Diagnosis and Management of the Cancer of the Uterus

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Abstract

Uterine cancer is the most common malignancy of the female genital tract. Treatment of uterine cancer is related to cell type, grade, and stage. However, the vast majority of uterine cancers will be low grade, early stage endometrial cancers with obesity being the primary risk factor associated with these cancers. Surgery is an important part of staging and management of uterine cancers.

Keywords

Uterine cancer • HNPCC • Lynch syndrome • Endometrial cancer • Sarcoma • Staging endometrial stromal cancer

Contents

1 Introduction

As the most common gynecologic cancer seen in North America and Europe, uterine cancer can be encountered by anyone who provides healthcare to women. While the majority of these cancers will be cured with treatment, management can be controversial and confusing. This chapter will discuss the epidemiology, pathology, genetics, and treatment of this common malignancy.

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2 Epidemiology

Uterine cancer is the 6th most common cancer in women worldwide, with over 218,100 new cases diagnosed each year. In North America and Europe, endometrial cancer is the most common malignancy of the female reproductive tract, the 4th overall most common cancer diagnosed in women, and the 8th most likely cause of cancer death (Jemal et al. 2011). It is estimated that 49,560 US women will be diagnosed with uterine cancer in 2013 (age-adjusted incidence rate 24.5/100,000) and 8,190 will die of their disease (SEER 2013).

Ninety-five percent of cancers of the uterine corpus arise from the epithelial cells of the endometrium. Endometrial cancer is more common in postmenopausal women, with the mean age of diagnosis of 60 and the majority of patients being over the age of 50 (Sorosky 2012). The greatest risk factor for endometrial cancer is hyperestrogenic states including estrogen producing tumors, unopposed exogenous estrogen, and increased adiposity. Early menarche, late menopause, and nulliparity also increase exposure to estrogen and are associated with an increased risk of uterine cancer.

Among obesity-related cancers in women, endometrial cancer is most strongly associated with increasing body mass, with 49% of cases in the US attributable to obesity (Renehan et al. 2008). Regional and racial differences in rates of endometrial cancer are additionally linked to rates of obesity and hormone use. Conversely, factors that reduce estrogen levels such as smoking, physical activity, oral contraceptive usage, and multiparity are protective against endometrial cancer.

Uterine sarcomas originate from the muscle and connective tissue of the myometrium. They comprise 2–5% of uterine cancers and less than 1% of all gynecologic malignancies. In the USA, approximately 1,500 uterine sarcomas were diagnosed in 2013. Risk factors include a history of pelvic irradiation and black race. The peak incidence differs for the type of sarcoma. Leiomyosarcomas affect women at a mean age of 53, with many being premenopausal at diagnosis (SEER 2013; Pautier et al. 2014).

3 Genetics

The majority of uterine cancers are sporadic with approximately 1 in 10 associated with a genetic syndrome. Hereditary nonpolyposis colon cancer (HNPCC) syndrome is the most common genetic syndrome associated with endometrial cancer. The NCCN recommends genetic counseling should be considered in women diagnosed under the age of 55, and those who have a family history of colon cancer and endometrial cancer. HNPCC, also known as Lynch Syndrome, is associated with microsatellite instability in the mismatch repair genes MLH1, MSH2, MSH6, PMS2, or EPCAM, predisposing to cancers arising from the endometrium, colon, ovary, upper gastrointestinal tract, genitourinary tract, and other sites (ACOG 2014).

Approximately 50% of women with Lynch syndrome will present with endometrial cancer. Women with Lynch syndrome should be offered a risk reducing hysterectomy and bilateral salpingo-oophorectomy after child bearing is complete. For women who wish to maintain their fertility, there is no clear evidence that screening for uterine cancer is effective but annual pelvic ultrasound and/or endometrial sampling is common practice (ACOG 2014). The National Comprehensive Cancer Network (NCCN) states that annual endometrial biopsies are an option for cancer screening (NCCN 2012). The American College of Obstetricians and Gynecologists (ACOG) recommends endometrial sampling every 1–2 years starting at age 30–35 (ACOG 2014). Risk reduction via progestin-based contraception should also be considered in women that do not desire surgery. Surveillance for other cancers should be encouraged in these patients and genetic counseling should be considered for themselves and family members (Sorosky 2012; Lynch syndrome 2014).

Cowden Syndrome is associated with multiple hamartomas and increased risk of cancers including endometrial, breast, and thyroid. The most

common mutation in Cowden Syndrome is PTEN, but mutations in SDHB, SDHD, and KLLN have also been seen. There is no evidence to support risk reducing hysterectomy, but this should be discussed with women with this syndrome (Cowden syndrome 2014).

Women with a history of retinoblastoma are at an increased risk for leiomyosarcoma. Retinoblastoma is associated with inactivation of the RB1 tumor suppressor gene. When the gene mutation involves all cells, there is increased risk for pinealoma, osteosarcoma, melanoma, and other muscle tumors (Retinoblastoma 2014).

4 Histology

Based on clinicopathological characteristics, Bokhman devised a dualistic classification of endometrial cancers. Type 1 lesions are the most common, comprising 80% of endometrial cancers. They include endometrioid cell type or variants (such as squamous differentiation, villoglandular, and secretory), are usually well to moderately differentiated, and are less likely to metastasize outside of the uterus. These tumors often occur in women with a history of anovulatory uterine bleeding and can be found in a background of endometrial hyperplasia. Women with a biopsy of complex endometrial hyperplasia with atypia have a 40% likelihood of having malignancy found in the hysterectomy specimen (Trimble et al. 2006).

Type II lesions include clear cell carcinoma, serous adenocarcinoma, and carcinosarcoma and are not associated with hyperestrogenism. These malignancies are poorly differentiated and more aggressive; deep myometrial invasion and metastic disease are more common than with type I tumors. Recurrence is more likely and survival is worse for type II uterine cancers. Serous carcinoma is characterized by papillae and has highly pleiomorphic tumor cells with necrosis and many mitoses. Endometrial intraepithelial carcinoma (EIC) is a rare finding, but it is thought to be the precursor lesion in serous tumors of the uterus. It involves pleiomorphic but noninvasive tumor cells (Trimble et al. 2012). Carcinosarcoma, also known as malignant mixed mullerian tumors, contain mixed components of sarcoma and adenocarcinoma. While it historically had been grouped with sarcomas, more recent evaluation has suggested that it is more similar to a dedifferentiated carcinoma than a sarcoma. Staging of carcinosarcoma is now included in the FIGO staging of endometrial carcinomas (Mutch 2009).

Uterine sarcomas include leiomyosarcomas, mixed epithelial and stromal tumors (carcinosarcoma and adenosarcoma), and endometrial stromal sarcomas. Leiomyosarcomas make up 30% of all uterine sarcomas. Sarcomas arising in the endometrial stroma account for 15% of all uterine sarcomas. Other sarcomas include mixed endometrial stromal and smooth muscle tumors, adenosarcomas, embryonal botryoides or rhabdomyosarcomas, and perivascular epithelial-cell tumors (PEComas) (D'Angelo and Prat 2009).

5 Diagnosis/Screening

Clinical features associated with uterine cancer include abnormal uterine bleeding, abnormal cervical cytology (e.g., atypical glandular cells on a cervical cytology), pelvic pain, and an enlarging pelvic mass. Approximately 90% of women with endometrial cancer present with abnormal bleeding. The diagnosis is obtained by pathological review of tissue, preferably obtained by endometrial biopsy, dilation and curettage, or hysteroscopy and biopsy. While these methods are very efficacious for detecting uterine cancers, if the lesion does not invade into the endometrial cavity, leiomyosarcoma may only be diagnosed after hysterectomy or myomectomy. Screening asymptomatic women for uterine cancer is not recommended (NCCN 2012).

6 Staging

The NCCN recommends a history and physical examination, chest x-ray, endometrial sampling, and cervical cytology for the initial workup for uterine cancer. Traditionally, staging of endometrial cancer involves an exploratory laparotomy, total

Table 1 2009 FIGO staging of endometrial carcinoma (Mutch 2009)

Stage 1	Tumor confined to the corpus uterus
1a	No or less than ½ myometrial invasion
1b	Invasion ≥ half of the myometrium
Stage 2	Tumor invades cervical stroma
Stage 3	Local and/or regional spread of tumor
3a	Tumor invades serosa of the uterus and/or adnexae
3b	Vaginal and/or parametrial involvement
3c	Metastases to pelvic and/or paraaortic lymph nodes C1: positive pelvic nodes C2: positive paraaortic nodes with/without positive pelvic nodes
4	Tumor invades bladder and/or bowel mucosa and/or distant metastases
4a	Tumor invasion of bladder and/or bowel mucosa
4b	Distant metastases including intra-abdominal metastases and/or inguinal lymph nodes

Table 2 2009 FIGO staging of uterine sarcoma (Mutch 2009)

Stage 1	Tumor confined to the corpus uterus
1a	Less than 5 cm
1b	≥5 cm
Stage 2	Tumor extends to the pelvis
2a	Adnexal involvement
2b	Tumor extends to extrauterine pelvic tissue
Stage 3	Tumor invades abdominal tissue
3a	One site
3b	More than one site
3c	Metastasis to pelvic and/or paraaortic lymph nodes
4	Tumor invades bladder and/or rectum and/or distant metastases
4a	Tumor invasion of bladder and/or rectum
4b	Distant metastases
*Endometrial stromal sarcoma	Simultaneous tumors of the uterine corpus and ovary/pelvis in association with ovarian/pelvic endometriosis should be classified as independent primary tumors
*Adenosarcoma Stage 1	1a: tumor limited to endometrium/endocervix (without myometrial invasion) 1b: tumor invades ≤ ½ of myometrium 1c: tumor invades > ½ of myometrium

abdominal hysterectomy, bilateral oophorectomy, and pelvic and paraaortic lymph node dissections (NCCN 2012).

Grade 1 tumors are well differentiated, with formed glands and no more than 5% of non-squamous solid components. Grade 2 contains 6–50% solid components and grade 3 has greater than 50% non-squamous solid components. If there is significant cytologic atypia, the tumor should be upgraded. Currently, nearly 70% of patients are diagnosed and treated at early stage with 5-year survival estimated at 95.8%, and an additional 20% are diagnosed with only regional disease with a 5-year survival estimated at 67.0% (SEER 2013) (Tables 1 and 2).

7 Management of Endometrial Cancer

Unless prohibited by patient comorbidities, surgery is usually the first step in the management of endometrial cancer. Comprehensive surgical staging traditionally includes a hysterectomy, bilateral salpingo-oophorectomy, lymph node assessment, and intraperitoneal cytology. However, much of the traditional recommendations for surgical management of endometrial cancer have been challenged recently.

While hysterectomy is indicated for women with endometrial cancer, the best surgical approach has been questioned. There have been multiple studies demonstrating the safety and efficacy of laparoscopic surgery for endometrial cancer staging. Proven benefits include improved quality of life, shorter hospital stay, and less blood loss than exploratory laparotomy. In addition, laparoscopy does not impact recurrence rates or survival (Zullo et al. 2012; Walker et al. 2012). Since the introduction of the DaVinci robotic surgical platform, its use has continued to climb. The literature demonstrating the safety and efficacy of robotic staging is growing. A clear benefit of utilizing the robot is the

ability to stage obese patients minimally invasively (Seamon et al. 2009).

7.1 Lymphadenectomy

There continues to be significant debate regarding what population is at risk for nodal disease and warrants a lymphadenectomy. There is considerable variability in practice patterns amongst gynecologic oncologist with respect to indications for staging and extent of dissection. While lymphadenectomy guides staging and treatment, trials have failed to demonstrate either an overall survival or recurrence free survival benefit for pelvic lymphadenectomy (Mariani et al. 2000).

7.2 BSO

Several studies have retrospectively evaluated the outcomes of premenopausal women with ovarian preservation during surgery for endometrial cancer without finding any adverse survival impact. Given the impact on quality of life and increase in cardiovascular risk factors, it may be reasonable to forgo oophorectomy in premenopausal women with early-stage low-risk endometrial cancer (Lau et al. 2014; Lee et al. 2013; Wright et al. 2009). This should be carefully considered by the patient and her gynecologic oncologist. The benefit of retaining the ovaries in a postmenopausal woman has not been evaluated and bilateral salpingo-oophorectomy is recommended.

7.3 Cytologic Assessment

Pelvic washings were included in surgical staging for endometrial cancer prior to the 2009 FIGO staging. The findings of positive cytology are not correlated with clinical outcomes, and their utility has been questioned. As of the 2009 FIGO staging, pelvic washings are no longer required as part of surgical staging for endometrial cancer, and many gynecologic oncologists no longer include intraperitoneal cytology as part of their staging surgery (NCCN 2012).

8 Risk Assessment

Surgical stage and other significant pathologic risk factors are utilized to determine patients' risk for persistent disease or recurrence. This risk assessment is often utilized to determine the need for adjuvant therapy. Risk assessment and determination of adjuvant therapy can be complex and should be managed by an oncologist experienced in the treatment of uterine cancer.

8.1 Low Risk

Patients at low risk of recurrence have endometrioid histology with disease confined to the endometrium. This includes a subset of patients with stage IA and grade 1 or 2 endometrial cancer. Typically these patients are managed with close surveillance alone following surgery (NCCN 2012).

8.2 Intermediate Risk

Patients with an intermediate risk for recurrence have disease confined to the uterus, including the cervix (stage II) with myometrial invasion (stage IA or IB). Other prognostic factors such as deep myometrial invasion, grade 2 or 3 histology, and the presence of lymphovascular invasion can further subdivide this group into low or high intermediate risk. Recurrence rates range from 5% to 30% with or without radiation therapy. As such, consideration for adjuvant radiation therapy is warranted (NCCN 2012; Keys et al. 2004; Creutzberg et al. 2000) (Table 3).

Patients with a high risk for disease recurrence have advanced stage disease, and grade 3 carcinomas (including serous and clear cell) of any stage. This category is associated with a high rate of recurrence and death from endometrial cancer. As such, adjuvant chemotherapy is often utilized postoperatively (NCCN 2012).

Table 3 Risk assessment of local stage endometrial cancer (high intermediate risk (HIR)group determination)

Study	Risk factor	Determination of HIR
Gynecologic Oncology Group	Deep myometrial invasion Grade 2 or 3 Lymphovascular space invasion	Any age with all 3 50–69 with 2/3 70 or older with 1/3
PORTEC	Deep myometrial invasion Grade 3	Age > 60 with both risk factors

8.3 High Risk

Currently there is not a "standard" approach for high-risk disease. Often adjuvant therapy is dictated by surgical and pathologic factors such as uterine or extra uterine disease. Since multiple questions remain, enrollment on a clinical trial may be the most appropriate option for patients in this risk category.

In advanced stage disease, chemotherapy with carboplatin and paclitaxel is the most use regimen. Other active agents include doxorubicin, ifosfamide, topotecan, oxaliplatin, docetaxel, ixabepilone, and pegylated liposomal doxorubicin (NCCN 2012). The role of combined chemotherapy and radiation therapy has not been defined in advanced disease.

8.4 Recurrent or Metastatic Disease

Chemotherapeutic options for recurrent or metastatic disease are the same as for advanced disease. In localized recurrence in patients without prior radiation, radiation therapy can be utilized. For patients in whom radiation or cytotoxic therapy is not a reasonable option, hormonal therapy is an acceptable alternative for therapy in recurrent disease. In tumors that express estrogen and progesterone receptors, a favorable response to endocrine therapy is likely (Decruze and Green 2007). Tamoxifen is currently the only selective estrogen receptor modulator to demonstrate activity (Thigpen et al. 2001). Aromatase inhibitors are currently under investigation.

9 Non-Endometrioid Histologies

9.1 Uterine Papillary Serous Carcinoma (UPSC)

UPSC represents a histologically aggressive subtype of endometrial carcinoma that typically presents with extrauterine disease with a spread pattern similar to papillary serous ovarian cancer. Although this histology accounts for 10% of all endometrial cancers, it accounts for the majority of recurrences. Comprehensive staging for early stage UPSC is recommended in *all* patients. Multiple studies have clearly demonstrated that optimal resection of metastatic disease confers a survival benefit and should be the goal at the time of primary surgery. Any myometrial invasion is associated with higher risk of recurrence. Controversy also persists regarding the benefit of adjuvant therapy for disease confined to a polyp. Although the risk of recurrence is low in this population, it is not negligible (Rauh-Hain et al. 2010). Due to the propensity for uterine serous cancer to recur distantly, chemotherapy has been considered as an essential component of adjuvant therapy (Fader et al. 2009).

For advanced stage disease, following optimal cytoreduction, chemotherapy is the recommended adjuvant therapy due to high risk of distant recurrence. Currently, the combination of paclitaxel and carboplatin is an appropriate choice of cytotoxic therapy for advanced stage UPSC. The role of radiation therapy is limited and not typically recommended (NCCN 2012).

9.2 Uterine Carcinosarcoma

As with endometrial carcinoma, surgery is the primary management for carcinosarcoma. Surgical staging is recommended. For advanced stage disease confined to the abdomen, cytoreduction is also recommended (Tanner et al. 2011). For stage I and II uterine carcinosarcoma, there is a relative paucity of quality data to recommend adjuvant therapy. In the limited number of trials that do exist, there is a consistent improvement in

progression free survival but not overall survival (Cantrell et al. 2012). Chemotherapy was associated with improved progression free survival compared to observation or radiation therapy (Omura et al. 1985). The role for radiation therapy or chemotherapy is questionable for early stage disease. Given the paucity of data, consideration should be given to enrollment on a clinical trial. For stage III and IV uterine carcinosarcoma, chemotherapy is recommended as adjuvant therapy. Ifosfamide, cisplatin, adriamycin, and paclitaxel have had the most significant evidence of activity (NCCN 2012).

10 Sarcomas

10.1 Leiomyosarcoma

Uterine leiomyosarcoma is often identified incidentally following a hysterectomy or myomectomy for presumed uterine leiomyomas. The standard surgical management for women with known leiomyosarcoma is a hysterectomy often coupled with a bilateral salpingo-oophorectomy (BSO) in postmenopausal women. The role of a BSO has been questioned due to a growing body of literature failing to demonstrate a survival benefit. For those with disease outside of the uterus, the role of cytoreduction is controversial and not clearly understood. The role of a lymphadenectomy is also uncertain. Any bulky nodes should be removed. Standard staging when disease is confined to the uterus is questionable since the risk of nodal metastasis is low (Kapp et al. 2008; Major et al. 1993). In patients with an incidental finding of leiomyosarcoma on final pathology, a return to the operating room for "staging" is not indicated. Imaging to identify extrauterine disease is recommended.

The role of chemotherapy, radiation therapy, or a combination of the two is undetermined. Adjuvant therapy for early stage disease is especially controversial. As such, enrollment on a clinical trial should be recommended. The NCCN recommends observation versus consideration for chemotherapy, with docetaxel and gemcitabine being the preferred regimen. Other suggested regimens are listed in the Uterine Cancer guidelines (NCCN 2012).

With respect to recurrent disease, leiomyosarcoma commonly recurs in the lungs, liver, abdomen, pelvis, and retroperitoneal lymph nodes. Local recurrences in patients with a prolonged progression free survival can be managed with surgical intervention. For patients with a local recurrence who are not ideal surgical candidates, radiation therapy can be considered. Chemotherapy is the recommended approach for women with recurrent metastatic disease. The combination of gemcitabine and docetaxel is supported by multiple clinical trials. In the setting of recurrent disease, the chemotherapeutic agent of choice is often dictated by performance status, medical history, and patient choice. In the setting of recurrent metastatic disease, palliation is the goal of chemotherapy (NCCN 2012).

10.2 Adenosarcoma

Treatment for adenosarcoma of the uterus is hysterectomy with bilateral salpingo-oophorectomy in postmenopausal women. As ovarian metastasis is uncommon, the ovaries can be left in premenopausal women. Lymphadenectomy is not required in disease confined to the uterus. As most adenosarcomas contain an endometrial stromal sarcoma component, adjuvant therapy should follow the ESS guidelines (Friedlander et al. 2014).

10.3 Endometrial Stromal Sarcoma

Hysterectomy is the primary treatment for early endometrial stromal sarcoma. Ovarian conservation may be considered in young women with small tumors. The role of lymphadenectomy is not well defined in this disease. In recurrent or advanced disease, cytoreductive surgery should be considered. As the rate of hormone receptor positivity is very high in endometrial stromal sarcoma, hormone therapy is recommended in

advanced or recurrent low-grade disease. In high-grade disease, cytotoxic chemotherapy should be considered (NCCN 2012). Radiation therapy is often used for palliation as adjuvant pelvic radiation has not been shown to improve survival (Amant et al. 2014).

11 Conclusion

Uterine cancer is the most common gynecologic malignancy with a rising incidence in the United States. Endometrial cancers are associated with obesity and genetic syndromes such as HNPCC. They are histologically divided into type I and type II malignancies, with type I cancers usually being early stage and often curable. Type II cancers tend to be more aggressive and more often diagnosed at later stages of disease. Cancers of the uterine body include sarcomas such as leiomyosarcoma, adenosarcoma, and endometrial stromal sarcoma.

Abnormal uterine bleeding is the most common presenting symptom and should be evaluated with an endometrial biopsy. Following a diagnosis of uterine cancer, surgical staging is often performed. There are still many controversies regarding the need for a lymphadenectomy, and it is uncertain which patients need a complete lymph node dissection for prognostic information and guidance of therapy. Laparoscopic, robotic, and open approaches to staging are considered equivalent for cancer therapy and only differ in their operative risks.

The need for adjuvant therapy is determined by pathologic risk factors for recurrence. Patients at low risk for disease recurrence need no treatment after surgery. Those with an intermediate risk may benefit from chemotherapy and/or radiation. Patients with a high risk of recurrence need chemotherapy and radiation. All patients with a history of uterine cancer will need surveillance for recurrence of disease with frequent exams and biopsy of any suspicious lesion. Treatment of recurrent disease depends on the timing and location of recurrence.

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