara, late menopause and early menarche may be related to increased risk [9].

Endometrial carcinoma can be divided into two categories based on clinicopathologic and molecular genetic features referred to as type I and type II. Type I is associated with unopposed oestrogen stimulation and is often accompanied by atypical hyperplasia. It is usually a low-grade carcinoma of favourable prognosis and more commonly occurs in perimenopausal white women. Type II has no association with exogenous oestrogen or endometrial hyperplasia. It is usually high grade and has an unfavourable prognosis and occurs in postmenopausal women, often of African-American or Asian descent [4, 5, 10–12].

Macroscopy

Endometrial carcinoma presents as an exophytic mass, usually seen in an enlarged uterus, or the tumour presents as a diffuse thickening of the endometrium with a shaggy, glistening and tan surface and presents more frequently on the posterior than on the anterior wall [13]. The tumour may be focal, at times presenting as polypoidal mass. Myometrial invasion usually appears as firm grey-white area in the form of linear extensions. The tumour may penetrate the serosa, and extension into the cervix is common.

Microscopy

Endometrial carcinoma has various histological types based on the cell morphology (Table 4.2).

Table 4.2 Histological classification of endometrial carcinoma [14]

Endometrioid adenocarcinoma
Variant with squamous differentiation
Villoglandular variant
Secretory variant
Ciliated cell variant
Mucinous adenocarcinoma
Serous adenocarcinoma
Clear cell adenocarcinoma
Mixed cell adenocarcinoma
Squamous cell carcinoma
Transitional cell carcinoma
Small cell carcinoma
Undifferentiated carcinoma

Table 4.3 FIGO – grading of endometrial carcinoma [12]

Grade 1	Less than 5 % of solid areas (excludes squamous differentiation)
Grade 2	6–50 % solid areas
Grade 3	More than 50 % solid areas

The tumour grade is increased by one if the nuclei are enlarged with prominent nucleoli (excluding serous or clear cell differentiation)

Endometrioid Adenocarcinoma

Endometrioid adenocarcinoma is the most common type accounting for almost three-fourths of the cases [11]. It resembles a proliferative phase endometrium with small, back-to-back glands without the stroma intervening. The grade of the tumour is based on nuclear features and architectural pattern. The nuclear grade is determined by the variation in nuclear size and shape, nucleoli and distribution of chromatin. The architecture grade and pattern are seen as how well the gland formation is seen as compared to solid clusters of tumour cells. Glandular complexity may be seen as luminal budding, papillae and cribriform patterns. Mitotic activity usually increases with the increase in nuclear grade and is an independent variable. The grading of the tumour is done according to the degree of gland formation by the tumour (Table 4.3). In grade 1 lesions, nuclei of the lining epithelial cells are uniform with minimal atypia and small discrete nucleoli (Fig. 4.2). The degree of tumour necrosis is usually mild to moderate. Marked amount of necrosis is unusual, even in high-grade endometrioid adenocarcinoma (Fig. 4.3).

Variants

Different morphologic patterns of endometrioid adenocarcinoma are seen including villoglandular, secretory, ciliated cell and adenocarcinoma with squamous differentiation. These patients share similar epidemiologic characteristics of typical endometrioid carcinoma, and these patterns may be seen in association with the usual form of endometrioid cell type.

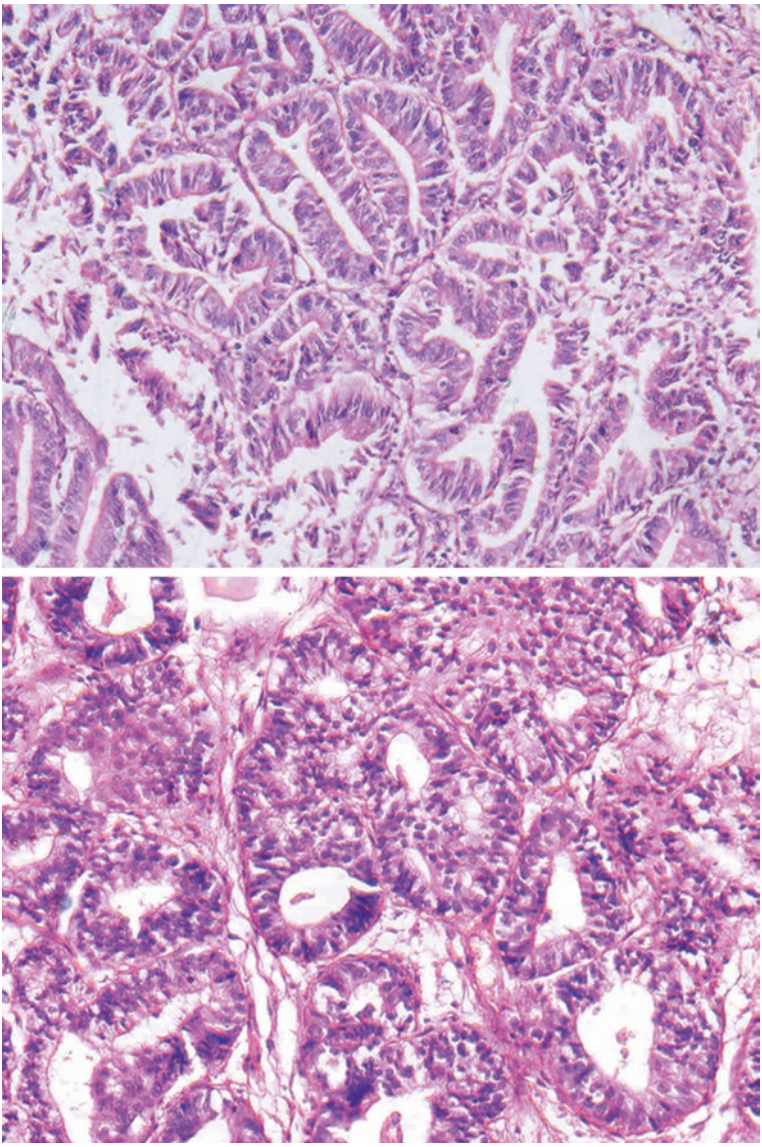

Fig. 4.2 Photomicrograph of endometrioid adenocarcinoma – grade 1

Endometrioid Adenocarcinoma with Squamous Differentiation

Endometrioid adenocarcinoma may contain squamous epithelium. The proportion of squamous element can be variable. At least 10 % of the tumour should have a squamous element in a well-sampled tumour to qualify as endometrioid carcinoma with squamous differentiation. There are no differences in clinical features of this

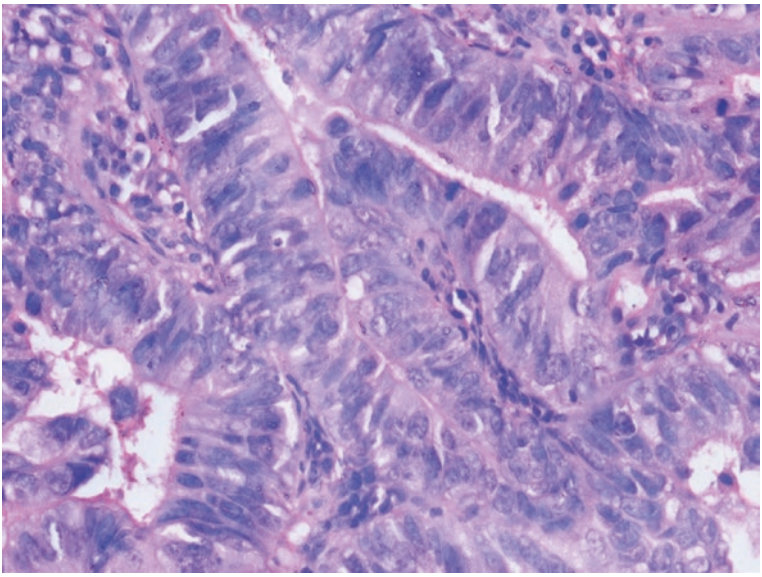

Fig. 4.3 Photomicrograph of endometrioid adenocarcinoma – grade 3 (high grade)

variant. It is graded on the basis of glandular component of the tumour as well, moderately or poorly differentiated. The treatment of this variant is the same as for endometrioid carcinoma of comparable stage.

Villoglandular Carcinoma

This variant displays papillary architecture with cells resembling usual endometrioid carcinoma. The papillary fronds comprise delicate fibrovascular cores covered by columnar cells with oval nuclei that generally show mild to moderate nuclear atypia. Occasionally high-grade nuclear atypia is seen where one has to differentiate it from serous carcinoma as both have distinct papillary pattern. Mitosis is variable and myometrial invasion is usually superficial.

Secretory Carcinoma

This variant appears histologically similar to secretory phase endometrium with columnar cells that have abundant vacuolated cytoplasm. They may have a cribriform or villoglandular pattern. Glands are back to back with presence of stromal invasion. Cellular atypia is minimal. The neoplasm is of low grade, and the prognosis is good. It is important to differentiate it from clear cell carcinoma.

Ciliated Cell Carcinoma

This is a rare variant of endometrioid carcinoma. Ciliated cells may be seen occasionally in endometrioid adenocarcinoma, but the majority of the malignant glands should be lined by ciliated cells to categorise it as this variant. One has to be just careful that endometrial proliferations with cilia may be carcinomatous too.

Mucinous Carcinoma

Mucinous carcinoma is an adenocarcinoma with abundant intracellular mucin. To categorise it as mucinous carcinoma, more than 50 % of the cell population must contain mucin which should be PAS positive and diastase resistant. Its appearance is similar to the mucinous endocervical adenocarcinoma, and it has to be differentiated from the clear cell carcinoma where the pattern is usually papillary or solid as compared to glandular in this variant. Endometrioid and clear cell adenocarcinoma may have large amounts of intraluminal mucin, but only mucinous adenocarcinoma contains the mucin within the cytoplasm. They tend to be of low grade with a good prognosis.

Serous Carcinoma

Serous carcinoma usually involves older women and is uncommon as compared to endometrioid carcinoma. It often displays papillary architecture like the variants of endometrioid carcinoma, but the papillae here have broad cores, and the pattern may be even solid. The cytologic atypia is marked (Fig. 4.4). Psammoma bodies may be present. These tumours are aggressive and have a poor prognosis. They are considered as high-grade neoplasms and are not graded. These tumours have a predilection for peritoneal spread, akin to ovarian serous adenocarcinoma [15].

Clear Cell Carcinoma

The prevalence of clear cell carcinoma is low and like serous carcinoma occurs in elderly women. It may exhibit solid, tubular, papillary and cystic pattern with typically hobnail-shaped cells. Nuclear atypia is moderate to marked. The clear cytoplasm is the result of glycogen present in the cells which can be demonstrated by

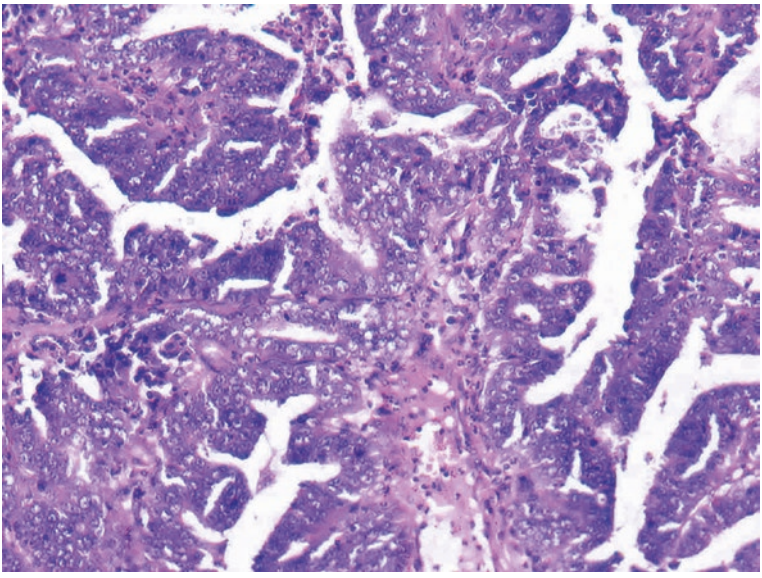

Fig. 4.4 Photomicrograph of serous adenocarcinoma – nuclei are typically poorly differentiated, macronucleoli

PAS staining with diastase digestion. They are not graded; per se they are high-grade tumours with aggressive behaviour and poor prognosis.

Squamous Cell Carcinoma

Endometrial squamous cell carcinoma (SCC) is extremely rare. To qualify it as squamous cell carcinoma, there should be no connection with the squamous epithelium of the cervix, squamous cell carcinoma should not be present in the cervix, and endometrial carcinoma should not be present in the endometrium. A strong association with pyometra and cervical stenosis and ichthyosis uteri has been seen in postmenopausal women. Primary SCC of the endometrium is an aggressive tumour and is associated with deep myometrial invasion and extrauterine extension.

Transitional Cell Carcinoma

Transitional cell carcinoma in the endometrium is extremely uncommon. In this 90 % or more is composed of cells resembling urothelial transitional cells. It is found admixed with another type of carcinoma, usually endometrioid. The immunoprofile supports Müllerian rather than urothelial differentiation.

Small Cell Carcinoma

Small cell carcinoma is an uncommon tumour of the endometrium. It resembles small cell carcinoma of the lungs and other organs. These are positive for neuroendocrine markers and for cytokeratin.

Undifferentiated Carcinoma

The tumour lacking any evidence of differentiation is defined as undifferentiated carcinoma as per WHO. These tumours have to be differentiated from small cell neuroendocrine tumours, large cell lymphoma, lymphoepithelioma-like carcinoma and undifferentiated component of other endometrial carcinomas.

Immunohistochemistry of Endometrial Carcinomas

Interpretation of tumour type in endometrial carcinoma can be difficult especially when biopsy material is scant, or there is abundant necrosis or poorly preserved architectural and cytologic detail. Some cases are morphologically ambiguous, even in a well-preserved biopsy specimen. In such circumstances, immunostains are useful.

Endometrial carcinomas usually express pan-cytokeratins, EMA, CA125, Ber-EP4, B72.3, CK7 and vimentin, whereas they are usually negative for CK20, WT1 and CEA (carcinoembryonic antigen). Endometrioid endometrial carcinomas express ER and PR. Squamous differentiation in endometrioid carcinomas often shows strong positivity with CEA. The serous carcinomas show strong p53 expression (intense nuclear staining of almost all nuclei) [16]. Only in some specific situations is immunohistochemistry of importance in the diagnosis of endometrial carcinomas. Importance of IHC lies in distinguishing endometrial and cervical adenocarcinoma in biopsies and curettings. To distinguish

endometrioid endometrial carcinoma from endocervical adenocarcinoma, ER, PR and P16 have been shown to be useful [17–19]. Most of the endocervical adenocarcinomas are HPV (human papilloma virus) related, and they express diffuse, moderate to strong P16 expression. Finally, an important difference between the immunophenotype of endometrial with ovarian and tubal serous carcinoma is the WT1 expression. Seventy percent of ovarian and tubal serous carcinomas express WT1 as against at most 20–30 % of endometrial serous carcinomas [20–22].

Prognostic Factors of Endometrial Carcinoma

Postoperative study of hysterectomy specimen in endometrial carcinoma requires evaluation of features (Tables 4.4 and 4.5) like cervical involvement, adnexal involvement, depth of myometrial involvement, histology type, grade and lymphovascular invasion. Myometrial invasion is an important issue. FIGO divides stage I tumours on the basis of the depth of invasion into IA (limited to the endometrium), IB (invasion of less than half of the myometrium) and IC (invasion of more than half of the myometrium) [23, 24]. Positive peritoneal cytology, pelvic and para-aortic lymph node metastasis and parametrial involvement are important extrauterine factors.

Table 4.4 Important parameters to be evaluated in surgical specimen

Cervical involvement
Tubes and ovaries
Parametrium
Depth of invasion
Histologic type
Histologic grade
Lymphovascular invasion
Peritoneum/omentum
Regional lymph nodes

Table 4.5 FIGO – staging of endometrial carcinoma [25]

I Tumour limited to the endometrium
IA No or less than half myometrial invasion
IB Invasion equal to or more than half of the myometrium
II Tumour invades cervix, but does not extend beyond the uterus
III
IIIA Tumour invades the serosa and/or adnexae
IIIB Vaginal involvement and/or parametrial involvement
IIIC Metastases to pelvic and/or para-aortic lymph nodes
IV
IVA Tumour invasion of bladder and/or bowel mucosa
IVB Distant metastasis including intra-abdominal metastases and/or inguinal nodes)
Endocervical gladular involvement only should be considered as stage I and no longer as stage II. Positive cytology has to be reported separately without changing the stage

Genetics of Endometrial Carcinoma

A number of cancer-causing genes have been analysed in endometrial carcinoma.

PTEN tumour suppressor gene has been the most frequently altered gene studied in endometrioid carcinoma [26, 27]. PTEN mutations are as well documented in endometrial hyperplasia with and without atypia too [28]. Another molecular alteration in endometrioid endometrial cancers includes microsatellite instability. It is found in tumours of patients affected by hereditary nonpolyposis colorectal carcinoma. Few oncogenes are altered in endometrial carcinoma like mutation in the *KRAS* proto-oncogene. Mutation in the *CTNNB1* gene too has been noted in tumours with squamous differentiation. Other oncogenes have been found to be overexpressed like *EGFR*, *c-Myc*, *CFMS, HER2/neu* and *BCl2* [29–32].

In contrast to endometrioid carcinoma, mutations in *KRAS* and *PTEN* appear to be uncommon in serous carcinoma, and microsatellite instability has not been detected in this type of tumour.

The most common genetic alteration in type 2 serous carcinomas is in p53, the tumour suppressor gene. Other frequent genetic alterations are inactivation of *p16* and overexpression of *HER2/neu* [33].

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Diagnosis and Pre-management Workup of Endometrial Carcinoma

5

P. Veena and Amita Maheshwari

Abstract

- Advanced age, postmenopausal status, obesity, polycystic ovarian syndrome/chronic anovulation, and tamoxifen use are the important risk factors for endometrial carcinoma (EC).
- Transvaginal ultrasonography is the imaging modality of first choice while evaluating women with postmenopausal bleeding.
- Office endometrial biopsy (EB) is the first step for evaluating the endometrium among women with postmenopausal bleeding.
- Once diagnosis of EC is confirmed, MRI is the most effective imaging modality for pre-management staging of EC especially in early stages, whereas CECT is effective in determining peritoneal deposits and parenchymal liver deposits.
- PET-CT is found to be effective for distant metastases, more so in recurrent diseases.

Abbreviations

ACOG	American College of Obstetricians and Gynecologists
ASR	Age-standardized rate
ATLAS trial	Adjuvant tamoxifen: longer against shorter trial
CECT	Contrast-enhanced computed tomography
EB	Endometrial biopsy

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EC	Endometrial carcinoma
ESMO	European Society for Medical Oncology
FDG PET [18F]	18-2-Fluoro-2-deoxy-D-glucose positron emission tomography
FIGO	International Federation of Gynecology and Obstetrics
HNPCC	Hereditary nonpolyposis colon cancer
MRI	Magnetic resonance imaging
NCCN	National Comprehensive Cancer Network
TVUS	Transvaginal ultrasound
USG	Ultrasonography

Introduction

The incidence of endometrial cancer is very low in India; the highest age-standardized rate (ASR) was observed in Delhi (ASR = 4.3) and Bangalore (ASR = 4.2), while in Mumbai it was 2.8 per 100,000 vs 25.1 per 100,000 in the western world [1]. Endometrial carcinoma is essentially a disease of postmenopausal woman, with median age at cancer diagnosis of 60 years. Usually it is diagnosed early as it is symptomatic in early stages, and diagnosis is easily accomplished.

Diagnosis

The most common symptom among women with endometrial carcinoma is abnormal uterine bleeding, mainly postmenopausal bleeding. Evaluation for this symptom can be done in different ways to gain different information and are enumerated below:

- History and clinical examination
- Pap smear
- Office endometrial biopsy
- Transvaginal ultrasound
- Color Doppler
- Sonohysterogram
- Hysteroscopy and guided biopsy
- Dilatation and curettage
- CECT of the abdomen and pelvis
- MRI of the abdomen and pelvis

History and Clinical Examination

Postmenopausal bleeding is an important symptom which needs to be evaluated thoroughly. Among women with postmenopausal bleeding, age and the duration from the menopause are directly proportional to the risk of endometrial carcinoma

(9 % at 50 years, 16 % in 60 years, 28 % in 70 years, and 60 % in 80 years) [2]. Even though endometrial carcinoma mainly occurs in postmenopausal women, it is vital to note that 25 % of the cases occur in premenopausal women and 5 % occur in women who are <40 years old [3]. Any irregular bleeding in these women should be investigated thoroughly after ruling out pregnancy-related conditions.

A thorough clinical history identifies women at increased risk of endometrial cancer. Any condition which leads to prolonged unopposed estrogen exposure of the endometrium puts the woman at an increased risk of endometrial hyperplasia and endometrial carcinoma. Chronic anovulation due to polycystic ovarian syndrome is an important cause [4]. Other hyperestrogenic states are morbid obesity (aromatization of androgens to estradiol and the conversion of androstenedione to estrone in peripheral adipose tissue), exogenous estrogen intake as in hormone replacement therapy, estrogen-secreting tumors of the ovary, and diabetes mellitus [5].

Tamoxifen use in women with breast cancer is an important risk factor for endometrial cancer. Tamoxifen, being a selective estrogen receptor modulator, has antiestrogenic action on tissues like the breast and estrogenic action on the endometrium. In standard doses used in adjuvant treatment of breast cancer, it is known to cause endometrial hyperplasia and polyps, invasive endometrial carcinoma, and uterine sarcoma. Tamoxifen is known to cause subepithelial stromal hypertrophy, which gives a false impression of a thick endometrium on ultrasonography [6] (Fig. 5.1).

Hence, in asymptomatic women, there is a poor correlation between ultrasonographically measured endometrial thickness and abnormal pathology, and screening them has not shown to be beneficial. Thus, evaluation of the endometrium should be performed only in postmenopausal women with abnormal uterine bleeding. However, the risk of developing endometrial carcinoma is estimated to be only 1.26 for 1000 patient-years after 5 years of tamoxifen intake. Further, based on the findings of the ATLAS study [7], ACOG recommends that tamoxifen use may be extended to 10 years rather than 5 years [8]. ACOG does not recommend screening in premenopausal women and asymptomatic postmenopausal women taking tamoxifen [8].

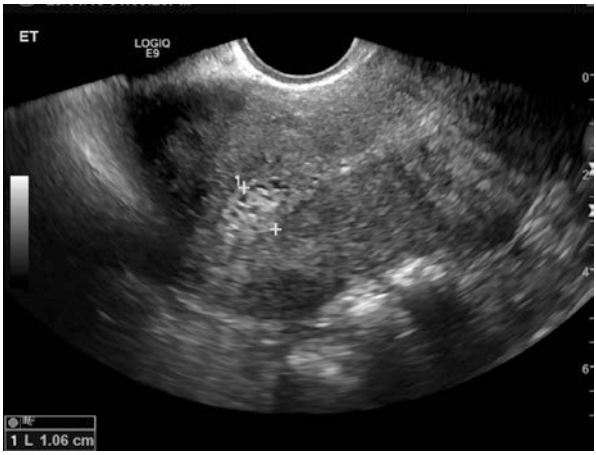

Fig. 5.1 Tamoxifen-induced cystic hyperplasia of the endometrium

Family history of malignancies among other members should not be overlooked, especially endometrial, breast, and colon cancers. Lynch syndrome or HNPCC (hereditary nonpolyposis colon cancer) is known to be associated with 40–60 % increased risk of endometrial malignancy, and 5 % of all endometrial cancers may be attributed to it. Germline mutation in one of four genes in the DNA mismatch repair family MLH1, MSH2, MSH6, or PMS2 is known to be associated with Lynch syndrome. Endometrial cancer occurs at an earlier age in these women, 47 years when compared to 60 years in general population [9]. Although BRCA1 and BRCA2 are known to be significantly associated with breast and ovarian cancers, lifetime risk of endometrial carcinoma is not increased in these women [10].

General examination should focus on detecting anemia, icterus, edema, and supraclavicular and inguinal lymph node enlargement. Clinical examination should aim at ruling out obvious causes of postmenopausal bleeding like those caused by lesions of the vulva, vagina, and cervix. This can be effectively done by visual inspection of the external genitalia in good light followed by a speculum examination. This should be followed by a bimanual examination to look for uterine size, tenderness, and irregularity, to rule out benign lesions, more so in premenopausal women. A rectovaginal examination aids in assessing the pouch of Douglas, the parametrium, and the adnexal pathology.

Pap Smear

If clinical examination does not reveal any obvious cause of postmenopausal bleeding, a Pap smear should be taken before doing the bimanual examination. Atypical glandular cells (AGC) reported on Pap smear are known to be associated with endocervical, endometrial, ovarian, or fallopian tube cancers 3–17 % of the time. These women should undergo a fractional curettage and pelvic imaging to rule out these cancers [11].

Office Endometrial Biopsy

The first step in the evaluation of the endometrium is invariably an office endometrial biopsy. Different devices which are available for performing the same are Novak curette, Pipelle endometrial suction curette, and Vabra aspirator (Fig. 5.2). Multiple studies have been done to determine the better device among these three, but it has been found that the accuracy for diagnosis of endometrial cancer is almost similar among these three (Novak curette, 67–97 %; Pipelle endometrial suction curette, 79–94 %; Vabra aspirator, 80–98 %) [12].

The success of the procedure is affected by many factors like cervical stenosis, alteration of the endometrial cavity by the submucous fibroids, and the size of the lesion itself. The yield of office endometrial biopsy can be increased by combining it with office hysteroscopy especially in small lesions [12]. False-negative rate of office endometrial biopsy is around 10 %, so further evaluation is recommended if the results come back as normal with persistent symptoms or abnormal pelvic imaging [13].

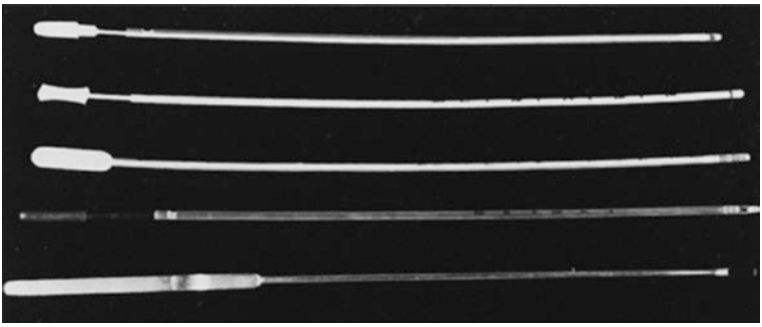

Fig. 5.2 Endometrial biopsy curettes

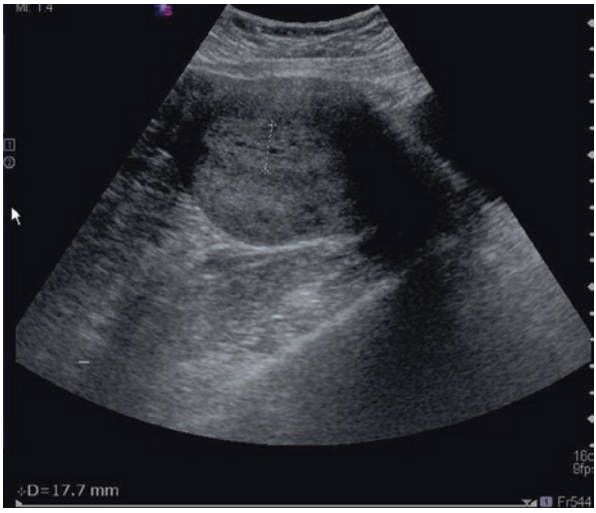

Fig. 5.3 Thickened endometrium by ultrasonogram

Transvaginal Ultrasound

Transvaginal ultrasound (TVUS) examination is a useful adjunct to office endometrial biopsy in the initial evaluation of endometrial pathology. The endometrium is usually evaluated by examining the thickness and morphology. Endometrial thickness of more than 5 mm is abnormal in postmenopausal women [14] (Fig. 5.3).

A normal TVUS decreases the pretest probability of endometrial cancer from 10 to 1 % posttest among postmenopausal women with vaginal bleeding [15]. Endometrial thickness is dynamic in premenopausal women; nevertheless, transvaginal ultrasound examination can be helpful in diagnosing benign conditions like fibroids and adenomyosis which can also present with abnormal uterine bleeding. At this juncture, it is prudent to mention that 17 % of type II endometrial cancers will have a thin endometrium as these cancers develop in a background of atrophy [16]. TVUS has good negative predictive value (99 %) but a poor positive predictive

value (57 %) in the diagnosis of endometrial cancer which further decreases to 37 % in women taking hormone replacement therapy [15].

Endometrial thickness can be morphologically classified as diffuse or focal. Diffuse endometrial thickness may be due to endometrial hyperplasia or carcinoma, and a non-focal blind biopsy is sufficient for diagnosis, whereas focal endometrial biopsy can be due to lesions like polyps, either benign or malignant, and requires hysteroscopic-guided biopsy. Other morphological features described by researchers to indicate malignancy are heterogeneous and hyperechoic with irregular borders. It is recommended that combined assessment of endometrial thickness and morphology should be done to improve detection of endometrial pathology [17].

Color Doppler

Color Doppler used along with TVUS aids in the diagnosis of endometrial malignancy. The pattern of vascularity in the thickened endometrium or a focal lesion helps in distinguishing between malignant and benign conditions. Broad-based lesions with diffuse high level of vascularity indicate malignant lesions, and single feeding vessel in the stalk of a focal lesion with low vascularity indicates a benign condition like polyps [18]. When Doppler analysis was compared to conventional gray-scale TVUS, researchers found that abnormal endometrial thickness alone is a better predictor of endometrial pathology than Doppler analysis [19].

Sonohysterography

Transvaginal ultrasound examination is performed after installing sterile normal saline into the endometrial cavity to enable better visualization of lesions like endometrial polyps, submucous fibroids, adhesions, and others. This is especially recommended in women who are on tamoxifen as they tend to have endometrial polyps [14]. Sonohysterography accurately identifies endometrial pathology with reported sensitivities of 89–98 % and specificities of 46–88 % with a good negative predictive value for detecting malignancy. But the positive predictive value for cancer prediction is very poor (16 %) which implies that it is very good at detecting benign conditions [20].

Hysteroscopy and Guided Biopsy

Hysteroscopy enables visualization and guided biopsy especially in small early lesions which can be easily missed on routine office endometrial biopsy (Fig. 5.4).

It is also useful in evaluating falsely thickened endometrium of women on tamoxifen which is due to subendometrial edema [14]. Hysteroscopy has good sensitivity and specificity at 86 % and 99 %, respectively. Like other modalities

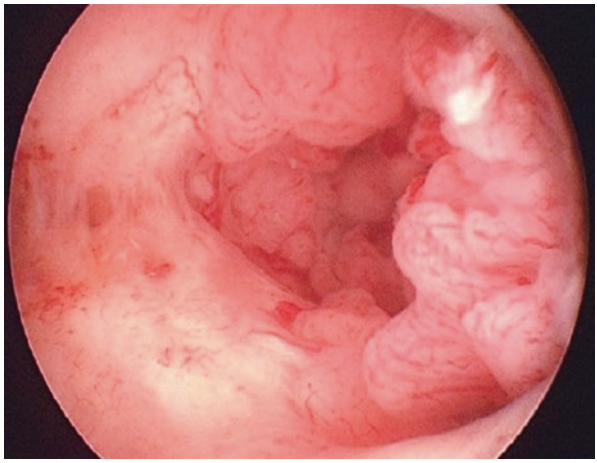

Fig. 5.4 Hysteroscopic image of endometrial malignancy

described above, the negative predictive value of hysteroscopy for detecting malignancy is up to 99 % with positive predictive value of 72 % [21].

Dilatation and Curettage

Dilatation and curettage was the recommended diagnostic test for evaluation of abnormal bleeding before office endometrial biopsy took over. Currently the indications for dilatation and curettage are inability to perform office endometrial biopsy due to patient distress, cervical stenosis, and anatomical factors like submucous fibroids. It is a day care procedure done under anesthesia, either local (paracervical block) or general. Hysteroscopic visualization during the procedures enables sampling of smaller lesions.

CECT, MRI, and PET-CT of the Abdomen and Pelvis

None of these imaging tests are indicated in screening or diagnosis of endometrial cancer. They are useful in pre-management workup of the patients as discussed in the next section.

Pre-management Workup

In a patient who is diagnosed with endometrial cancer, pre-management workup is essentially directed toward assessing the clinical stage of disease to decide the mode of initial treatment. In patients for surgery, pre-op workup also aims at determining medical fitness for surgery and deciding the extent of surgery. NCCN (2016) and ESMO 2015 [22] recommend following investigations in the initial evaluation of endometrial cancer (Table 5.1).

Table 5.1 Initial evaluation of endometrial cancer (NCCN 2016 and ESMO 2015 [22])

Recommended	Optional
Clinical and gynecological examination	Genetic counseling in women <50 years and in those with family history of endometrial cancer and colon cancer
Histopathology of endometrial biopsy	Cervix biopsy or MRI in suspected cases of cervical involvement
CBC including platelets	CA-125 (optional), MRI, CECT in suspected extrauterine disease
Chest X-ray	FDG PET-CT ([18F] 2-fluoro-2-deoxy-D-glucose positron emission tomography) in suspected distant metastases
Liver function and renal function tests	Immunohistochemistry (IHC) and microsatellite instability (MSI) screening to identify individuals at risk for Lynch syndrome

Table 5.2 Staging of endometrial cancer (FIGO: 2009) [23]

Stage I	Tumor confined to the corpus uteri		
	IA	NO or less than half myometrial invasion	
	IB	Invasion equal to or more than half of the myometrium	
Stage II	Tumor invades cervical stroma, but does not extend beyond the uterus		
Stage III	Local and/or regional spread of the tumor		
	IIIA	Tumor invades the serosa of the corpus uteri and/or adnexa	
	IIIB	Vaginal and/or parametrial involvement	
	IIIC	Metastasis to pelvic and/or para-aortic lymph nodes	
		C1	Positive pelvic nodes
		C2	Positive para-aortic lymph nodes with or without positive pelvic lymph nodes
Stage IV	Tumor invades bladder and/or bowel mucosa and/or distant metastases		
	IVA	Tumor invasion of bladder and/or bowel mucosa	
	IVB	Distant metastases, including intra-abdominal metastases	

Staging of Endometrial Cancer

Endometrial cancer is generally staged according to the International Federation of Gynecology and Obstetrics (FIGO) system [23]. In May 2009, a new staging system was published, replacing the previous staging of 1988 (Table 5.2).

Imaging in the Pre-op Workup of Endometrial Cancer

Although staging of endometrial cancer is recommended to be done surgically, imaging plays an important role in the treatment planning and predicting prognosis of the disease. Pre-op staging also helps in determining the need for lymphadenectomy, radical hysterectomy, and preoperative radiotherapy and in assessing for hormonal treatment in women who are desirous of further childbearing. Various imaging modalities like TVUS, Doppler, CECT, MRI, and FDG PET have been studied in predicting the extent of disease.

TVUS

Tumor spread within the uterus can be assessed by TVUS by the virtue of its high resolution, but extrauterine spread and nodal involvement cannot be assessed efficiently owing to its poor tissue penetration. Researchers have found high levels of accuracy in detecting deep myometrial invasion (99 %) and cervical extension (96 %) using TVUS [24]. In another study where TVUS was compared with MRI, the accuracy of TVUS for detecting deep myometrial invasion was 68 %, and cervical extension was 69 % [25]. This wide variation in reported accuracies can be attributed to operator expertise, technical factors, and patients' body habitus. Researchers have even studied intrauterine sonography using high-frequency micro-tip probe inserted transcervically and have reported improved accuracy in assessing depth of myometrial invasion when compared to TVUS [26].

Doppler

Inconclusive data exist in the literature regarding the use of Doppler in pre-op staging of endometrial cancer. Some researchers have found it to be useful in predicting deep myometrial invasion, but not for tumor grade or nodal spread [19]. Yet others have reported a statistically significant association between pelvic lymph node metastases and vascular density [27].

Magnetic Resonance Imaging (MRI)

MRI is the most important imaging investigation for pre-op staging of EC. The accuracy of MRI in determining myometrial invasion, cervical involvement, and extrauterine spread is reportedly better than that of CECT or TVUS [28] (Figs. 5.5 and 5.6).

These investigators have also compared MRI with visual inspection of a surgical specimen in evaluation of myometrial invasion and cervical involvement and found that MRI is 90 % accurate in predicting myometrial invasion and 80 % accurate for cervical involvement. Errors in assessing myometrial invasion can occur in women with fibroids and adenomyosis and in women with distension of the endometrial cavity. They also mention that contrast-enhanced MRI (gadolinium) performs better than plain MRI.

Evaluation of lymph nodes by MRI was improved by addition of ferumoxtran-10, which evaluates nodal function rather than size [29] as normal-sized nodes can harbor micro-metastatic disease, whereas enlarged nodes may be reactive in nature.

CECT

CECT has a limited role in evaluating patients with early disease. Advantage of CECT is that its resolution is not compromised by bowel or patient motion when compared to MRI, and this property enables CECT to reliably detect distant parenchymal metastases, peritoneal implants, and malignant ascites [30]. Table 5.3

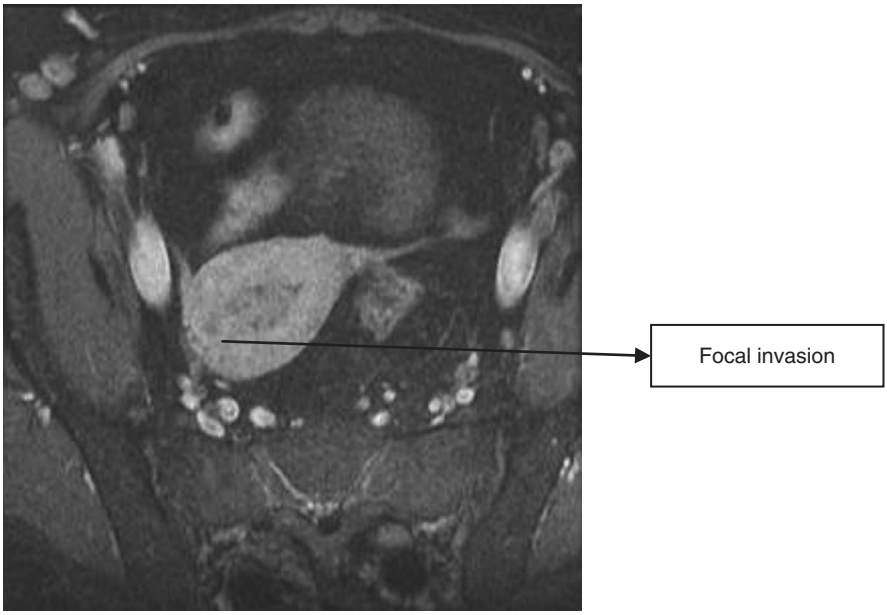

Fig. 5.5 MRI showing superficial myometrial invasion

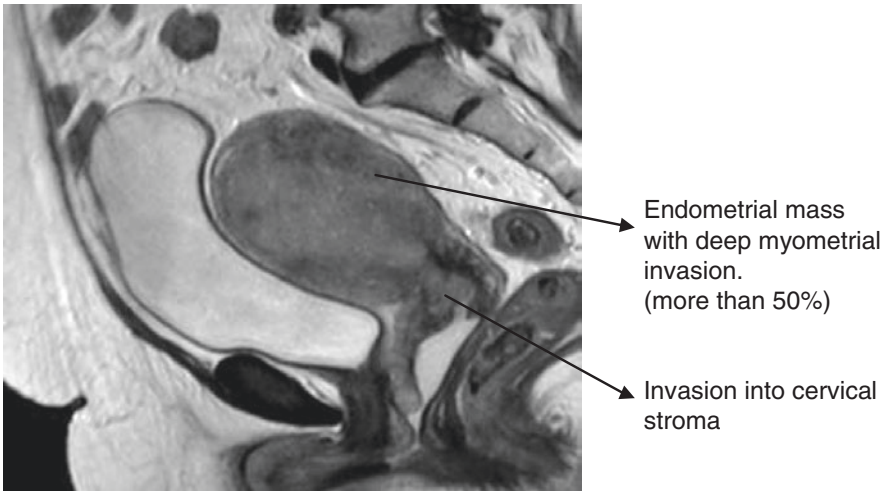

Fig. 5.6 MRI showing deep myometrial invasion and cervical stromal involvement

Table 5.3 Accuracy of imaging in the workup of endometrial Ca

Imaging modality	Cervical stromal involvement %	Myometrial invasion %	Distant spread
USG [27]	69	68	Poor
MRI [30]	80	90	Good
CECT [31]	58	76	Good

summarizes three important modalities in the pre-management evaluation of endometrial carcinoma.

PET

Positron emission tomography (PET) with the radioactive glucose analogue 18-2-fluoro-2-deoxy-D-glucose (FDG PET [18F]) has been used in various malignancies to detect nodal involvement, but it was not found to be useful in early endometrial cancer because of its limited ability in detecting micro-metastases in normal-sized nodes with sensitivity for nodal metastases of 63 % and a specificity of 98 % [32]. However, when used along with CECT or MRI, FDG PET images performed better in detecting extra-pelvic and nodal metastases, and currently research is ongoing regarding the role of fusion PET-CT scanning for pre-op staging of endometrial Ca [33].

Workup for Fertility-Preserving Therapy

Around 4 % of patients with endometrial carcinoma are <40 years of age, and majority of them may be desirous of future childbearing. The standard approach for the management of endometrial cancer in young women of childbearing age is hysterectomy and bilateral salpingo-oophorectomy with or without lymphadenectomy. Although this treatment is highly effective, it also results in a permanent loss of reproductive potential. In such patients, fertility-preserving approach using high-dose oral progestins could be considered when the tumor is of low grade and confined to the endometrium. D&C is superior to Pipelle biopsy in terms of accuracy of the tumor grade, and the initial stage should be confirmed by an enhanced pelvic magnetic resonance imaging (MRI) to exclude overt myometrial invasion, as well as adnexal or pelvic nodes involvement. Patients should be informed that this is a nonstandard approach, and they should be willing to accept close follow-up during and after the treatment. They should also be informed of the need for future hysterectomy in case of failure of the treatment and/or after pregnancies [22].

Conclusion

Diagnosis of endometrial carcinoma is easily accomplished by simple modalities like transvaginal ultrasonography and endometrial biopsy. Advanced imaging techniques like MRI, CECT, and FDG PET have no role in diagnosis but serve to stage the disease preoperatively to optimize treatment.

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Surgical Management of Early-Stage Endometrial Cancer

6

Hemant Tongaonkar, Samar Gupte, Devyani Mahajan, and Jyoti Kulkarni

Abstract

Most endometrial cancers are diagnosed with early-stage/uterus-confined disease and are usually cured by surgery alone.

Extrafascial hysterectomy with bilateral salpingo-oophorectomy along with comprehensive surgical staging including pelvic and para-aortic lymphadenectomy (except in low-risk disease) and peritoneal wash cytology remains the mainstay of surgical treatment of endometrial carcinoma.

Ovarian preservation may be done in young patients with low-stage, low-grade endometrial cancer after thorough counselling.

Minimally invasive surgery is recommended in low- to intermediate-risk patients with early-stage endometrial carcinoma in a skilled set-up.

Tumour stage and pathological tumour grade appear to be the most important factors influencing lymph node metastasis.

Sentinel node mapping for uterine cancer is currently being widely studied.

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Introduction

Endometrial cancer is the most common malignancy of the female genital tract in developed countries and fourth most common cancer in women after breast, lung and colorectal cancers. The incidence rate in India is much lower, it being the third commonest gynaecological cancer in India after cervical and ovarian cancers.

Most cancers are diagnosed with uterus-confined disease, which are usually cured by surgery alone. The presence of extrauterine disease significantly affects recurrence rates and survival, which emphasizes the importance of sites of disease spread and provision of appropriate adjuvant post-operative therapy.

The surgical management of early endometrial cancer has evolved over the past two decades, with introduction of comprehensive surgical staging to identify patients with extrauterine disease and an emphasis on individualization of treatment based on clinicopathological risk groupings and risk of recurrence. Surgical approaches aimed at limiting morbidity and improving quality of life in these patients without affecting cure rates are now introduced at specialist centres. Several other such approaches are being investigated for their safety and efficacy before they can be considered a part of standard clinical practice. In this chapter, we review the current "state of the art" of surgical management of early stage endometrial cancer.

Assessment of Early-Stage Endometrial Cancer

Accurate assessment of tumour stage and histology is essential to plan optimum therapy for patients with early stage endometrial cancer.

Although endometrial cancer is generally diagnosed with the help of pelvic ultrasonography followed by hysteroscopic evaluation and endometrial biopsy or curettage, additional imaging may be considered in order to better define the myometrial invasion, cervical, ovarian, peritoneal, nodal involvement and distant spread. An MRI is most accurate in defining the local extent of the disease within the uterus [1], while a CT scan [2] or a PET-CT scan is necessary to define extrauterine spread of the disease [3–6]. However, since endometrial cancer is a surgically staged disease, it is not mandatory to do these pre-operative imaging studies, since these imaging studies have been rarely found to alter the management of patients with uterine cancers especially of the endometrioid variety [7].

Pre- and intraoperative assessment of histology in terms of histological subtype and the tumour grade by an experienced oncopathologist cannot be overemphasized as the management strategy, and prognosis depends on these factors [8, 9].

Surgical Management of Apparent Stage I Endometrial Cancer

Extrafascial hysterectomy with bilateral salpingo-oophorectomy along with comprehensive surgical staging including pelvic and para-aortic lymphadenectomy and peritoneal wash cytology remains the mainstay of treatment of endometrial cancer.

The need for a comprehensive staging is based on the fact that nearly 20 % of women believed pre-operatively to have early stage uterine cancer are found to have advanced (stage III–IV) disease [10]. It is no longer considered necessary to remove a vaginal cuff along with extrafascial hysterectomy at surgery.

Radical hysterectomy for stage II endometrial cancer has not been found to impart survival benefit as compared to extrafascial hysterectomy but was associated with more adverse events. However, radical hysterectomy is recommended in the presence of parametrial spread.

Ovarian preservation may be done in young patients with endometrial cancer who are more likely to have low-stage, low-grade tumours, after a thorough discussion of the benefits and risks of preserving the adnexa. This is important to avoid an early surgical menopause and the early and late consequences thereof. Before contemplating ovarian preservation, it is essential to rule out a synchronous ovarian cancer or ovarian metastases from endometrial cancer intraoperatively. Numerous studies have reported that ovarian preservation may be safe and has no adverse impact on overall survival of these young patients with early stage endometrial cancer [11]. Ovarian preservation is not recommended in patients with family history of breast/ovarian/uterine cancers, in non-endometrioid histology and in advanced stages.

Omentectomy is also considered a part of the standard surgical protocol for papillary serous carcinomas especially where peritoneal implants may be present. However, it is not recommended for clear cell carcinomas.

Current literature suggests that management of women by a gynaecologic oncologist in high-volume institutions results in improved disease-specific survival [12].

Surgical Approach

Surgery may be carried out by the open, laparoscopic or robotic approach.

Traditionally, surgical staging of endometrial cancer has been accomplished by laparotomy. Many prospective and retrospective studies in 1990s demonstrated feasibility of laparoscopic surgery for endometrial cancer [13, 14]. Numerous randomized controlled trials have compared the surgical- and disease-related outcomes after open versus laparoscopic surgery for endometrial cancer. The largest amongst these, the LAP-2 study, accrued 2626 patients of stage I–IIA endometrial cancer, who were randomized to open (n = 920) versus laparoscopic (n = 1696) [15]. All patients underwent hysterectomy, bilateral salpingo-oophorectomy, pelvic and para-aortic lymphadenectomy and peritoneal cytology. The laparoscopic arm was associated with a longer operative time but a shorter post-operative stay. The post-operative adverse events were similar in both the arms, with a lesser incidence of moderate to severe side effects in the laparoscopic arm (14 % vs. 21 %, $p < 0.0001$). Although there was a high (25.8 %) conversion rate to laparotomy in the laparoscopy arm, there was no significant difference in the overall detection of advanced-stage disease between the two arms. The high rate of conversion to laparotomy was more related to the lymphadenectomy part of the surgery and dependent on the learning curve of the operator. Long-term outcomes of the LAP-2 study published

in 2012 showed a non-inferiority (defined as no more than 40 % increase in the risk of recurrence with laparoscopy compared to laparotomy) of recurrence-free interval (HR for laparoscopy vs. laparotomy 1.14) and equivalent estimated overall survival (89.8%) [16].

Two meta-analyses have compared the outcomes between the two approaches. Zullo et al. [17] in a meta-analysis of eight trials concluded that the estimated blood loss and the post-operative complications were significantly lower in the laparoscopic arm, while the operative time was significantly longer in the laparoscopy arm. Intraoperative complications were no different in the two groups and were related to the training of the operative surgeon [17]. The updated meta-analysis published by Palomba in 2009 observed that there was no difference in the adverse events as well as in the disease-free survival, overall survival or cancer-related survival [18]. Although there is a paucity of published data from RCTs comparing robotic with open/laparoscopic approach, one expects the results of robotic approach to be equivalent to the older approaches. However, the cost [19, 20], limited availability and learning curve [21, 22], along with lack of significant measurable benefits to the patient, are limiting factors to recommend routine robotic surgery in all patients.

The findings of the randomized trials and the meta-analysis provide definitive evidence of short-term safety benefit and cost-effectiveness of laparoscopic surgery in all patients, including those with co-morbidities, obesity and advanced age, along with similar recurrence-free and overall survival [23, 24]. From the available evidence, one can conclude that minimally invasive surgery is recommended and in fact considered the preferred surgical approach in low- to intermediate-risk patients with early stage endometrial cancer, provided the surgeon is trained in advanced surgical techniques needed to perform retroperitoneal lymphadenectomy. The extrapolation of the same to high-risk patients is debatable.

In patients who are medically unfit to undergo standard open or minimally invasive surgery for endometrial cancer, vaginal hysterectomy with bilateral salpingo-oophorectomy may be considered, especially in low-risk patients who may not need systematic lymphadenectomy [25]. For some women who are old, obese or have severe medical co-morbidities, the risk associated with open or laparoscopic surgical staging may overweigh its potential benefit [12]. The vaginal approach does not allow a thorough exploration of the abdominal cavity, peritoneal washings, lymphadenectomy and omentectomy and hence is not suitable for patients at risk of extrauterine disease. Several studies have reported similar survival rates with vaginal hysterectomy versus abdominal hysterectomy for early stage endometrial cancer in patients with a high surgical risk [26–28].

Lymphadenectomy

The indications, extent and therapeutic impact of lymphadenectomy remains one of the most controversial and contentious issues in management of endometrial cancer. Undoubtedly, it is an integral part of the comprehensive surgical staging,

endometrial cancer being a surgico-pathologically staged cancer. Currently, a systematic pelvic and para-aortic lymphadenectomy is the only way to accurately identify the presence of nodal disease in women with endometrial cancer [29, 30]. Nearly 20 % of patients with endometrial cancer are understaged in the absence of systematic lymphadenectomy [10]. It is also useful for prognostication (90 % 5-year survival in node-negative versus 54 % for node-positive patients) and for appropriate triage of patients for adjuvant therapy as the results of lymphadenectomy can identify patients at high risk of recurrence and guide the decision about appropriate adjuvant therapy (radiation therapy, chemotherapy, etc.). It thereby helps to individualize treatment and prevent unnecessary overtreatment or inappropriate undertreatment. The therapeutic value of lymphadenectomy, however, remains unclear and debated.

Risk of Lymph Node Metastases

Endometrial cancer is a surgico-pathologically staged cancer. The GOG 33 protocol, a prospective surgico-pathological study published in 1987, clearly showed the limitations of clinical staging compared with surgico-pathological assessment. Metastatic disease was identified in a significant percentage of patients, when comprehensive staging was performed in apparently stage I patients with disease confined to the uterus. Based on this, the FIGO changed over to a surgical staging system for endometrial cancer in 1988 [31].

Tumour stage and pathological tumour grade appear to be the most important factors influencing lymph node metastases. Creasman et al. [10] reported that the overall incidence of lymph node metastases in clinically uterus-confined endometrial cancer was about 3 % in grade I, 9 % in grade II and 18 % in grade III tumours and less than 5 % in <50 % myometrial invasion, 15 % of grade I–II tumours with >50 % myometrial invasion or grade III with <50 % of myometrial invasion and >40 % in grade III >50 % myometrial invasion. Boronow et al. noted that patients with outer one third of myometrial involvement had a 25 % incidence of pelvic node metastases and 17 % para-aortic lymph node metastases as compared to only 1 % incidence of nodal metastases in patients without myometrial invasion [32]. Chi et al. reporting on the incidence of lymph node metastases in patients with surgically staged endometrioid endometrial cancer confirmed that as the tumour grade increased, the risk of myometrial invasion also increased. In their series, no patient with grade I tumour on final pathology and only 2 % of patients with no myometrial invasion had lymph node metastases [33].

An intraoperative assessment of histological subtype, grade and depth of myometrial invasion in the operative specimen of hysterectomy visually and by frozen section examination is found to be fairly accurate (84–88 % accuracy) and often recommended to better define the risk of regional and distant spread and has the ability to identify patients who will benefit from systematic lymphadenectomy and adjuvant therapy [34].

Indications for Lymphadenectomy

Patients with stage I endometrial cancer are stratified into different risk groups according to their risk of extrauterine spread and relapse. This risk stratification also serves as an aid to guide optimum adjuvant therapy. Although various risk stratification models are available, the one defined by endometrial cancer consensus conference guidelines probably defines the risk groups best and is given below:

Low risk	Stage I endometrioid, grade I–II, <50 % myometrial invasion, LVSI – ve
Intermediate risk	Stage I endometrioid, grade I–II, > 50 % myometrial invasion, LVSI – ve
High-intermediate risk	Stage I endometrioid, grade III, <50 % myometrial invasion, regardless of LVSI status
	Stage I endometrioid, grade I–II, LVSI +ve, regardless of depth of invasion
High risk	Stage I endometrioid, grade III, >50 % myometrial invasion, regardless of LVSI status
	Stage II
	Stage I with non-endometrioid histology

Patients with low-risk endometrial cancer have a low risk of lymph node involvement and do not benefit with systematic lymphadenectomy, and hence it is not routinely recommended in them [25, 35, 36].

Patients with intermediate-, high-intermediate- and high-risk endometrial cancer have a higher probability of having extrauterine disease and also have demonstrated survival benefit with systematic lymphadenectomy. Hence, a comprehensive pelvic and para-aortic lymphadenectomy is recommended in them for staging and therapeutic planning purposes [25].

Extent of Lymphadenectomy

In published literature, the extent of lymphadenectomy for endometrial cancer has been extremely variable, ranging from no lymphadenectomy to pelvic and/or para-aortic lymph node sampling to a comprehensive pelvic and para-aortic lymphadenectomy. Although there is no standard definition of "optimum lymphadenectomy" for endometrial cancer, it is clear that lymph node sampling has a low sensitivity for detecting lymph node metastases, since para-aortic lymph nodes may be involved in the absence of positive pelvic nodes [10].

The question of the optimal extent of lymphadenectomy was answered in a retrospective study of 281 patients with endometrial cancer who underwent comprehensive pelvic and para-aortic lymphadenectomy. Twenty-two percent of patients with high-risk endometrial cancer had lymph node metastases – 51 % of these had metastases in both pelvic and para-aortic nodes, 33 % had positive pelvic nodes only, while 16 % had isolated positive para-aortic nodes in the absence of metastatic

pelvic nodes, with majority of patients with para-aortic metastatic nodes (77 %) having positive nodes above the level of inferior mesenteric artery [37]. On the other hand, they also found that patients with low-risk disease had no lymph node metastases and did not benefit from a systematic lymphadenectomy. Similar findings have been reported by other authors [38]. This suggests that para-aortic nodes should be removed whenever lymphadenectomy is indicated and that it is essential to extend the upper limit of lymphadenectomy to the level of renal vessels.

There are two ways to judge the adequacy of lymphadenectomy. The more accurate way is to perform a complete pelvic and para-aortic lymphadenectomy as per the anatomic templates. The other is to measure the lymph node count in the surgical specimen, which is a surrogate marker for adequacy of lymph node dissection (it has been shown that patients with more than 10–12 nodes removed during lymphadenectomy have an improved survival). In the collated data of 16,995 patients of endometrial cancer from two randomized controlled trials and seven observational studies, Kim et al. demonstrated an improved overall survival with systematic lymphadenectomy (i.e. removal of more than 10–11 nodes) in patients with intermediate- and high-risk endometrial cancer but limited survival benefit in low-risk patients [39–41]. Based on this, lymph node counts have become a surrogate for adequacy of lymphadenectomy with the recommendation that more than ten nodes should be removed in an adequate lymphadenectomy [42, 43].

Does Lymphadenectomy Improve Survival?

Two randomized studies [44, 45] comparing systematic pelvic lymphadenectomy to no lymphadenectomy in the surgical management of patients with endometrial cancer demonstrated that lymphadenectomy improved surgical staging but had no impact on overall survival.

However, despite the randomized trials showing no survival benefit with comprehensive surgical staging, controversy still exists regarding the role of lymphadenectomy, mainly due to the criticisms of the ASTEC trial [46]. This trial was criticized for a faulty trial design, a high rate of crossover to radiation therapy and selection bias. Neither trial included para-aortic lymphadenectomy, and the ASTEC trial also had low lymph nodal counts. This omission of para-aortic lymphadenectomy may have negated the therapeutic effect of lymphadenectomy since more than half of the patients with positive pelvic nodes have para-aortic nodal metastases, and about 10 % of lymph node metastases occur exclusively in the para-aortic region without pelvic lymph nodal involvement as shown by the sentinel node studies [47]. Removal of para-aortic lymph nodes could probably explain the significant effect of para-aortic lymphadenectomy as shown by Todo et al. [48]. They analyzed their study of intermediate and high-risk patients who underwent surgery with pelvic lymphadenectomy with or without para-aortic lymphadenectomy. Those who had para-aortic lymphadenectomy had a survival benefit as compared to those who did not [48]. The findings of this SEPAL study, similar to the ASTEC trial, suggested that the survival effect of

lymphadenectomy is rather limited in low-risk patients but is quite substantial in the intermediate- or high-risk patients, with reduction in the risk of death (HR 0.44, $p < 0.0001$). In the ASTEC trial, patients were secondarily randomized to radiation therapy based on uterine pathology only without considering the nodal status, leaving some patients with metastatic nodes with no adjuvant therapy. The clinical benefit of triage to adjuvant therapy was obscured as 50 % of patients with lymph node metastases were randomized to no adjuvant therapy. Besides, the lymphadenectomy versus no lymphadenectomy arms were unbalanced in terms of high-risk criteria, with the lymphadenectomy arm having a greater percentage of patients with high-risk histology, high-grade tumours, presence of lymphovascular invasion and deep myometrial invasion. Lastly, this trial did not address the issue of benefit from para-aortic lymphadenectomy as patients underwent para-aortic node palpation with selective sampling rather than systematic lymphadenectomy.

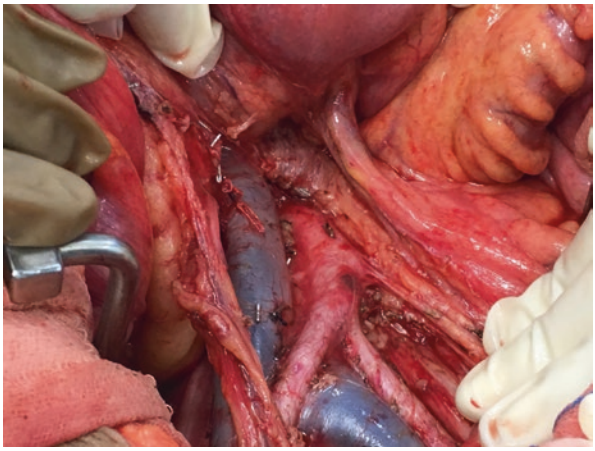
Retrospective data suggests that patients undergoing systematic lymphadenectomy had improved survival over those who had limited or no lymphadenectomy [43]. An analysis of 42,184 patients from the SEER database revealed that systematic lymphadenectomy was associated with overall and cancer-specific survival benefit (HR 0.81 and 0.78, respectively), and removal of more than 11 nodes was associated with HRs of 0.74 and 0.69, respectively [49]. Although statistically significant, the retrospective nature of the data was subject to selection bias and stage migration. Trimble et al., using a large national database, reported benefit with lymphadenectomy in grade III tumours only [50].

Sentinel Node Mapping

The lymphatic drainage of uterus is complex, with several anatomical areas at risk for metastases. The sentinel node is defined as the first node in the lymphatic basin that receives the lymphatic flow. If the SLN is negative for metastatic disease, other nodes in the template are expected to be free of disease involvement. The advantage of SLN biopsy is the potential for improved diagnostic accuracy with use of ultrastaging while lowering morbidity [51, 52]. Sentinel node biopsy in particular has the advantage of limiting the risk of lymphedema, which is seen in 6–38 % of patients following pelvic lymphadenectomy [53, 54].

Sentinel node mapping for uterine cancer was first described by Burke et al. [55]. They reported on 15 patients who had SLN mapping followed by complete pelvic and para-aortic lymphadenectomy. They reported an overall SLN detection rate of 67 %. Four patients had positive lymph nodes – two of these were detected by SLN mapping with blue dye, one had a positive non-sentinel node and one had bulky nodes without dye uptake. Khoury-Collado et al. (2011) could successfully identity the sentinel node in 84 % of the cases in their study of 266 cases of endometrial cancer, with 12 % incidence of metastatic nodes and 3 % metastatic nodes being confirmed by immunohistochemistry [56]. Ballester et al. [51] in their multicentre SENTI-ENDO trial showed that 10 % of low-risk and 15 % of intermediate-risk patients were upstaged using the sentinel node technique [51].

The greatest challenge in using the SLN technique in endometrial cancer is to identify the optimum injection site that properly represents the drainage of the tumour. Most large series till date have used cervix as the injection site. In recent times, endometrial site of injection using the hysteroscopic, ultrasound-guided, laparoscopic and open approaches has been investigated. Hysteroscopy allows injection of the tracer in the mucosal space just around the tumour and at least conceptually should be the best way to delineate the drainage of the tumour. Hysteroscopic injection also allows a complete detection of the drainage of the uterine corpus directed to both pelvic and para-aortic nodes, thereby decreasing the false-negative rates. The first report of hysteroscopy-guided SLN technique by Nilkur et al. [47] showed a detection rate of 82 % with no false negatives. Subsequently, Maccauro et al. [57] and Raspagliesi et al. [58] reported a detection rate of 100 % with no false negatives [57, 58]. Presently, however, there is no definite evidence that these technically more demanding injection approaches have a definite benefit over cervix as the injection site [59].



Para Aortic Lymphadenectomy

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Minimally Invasive Surgery for Endometrial Cancer

7

S.P. Somashekhar

Abstract

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. Laparoscopic method is established as a standard technique with the landmark trial of GOG LAP2.

Robotic approach further enhances the benefits of laparoscopy with similar results especially in obese women. However, randomized trials are awaited in this regard. Early case series thus far reported suggest robotic surgery for endometrial cancer is feasible.

Main advantages of robotic technology over laparoscopy include 3D vision with better camera, more flexible instruments, less conversion rate, ease of surgery, surgeon's comfort, and shorter learning curve.

Current limitations of robotic surgery are mostly due to mechanical/energy source-related instrument problems, high cost, and longer operating time.

The extent of surgery depends on the stage and extent of disease.

Adjuvant treatment is offered based on surgical stage and adverse factors.

Chemoradiation shows promising results in high-risk and advanced-stage disease.

Systemic treatment of metastatic and relapsed disease may consist of endocrine therapy or cytotoxic chemotherapy.

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Introduction

Endometrial cancer is the sixth most common malignancy among females worldwide. In developed countries, endometrial cancer is the fourth most common cancer in women [1]. Endometrial cancer is common in western women, and the rates are very high; however, in India, the rates are as low as 4.3 per 100,000 (Delhi) [2]. More than 90 % of cases occur in women older than 50 years of age, with a median age of 63 years. Chronic estrogen exposure is the most common risk factor followed by genetic predisposition (10 %), e.g., HNPCC/Lynch syndrome and chronic liver disease like cirrhosis. Most cases of endometrial cancer are diagnosed in early stages since abnormal uterine bleeding is the presenting symptom in 90 % of cases.

Endometrial cancer is staged according to the International Federation of Gynecology and Obstetrics (FIGO 2009) system [3]. Preoperative imaging is not mandatory. Dynamic contrast-enhanced magnetic resonance imaging (MRI) is the best tool to assess the cervical involvement [4, 5]. In a few studies, MRI has been shown to accurately evaluate the depth of myometrial invasion. A prospective collaborative trial, comparing MRI and ultrasonography (US), reported that the accuracy of US is comparable to that provided by MRI [6], but US is highly operator dependent. CA-125 marker is raised in extrauterine disease and is a bad prognostic marker.

Multiple factors have been identified for high risk of recurrence in apparent early-stage disease: histological subtype, grade 3 histology, myometrial invasion ≥50 %, lymphovascular space invasion (LVSI), lymph node metastases, and tumor diameter >2 cm. In this regard, stage I can be subdivided into three risk categories:

Low risk: stage IA (G1 and G2) with endometrioid type
Intermediate risk: stage IA G3 with endometrioid type and stage IB (G1 and G2) with endometrioid type
High risk: stage IB G3 with endometrioid type, all stages with non-endometrioid type

Two main clinicopathological types of endometrial cancer have been recognized, corresponding to estrogen-dependent, more common endometrioid (type 1) and estrogen-independent non-endometrioid carcinomas (type 2). Type 2 endometrial cancer carries bad prognosis. Both type 1 and type 2 have different etiopathogenesis through different molecular pathways. Unlike typical (or "prototypical") tumors, several cases still remain morphologically ambiguous, indeterminate, or hybrid adenocarcinomas, requiring immunohistochemistry (ER, PR, p53, p16, PTEN) and eventually mutational analysis to allow for a correct interpretation.

Surgical Treatment

The surgical approach for the treatment of endometrial cancer has traditionally been laparotomy. Nevertheless, in the last 15 years, the use of minimally invasive techniques has been widely accepted by many authors. A recent publication of the

Gynecologic Oncology Group (GOG) LAP2 study has shown similar operative outcomes in the minimally invasive surgery and in the laparotomy group. Laparoscopy seems to provide equivalent results in terms of disease-free survival and overall survival compared with laparotomy, with further benefits: shorter hospital stay, less use of pain killers, lower rate of complications, and improved quality of life. A potential enhancement to laparoscopy has been provided by the robotic approach with a high "benefit" in obese women. Since 2002, the use of robotic-assisted laparoscopy has advanced rapidly, particularly in the United States. The largest published series of robotic surgery was reported in 2011 by Paley et al. [10]. The major complication rate was significantly less with robotic surgery (20 % vs. 6.4 %) compared with laparotomy, particularly related to wound complications and infections.

Surgical Treatment in Stage I Endometrial Cancer

The standard surgical approach for stage I endometrial cancer consists of total hysterectomy and bilateral salpingo-oophorectomy (BSO) with or without lymphadenectomy [I, A]. Lymphadenectomy could be important in determining a patient's prognosis and in tailoring adjuvant therapies. Hence, many authors suggest a complete surgical staging for intermediate high-risk endometrioid cancer (stage IA G3 and IB) [II, B]. Randomized trials have failed to show a survival or relapse-free survival benefit in stage I endometrial cancer [I, A], and the role of systematic pelvic lymphadenectomy is an issue of current debate. In an Italian study, 514 patients with stage I endometrial cancer were randomized to receive lymphadenectomy or not (excluding stage IA–IB G1 and non-endometrioid histotype). In this study, systematic lymphadenectomy did not improve disease-free or overall survival [11]. In the ASTEC trial, 1408 women with malignancies confined to the uterus were randomized. In this trial, there was no evidence of a benefit on overall survival or recurrence-free survival when pelvic lymphadenectomy was carried out [12]. The authors concluded that routine systematic pelvic lymphadenectomy cannot be recommended in women with stage I endometrial cancer, unless enrolled in clinical trials. However, the design of these studies has not addressed the most important impact of lymphadenectomy in the high-risk population in order to identify patients who can safely avoid or benefit from adjuvant treatment. A large retrospective study published in 2010, comparing systematic pelvic lymphadenectomy vs. systematic pelvic and para-aortic lymphadenectomy (SEPAL) study, has suggested that overall survival was significantly longer in patients undergoing pelvic and para-aortic lymphadenectomy [13]. The SEPAL study suggests that high-risk patients may benefit from aggressive surgery. Sentinel lymph node identification in endometrial cancer has been described with interesting preliminary results, which deserve further investigation in properly designed clinical studies. Further randomized trials will be focused on investigating the role of lymphadenectomy for patients with high-risk endometrial cancer to direct subsequent treatment and the role of sentinel node biopsy.

Surgical Treatment in Stage II Endometrial Cancer

Traditionally, the surgical approach consists of radical hysterectomy with bilateral salpingo-oophorectomy and systematic pelvic lymphadenectomy with or without para-aortic lymphadenectomy. In stage II, lymphadenectomy is recommended to guide surgical staging and adjuvant therapy.

Robotic-Assisted Surgery for Endometrial Cancer

The benefits of robotic surgery as a minimally invasive surgical technique parallel those of traditional laparoscopy, with the added advantages of overcoming several barriers to the use of laparoscopy.

Basics of Robot

Surgeon performs 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 were once only possible with open surgery. Robotic machine has three parts – surgeon's console (Fig. 7.1), patient cart (Fig. 7.2), and optical cart. Surgeon's 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 robot have better surgeon's console and patient cart.

Robotic surgery enables surgeons to be more precise, advancing their technique and enhancing their capability in performing complex minimally invasive surgery.

Binocular stereoscopic 3D vision with stability of camera and 10× magnification allows the surgeon better visualization of the anatomy, which is especially 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.

It mimics the human hand in its flexible movement and also overcomes limitations of it, like 7° of movement and 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 laparoscopy for complex procedures because they generally find that fine-tissue manipulation such as dissecting and suturing to be more difficult. Intuitive technology, however, enables the use of robot for complex procedures. The robot allows for 7° 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).

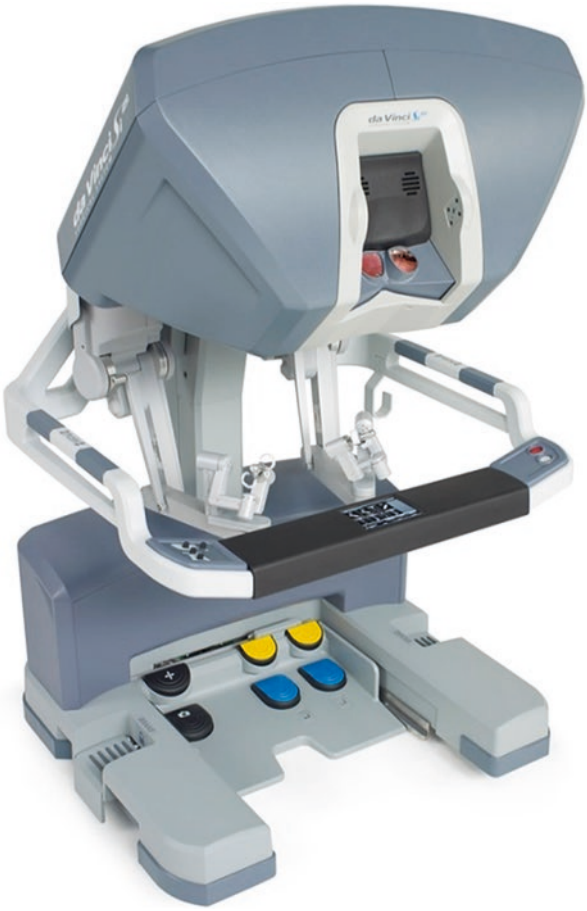


Fig. 7.1 Surgeon's console

Motion scaling and precision of surgical movements during robotic surgery improve the quality of surgery. Extremely easy and fast suturing and knotting and multitasking instrumentations decrease operative time. Surgeon sits and operates at ease with less fatigue, translating to safe surgery.

Surgical Technique

Preoperative Preparation

Patient takes clear liquids a day prior to surgery. Proctoclysis enema and two Dulcolax (bisacodyl) tablets are given per oral a night before the surgery. We do not administer Peglec which causes dilatation of the bowel.

Port placement (Figs. 7.3 and 7.4) and instrumentation (Fig. 7.8)

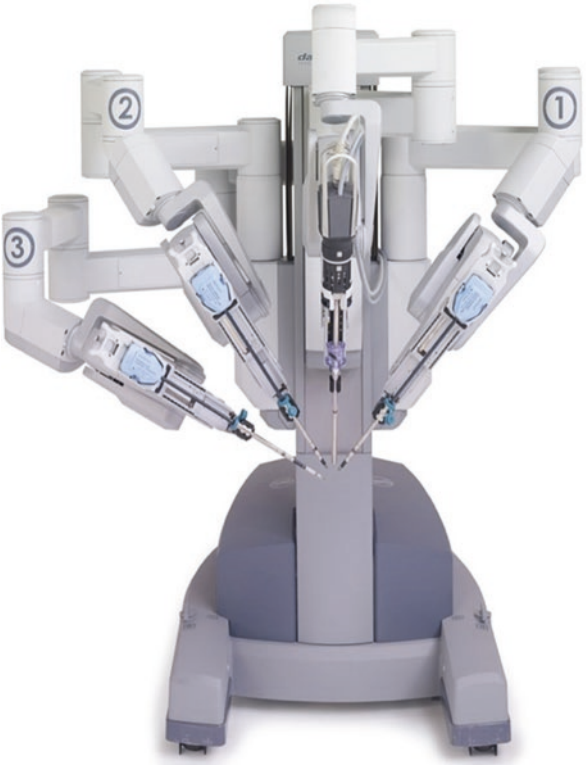


Fig. 7.2 Patient cart

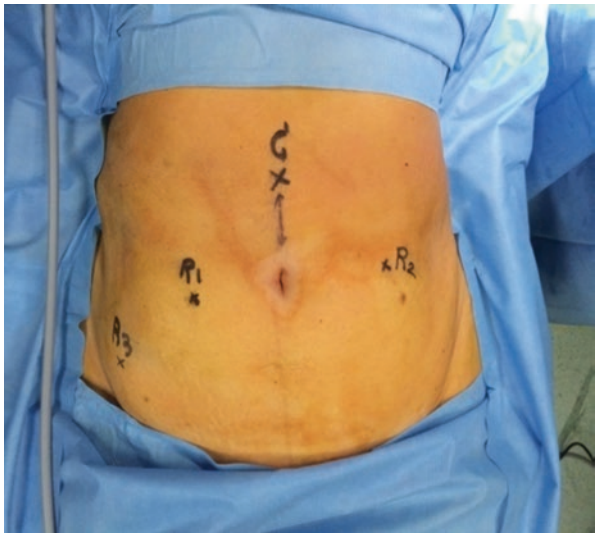


Fig. 7.3 Abdominal marking of port placement

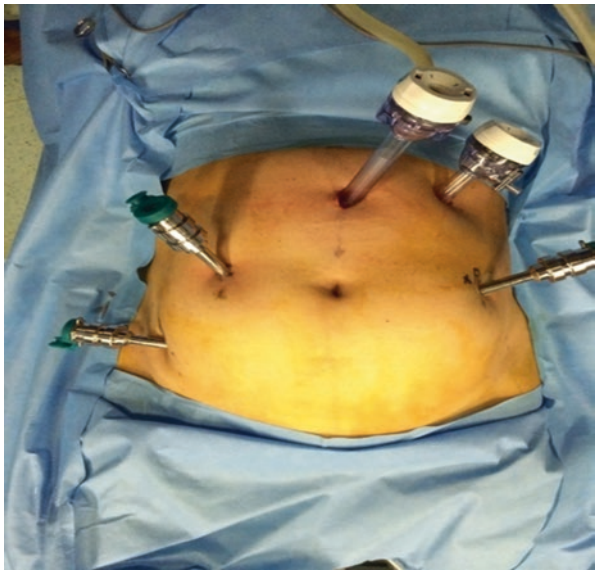


Fig. 7.4 Port placement

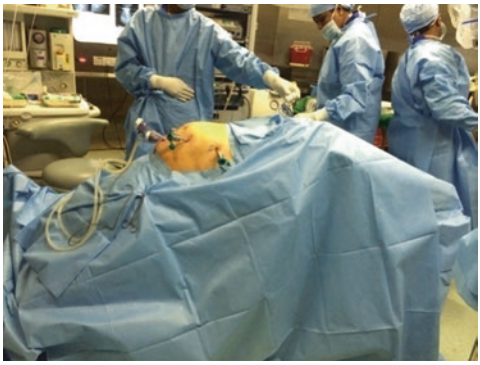
Vaginal-Cervical Ahluwalia Retractor-Elevator (VCARE) uterine manipulator is fixed to the cervix after placing patient in lithotomy position. Intraoperatively, it helps in manipulating the uterus. A 12 mm camera port is placed 3 cm above the umbilicus in the midline with optical trocar. The rest of the ports are placed after insufflating the abdomen with gas and marking the port measurements. Arm-one (8 mm) port is placed on 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 patient's left side, 8 cm lateral and 3–5 cm below the level of the camera port. Arm-three (8 mm) port is placed on patient's right side, 2 cm above the anterior superior iliac spine and 8 cm away from the first port. Assistant port (12 mm) is placed on 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.

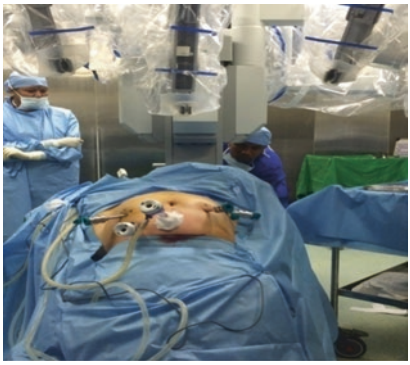
Zero-degree scope is used for all the steps, except for para-aortic lymph node dissection where 30° down scope is used. In arm-one hot shears (monopolar curved scissors), in arm-two fenestrated bipolar forceps, and in arm-three prograsp forceps is used (Figs. 7.5 and 7.6, 7.7).

After placing all the ports, the patient is positioned before docking the robot. Head end side 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 (Fig. 7.8).

Surgical Steps

Dissection is done in a circular fashion from one round ligament to the other.





Figs. 7.5 and 7.6 Patient positioning and Docking in progress

Fig. 7.7 Post docking

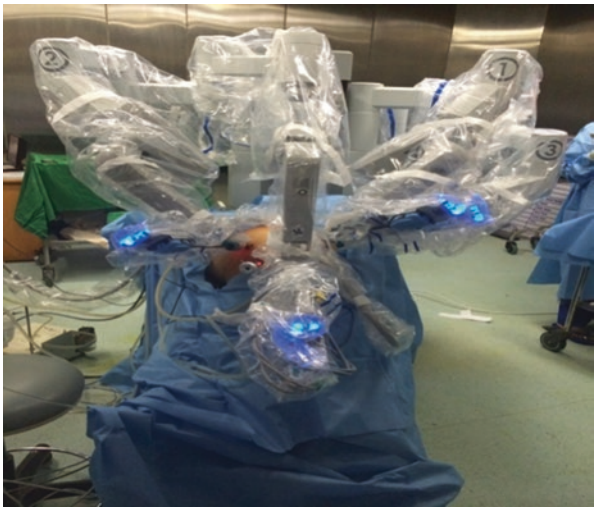
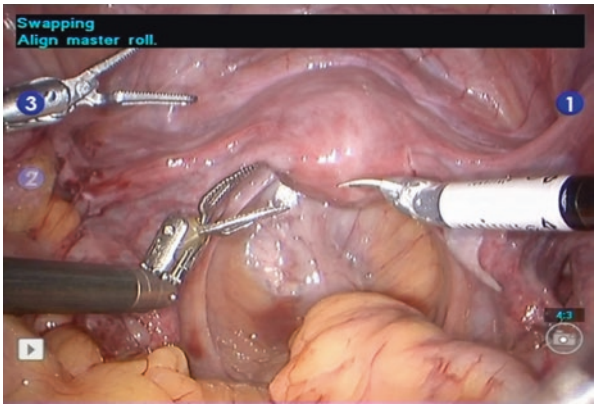


Fig. 7.8 Robotic instruments with endowrist technology



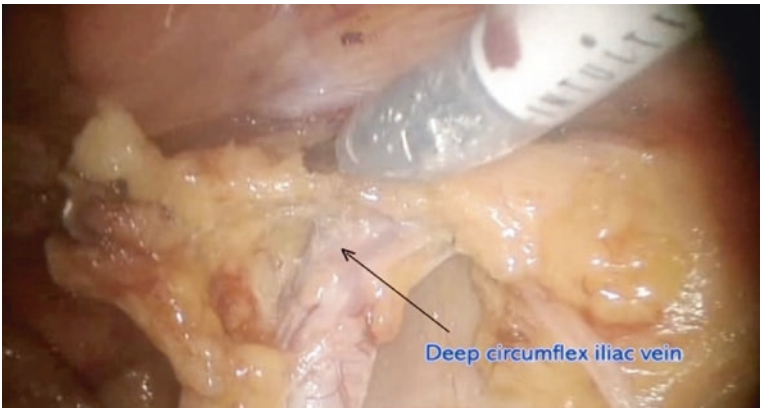


Fig. 7.9 Pelvic lymphadenectomy – distal boundary

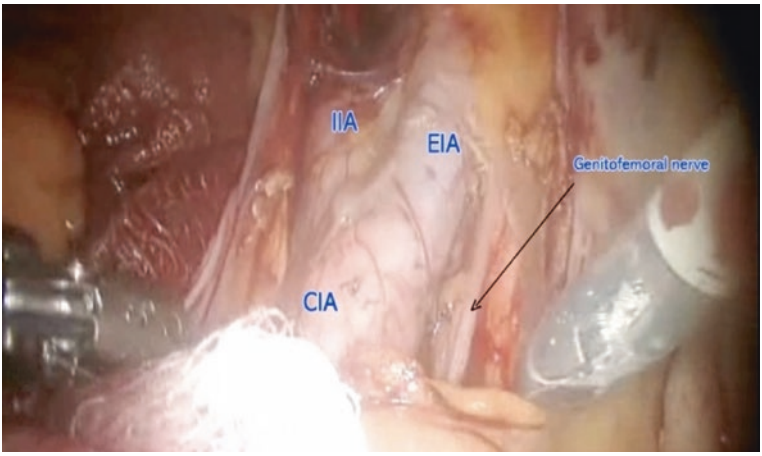


Fig. 7.10 Pelvic lymphadenectomy – lateral and proximal boundary

Step 1: The uterus is retracted to the patient's left side with the help of uterine manipulator. Dissection starts with incising the peritoneum over the 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. Pay careful attention to the course of the ureter.

Step 2:The urinary bladder is lifted up with third arm, and the uterus is retroverted with the help of 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 the 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 size ball made of mop inside a surgical hand glove.

Step 6: Bilateral pelvic lymphadenectomy (Figs. 7.11 and 7.12) is done by exposing the pararectal and paravesical spaces. Separate specimen bag is used for each side of the lymph nodes, and specimen is delivered through the vagina. Para-aortic lymph node dissection is done when indicated. The vaginal cuff is closed with a 15 cm long self-retaining polydioxanone (monofilament, violet) barb suture, and uterosacral ligaments are included laterally.

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 support 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.

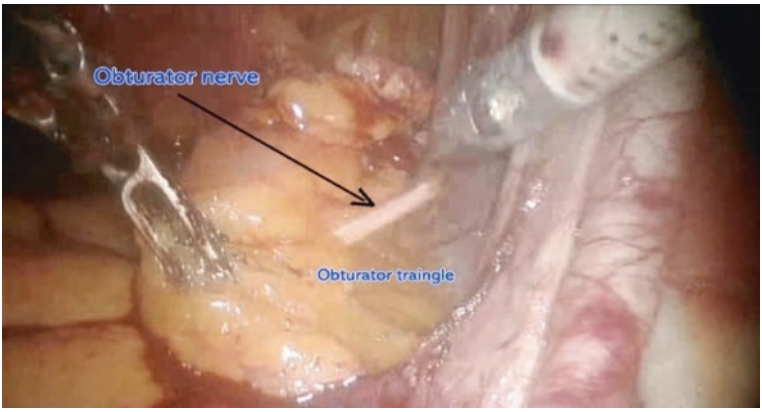


Fig. 7.11 Pelvic lymphadenectomy – inferior boundary

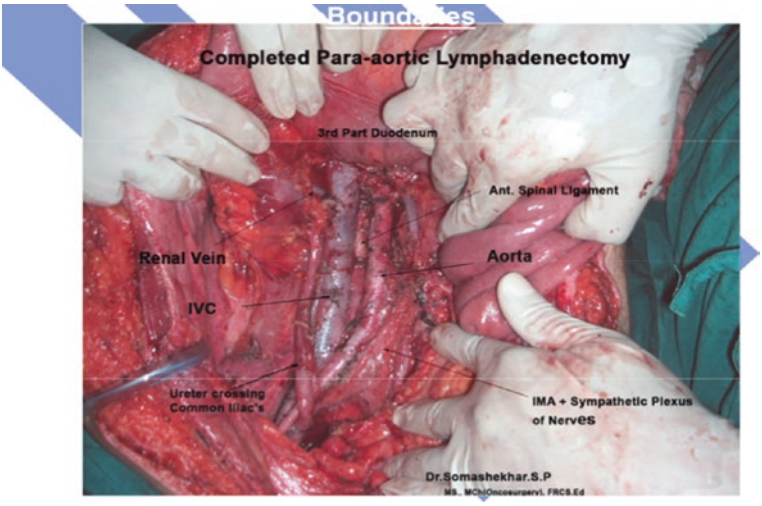


Fig. 7.12 Completed paraortic lymphadenectomy with critical structures

Anatomical spaces in pelvic dissection:

1. Paravesical space
2. Pararectal space

Anatomical boundaries:

Distal – deep circumflex iliac vein
Proximal – common iliac vessels
Laterally – genitofemoral nerve
Inferiorly – obturator fossa (Figs. 7.9 and 7.10)

Para-aortic Lymphadenectomy

Boundaries

Superiorly – renal vein
Inferiorly – common iliac vessels
Laterally – ureter

Evolving Evidence

Efficacy of Laparoscopy

The Gynecologic Oncology Group (GOG) has completed a phase III randomized study (lamina-associated polypeptide 2 (LAP2)) comparing laparoscopy vs.

laparotomy in endometrial cancer [9]. Patients with clinical stage I–IIA uterine cancer were randomly assigned to laparoscopy ($n = 1696$) 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 % *v* 21 %, respectively; $P = .0001$) but similar rates of intraoperative complications, despite having a significantly longer operative time (median, 204 *v* 130 min, respectively; $P = .001$). Hospitalization of more than 2 days was significantly lower in laparoscopy vs. laparotomy patients (52 % *v* 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 pre-specified 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 the UK institutions, the Laparoscopic Approach to Cancer of the Endometrium (LACE) trial anticipated to randomize 590 patients to total laparoscopic hysterectomy and lymph nodal staging vs. standard, open surgery [11].

Disadvantages of laparoscopy:

- Steep learning curve
- Limited dexterity
- Counterintuitive motion
- Two-dimensional field
- Limited depth perception
- Ergonomic difficulty

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 problems. However, at the same time, obesity increases the degree of difficulty of management via laparoscopy, maybe to the extent that the level of difficulty may become prohibitive in accomplishing the operation. 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. These patients were compared 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 vs. 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; $P = 0.001$). 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 were 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 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 chronologic order of each group of 20 cases demonstrated a decrease in operative time: 183.2 (69) min (95 % CI, 153.0–213.4) for cases 1–20, 152.7 (39.8) min (95 % CI, 135.3–170.1) for cases 21–40, and 148.8 (36.7) min (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 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-assisted surgery 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 oncological 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. 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.

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 camera arm.
- Filters human tremor.
- Ergonomic with equal access with both left- and right-sided ports.

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. Mean number of lymph nodes removed were 30.56 vs. 27.6 which is suggestive of significant difference statistically. Operative time decreased as the experience of the surgeon increased but still significantly remained higher than the open procedure after 25 robotic-assisted surgeries. All robotic surgeries were completed successfully without converting to open method. Robotic-assisted staging procedure for endometrial cancer is feasible without converting to open method, with the advantages of decreased blood loss, short duration of hospital stay, and less postoperative minor 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. two 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 operating time (242 vs. 287 min, $P < 0.001$) and total room time (305 vs. 336 min, $P < 0.001$) was shorter for the robotic cohort. It was concluded that robotic hysterectomy and lymphadenectomy for endometrial cancer can be accomplished in heavier patients and result in shorter operating times and hospital length of stay, lower transfusion rate, and less frequent conversion to laparotomy when compared to laparoscopic hysterectomy and lymphadenectomy.

Magrina 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 ($p = 0.008$); and 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 robotic 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/laparotomy due to a reduced hospitalization.

Ran et al. recently reported a meta-analysis which included 22 studies [20]. These studies involved a total of 4420 patients, 3403 of whom underwent both robotic surgery and laparoscopy and 1017 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 ($p < 0.00001$) was significantly longer in robotic surgery than in laparotomy. The TLNH showed no significant difference between robotic surgery and laparotomy. Conclusions: 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 than laparotomy.

Limitations of Robotic Surgery

Apart from the absence of level 1 evidence regarding robotic-assisted laparoscopy 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]

- Additional surgical training
- Increased costs and operating room time
- Bulkiness of the devices
- Instrumentation limitations (e.g., lack of a robotic suction and irrigation device, size, cost)

- Lack of haptics (tactile feedback)
- Risk of mechanical failure
- Limited number of energy sources (i.e., less than with conventional laparoscopy)
- 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, 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 ports are typically higher in a patient than compared to traditional laparoscopy in order to have access to both the pelvis and to 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's 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.

Surgical Treatment in Stage III–IV Endometrial Cancer

Maximal surgical debulking is indicated in patients with a good performance status and resectable tumor [III, B]. For distant metastatic disease, palliative surgery could be considered in patients with a good performance status. When surgery is not

Table 7.1 Stage wise treatment protocol for endometrial cancer

Stage		Surgical treatment	Adjuvant treatment
I	IA G1–G2	Hysterectomy + BSO	
	IA G3	Hysterectomy + BSO + bilateral pelvic and para-aortic lymphadenectomy	
	IB G1–G3	Hysterectomy + BSO + bilateral pelvic and para-aortic lymphadenectomy	
II		Hysterectomy + BSO + bilateral pelvic and para-aortic lymphadenectomy	
III		Maximal surgical cytoreduction with good performance status	
IV	IVA	Anterior and posterior pelvic exenteration	
	IVB	Systemic therapy with palliative surgery	

feasible due to medical contraindications (5–10 % of patients), or because of irresectable disease, external radiotherapy with or without intracavitary brachytherapy to the uterus and vagina is suitable for individual clinical use [IV, B] (Table 7.1).

Adjuvant Treatment

Adjuvant treatment for endometrial cancer is offered based on surgical stage and adverse factors.

Radiotherapy

In 2009, a randomized trial compared vaginal brachytherapy vs. observation in stage IA G1–2 endometrial cancer with a similar overall recurrence rate, survival, and late toxic effect in the two groups. The optimal adjuvant treatment (Table 7.2) of intermediate-risk endometrial cancer is still to be defined. External beam radiation has been shown to reduce the rate of locoregional recurrence in intermediate-risk endometrial cancer. However, three large randomized studies (PORTEC-1 [13], GOG 99 [14], and ASTEC MRC-NCIC CTG EN.5 [15]) failed to demonstrate that radiation improves overall or disease-specific survival. A randomized clinical trial (PORTEC-2) comparing vaginal brachytherapy and external beam radiation in intermediate-risk patients showed that the two radiation therapies were equally effective but that the quality of life was better in the vaginal brachytherapy arm [16].

Chemotherapy

Platinum-based chemotherapy can be considered in stage I G3 with adverse risk factors (patient age, lymphovascular space invasion, and high tumor volume) and in

Table 7.2 Risk stratification and adjuvant Rx

Risk Category	Extent of disease	Adjuvant treatment
Low Risk	Superficial invasion (<1/2)	No further Rx
	Low grade (1/2)	
Intermediate Risk	High Grade	Vaginal Brachytherapy
	Deep Invasion	
	LVSI	
	Negative Lymph Nodes	
High Risk	Positive Lymph Nodes	External pelvic irradiation and vaginal brachytherapy – /+CT CT + Extended field RT
	Stage II	
	UPSC, CCCa	
	Positive P- A LNs	
PORTEC II Trial		

patients with stage II–III endometrial cancer [II, B]. Maggi et al. conducted a randomized trial in 345 high-risk patients comparing five courses of cisplatin, doxorubicin, and cyclophosphamide with external pelvic radiation. The authors reported no difference between therapies in terms of PFS or overall survival [17], a result which is also related to the insufficient sample size. A Japanese multicenter randomized trial compared whole-pelvic irradiation with three or more courses of cyclophosphamide, doxorubicin, and cisplatin chemotherapy in patients with old stage IC–IIIC endometrioid adenocarcinoma. No difference in overall survival, relapse rate, or PFS was observed [18]. In a subgroup analysis, chemotherapy appeared superior to pelvic radiotherapy in patients aged >70 years with outer half myometrial invasion, those with grade 3, those with stage II, or those with stage I disease and positive peritoneal cytology.

Combined Radiotherapy and Chemotherapy

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 radiotherapy alone in high-risk endometrial cancer patients (stage I–IIA, IIIC, any histology). The results of the two studies were pooled for analysis [19]. 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. The ongoing PORTEC-3 study is comparing radiotherapy with the concomitant and sequential use of chemotherapy and radiotherapy in patients with endometrioid stage I G3, stage II–III, and any stage serous and clear-cell carcinomas. Current evidence does not support the use of progestins in the adjuvant treatment of endometrial cancer [I, A].

Locoregional Recurrence

The standard treatment of vaginal recurrence in women who have not taken prior RT is radiotherapy (external beam plus vaginal brachytherapy) with high rates of local control, complete response (CR), and a 5-year survival of 50 %. For central pelvic recurrence, the treatment of choice is surgery or radiotherapy (no prior RT), while for regional pelvic recurrences, it is radiotherapy (no prior RT), associated with chemotherapy/hormone therapy.

Advanced Disease

There is no agreement on the standard treatment of women with advanced endometrial cancer. Typically, a combination of surgery, radiotherapy, and/or chemotherapy is employed.

In the GOG-122 trial, there were 396 patients with stage III and optimally debulked stage IV disease who were randomized to whole abdominal radiation or to doxorubicin-cisplatin chemotherapy; there was a significant improvement in both PFS (50 % vs. 38 %; $P = 0.07$) and overall survival (55 % vs. 42%; $P = 0.004$) in favor of chemotherapy [20].

Treatment of Metastatic Disease and Relapse

Systemic treatment of metastatic and relapsed disease may consist of endocrine therapy or cytotoxic chemotherapy. Hormonal therapy is recommended for endometrioid histologies only and involves mainly the use of progestational agents; tamoxifen and aromatase inhibitors are also used. The main predictors of response in the treatment of metastatic disease are well-differentiated tumors, a long disease-free interval, and the location and extent of extrapelvic (particularly pulmonary) metastases. The overall response to progestins is ~25 %. Single cytotoxic agents have been reported to achieve a response rate up to 40 % in chemotherapy-naïve patients with metastatic endometrial cancer. Among those, platinum compounds, anthracyclines, and taxanes are most commonly used alone and in combination [21]. In nonrandomized trials, paclitaxel with carboplatin or cisplatin demonstrated a response rate of >60 % and a possibly prolonged survival compared with historical experience with other non-paclitaxel-containing regimens. Based upon these results, many consider that paclitaxel-based combination regimens are preferred for first-line chemotherapy of advanced and recurrent endometrial cancer. The GOG has completed accrual to a non-inferiority randomized phase III study evaluating carboplatin/paclitaxel vs. cisplatin/doxorubicin/paclitaxel in patients with stage III, IV, or recurrent endometrial cancer (GOG 209), and published results should be available soon. Preliminary results showed that the two-drug regimen was as good as the three-drug regimen in terms of activity against the cancer and overall survival, whereas it was less toxic. Endometrial cancer recurring after first-line chemotherapy is largely a chemoresistant disease. Various agents have been tested in a number

of small phase II trials in patients previously exposed to chemotherapy. Only paclitaxel has consistently shown a response rate of >20 %. Preliminary data for several molecularly targeted agents for endometrial cancer are emerging. The PI3K/Akt/mTOR pathway is frequently upregulated in women with endometrial cancer because of loss of the tumor suppressor gene PTEN. Inhibitors of the mammalian target of rapamycin (mTOR) have shown promising early results. The mTOR inhibitor temsirolimus was associated with a 24 % response rate in chemotherapy-naïve patients. In patients with previous treatment, a 4 % response rate with disease stabilization in 46 % has been reported [22]. A recent phase II clinical trial demonstrates that single-agent ridaforolimus has antitumor activity in women with advanced endometrial cancer, most of whom had received two prior chemotherapy regimens [23]. The study met its primary end point, as 29 % of patients achieved a clinical benefit, defined as an objective response or prolonged stable disease of 16 weeks or more. Ridaforolimus also showed an acceptable toxic effect profile. Unfortunately, predictive factors have not yet been identified to select patients most likely to benefit from mTOR inhibitor therapy.

Serous Carcinoma and Clear-Cell Carcinoma

Serous and clear-cell carcinoma requires complete staging with total hysterectomy, bilateral salpingo-oophorectomy, pelvic and para-aortic lymphadenectomy, omentectomy, appendectomy, and peritoneal biopsies. They are more aggressive with higher rates of metastatic disease and lower 5-year survival rates [I, A]. There is considerable evidence from retrospective series that platinum-based adjuvant chemotherapy for early (stage I and II) disease improves PFS and overall survival [III, B] [24]. Platinum-based chemotherapy is recommended in patients with stage III or IV [I, A]. The same chemotherapy regimens usually employed for epithelial ovarian cancer can be considered in women with advanced or recurrent serous or clear-cell uterine cancer. Historically serous endometrial cancers have not been considered to be hormone responsive.

Prognosis

Endometrial cancer is generally associated with a favorable prognosis. In the EUROCARE-4 study, age-adjusted 5-year relative survival estimates reached 76 % in 1995–1999 and 78 % in 2000–2002 in Europe. Survival for patients treated in 2000–2002 was highest generally in Northern Europe (especially in Sweden) and lowest in Eastern Europe (Czech Republic and Poland) [25]. A key factor leading to this good prognosis is that most cases are diagnosed at an early stage. The most important prognostic factors at diagnosis are stage, grade, depth of invasive disease, LVSI, and histological subtype. Endometrial tumors have a 5-year survival of 83 % compared with 62 % for clear-cell and 53 % for papillary carcinomas. LVSI is present in 25 % of cases. Five-year overall survival is 64 and 88 % with or without LVSI, respectively.

Given the importance of tumor stage for both prognosis and adjuvant treatment, it is necessary to compare the performance of the 1988 and 2009 FIGO staging systems. Based on the 2009 system, survival was 89.6 and 77.6 % for stage IA and IB. The newly defined stage IIIC substages are prognostically different. Survival for stage IIIC1 was 57 % compared with 49 % for stage IIIC2 [26]. The first Indian prospective randomized trail comparing open and robotic assisted surgery in endometrial cancers revealed that minimally invasive method is similar to open method with respect to oncological outcomes. It has the additional benefit of decreased blood loss, shorter duration of hospital stay and less postoperative complications [27].

Follow-Up and Long-Term Implications

Most recurrences will occur within the first 3 years after treatment. The suggested frequency of follow-up is every 3–4 months with physical and gynecological examination for the first 2 years and then with a 6-month interval until 5 years. Further investigations can be carried out if clinically indicated. PET/CT has been shown to be more sensitive and specific than CT alone for the assessment of suspected recurrent endometrial cancer. The utility of Pap smears for the detection of local recurrences has not been demonstrated.

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Endometrial Cancer: Advanced Stage

8

Rama Joshi

Abstract

For patients with stage III/IV endometrial carcinoma, prognosis remains poor and an optimum therapy is yet to be established. Treatment is individualized based on disease extent at presentation, patient's performance status, and hormonal status of the tumor. Surgery is often the mainstay of treatment in stage III disease. The role of adjuvant radiotherapy in conferring survival is controversial. Chemotherapy is fast emerging as an effective adjuvant treatment for advanced endometrial cancer. Hormonal therapy with variable response rates has been used for metastatic and recurrent endometrial carcinoma. The GOG continues to investigate multimodality therapy.

Endometrial carcinoma is the most common malignancy of the female genital tract in the western world and the fourth most common cancer in the women after breast, lung, and colorectal cancer. Developing countries and Japan have incidence rates 4–5 times lower than western industrialized nations with the lowest rates being in India and South Asia [1].

In 2/3 cases of endometrial cancer, the tumor is confined to the corpus at the time of diagnosis where uncorrected survival rates of 75 % or more are expected [2]. In patients of advanced endometrial cancer with documented extrauterine disease of stage III or IV, the prognosis remains poor.

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In the past 50 years, the treatment of endometrial cancer has evolved from a regime of preoperative intracavitary radium packing or external pelvic radiation therapy (RT) followed in 6 weeks by hysterectomy to customized treatment program of primary surgery where hysterectomy with bilateral salpingo-oophorectomy and surgical staging has now become the standard of care management. The adjuvant treatment is employed subject to the stage of the disease and other histological risk factors. The patients of endometrial cancer are staged according to FIGO 2009 (Table 8.1) [3].

In the past 30 years, the role of chemotherapy has emerged, and various chemotherapeutic regimes have been tried and tested as the adjuvant treatment in primary setting.

Diagnosis and Staging Studies

The diagnosis of endometrial cancer is confirmed by the histopathology of endometrial curettage/endometrial biopsy. Thorough evaluation of patient, including complete physical examination, and metastatic workup can define the extrauterine spread of the disease within the pelvis or outside the pelvis, in the abdomen, and in supraclavicular or inguinal nodal areas. These patients often have comorbid conditions of obesity, diabetes, and hypertension which require to be evaluated prior to the treatment decision of the disease.

The workup includes imaging ultrasonography (USG), magnetic resonance imaging (MRI), CA125, and PET–CT when indicated. The ultrasonography and magnetic resonance imaging appear to be able to diagnose the myometrial invasion and lymph node metastasis with accuracy of 75–95 % [4–7]. The only way of accurately diagnosing the depth of myometrium invasion is by histological examination of the hysterectomy specimen.

Serum levels of CA125 are elevated in most of the patients with advanced or metastatic endometrial cancer [8]. Multivariate analysis showed lymph node metastasis had the most significant effect on elevation of CA125 levels (>40 u/ml), the sensitivity and specificity for screening lymph node metastasis being 78 % and 84 %, respectively. Thus, preoperative CA125 levels greater than 40 u/ml can be considered as an indication for full surgical staging with pelvic and para-aortic lymphadenectomy in endometrial cancer [9] and may be helpful in monitoring clinical response [10, 11].

Predicting Factors for Advance Stage

The two large prospective surgical staging GOG trials reported in 1984 and 1987 [12, 13] were the landmark trials in defining the prognostic factors of endometrial carcinoma and the current treatment approach for the patients of endometrial cancer.

Table 8.1 AJCC tumor–node–metastasis (TNM) and International Federation of Gynecology and Obstetrics (FIGO) surgical staging systems for endometrial cancer

Primary tumor (T)		
TNM categories	FIGO[a] stages	Surgical–pathological findings
TX		Primary tumor cannot be assessed
T0		No evidence of primary tumor
Tis[b]		Carcinoma in situ (preinvasive carcinoma)
T1	I	Tumor confined to the corpus uteri
T1a	Ia	Tumor limited to the endometrium or invades less than one-half of the myometrium
T2	II	Tumor invades stromal connective tissue of the cervix but does not extend beyond the uterus[c]
T3a	IIIA	Tumor involves the serosa and/or adnexa (direct extension or metastasis)[d]
TBb	IIIB	Vaginal involvement (direct extension or metastasis) or parametrial involvement
	IIIC	Metastases to pelvic and/or para-aortic lymph nodes[d]
	IV	Tumor invades the bladder and/or bowel mucosa and/or distant metastases
T4	IVA	Tumor invades the bladder mucosa and/or bowel (bullous edema is not sufficient to classify a tumor as T4)

Regional lymph nodes (N)		
TNM	FIGO	Surgical–pathological findings
NX		Regional lymph nodes cannot be assessed
N0		No regional lymph node metastasis
N1	IIIC1	Regional lymph node metastasis to pelvic lymph nodes (positive pelvic nodes)
N2	IIIC2	Regional lymph node metastasis to para-aortic lymph nodes, with or without positive pelvic nodes

Distant metastasis (M)		
TNM categories	FIGO stage	Surgical–pathological findings
M0		No distant metastasis
M1	IVB	Distant metastasis (includes metastasis to the inguinal lymph nodes, intraperitoneal disease, or lung, liver, or bone). It excludes metastasis to the para-aortic lymph nodes, vagina, pelvic serosa, or adnexa

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(continued)

Table 8.1 (continued)

Reprinted from: Pecorelli et al. [74] (Copyright 2009, with permission from International Federation of Gynecology and Obstetrics)
[a]Either G1, G2, or G3
[b]Note: FIGO no longer includes stage 0 (Tis)
[c]Endocervical glandular involvement only should be considered as stage I and no longer as stage II
[d]Positive cytology has to be reported separately without changing the stage

In addition to intrauterine risk factors of histological type, grade, myometrial invasion, isthmus–cervix extension, and vascular space invasion, the extrauterine factors of adnexal metastasis, intraperitoneal spread, pelvic node metastasis, and para-aortic node metastasis are important in defining the adjuvant treatment. Predicting factors help in selecting the patients who are likely to have advanced disease at presentation and should undergo the extensive surgical staging. The high-risk factors usually modify the survival by either lymph node metastasis or extrauterine spread of the disease.

The following factors can predict the advanced stage of the disease:

1. *FIGO stage* is the strongest single predictor of outcome in women with endometrial carcinoma as shown in multivariate analysis [14]. The probability of pelvic and para-aortic lymph node involvement and subsequent survival can be determined by the uterine risk factors as well as the extrauterine risk factors.
2. *Histologic cell types*

The cell type has consistently been recognized as an important factor in predicting the biological behavior of the disease and thus survival. The majority of the uterine corpus tumors are endometrioid adenocarcinoma and usually have relatively good prognosis. Adenocarcinoma with squamous differentiation and villoglandular carcinoma behave similarly with respect to the frequency of nodal metastasis and survival to that in endometrioid adenocarcinoma.

Serous carcinoma often has low survival rates from 40 to 60 % at 5 years [15–22]; clear cell carcinoma also has very aggressive behavior with a reported 5-year survival rate of 30–75 % [23–30] as the disease is often advanced at presentation.

3. *Grade*

The degree of histological differentiation is considered to be the most sensitive indicators of tumor spread to either lymph nodes or extrauterine sites. High-grade tumors will have deeper myometrial invasion and increased incidence of pelvic and para-aortic nodal metastasis (Table 8.2). More than half of grade 3 lesions are reported to have >50 % myometrial invasion, 30 % involvement of pelvic, and 20 % involvement of the para-aortic lymph nodes. Survival has also been consistently related to histological grade [13].

Table 8.2 Histological grade and depth of invasion grade and no. of patients

Depth	Grade 1 (%)	Grade 2 (%)	Grade 3 (%)	Total (% of total)
Endometrium only	44 (24)	31 (11)	11 (7)	86 (14)
Superficial	96 (53)	131 (45)	54 (35)	281 (45)
Middle	22 (12)	69 (24)	24 (16)	115 (19)
Deep	18 (10)	57 (20)	64 (42)	139 (22)
Total	180 (100)	288 (100)	153 (100)	621 (100)

Reprinted from Creasman et al. [13]

4. *Myometrial invasion*

The depth of myometrial invasion is one of the most important factors, and deep myometrial invasion has high probability of extrauterine disease spread including lymph node metastasis and treatment failure [12, 31, 32].

5. *Isthmus–cervix extension*

Site of the tumor within the uterus is important in predicting the nodal metastasis. Fundal lesions have 8 % pelvic nodal metastasis and 4 % para-aortic nodal metastasis. In addition, lower uterine segment lesions will have 16 % risk of positive pelvic node and 14 % risk of positive para-aortic nodes [13].

6. *Lymphovascular invasion*

The lymphatic invasion helps to identify the patients with lymph nodal metastasis and is a strong predictor of tumor recurrence. Vascular space invasion is reported in 15 % of uterus-confined adenocarcinoma [13] with pelvic node positivity in 27 % and para-aortic nodal positivity in 19 %, which is 4–6 times higher in comparison to lymphovascular space-negative patients.

7. *Adnexal involvement*

The clinical stage I and occult stage II patients have tumor spread to adnexa in 6 % [13] where pelvic and para-aortic nodal metastasis is reported in 32 % and 20 % cases, respectively, which is four times greater than in patients without adnexal metastasis.

8. *Intraperitoneal spread*

Gross intraperitoneal spread of the disease in absence of adnexal involvement correlates well with higher incidence of involvement of pelvic and para-aortic nodes in about 50 % of patients and 23 % patients, respectively [13, 33, 34]. The pelvic and para-aortic nodal positivity in absence of peritoneal spread is 7 and 4 % only.

Table 8.3 Frequency of nodal metastasis among risk factors

Risk factors	No. of patients	Pelvic no. (%)	Aortic no. (%)
Histology			
Endometrioid adenocarcinoma	599	56 (9)	30 (5)
Others	22	2 (9)	4 (8)
Grade			
1 well	180	5 (3)	3 (2)
1 moderate	288	25 (9)	14 (5)
3 poor	153	28 (18)	17 (11)
Myometrial invasion			
Endometrial	87	1 (1)	1 (1)
Superficial	279	15 (5)	8 (3)
Middle	116	7 (6)	1 (1)
Deep	139	35 (25)	24 (17)
Site of tumor			
Fundus	524	42 (8)	20 (4)
Isthmus–cervix	97	16 (16)	14 (14)
Capillary-like space involvement			
Negative	528	37 (7)	19 (9)
Positive	93	21 (27)	15 (19)
Other extrauterine metastases			
Negative	586	40 (7)	26 (4)
Positive	35	18 (51)	8 (23)
Peritoneal cytology			
Negative	537	38 (7)	20 (4)
Positive	75	19 (25)	14 (19)

Reprinted from Creasman et al. [13]

9. *Pelvic and para-aortic lymph node metastasis*

The frequency of pelvic and para-aortic nodal metastasis has been correlated well to various pathological risk factors as shown in Table 8.3. Para-aortic nodal metastasis was in 35 % of the cases where pelvic nodes were positive.

10. *Ploidy and steroid receptors*

Ploidy has remained the strong predictor of disease outcome. Diploid tumors show higher survival rates than aneuploid tumors [35]. Positivity and quantity of estrogen receptors and progesterone receptors have been correlated well with clinical stage, histological grade, absence of vascular invasion, and better outcome [36].

Treatment of Advanced Stage

Advanced stage endometrial cancer patients have stage III or stage IV disease. These have increased risk of locoregional as well as distant recurrence and poor prognosis. The use of multimodal approach in the treatment is required which can prevent these recurrences and thus improve survival. These patients may benefit from chemotherapy, tumor-directed radiation therapy, hormonal therapy, or combined treatment. Chemotherapy is regarded as the foundation of adjuvant treatment in advanced stage endometrial cancer.

Treatment of Stage III

Majority of the patients presenting with early-stage disease have good prognosis and survival [37]. Approximately 5–10 % of patients of endometrial cancer present in clinical stage III disease [38]. The patients in stage III include the heterogeneous group of patients of extrauterine disease involving the adnexa, serosa, vagina, or retroperitoneal pelvic or para-aortic nodes with varying risks.

Surgery

Patients presumed to be in advance stage are shown in Table 8.4. Surgery is the mainstay of treatment [38] and requires the following surgical procedures:

- Type I hysterectomy
- Type II hysterectomy when the cervix is involved by the disease
- Bilateral salpingo-oophorectomy
- Peritoneal washings for cytological study
- Pelvic and para-aortic lymphadenectomy
- Resection of grossly enlarged nodes when present (Figs. 8.1 and 8.2)
- Omental biopsy
- Omentectomy when histology is serous, clear cell, or poorly differentiated carcinoma
- Biopsy of any suspicious peritoneal nodule/lesion

Table 8.4 Risk factors in endometrial cancer

Uterine factors	Extrauterine factors
Histological type	Adnexal metastasis
Grade	Intraperitoneal spread
Myometrial invasion	Positive peritoneal cytology
Isthmus–cervix extension	Pelvic node metastasis
Vascular space invasion	Aortic node metastasis

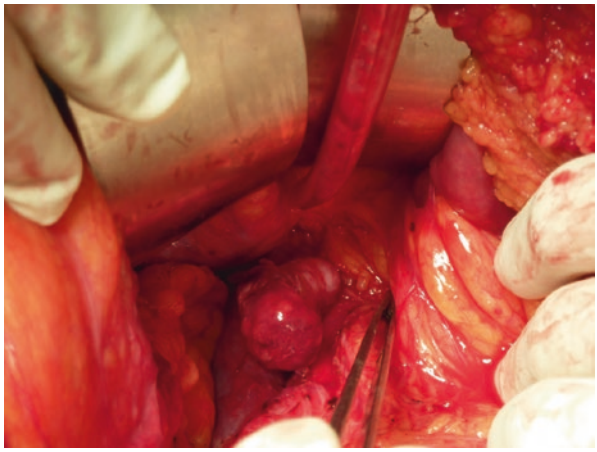

Fig. 8.1 Bulky para-aortic nodal disease in endometrial cancer stage IIIC2

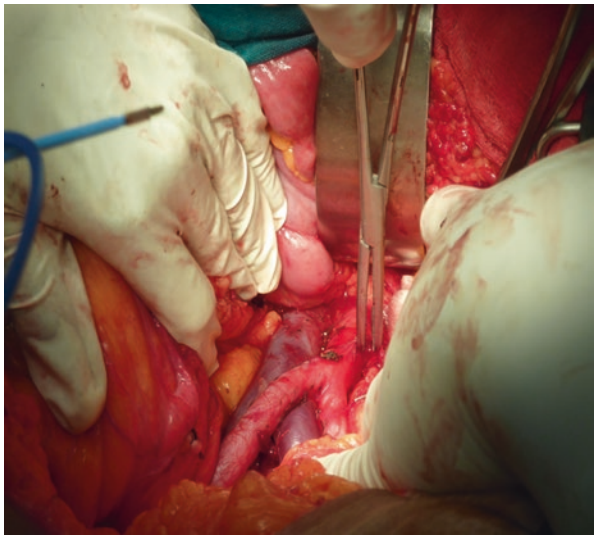

Fig. 8.2 Status post nodal mass excision in endometrial cancer stage IIIC2

Adjuvant Treatment

Patients with extrauterine disease confined to the adnexa or lymph nodes may be treated with systematic therapy and pelvic- or extended-field tumor-directed radiation therapy (RT).

The GOG 33 trial documented the 5-year survival rate of 36 % [39] for patients receiving para-aortic radiation therapy for para-aortic node positivity. The radiation dose which ranged from 4500 to 5015 cGy was delivered to the nodal area from the pelvic brim. In the same series, the 5-year survival rate for patients with para-aortic and pelvic nodal disease was 43 % compared with 47 % for those with para-aortic

nodal disease, though the difference was of no statistical significance [39]. Another series of 18 patients showed significantly better 5-year survival rate of 67 % in patients with para-aortic microscopic disease compared to 17 % for patients with gross nodal disease [40].

Adjuvant chemotherapy and hormonal therapy in stage III and IV endometrial cancer are discussed later in the chapter.

Treatment of Stage IV

The treatment of stage IV disease must be individualized. This usually involves multimodality treatment of surgery, radiation therapy, chemotherapy, and hormonal therapy. Endometrial cancer involving the bladder or rectum is uncommon and usually requires some type of modified pelvic exenteration with or without adjuvant radiation or chemotherapy.

Surgery

Cytoreductive surgery plays an important role in the management of stage IV endometrial cancer. The importance of cytoreductive surgery was studied in some series (Table 8.5) [41–43]. In these series, the successful cytoreduction was found to be a significant prognostic variable on multivariate analysis. Young age of <58 years and good performance status were also predictive of survival [41] in stage IV disease.

Importance of aggressive surgery with the optimal status of cytoreduction has been correlated with the improved survival in addition to the tumor biology [42]. The optimal status of cytoreduction was defined as the largest residual tumor nodule of diameter ≤2 cm. Surgery in these patients may include radical pelvic resection and some type of modified pelvic exenteration (Figs. 8.3, 8.4, 8.5 and 8.6). The radical pelvic resection and extended pelvic resection with or without pelvic radiation or chemotherapy in conjunction with intraoperative radiation have also been described [44].

Table 8.5 Surgical cytoreduction for stage IV endometrial cancer

Study	*n* of patients	Residual tumor diameter	Median survival (mos)
Goff et al. (1994) [43]	47	Resected	18
		Unresected	8
Chi et al. (1997) [42]	55	≤ 2 cm	31
		>2 cm	12
		Unresected	3
Bristow et al. (2000) [41]	65	Microscopic	40
		≤ 1 cm	15
		>1 cm	11

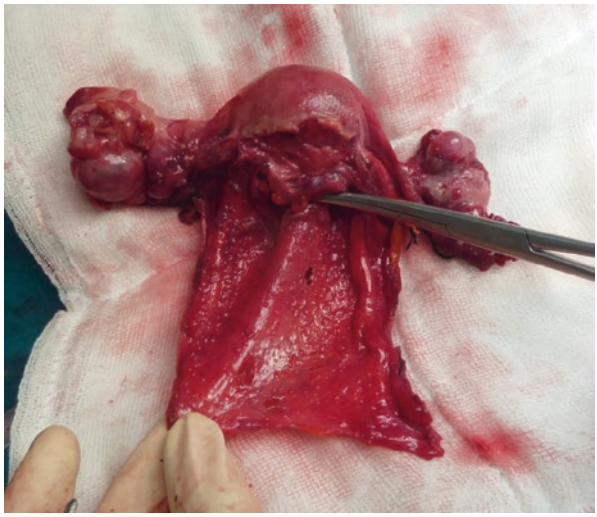

Fig. 8.3 Specimen of endometrial cancer involving the adnexa uterine surface and pelvic peritoneum

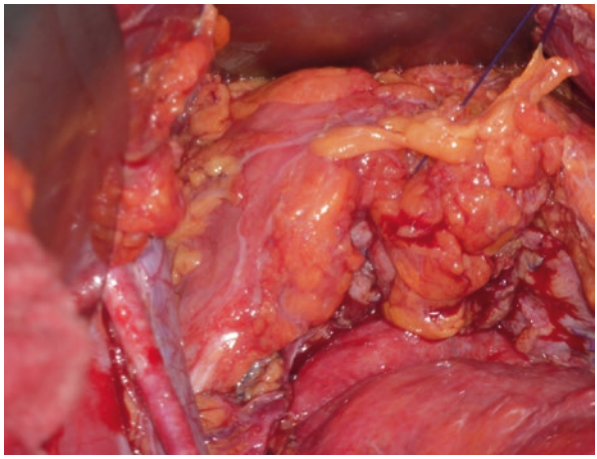

Fig. 8.4 No residual status postsurgical cytoreduction following radical pelvic resection

Chemotherapy

For improving the outcome of patients, chemotherapy was combined to the adjuvant radiation therapy as safety and efficacy of chemoradiation was established in cervical carcinoma patients [45–48]. The chemotherapy was combined to radiation therapy for improving survival in advanced endometrial cancer. Different combination chemotherapy schedules are shown in Table 8.6 [49–53]. These studies are limited with their small sample size.

The randomized phase III GOG trial [54] assessed optimal adjuvant therapy for patients with stage III and stage IV disease having minimal residual disease and was

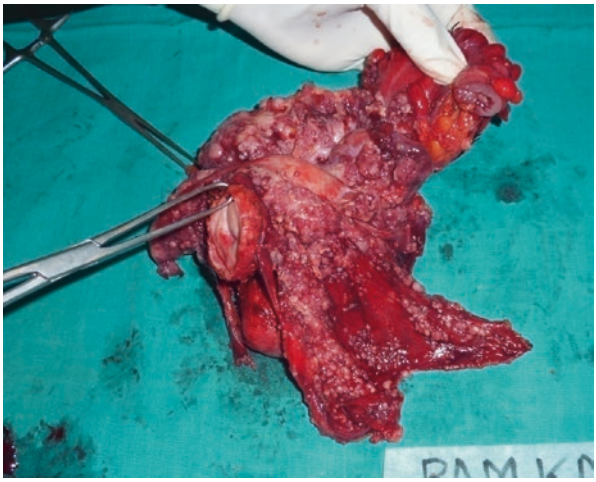

Fig. 8.5 Endometrial disease involving the adnexa, pelvic peritoneum, and rectosigmoid. The specimen of modified posterior exenteration

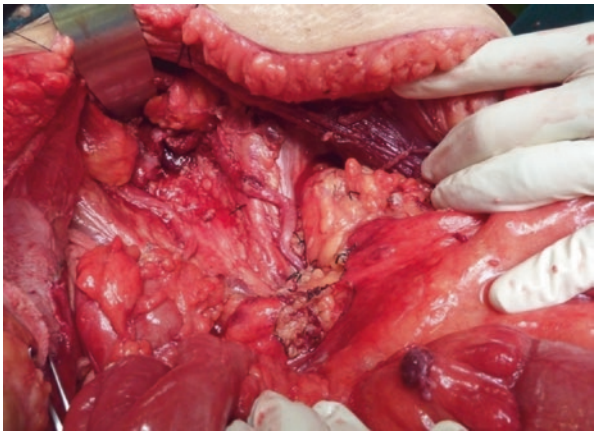

Fig. 8.6 No gross residual disease status following modified posterior exenteration as cytoreductive procedure

randomly assigned to either whole abdominal radiation therapy or seven cycles of combined doxorubicin (60 mg/m^2) and cisplatin (50 mg/m^2) chemotherapy. This study reported improved progression-free survival (PFS) and overall survival (OS) in patients receiving combination chemotherapy as compared to whole abdominal radiation therapy (RT) arm and has since established the role of adjuvant multiagent systemic chemotherapy in advanced endometrial cancer patients with the curative intent and raised the issue of appropriate combination of chemotherapy and radiation therapy [54].

Another GOG study compared the two chemotherapeutic arms of cisplatin, doxorubicin, paclitaxel, and cisplatin and doxorubicin arms. The three-drug regimen arm showed improved survival but with increased toxicity of peripheral neuropathy [55].

GOG 209 compared the outcome of chemotherapeutic regimes of carboplatin and paclitaxel versus cisplatin, doxorubicin, and paclitaxel which reported similar

Table 8.6 Phase I and II trials evaluating combination chemotherapy and radiation therapy in the management of stage III/IV and high-risk endometrial carcinoma patients

Study	Stages	Patients	Regimen	Comments
Duska et al. (2005) [33]	III/IV, HR	20	TAC f/b 45 Gy WPRT	SBO X2; 13 NED at median follow-up of 16 mos
Soper et al. (2004) [34]	III/IV	10	30 Gy WART + CDDP f/b Dox + CDDP	7 of 10 patients received CT; grade 4 neutropenia, 10 of 10 patients; 5 episodes of FN; median survival, 14 mos
Bruzzone et al. (2004) [35]	III/IV	45	CDDP + Epidox + cyclophosphamide f/b 50 Gy WPRT	Grade 4 neutropenia, 8 % 9-year PFS, 30 %; OS, 53 %
Frigerio et al. (2001) [36]	HR	13	Paclitaxel + 50 Gy WPRT	Minimal toxicity; no survival data
Greven et al. (2004) [37]	HR	46	45 Gy WPRT + CDDP f/b CDDP + paclitaxel	Grade 4 hematologic toxicity: RT, 2 %; CT, 62 %; 2-year DFS, 83 %; OS, 90 %

CT regimens: Duska et al. [33], TAC paclitaxel (160 mg/m^2), Dox (45 mg/m^2), carboplatin (AUC 5); Soper et al. [34], CDDP (15 mg/m^2) with RT, Dox (50 mg/m^2), CDDP (50 mg/m^2); Bruzzone et al. [35], CDDP (50 mg/m^2), Epidox (60 mg/ m^2), cyclophosphamide (600 mg/m^2); Frigerio et al. [36], paclitaxel (60 mg/m^2); Greven et al. [37], CDDP (50 mg/m^2) on days 1 and 28 of WPRT, CDDP (50 mg/m^2), paclitaxel (175 mg/m^2)

Abbreviations: *AUC* area under the concentration–time curve, *CDDP* cisplatin, *CT* chemotherapy, *DFS* disease-free survival, *Dox* doxorubicin, *Epidox* epidoxorubicin, *f/b* followed by, *FN* febrile neutropenia, *HR* high-risk endometrial cancer (papillary serous, clear cell, advanced stage), *NED* no evidence of disease, *OS* overall survival, *PFS* progression-free survival, *RT* radiotherapy, *SBO X2* two small-bowel obstruction events, *WART* whole abdominal radiotherapy, *WPRT* whole pelvic radiotherapy

outcomes with less toxicity in carboplatin and paclitaxel chemotherapy arm and reported the response rate of 40–62 % and overall survival of 13–29 months [56].

Hormonal and Chemohormonal Therapy

The role of hormonal therapy in metastatic endometrial cancer has been primarily evaluated in endometrioid adenocarcinoma expressing estrogen (ER) and progesterone receptors (PR), not in the papillary serous carcinoma, clear cell, and poorly differentiated carcinoma. Well-differentiated tumors with expression of ER/PR and location and extent of extrapelvic metastasis are the main predictors of hormonal treatment response.

Progestational agents are mainly used in the treatment of advanced stage endometrial cancer [57]. Medroxyprogesterone acetate (MPA), megestrol acetate, and hydroxyprogesterone caproate have shown the response rates of 14–53 %, 11–56 %, and 9–36 %, respectively [57–65]. The responses are usually of short duration, the median being 4 months [66].

Tamoxifen and aromatase inhibitors have also been used as the hormonal therapy. Tamoxifen has been studied in combination of progestational agents [67, 68]. The response rate was not significantly different when treated with megestrol acetate as the single agent compared with those treated with combination of tamoxifen and megestrol acetate [69]. Sequential hormonal treatment of megestrol acetate in the dose of 80 mg twice daily for 3 weeks, alternating with tamoxifen 20 mg daily for 3 weeks, reported an overall response rate of 26 % [70]. Another GOG study reported a response rate of 33 % with progression-free survival of 3 months and median overall survival of 13 months when tamoxifen was given in the dose of 20 mg daily combined with medroxyprogesterone acetate 100 mg twice daily in alternate week [71].

The combination hormonal therapy is the potential treatment alternative in selected asymptomatic advanced endometrial cancer patients expressing estrogen and progesterone receptors. The adjuvant therapy with hormonal agents has not been compared with chemotherapy in advanced disease.

Combination chemohormonal therapy has been studied in some phase II trials [72, 73]. A response rate of 40–50 % was noted which was similar to the response rates reported by combination chemotherapeutic treatment. Further randomized trials are required to establish the superiority of either chemohormone or paclitaxel-containing combination chemotherapy.

Intraoperative/specimen photographs of the advanced endometrial cancer patients in stage III and stage IV disease contributed by author of the chapter

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Recurrent Endometrial Cancer

9

Yogesh Kulkarni and Harshavardhan

Abstract

Women who present with recurrent disease are not curable. Treatment options are dependent on prior therapy.

For women who did not receive radiation after primary surgery and who presented with isolated vaginal recurrence, RT rather than surgery or medical treatment is preferred (Grade 2C). For women who decline RT or are not candidates for RT, surgical resection is a reasonable alternative.

Surgery is the treatment of choice for patients with prior radiation and isolated vaginal recurrence, if surgery is feasible and patient is fit to undergo surgery (Grade 2C). For women who are not surgical candidates (due to disease location or medical contraindications), re-irradiation can be considered provided that local expertise is available (Grade 2C).

For women who are not candidates for local therapy, medical treatment is recommended.

For chemotherapy naïve patients, a platinum-based combination regimen rather than endocrine therapy or single-agent chemotherapy (Grade 2B) is preferred.

Carboplatin and paclitaxel are the preferred combination regime.

For some women with recurrent endometrial cancer, endocrine therapy is a reasonable alternative to combination chemotherapy as initial treatment *if any of the following factors are present: grade 1 or grade 2 endometrial cancer, tumors positive for estrogen (ER) and progesterone (PR) receptors, and women without*

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(or with minimal) cancer-related symptoms. If endocrine therapy is administered, megestrol acetate alternating with tamoxifen is preferred (Grade 2C).

Disease progression on endocrine therapy – chemotherapy given

Second-line chemotherapy – relapse interval is taken into account. For a long treatment-free interval (e.g., ≥6 months), platinum-based combination chemotherapy rather than single-agent therapy is used (Grade 2C).

For relapse within 6 months of completion of first-line chemotherapy – single-agent chemotherapy

Women, who relapse following first- or second-line chemotherapy, have a poor prognosis. The median overall survival in clinical trials of first- or second-line agents is generally 12 months or less.

Introduction

Seventy to eighty percent of endometrial cancers are diagnosed at an early stage. As a result, treatment with surgery with or without adjuvant radiation results in fewer treatment failures. Treating women with recurrent endometrial cancer can be challenging, and clear understanding of the management options is essential.

Factors that impact survival in patients with recurrent endometrial cancer include site of relapse, prior radiation exposure, time to relapse, and the histological type/grade of tumor. A longer disease-free interval, type I/grade I endometrioid carcinoma, and isolated site of recurrence are associated with prolonged survival in recurrent endometrial carcinoma cases. Non-endometrioid histology and high-grade tumors have a worse prognosis than endometrioid carcinoma. Women with endometrial carcinoma who did not receive radiation therapy after primary surgery and with isolated vault recurrences are appropriate candidates for radiation therapy [1].

Aalders et al. [2] *reported a large series of 379 recurrent endometrial carcinoma cases from the Norwegian Radium Hospital. Local recurrence was observed in 50 % of cases, distant metastasis was seen in 29 %, and 21 % of patients had both local and distant relapse. The time to detect the recurrence was 14 months for patients with local recurrence and 19 months for those with distant recurrence*. Three-fourths (76 %) of the recurrences were detected within 3 years. The disease was symptomatic only in 68 % of patients. Among the patients with local recurrence, 36 % were asymptomatic, 37 % had vaginal bleeding, and 16 % had pelvic pain.

A diagnosis of endometrial cancer generally portends a favorable prognosis. A majority (75 %) are diagnosed in FIGO stage I and have a 5-year survival of 85 %. Women diagnosed in FIGO stage II have a 5-year survival of 75 %, 40 % for FIGO stage III, and 20 % for FIGO stage IV [3, 4].

The reported recurrence rate for endometrial carcinoma is 6–14 %, and almost 80 % of recurrences are seen within 3 years of completion of treatment [5, 6].

Isolated Vaginal Vault Recurrences

These are the recurrences which are most amenable to treatment, possibly even with a curative intent. Prior to initiation of any kind of therapy, metastatic workup is necessary. PET/CT scans achieve this in the best possible way.

Treatment approaches usually vary with prior history of radiation therapy:

No Prior Radiation Therapy

Evidence in support of radiation therapy for isolated vaginal vault recurrences comes in from a multi-institutional study in the United States which identified 69 patients *diagnosed with stage I endometrial carcinoma* who were treated without adjuvant radiation and who went on to develop an isolated vaginal recurrence [6]. Radiation therapy controlled 81 % of these vault recurrences.

In the Danish endometrial cancer study in which low-risk patients were followed without radiation, 17 vaginal recurrences were reported, and 15 of these (88.2 %) responded completely to radiation therapy. By contrast, none of the seven patients with a pelvic recurrence could be cured [7].

Prior Radiation Therapy

Vaginal recurrences are less common in women treated with prior RT, but are associated with a poor prognosis. In the PORTEC trial, there were only seven vaginal recurrences out of 354 women treated with RT [8]. However, the actuarial OS rate at 3 years among these patients was 43 %. Treatment options among these women depend on whether surgery is an option or no.

Operative Candidates Pelvic exenteration may be required as prior radiotherapy, and surgery might have rendered anatomical planes obsolete. However, the decision to proceed with pelvic exenteration should be considered carefully due to the associated short- and long-term morbidity, including urinary tract and bowel dysfunction, the need for diversion (colostomy and/or nephrostomy), and sexual dysfunction. Wide excision and primary closure might be possible in a few cases.

The reported 5-year OS rates for pelvic exenteration range from 14 to 50 %. In the largest series of 44 women with recurrent endometrial cancer, the median OS was 10.2 months, and 5-year OS was 20 % [9]. In a more recent review, Khoury-Collado F et al. describe their experience with 21 patients and report an overall 5-year survival of 40 % [10].

Nonoperative Candidates In general, reradiating is not an option for women with a vaginal recurrence, particularly after pelvic radiation, given the risks to the normal surrounding tissue. However, tailored treatment approaches may allow for

re-treatment with limited toxicity to surrounding normal tissue. As an example, a case series of 27 patients treated with stereotactic RT after conventional RT found no serious (grade 3, 4, or 5) toxicity associated with re-treatment, and a 96 % symptomatic response (measured by reduced tumor size, decrease in pain, or decrease in bleeding) was reported [11]. Unfortunately, due to limited experience, the practice is not universal, and some form of medical treatment is recommended.

Systemic Recurrence: Role of Surgery

Surgery – in combination with radiation, chemotherapy, or hormonal therapy – may play a role in selected patients with recurrent endometrial cancer, particularly if all R0 status can be achieved.

Johns Hopkins Medical Center has reported complete cytoreduction in 23 patients (66 %) [12]. Median OS was 39 months compared to 13.5 months in residual disease group. Completeness of salvage surgery and residual disease was significantly associated with survival. A smaller study from MSKCC also had the same conclusions [13].

Ideal candidates for this approach are patients with long disease-free interval (>2 years) and oligometastases.

Systemic Recurrence: Role of Hormonal Therapy

Progestational Agents Both parenteral and oral have been used in patients with recurrent and metastatic endometrial cancers. The objective response rate, however, has been of the order of 15–20 %. Features that predict a better response are hormone receptor expression, low-grade histology, and a long disease-free interval. The GOG randomized 299 patients with advanced or recurrent endometrial cancer to receive either 200 mg/d or 1,000 mg/d of oral MPA. Overall response was better with the low-dose regime (25 % vs 15 %). Median survival durations were 11.1 months and 7 months (low vs high dose). Patients with poorly differentiated or PR-negative tumors had only an 8–9 % response rate [14]. Progestins are to be continued lifelong in responders. Adverse effects from progestin include weight gain, edema, thrombophlebitis, tremor, headache, and hypertension. There is also an increased risk of thromboembolism.

Tamoxifen Tamoxifen is a first-generation selective estrogen response modulator (SERM) and inhibits the binding of estradiol to uterine ER, presumably blocking the proliferative stimulus of circulating estrogens. Dose is 20 mg daily or twice daily and is continued for as long as the disease is responding. Adverse effects include hot flashes, vaginal dryness, DVT, and increased risk of cardiovascular events. Moore et al. [15], in a review of literature, reported a pooled response rate of 22 % for single-agent tamoxifen.

Aromatase Inhibitors These have a response rate of only about 10 % in recurrent and metastatic endometrial cancers, but the majority of patients in the reported studies have had high-grade, hormone receptor-negative cancers, where the likelihood of response is low [16].

Systemic Recurrence: Role of Cytotoxic Chemotherapy

The role of cytotoxic chemotherapy in recurrent endometrial cancers is palliative at best. Considerations to be noted prior to initiation include:

- Performance status
- Comorbidities such as obesity, diabetes mellitus, and cardiovascular disease
- Pelvic radiation – can limit bone marrow reserve
- Prior therapy with cytotoxic agents

Initial Therapy

Platinum-based combination is preferred. The two most commonly used regimens to treat recurrent endometrial cancer are:

- Carboplatin plus paclitaxel
- The triple drug combination of cisplatin, doxorubicin, plus paclitaxel (TAP)

A 2012 meta-analysis [18] of trials that compared administration of two or more agents ("more intensive" regimens) to one agent or two agent combinations ("less intensive" regimens):

- Improvement in PFS from 6 to 7 months (HR 0.82, 95 % CI 0.74–0.90) and OS from 9 to 10.5 months (HR 0.86, 95 % CI 0.77–0.96) in favor of "more intense regimens."
- "More intensive" chemotherapy significantly increased the risk of serious nausea and vomiting (odds ratio [OR] 2.64, 95 % CI 1.71–4.09) and diarrhea (OR 2.25, 95 % CI 1.09–4.63) (Figs. 9.1, 9.2, 9.3, 9.4, 9.5, and 9.6).

Cisplatin, Doxorubicin, Plus Paclitaxel GOG 177 enrolled 273 women with previously untreated stage III/IV or recurrent endometrial cancer and randomized them to treatment with AP (cisplatin [50 mg/m2] plus doxorubicin [60 mg/m2] administered on day 1 every 3 weeks) or to TAP (doxorubicin [45 mg/m2 on day 1], cisplatin [50 mg/m2 on day 1] plus paclitaxel [160 mg/m2 over 3 h on day 2] every 3 weeks) [17]. Compared to AP, TAP resulted in:

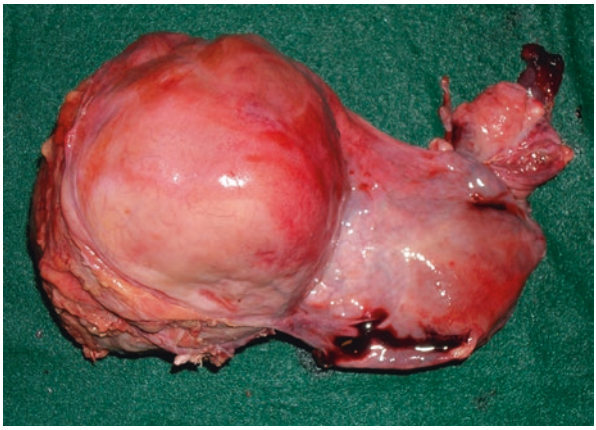

Fig. 9.1 Anterior exenteration for a case of recurrent endometrial carcinoma treated primarily by radiation

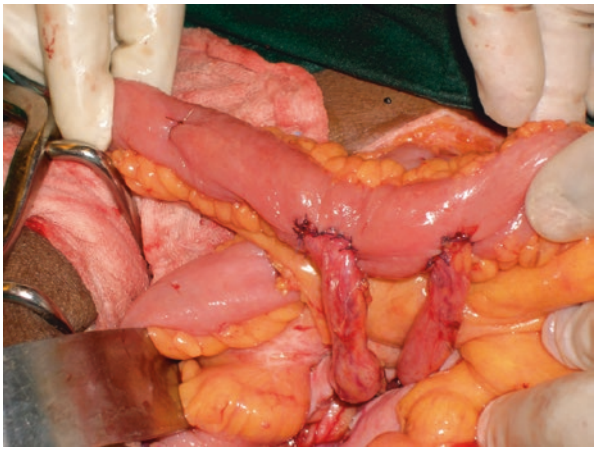

Fig. 9.2 Ileal conduit with ureteric anastomosis

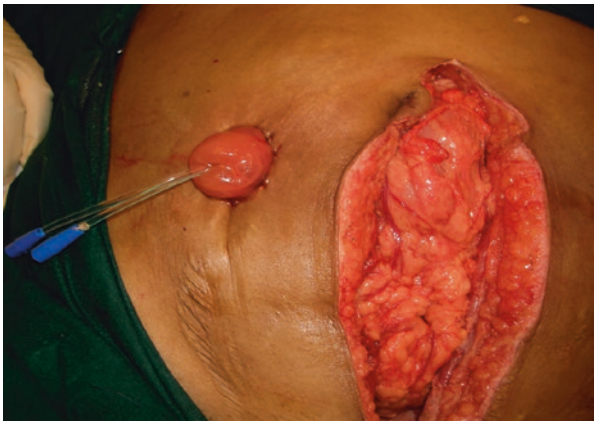

Fig. 9.3 Ileal conduit

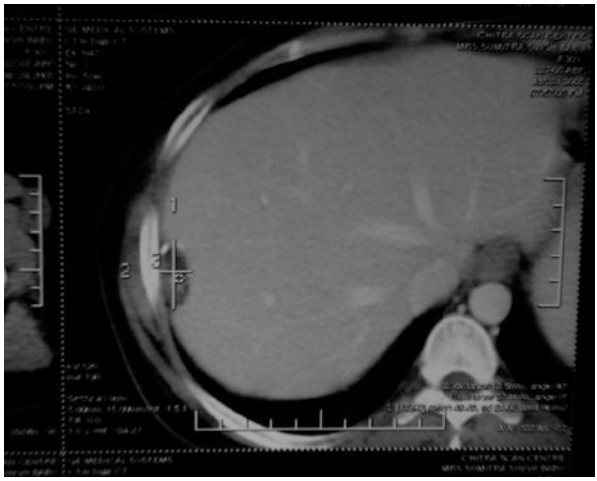

Fig. 9.4 Recurrence on liver surface in a case of papillary serous adenocarcinoma of endometrium

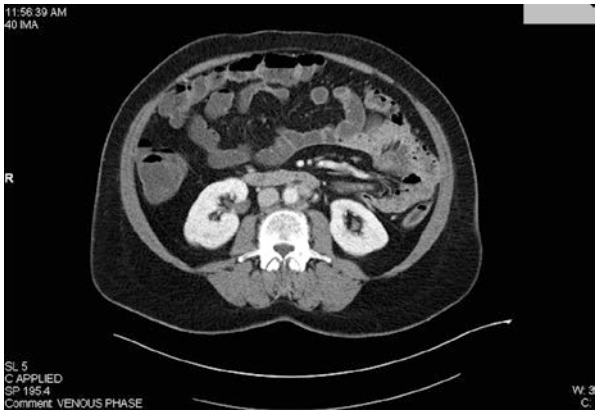

Fig. 9.5 Para-aortic nodal recurrence in endometrial carcinoma case after 3 years

- Overall response rate (ORR) – 57 % vs 34 %
- PFS – 8 months vs 5 months
- OS −15 months vs 12 months
- TAP – increased incidence of grade 3 neuropathy (12 % vs 1 %)

Carboplatin Plus Paclitaxel GOG 209 (which was not included in the 2012 meta-analysis) administered carboplatin (area under curve = 6) plus paclitaxel (175 mg/m^2) every 21 days and was compared to TAP in a trial that enrolled 1300 women with chemotherapy naive stage III, IV, or recurrent endometrial carcinoma [17]:

- ORR – 51 % in both arms
- PFS – 13 months in both arms
- OS – 37 months vs 40 months (AP vs TAP)

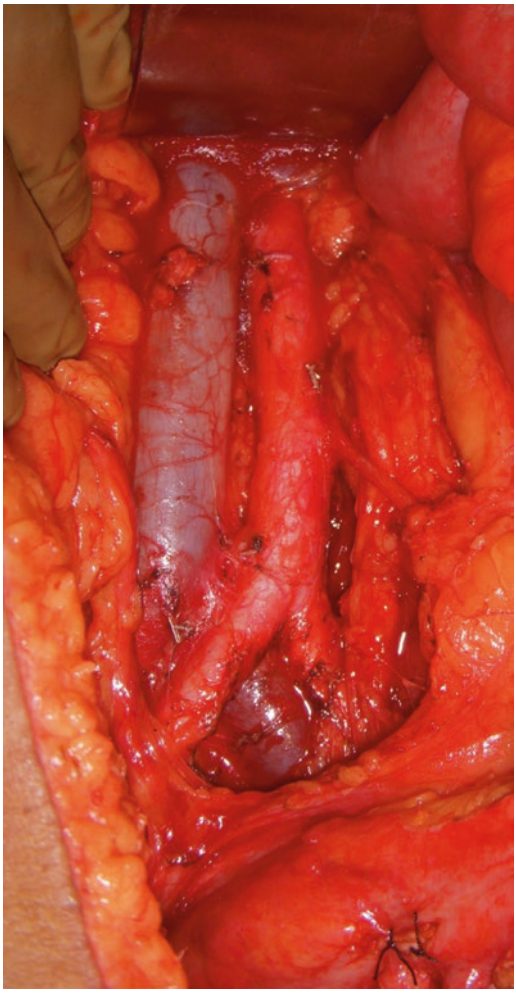

Fig. 9.6 Complete retroperitoneal node dissection in endometrial carcinoma with isolated nodal recurrence

- A statistically significant reduction in the incidence of grade 2 or greater toxicity, including sensory neuropathy (19 % vs 26 %), thrombocytopenia (12 % vs 23 %), emesis (4 % vs 7 %), diarrhea (2 % vs 6 %), and metabolic derangements (8 % vs 14 %)

Second-Line Therapy

For women who have received adjuvant chemotherapy, the approach to second-line treatment depends on the interval between the end of adjuvant treatment and the diagnosis of relapse:

- Greater than 6 months – repeat treatment with a platinum-based combination
- Short treatment-free interval (<6 months) – single-agent therapy rather than a combination chemotherapy regimen. Commonly used agents include:
  - Doxorubicin
  - Ifosfamide
  - Ixabepilone
  - Docetaxel
  - Topotecan
  - Oxaliplatin

Novel Agents

- Bevacizumab
- Temsirolimus

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Newer Perspectives in the Management of Endometrial Cancer

10

Sampada Dessai and Anant Ramaswamy

Abstract

CT, MRI, or PET have similar efficacy in detecting extrauterine disease and should be performed when extrauterine disease is suspected in carcinoma endometrium.

Systematic lymphadenectomy is associated with an improvement in overall survival in patients with intermediate- or high-risk endometrial cancer.

Adjuvant RT and chemotherapy in stage I disease with intermediate- or high-risk features prevent recurrence but are not associated with improvement in overall survival.

Introduction

Endometrial cancer is the commonest female malignancy in the western world, but in India, it ranks third after breast and cervical cancer, respectively. Incidence of endometrial cancer in India is 12,335 cases per year, and 4773 persons die because of this malignancy every year [1]. Advances in endometrial cancer at a national level are slow to occur in view of its rarity. However, management of this cancer remains challenging. The aim of this chapter is to comprehensively describe the advances in the management of endometrial cancer.

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Methods

A PubMed search was carried out using the following MeSH terms and filters, "endometrial neoplasm's"[MeSH Terms] OR ("endometrial"[All Fields] AND "neoplasms"[All Fields]) OR "endometrial neoplasms" [All Fields] OR ("endometrial"[All Fields] AND "cancer"[All Fields]) OR "endometrial cancer"[All Fields]) AND ((Clinical Trial[ptyp] OR Comparative Study[ptyp] OR Meta-Analysis[ptyp]) AND "2010/07/19"[PDat]: "2015/07/17"[PDat] AND "humans"[MeSH Terms] AND English[lang]).

Eight hundred and sixty-one articles were available for selection. These articles were manually screened, and relevant articles are compiled under the subheadings of surgical, medical, and radiation oncology.

Recent Perspective in Imaging

Imaging in Carcinoma Endometrium

Detection of extrauterine disease mandates an imaging in carcinoma endometrium. CECT has been traditionally used for this purpose. Whether PET-CT or PET-CECT would improve the rate of detection of extrauterine disease is an open question. A part of this question with regard to nodal involvement was answered by Kitajima et al. [2]. A cohort of 41 patients underwent CECT, PET-CT, and PET-CECT. The sensitivity and specificity of PET-CECT, PET-CT, and CECT were 61.4 % and 98.1 %, 52.3 % and 96.8 %, and 40.9 % and 97.8 %, respectively. The authors concluded that PET-CECT was not significantly superior to PET-CT for nodal staging of uterine cancer. Nodal metastasis cannot be excluded even if PET-CECT findings are negative. A systematic review and meta-analysis were performed by Chang et al. to assess the performances of PET or PET-CT in detecting pelvic and/or para-aortic lymph nodal metastasis [3]. The sensitivity and specificity of PET or PET-CT scans in the detection of nodal metastasis (pelvic and/or para-aortic LN) were 63.0 % and 94.7 %, respectively. Chang et al. concluded that it may help surgeons in selecting appropriate patients for pelvic and/or para-aortic lymphadenectomy.

The value of 18 FDG-PET in preoperative risk determination and prognosis was evaluated in a systematic review by Ghooshkhanei et al. [4]. Pooled mean SUVmax in patients with high-risk factors [grade 3, lymphovascular invasion (LVI), cervical invasion (CI), myometrial invasion (MI) $\geq$ 50 %] was statistically higher than those in patients without risk factors. Higher preoperative SUVmax was predicted for a lower disease-free survival. However, these findings need large multicentric studies for confirmation.

The current NCCN guidelines suggest that CT, MRI, or PET can be performed as clinically indicated when extrauterine disease is suspected in carcinoma endometrium. On the basis of evidence, it seems that PET-CECT is slightly better in identifying patients with extrauterine nodal disease than CECT.

Recent Perspective in Surgical Oncology

Fertility-Preserving Surgery

Fertility-preserving surgery seems an option for FIGO stage IA endometrial cancer. Laurelli et al. selected patients with age ≤40 years, without Lynch II syndrome, with G1 and ER+/PR+ endometrioid histology, without myometrial invasion, without multifocal tumor, without node metastasis, without ovarian mass, and with normal serum CA 125 for fertility-preserving surgery. They underwent hysteroscopic ablation of the lesion and the myometrial tissue below, followed by either oral megestrol acetate 160 mg/day for 6 months or 52 mg levonorgestrel-medicated intrauterine device for 12 months. Only one patient out of 14 recurred within a median follow-up of 40 months [5]. The Turkish gynecologic oncology group also collected their data on fertility-preserving strategy in early endometrial cancers. They had 43 patients, and with average follow-up of 50 months, 81.4 % patients were disease-free, and 41.9 % patients had conceived [6].

NCCN currently recommends that fertility-preserving treatment can be provided in selected patient cohorts. These patients include those with stage IA G1 endometrioid histology, with endometrial cancer limited to the endometrium, without any myometrial invasion, without Lynch type 2 syndrome or any other genetic syndrome, without any extrauterine disease, and without any medical contraindication for progesterone therapy. These patients need to be counseled that this is not the standard option, and if they still insist, it can be offered. If post 6 months they have a complete response, then they should be encouraged for conception with continuous surveillance.

Extent of Surgery

Prediction of Lymph Nodal Disease

Nomograms

The role of complete prophylactic lymphadenectomy in early stage endometrial cancer is a matter of controversy. Around 5–10 % of early stage endometrial cancers harbor lymph nodal metastasis. Hence, it would be useful to know if we can identify patients who may benefit from lymphadenectomy either preoperatively or intraoperatively. The prediction of nodal disease preoperatively by PET scan has been discussed in the above section. In this section, we would look at other characteristics which have been reported to be important predictors of lymph nodal metastasis. Bendifallah et al. validated two nomograms made and were internally validated by ALHilli et al. [7]. The overall rate of lymphatic spread was 9.9 %. Predictive accuracy was 0.65 (95 % Cl, 0.61–0.69) for the full nomogram and 0.71 (95 % Cl, 0.68–0.74) for the alternative nomogram. The correspondence between recurrence rate and the nomogram prediction suggested only a moderate calibration of the nomograms. The authors concluded that additional parameters are needed to improve upon the accuracy of the nomograms.

In India, patients are commonly seen after incomplete staging surgery, i.e., only TAH-BSO without lymph node dissection. Whether to do para-aortic nodal staging in them is a matter of debate in this situation. Kang et al. addressed this issue and tried to prepare a web-based nomogram which could be utilized to individualize treatment in such cases [8]. Four variables – deep myometrial invasion, non-endometrioid subtype, lymphovascular space invasion, and log-transformed CA-125 levels – were part of the nomogram. It showed good discrimination. The nomogram is available on the website (http://www.kgog.org/nomogram/empa001.html). It can be helpful in individualizing treatment in these patients.

Sentinel Lymph Node

Sentinel lymph node procedure is one of the known ways of predicting lymph node status. It has established itself in breast cancer, melanoma, and carcinoma vulva. The utility of sentinel lymph node dissection in endometrial cancers was studied by Kang et al. in 2011in a meta-analysis [9]. The detection rate and the sensitivity were 78 % (95 % CI=73–84 %) and 93 % (95 % CI=87–100 %), respectively. Paracervical injection technique was associated with the increase in detection rate ($P = 0.031$). While hysteroscopic injection technique and the subserosal injection technique were associated with decrease in detection rate and decreased sensitivity, respectively, if they were not combined with other injection techniques. The authors concluded that SLN biopsy had shown good diagnostic performance, but this should be interpreted with caution.

Ballester et al. evaluated sentinel lymph node in presumed low- and intermediate-risk endometrial cancers. The detection rates in low and intermediate risk were 61.2 % and 37.1 %, respectively. 21.4 % and 21.2 % of patients in low risk and intermediate risk were upstaged by the procedure. Ultrastaging detected metastases which were undetected by conventional histology in 42.8 % of patients [10].

A repeat systematic review and meta-analysis of sentinel LN sampling by Ansari et al. revealed a detection rate of 77.8 % and sensitivity of 89 % [11]. Similar to Kang's review, it also observed that paracervical injections were associated with higher detection rates [9]. The authors concluded that sentinel node mapping was feasible in endometrial cancer. Using blue dye, radiotracer, and cervical injection can optimize the sensitivity and detection rate of this technique.

All these reviews had concluded that a large study would be required to confirm these benefits of these techniques. The SENTI-ENDO study was reported by Daraï et al. in 2015 [12]. It was a study evaluating the impact of sentinel lymph node dissection on adjuvant therapy. There was no difference in recurrence-free survival (RFS) whether sentinel LN was detected or not in patients with stage I–II endometrial cancer. Similarly there was no difference in RFS in patients whether the sentinel LN detected was negative or positive. Adjuvant therapies were more frequently administered in patients with a sentinel lymph node-positive status. It seems that these adjuvant therapies may have altered the course of sentinel lymph node-positive cases.

The current NCCN guidelines suggest doing sentinel lymph node dissection as category 3 recommendation.

Role of Lymphadenectomy

The role of lymphadenectomy has also been debated in endometrial cancers especially after the publication of ASTEC studies. Kim et al. did a systematic review and meta-analysis to address this issue. In all the studies, systematic lymphadenectomy improved overall survival, compared with unsystematic lymphadenectomy (hazard ratio, 0.89; 95 % confidence interval, 0.82–0.97). The systematic lymphadenectomy was associated with an improvement in overall survival in patients with intermediate- or high-risk endometrial cancer (hazard ratio, 0.77; 95 % confidence interval, 0.70–0.86). No such benefit was seen in those with low-risk endometrial cancer (hazard ratio, 1.14; 95 % confidence interval, 0.87–1.49) [13]. The impact of systematic lymphadenectomy was studied by Angioli et al. Lymphadenectomy had no negative influence on global health status [14]. Hence, systemic lymphadenectomy should be performed in patients with intermediate to high risk of lymph nodal metastasis.

The current NCCN guideline suggests doing pelvic and para-aortic lymph node removal for staging in patients with high-risk factors.

Technique of Surgery

Laparoscopic Versus Open Surgery

Lu et al. reported a randomized study comparing the outcomes of open versus laparoscopic surgery in endometrial cancers [15]. Laparoscopic surgery was found to be a safe and reliable alternative to laparotomy, with significantly reduced hospital stay and postoperative complications; however, it did not seem to improve the overall survival and 5-year survival rate. A Cochrane review done on the same topic too had similar conclusions [16]. In early stage carcinoma, laparoscopy was associated with similar overall and disease-free survival. Laparoscopy had reduced operative morbidity and hospital stay. There was no difference in severe postoperative morbidity between the two techniques.

Robotic Versus Laparoscopic Surgery

Gala et al. did a systematic review of robotic versus laparoscopic versus laparotomy in endometrial cancer [17]. They revealed that, compared with open surgery, robotic surgery has a shorter hospital stay. The learning curve seems to be lower for robotic surgery than for laparoscopy. There was a conflicting data regarding comparison of robotics and laparoscopy. He concluded that whether to select laparoscopy or robotic surgery should be individualized for a patient taking into consideration surgeons' proficiency and equipment available.

Recent Perspective in Radiation Oncology

Radical Radiation

Surgery is the standard treatment option in endometrial cancer. Radical radiation is an option in patients with medically inoperable endometrial cancers. A retrospective experience with radical radiation was published by Podzielinski [18]. The median PFS and OS were 43.5 and 47.2 months, respectively. Majority of patients in this review died due to comorbidities. Among the surviving patients, only 16 % had recurrence.

NCCN recommends a tumor-directed RT in medically inoperable patients. However, in these patients, control of comorbidities seems to be an important aspect of management.

Adjuvant Radiation

Sorbe et al. reported a randomized study of intermediate-risk endometrial cancer randomized postsurgery between vaginal brachytherapy and external beam radiation. Five-year locoregional relapse rates were 1.5 % after EBRT + VBT and 5 % after VBT alone ($p = 0.013$), and 5-year overall survival rates were 89 % and 90 %, respectively ($p = 0.548$). There was no survival benefit associated with EBRT +VBT, and it had incremental complications. Hence, the author concluded that combined RT should probably be used for high-risk cases with two or more high-risk factors. VBT alone should be the adjuvant treatment option for purely medium-risk cases [19].

A Cochrane review was done by Kong et al. to address the issue of adjuvant RT in stage I endometrial cancer. EBRT significantly reduced locoregional recurrence compared with no EBRT or VBT alone ($P < .001$), but there was no improvement in OS or endometrial cancer-specific survival or distant recurrence rates. EBRT in addition increased risk of severe acute toxicity, severe late toxicity, and reduced quality of life scores [20].

The NCCN recommends the use of external RT and vaginal brachytherapy on the basis of risk stratification. To summarize, in the absence of risk factors for recurrence, observation is recommended; in case of intermediate risk, vaginal brachytherapy is recommended; and in case of high-risk status, both EBRT and vaginal brachytherapy are recommended.

Recent Perspective in Medical Oncology

Adjuvant Chemotherapy

Endometrial cancers with poor differentiation, deep myometrial invasion, and high-grade histologies or with advanced disease are associated with poor prognosis. Adjuvant radiation has shown to improve locoregional control rates in these patients, but not overall survival. Whether addition of adjuvant chemotherapy helps in

improving outcomes in these patients is not known. A combined analysis of two randomized studies evaluating adjuvant chemotherapy was reported by Hogberg et al. In both these studies, patients with high-risk features were randomized to either adjuvant RT or adjuvant RT + sequential chemotherapy. In the combined analysis, overall survival was not improved by adjuvant chemotherapy (HR 0.69, CI 0.46–1.03, $P = 0.07$); however, it had significant impact on cancer-specific survival (CSS) (HR 0.55, CI 0.35–0.88, $P = 0.01$). The chemotherapy used in these studies was paclitaxel+ carboplatin or doxorubicin + carboplatin or paclitaxel + epirubicin or doxorubicin + cisplatin [21].

Two drug regimens have been used as adjuvant therapies; whether addition of a third agent would improve the outcomes is not known. Addition of an anthracycline to paclitaxel and carboplatin has been tried. In a feasibility study, the combination of paclitaxel 150 mg/m^2, epirubicin 50 mg/m^2, and carboplatin AUC 4 was associated with a response rate of 74 % and median survival of 37 months [22]. Similar efficiency has also been shown for doxorubicin (45 mg/m^2), cisplatin (50 mg/m^2), and paclitaxel (160 mg/m^2) [23]. These studies need evaluation in large multicentric studies prior to their routine use.

NCCN recommends adjuvant chemotherapy in advanced endometrial cancer and stage IB with high-risk features and stage II G3.

Palliative Chemotherapy

Palliative chemotherapy in recurrent, metastatic, and advanced endometrial cancer is associated with an increment in overall survival. A Cochrane review showed that treatment consisting of chemotherapy regimen has better overall survival (OS) (hazard ratio (HR) 0.86, 95 % confidence intervals (CI) 0.77–0.96, $P = 0.005$) and progression-free survival (PFS) ($n = 1526$, HR 0.82, 95 % CI 0.74–0.90, $P < 0.0001$). But these regimens are associated with more serious side effects. There was no particular single agent or doublet regimen which would be labeled as a regimen with better response rates [24].

Multiple newer agents including lapatinib, gefitinib, and aflibercept have been tested, but none of them had a survival benefit [25–29].

Palliative Hormonal Therapy

Hormonal therapy has been used in endometrial cancer. The resistance to these does develop over time. m-TOR inhibitors have been suggested – in such situations. The addition of temsirolimus and everolimus to aromatase inhibitors has shown promising activity in phase II studies [30, 31]. Fulvestrant, an estrogen receptor inhibitor, was tested in phase II studies, but it failed to improve the results [32].

Conclusion

In the last 5 years, the treatment of endometrial cancer has shown minimal progress. Major advances have been reported in minimal invasive techniques.

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