Radiation Therapy in Endometrial Cancer

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Abstract
Endometrial cancer is one of the most common malignancies among females, with multiple risk factors and environmental exposures associated with the diagnosis. Despite it being a common malignancy, early intervention and effective treatment helps in keeping disease-related mortality low compared to other gynecologic malignancies. Endometrial cancer typically presents with abnormal or postmenopausal bleeding (vaginal bleeding), which warrants further workup of endometrial biopsy and vaginal ultrasound. Surgery is the primary treatment for endometrial cancer and also
plays an important role in the staging. Adjuvant treatment with radiation and/or chemotherapy depends on a variety of patient and tumor-related risk factors. Adjuvant radiation can be in the form of vaginal cuff brachytherapy and/or external beam radiation. Advanced in radiation treatments over the years have led to a better therapeutic ratio, with a lower rate of toxicities and equivalent to improved disease control. It is important to understand the risk factors of a patient’s endometrial cancer that help guide her overall cancer management and use a multidisciplinary approach.

Keywords
Endometrial cancer · Management · Chemotherapy · Radiation · Brachytherapy

Epidemiology

Endometrial cancer is the most common gynecologic malignancy in women in developed countries and second-most common worldwide behind cervical cancer. In 2018, the estimated incidence of endometrial cancer is 63,230, ranking sixth in cancer mortality with an estimated 11,350 deaths in 2018 (Siegel et al. 2018). Despite the high prevalence of endometrial cancer, it ranks seventh in cancer deaths in women and accounts for 20% of gynecologic cancer deaths, in part due to early intervention and effective treatment. According to the Surveillance, Epidemiology, and End Results program (SEER) analysis, it is estimated that nearly 3% of women will be diagnosed with endometrial cancer during their lifetime, with a median age of 62 at diagnosis. Endometrial cancer incidence is greatest in white women; however, the incidence in black women is rising. Furthermore, black and Hispanic women tend to present with more advanced disease and more aggressive histologies. Despite a lower cancer incidence among black women, they have a cancer specific mortality twice that of white women. This is likely due to a combination of tumor biological factors, with higher rates of more aggressive disease as well as patient and systemic factors such as higher rates of comorbidities, access to care, and socioeconomic factors (Collins et al. 2014).

Estrogen exposure is the primary risk factor for most endometrial cancers, particularly endometrioid type, commonly referred to as Type 1 endometrial cancer. This includes both endogenous and exogenous sources of estrogen. Physiologic sources of higher exposure to estrogen include late menarche, nulliparity or low parity, late menopause or in rare cases, estrogen-secreting tumors (Dossus et al. 2010). Commonly, excess endogenous estrogen originates from a woman’s adipose tissue due to peripheral conversion of androgen precursors to estrogen. Due to this source originating in adipose tissue, women who are overweight or obese have an increased risk of endometrial cancer. Women with a BMI of 30 or higher are at a threefold increased risk of having endometrial cancer compared to a non-obese BMI population (Fader et al. 2009; Jenabi and Poorolajal 2015). Additionally, those patients with comorbidities including diabetes and hypertension have an increased risk as well, although the reason for this association is not well known (Fader et al. 2009).

Exogenous estrogen exposure also leads to an increased risk in endometrial cancer. Estrogen only oral contraception is associated with increased risk of endometrial cancer (Weiderpass et al. 1999). In more recent decades, oral contraception is more commonly combination estrogen/progestin formulas, which does not carry an increased risk, due to the protective effect of the progestins. Tamoxifen, an estrogen receptor agonist used in the treatment and prevention of breast cancer carries an increased risk of developing endometrial cancer. This risk is dependent on the duration of tamoxifen use, with up to a sevenfold increased relative risk in patients treated with tamoxifen for 5 years or more. These patients also tend to develop endometrial cancer with poorer histologies and more advanced stage disease (Bergman et al. 2000). Although, others report the absolute increase of endometrial cancer diagnosis is 2% (Segev et al. 2013).

Protective effects against endometrial cancer include limiting estrogen exposure: late menarche, early menopause, and multiparity reduce this risk. Combination oral contraceptive use with concurrent progesterone provides a protective effect from the progestins limiting
estrogen-induced endometrial hyperplasia and proliferation (Dossus et al. 2010).

Genetic predispositions represent about 5% of endometrial cancers. Lynch syndrome (or hereditary nonpolyposis colorectal cancer) is an autosomal dominant condition caused by a germline mutation in the mismatch repair genes, namely, MSH-2, MLH-1, MSH-6, and PMS-2, leading to defective mismatch repair and microsatellite instability. This leads to an increased risk of developing colon and endometrial cancer. Women with Lynch syndrome carry up to a 60% lifetime risk of endometrial cancer, with an average age at diagnosis of 45. These women are often recommended prophylactic hysterectomy in order to reduce their risk of endometrial cancer (Wang et al. 2013). Women with a BRCA mutation, which portends an increased risk of breast and ovarian cancer, may have a higher incidence of endometrial cancer (Segev et al. 2013). This may be related to tamoxifen use as a treatment of their breast cancer, although there is data suggesting a higher risk of more aggressive forms of endometrial cancer, serous carcinoma in particular, in women with BRCA mutations (Shu et al. 2016). Ultimately, BRCA positive women should be counseled on hysterectomy with prophylactic oophorectomies at diagnosis.

Symptomatology

The most common presenting symptom of endometrial cancer is vaginal bleeding. Despite this being the most common presentation, only 10–20% of postmenopausal bleeding is due to endometrial cancer, but all require further workup to rule out endometrial hyperplasia or carcinoma, regardless of bleeding severity (Alberico et al. 1989). Similarly, any premenopausal or perimenopausal female with abnormal uterine bleeding, including vaginal spotting, menorrhagia, or metrorrhagia should receive a similar workup. If the vaginal bleeding is severe enough, it can lead to anemia, either symptomatic or asymptomatic, which can be another presenting sign. Other presenting symptoms including pelvic cramping or pain, vaginal discharge, dyspareunia, and in more locally advanced cases affecting adjacent organs, bowel or bladder complaints.

Diagnostic Workup

Currently, there is no recommended screening for endometrial cancer. Rather, signs and symptoms must be monitored and addressed accordingly. The workup begins with a comprehensive history, concentrating on the duration of symptoms, genitourinary (GU) or gastrointestinal (GI) symptoms, review of constitutional systems including weight loss or fatigue, family history of malignancies or genetic disorders, and risk factors, as discussed previously. A detailed gynecologic exam should be performed, which is often normal in patients, especially those with early stage disease. Most women with suspicion of endometrial cancer undergo transvaginal ultrasonography to evaluate the thickness of the endometrial stripe; however, all women with postmenopausal bleeding require an endometrial pipelle biopsy to rule out carcinoma. A large UK trial demonstrated a sensitivity and specificity of 80.5% and 85.7%, respectively, of detecting endometrial cancer in women with an endometrial stripe of 5 mm or greater on vaginal ultrasound, hence the need for endometrial biopsy given the relatively low specificity and sensitivity with ultrasound alone (Jacobs et al. 2011). If the endometrial biopsy is nondiagnostic and vaginal bleeding or symptoms persist, then the patient should undergo dilation and curettage, as there may be sampling error with the pipelle biopsy. At the time of endometrial biopsy, a pap smear should also be performed to rule out any cervical abnormality. If there is suspicion on exam for cervical disease involvement, a cervical biopsy should also be performed.

Additional workup for endometrial cancer includes a complete blood count, serum chemistries, and liver function tests. A CA-125 level may be useful as well, as this can be elevated in endometrial cancer, particularly serous type, and can be utilized for prognostic information as well as a marker to monitor for recurrence after definitive treatment (Chen et al. 2011). The role of pretreatment imaging depends on a patient’s disease characteristics. For early stage, low risk patients, a CXR alone should be sufficient to rule out distant metastases; however, if there are concerns for more advanced disease or high risk histologies, then consideration of presurgical imaging with
Cross-sectional imaging should be considered. The ACR (American College of Radiology) appropriateness criteria provide evidence-based recommendations of when and what imaging modalities can aid in treatment planning (Lee et al. 2011). However, often times, the extent of disease and high risk features aren’t noted until after definitive surgical management, making pretreatment imaging selection somewhat challenging.

Most women without high-risk features proceed directly to surgery following a positive endometrial biopsy. Surgical resection consists of a total hysterectomy and bilateral salpingo-oophorectomies with or without pelvic node dissection or sampling, and cytologic evaluation of pelvic washings. Newer data suggest a sentinel pelvic node biopsy can be done in place of upfront dissection (Rossi et al. 2017). This is described in more detail below. Surgery is not only the primary treatment for endometrial cancer, but it is also required for staging, which helps guide treatment. While there is debate regarding the role of nodal dissection, it remains the gold standard of determining nodal staging. Many surgeons utilize tumor grade, histology, and the primary tumor size as an indication to proceed with nodal dissection (Mariani et al. 2000). Pelvic nodes that may be sampled or dissected include the common iliac, internal iliac, external iliac, and obturator nodes, which are the primary draining lymph node regions from the uterus. Para-aortic nodes may also be sampled, particularly in women with high-risk features and high risk of nodal involvement or if they appear suspicious. While rare, isolated para-aortic nodal metastases in the setting of negative pelvic nodes can occur, as there can be direct lymphatic drainage to the para-aortic nodes from the uterine fundus (Burke et al. 1996). The risk of nodal involvement can be estimated from surgical data from a randomized trial GOG 33, commonly referred to as the Creasman tables, based on depth of tumor invasion into the myometrium and grade of disease, as shown in Table 1 (Creasman et al. 1987). When to do a completion dissection of the pelvic nodes is discussed further in the surgery section.

### Classification

#### Histology

There are many histologic subtypes of endometrial carcinoma including the most common endometrioid type, as well as less common histologies of serous carcinoma, clear cell carcinoma, carcinosarcoma, and small cell carcinoma. Endometrial carcinoma is generally divided into two subtypes. Type I endometrial cancer, commonly grade 1 and 2 endometrioid histology, represents about 80–90% of all endometrial cancers, is related to estrogen exposure, and mostly occurs in younger, perimenopausal women. These tumors arise in hyperplastic endometrial glands. Type II cancers make up 10–20% of endometrial cancers. They tend to be more aggressive in nature and include high-grade endometrioid histology and other subtypes like clear cell carcinoma, carcinosarcoma, and serous carcinoma. Estrogen exposure does not seem to play as important a role in type II histologies compared to type I. Type II cancers arise in atrophic endometria, more often affecting older women. Mutations leading to malignancy are different as well: type I tends to have PTEN pathway mutations and type II often have p53 mutations (Di Cristofano and Ellenson 2007).

Endometrial sarcoma is a rare disease entity, comprising less than 0.2% of uterine malignancies,
with different staging and treatment strategies than endometrial carcinoma. Endometrial stromal sarcoma and leiomyosarcoma are histologic subtypes of endometrial sarcomas (Wais et al. 2017).

### Staging

Endometrial cancer is a surgically staged cancer, with histologic information ultimately providing the International Federation of Gynecology and Obstetrics (FIGO) stage. This requires surgical evaluation of the pelvic organs and lymph nodes, although there is no defined standard of extent of nodal dissection for endometrial cancer, both in terms of number of nodes removed and the superior extent of removal. FIGO stage is the standard international staging and utilizes physical exam findings and surgical staging to define the stage of disease but also allows the use of pelvic imaging (MRI or CT) to help determine stage and treatment, particularly in the more advanced stage patients. Some staging systems recommend preoperative MRI to help with staging as well (Freeman et al. 2012). The AJCC (American Joint Committee on Cancer) staging also allows imaging modalities to aid in defining stage of disease, particularly nodal involvement. Table 2 describes the current 2009 FIGO staging and eighth edition AJCC staging for endometrial carcinoma (Powell et al. 2017).

Endometrial sarcoma is staged per the FIGO staging, however, has a separate staging system in the AJCC system, as demonstrated in Table 3 (Dizon et al. 2017).

#### Table 2

| AJCC eighth edition staging | FIGO stage | Surgical/pathologic findings |
|---------------------------|------------|-------------------------------|
| T stage                   |            |                               |
| Tx                        |            | Primary tumor not assessed    |
| T0                        | I          | No evidence of tumor          |
| Tis                       | II         | Carcinoma in-situ             |
| T1                        | III        | Confined to uterine corpus including endocervical glandular involvement<sup>a</sup> |
| T1a                       | IIIA       | Tumor involves <50% of myometrium or endometrium alone |
| T1b                       | IIIB       | Tumor involves ≥50% of myometrium |
| T2                        | IV         | Cervical stromal involvement but does not extend beyond uterus |
| T3                        | III        | Tumor involving serosa, adnexa, vagina, or parametrium |
| T3a                       | IIIA       | Serosa and/or adnexal involvement (due to direct extension or metastasis) |
| T3b                       | IIIB       | Vaginal involvement or parametrical involvement |
| T4                        | IVVA       | Bladder and or bowel mucosal involvement |
| N stage                   |            |                               |
| Nx                        | IIIIC1     | Regional nodes not assessed   |
| N0                        |            | No regional node metastases  |
| N1                        | IIIIC1     | Pelvic nodes positive for metastases |
| N1mi                      | IIIIC1     | Pelvic node metastases >0.2 mm but ≤2 mm in size |
| N1a                       | IIIIC1     | Pelvic node metastases >2 mm in size |
| N2                        | IIIIC2     | Para-aortic nodes positive for metastases |
| N2mi                      | IIIIC2     | Para-aortic node metastases >0.2 mm but ≤2 mm in size |
| N2a                       | IIIIC2     | Para-aortic node metastases >2 mm in size |
| M stage                   |            |                               |
| M0                        | IVB        | Distant metastases (including to inguinal nodes) |

AJCC = American Joint Committee on Cancer; FIGO = International Federation of Gynecology and Obstetrics

<sup>a</sup>Endocervical glandular involvement is considered stage I
Patients with early stage, FIGO stage I endometrioid type carcinoma can be further characterized as having intermediate risk disease based on patient and tumor characteristics. Further stratification as “low-intermediate risk” or “high-intermediate risk” is routinely done, based on their disease characteristics, as this predicts for greater risk of locoregional failures and help guide adjuvant treatment recommendations. PORTEC 1 (Postoperative radiation therapy for endometrial carcinoma) and GOG (Gynecologic oncology group) 99, two large randomized trials of women with stage I–II endometrial carcinoma treated with surgery with or without adjuvant pelvic radiation defined these intermediate risk patients as described in Table 4 (Creutzberg et al. 2000; Keys et al. 2004).

In addition to those risk factors described in Table 4, additional risk factors for recurrent disease or nodal involvement include tumor size and LVSI (lymphovascular space involvement) (Bosse et al. 2015; Canlorbe et al. 2016). A pooled analysis of PORTEC-1 and PORTEC-2 demonstrated that extensive LVSI was the strongest independent risk factor predictive of distant metastases and locoregional failure (Bosse et al. 2015). Additionally, tumor size >2 cm has been associated with a higher rate of pelvic and para-aortic nodal involvement (Schink et al. 1991). More controversial data exists on the
risk of nodal involvement when disease is located in the lower uterine segment (Canlorbe et al. 2016). Ultimately, all of these risk factors should be considered when estimating risks of vaginal and pelvic recurrence and executing joint decision-making of adjuvant treatment for a patient.

**General Management Principles**

Endometrial cancer is primarily treated with surgery, including total hysterectomy, bilateral salpingo-oophorectomy, peritoneal washings, with or without lymph node evaluation, either with dissection or nodal sampling of the pelvic and/or para-aortic nodes, with new emerging data suggesting sentinel node biopsy can suffice (Rossi et al. 2017). Patients with early stage disease may not require further adjuvant treatment with either radiation or chemotherapy. Generally, patients with stage IA low-grade disease with no other risk factors have low rates of recurrence and generally are managed by observation alone. Patients with certain risk factors for recurrence may benefit from adjuvant radiation with or without chemotherapy as detailed below. There are several established risk factors predictive of recurrence, including increasing grade, depth of myometrial invasion, lymphovascular space involvement (LVSI), outer half (>50%) or outer third (>66.6%) of the myometrium, lymphovascular space invasion, lymphovascular space involvement (LVSI), outer half (>50%) or outer third (>66.6%) of the myometrium, lymphovascular space invasion, positive lymphovascular space involvement (LVSI), outer half (>50%) or outer third (>66.6%) of the myometrium, lymphovascular space invasion, positive lymphovascular space involvement (LVSI), outer half (>50%) or outer third (>66.6%) of the myometrium, lymphovascular space invasion, positive lymphovascular space involvement (LVSI), outer half (>50%) or outer third (>66.6%) of the myometrium, lymphovascular space invasion, positive lymphovascular space involvement (LVSI), outer half (>50%) or outer third (>66.6%) of the myometrium, lymphovascular space invasion, positive lymphovascular space 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The extent of pelvic and para-aortic lymph node assessment recommended in endometrial cancer remains a controversial topic and area of active research. Risks of surgical complications associated with performing a lymphadenectomy include vascular or nerve injury, or more commonly, a risk of lymphedema. There is some data suggesting a full pelvic and para-aortic lymphadenectomy may not be routinely needed. Many gynecologic oncologists use the Mayo criteria to determine whether to complete a lymphadenectomy. This criterion identifies women with minimal risk of lymph node metastasis and cancer recurrence who could safely forego lymphadenectomy. For patients with endometrioid grade 1 or 2 histology, less than 50% myometrial invasion, and tumor diameter < 2 cm, as determined by frozen section at the time of surgery, hysterectomy with bilateral salpingo-oophorectomy is often considered the optimal treatment (Mariani et al. 2000). However, this requires intraoperative assessment of pathology from the uterine specimen, as depth of invasion cannot be assessed accurately preoperatively. One randomized trial of 1408 women with endometrial cancer who underwent either standard surgery or standard surgery plus lymphadenectomy found no benefit for systematic lymphadenectomy in terms of overall, disease-specific, and recurrence-free survival, with an increase in the risk of lymphedema in those patients who underwent lymph node dissection. While this study concluded that lymph node dissections cannot be routinely recommended, approximately 10% of women with high grade and outer myometrial invasion were upstaged due to nodal involvement (ASTEC study group et al. 2009). Nodal upstaging has an important role in recommending adjuvant chemotherapy and/or radiotherapy.

There is growing research showing the successful use of sentinel lymph node assessment to determine if nodal metastatic disease is present in patients undergoing surgery for endometrial cancer. This technique of injecting blue dye into the cervix and identifying lymph nodes containing the dye, which has spread through the lymphatics, identifies metastases that would require adjuvant therapy while minimizing the morbidity of lymphadenectomy. Such a procedure has only been investigated since 2006 and currently has level 2A evidence in the National Comprehensive Cancer Network (NCCN) guidelines as a technique for staging of endometrial cancer (NCCN clinical practice guidelines 2018). Current evidence suggests sentinel lymph node mapping may be equivalent to lymphadenectomy with low false negative rates (Rossi et al. 2017).

Barlin et al. describe a surgical algorithm with sensitivity of 98.1%, false negative rate of 1.9%, and negative predictive value of 99.8%. Their algorithm requires peritoneal and serosal evaluation followed by retroperitoneal pathologic evaluation of mapped sentinel lymph nodes with ultrastaging, a technique where H&E and anti-cytokeratin stains are used to evaluate four slides per block. Additionally, suspicious lymph nodes were removed along with side-specific lymphadenectomy in the case of no mapping of a hemi-pelvis. In this algorithm, para-aortic lymph node dissection was performed at the discretion of the attending surgeon (Barlin et al. 2012). In a recent trial, sentinel lymph node biopsy was compared to standard lymphadenectomy. Three hundred and forty patients underwent injection of dye, attempted sentinel lymph node mapping and lymphadenectomy, and mapping identified at least one sentinel lymph node in 86% of patients. The sensitivity of sentinel lymph node mapping to identify metastases was 97.2%. There was also a high negative predictive value of 99.6% in the sentinel node biopsy cohort. Additionally, sentinel lymph nodes were significantly more likely to contain metastatic disease than other lymph nodes not identified with sentinel lymph node mapping \( p = 0.0001 \). This study suggests that sentinel lymph node biopsy may be considered equivalent to standard lymphadenectomy in the detection of endometrial cancer metastases to lymph nodes (Rossi et al. 2017). While there is no consensus on the standard use of sentinel lymph node dissection, the current body of literature illustrates a technique that may be increasingly adopted in the future to reduce the morbidity associated with complete lymphadenectomy.


**Systemic Therapy**

Chemotherapy is not a standard adjuvant treatment for most early stage endometrial cancers; however, its role has been established in locally advanced cases. Its role in early stage, high-risk disease remains a subject of debate. Historically, the rationale behind including adjuvant chemotherapy, either simultaneously with radiation or sequentially was the high rate of distant metastases despite lower pelvic failure rates with adjuvant radiation. FIGO 2009 in a paper from 2004 demonstrated a pelvic relapse rate of 14% but a distant metastasis rate of 31% in the analysis of a subset of patients with stage IB, grade 3 disease who had received adjuvant radiation in PORTEC 1, a trial treating patient with adjuvant pelvic RT vs. no further treatment (Creutzberg et al. 2004). In order to decrease the rate of distant metastasis, several trials tested the addition of chemotherapy to radiation. In RTOG 97-08, a phase II trial of women with high-intermediate and high-risk endometrial cancer treated with pelvic +/- para-aortic node radiation with a brachytherapy boost, concurrent and adjuvant chemotherapy was utilized. Patients received two cycles of concurrent cisplatin given during weeks 1 and 5, followed by sequential cisplatin/paclitaxel for four cycles. This treatment lead to a 4 year distant metastasis rate of 19% and pelvic recurrence rate of only 2%, both improved compared to historic controls. Overall, the chemoradiation and chemotherapy regimens were well tolerated, however, with 41% and 16% late grade 2 and grade 3 toxicities, respectively, higher than that reported with radiation alone historically (Greven et al. 2006). These promising results lead to the phase III randomized trial, RTOG 99-05, comparing this regimen in patients with high-intermediate and high-risk endometrial cancer treated with postoperative pelvic radiation with or without concurrent chemotherapy (RTOG 97-08 regimen). Unfortunately, this trial closed due to nonaccrual, likely due to omission of stage III patients from inclusion to this study due to a competing trial. Additionally, RTOG 0921 was a phase II trial with a similar design treating high risk patients delivering post-operative pelvic radiation delivered using intensity modulated radiation therapy (IMRT) with concurrent chemotherapy and bevacizumab followed by four cycles of carboplatin/paclitaxel. The results showed a 2 year survival of 96.7%, 2 year disease-free survival of 79.1%, and no failures within the radiation fields for stage I–IIIA patients (Viswanathan et al. 2015).

There are several more recently completed and ongoing trials testing adjuvant and concurrent chemoradiation in the treatment of endometrial cancer. The role of chemotherapy for stage I–II high-intermediate and high-risk patients (including ~20% serous and clear cell carcinomas) was studied in GOG 249, a phase 3 trial randomizing patients to either pelvic EBRT (control arm) or VBT and chemotherapy with three cycles of carboplatin and paclitaxel (study arm). At 2 years of follow-up, there was no difference in overall survival or distant metastasis rate with pelvic EBRT vs. VBT and chemotherapy. Patients receiving VBT and chemotherapy experienced greater overall toxicities, particularly with greater hematologic toxicity, neuropathy, and fatigue, while EBRT patients had a higher rate of diarrhea (McMeekin et al. 2014). Late results were presented at the American Society of Therapeutic Radiation Oncology (ASTRO) 2017 meeting. At a median follow-up of 53 months, there was no improvement in recurrence free survival or overall survival in the VBT + chemotherapy arm. Furthermore, there were similar rates of distant metastases (18% in both arms), but a higher rate of nodal failures of 9% vs. 4% in the patients treated with VBT followed by chemotherapy compared to pelvic EBRT alone, respectively. Also noted was significantly worse acute toxicity in the VBT + chemotherapy arm of 64% grade 3 or higher toxicities compared to 11% in the pelvic EBRT alone, with similar late toxicity rates of 12–13% grade 3+ toxicity (Randall 2017). Thus for this group of patients, based on early reports, adjuvant radiation alone is appropriate.

The use of multimodality adjuvant therapy in the locally advanced endometrial cancer patients is controversial. A combined analysis of two trials testing whether the addition of sequential chemotherapy to radiation improves disease outcomes suggests a benefit for combined therapy (Hogberg
et al. 2010). One trial (EORTC – 55,991) included patients with stages I–III disease, high intermediate and high-risk patients including serous and clear cell carcinomas. This trial tested the addition of doxorubicin/epirubicin and cisplatin to pelvic radiation with or without VBT; however, later trial amendment allowed alternative chemotherapy regimens. The other trial (MaNGO trial) used a doxorubicin/cisplatin chemotherapy regimen for three cycles and included patients with stages II–III but excluded unfavorable histologies. The combined analysis of these trials demonstrated an improvement in progression free survival with sequential radiation and chemotherapy compared to radiation alone, with a trend towards improved overall survival, supporting the role for combined modality therapy for patients at high risk for recurrence (Hogberg et al. 2010). PORTEC-3 randomized patients with high-risk endometrial cancer to whole pelvic radiation with or without chemotherapy (concurrent cisplatin, followed by four cycles of adjuvant carboplatin/paclitaxel). Early results were reported on 2 year toxicity and quality of life demonstrating a significant increase in both patient and physician reported toxicity, namely, acute hematologic toxicity and late neurotoxicity (neuropathy) in the chemoradiation arm compared to the radiation alone arm. At 2 years, only neuropathy persisted at a significantly higher rate in the chemoradiation arm. However, failure-free survival (FFS) trended toward improvement with combined modality treatment for the whole population, and FFS was significantly improved in stage III patients (de Boer et al. 2016, 2017). Overall, these trials demonstrate that the addition of chemotherapy to radiation carries both a higher risk of toxicity, but also an improvement in disease specific outcomes.

A few trials have sought to explore chemotherapy alone in the locally advanced setting. GOG 122 tested single modality treatment using whole abdomen radiation vs. chemotherapy following surgery. Those who received chemotherapy showed improved overall survival and progression free survival compared to the radiation arm; however, there were multiple issues with the radiation delivery methods, discussed further below (Randall et al. 2006). GOG 258 randomized advanced stage (stage III–IV) endometrial patients s/p maximal debulking to six cycles of adjuvant chemotherapy alone vs. pelvic +/- para-aortic nodal radiation with concurrent cisplatin, followed by four cycles of adjuvant carboplatin/paclitaxel. Early results demonstrated improved vaginal, pelvic, and para-aortic recurrence rates in the chemoradiation arm but inferior distant metastasis rates compared to chemotherapy alone. There were similar rates of grade 3+ toxicity as well. Long-term and overall survival results are still awaited (Matei et al. 2017).

Overall, the role of chemotherapy is well accepted for advanced stage endometrial cancer including women with stage III–IV disease but is probably not indicated in earlier stage disease.

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**Radiation Therapy**

**Early Stage Disease**

Multiple large randomized trials have demonstrated improved locoregional disease control for patients with early stage endometrial cancer treated with adjuvant radiation, compared to no further treatment following definitive surgery. Two large studies, PORTEC-1 and GOG 99 both explored the use of adjuvant pelvic radiation vs. observation in women with early stage, intermediate risk disease. These studies demonstrated an absolute risk reduction of ~10% of having a locoregional recurrence with the addition of pelvic radiation (3–4% with pelvic RT vs. 12–14% without RT) (Creutzberg et al. 2000; Keys et al. 2004). Furthermore, these studies helped establish the risk groupings of low-intermediate and high-intermediate risk disease based on patient and tumor factors, as described in Table 4. Of the patients who developed locoregional failure in these trials, approximately 75% occurred at the vaginal cuff. A follow-up trial, PORTEC-2 compared vaginal cuff brachytherapy (VBT) to pelvic external beam radiotherapy (EBRT) and demonstrated that VBT was noninferior to pelvic EBRT in preventing vaginal recurrences in PORTEC defined high-intermediate risk patients. While there was a relatively low rate of pelvic failures...
in both arms, this risk was still reduced with the use of pelvic EBRT (3.8% in VBT arm vs. 0.5% in pelvic EBRT arm, p = 0.02) (Nout et al. 2010). Patients with GOG 249 defined high-intermediate and high risk early endometrial cancer are probably best treated with pelvic EBRT, although we await the publication of the manuscript. Pelvic EBRT can also be considered based on a patient’s risk of pelvic and para-aortic node involvement. Pelvic nodal risk can be estimated from early surgical data from GOG 33 based on depth of involvement and grade (Table 1) or with the aid of nomograms predicting risks, based on factors including patient age, depth of invasion, grade, stage, presence of LVSI, and tumor size (AlHilli et al. 2013; Bendifallah et al. 2015; Creasman et al. 1987). Utilizing these data and predictive tools may help guide decision-making regarding pelvic EBRT vs. VBT for early stage patients.

Women with FIGO 2009 stage IB/grade 3 were excluded from the PORTEC trials of intermediate risk patients given their high risk of nodal involvement, thus, especially in the absence of nodal staging, they should be strongly considered for pelvic radiation with or without a vaginal cuff brachytherapy boost (Creasman et al. 1987; Creutzberg et al. 2004). A Norwegian study of stage I endometrial cancer also supports adjuvant radiation by demonstrating that patients with FIGO 2009 stage IB/grade 3 had improved survival with EBRT and VBT compared to VBT alone (Aalders et al. 1980).

Advanced Stage Disease

The use of radiation in locally advanced endometrial cancer continues to be studied in present day. Historically, when radiation was compared to chemotherapy as a monotherapy in GOG 122, a randomized trial of whole abdomen radiation vs. chemotherapy following surgery, those who received chemotherapy showed improved overall survival and progression free survival compared to the radiation arm. However, this trial had multiple issues including imbalanced crossover, used older radiation techniques, and was not well balanced between the two randomized groups (Randall et al. 2006). GOG 258 demonstrates improved locoregional control for stage III–IV patients treated with chemoradiation + adjuvant chemotherapy vs. chemotherapy alone although no improvement in relapse free survival (Matei et al. 2017).

In summary, the addition of radiation to adjuvant chemotherapy in patients with locally advanced endometrial cancer provides a locoregional control benefit, with more modern radiation techniques reducing historic toxicity rates associated with combination therapy and should be strongly considered in all locally advanced patients.

Radiotherapy Technique

CT Simulation: Patients undergoing EBRT for endometrial cancer should have their CT simulation performed with an immobilization device. Either a generous margin around the vaginal cuff should be used or one can create an internal target volume accounting for motion caused by changes bladder and rectal filling by obtaining both a full and empty bladder scan. Alternatively, image guidance with cone beam CT can be utilized to confirm appropriate bladder filling. The vaginal canal should be marked with either radiopaque marker or fiducials. IV and PO contrast can be helpful in delineating the pelvic vessels adjacent to nodal regions and small bowel, respectively.

EBRT Volumes: Target volumes for standard adjuvant pelvic EBRT should include the proximal 3–5 cm of the vaginal cuff, the pelvic nodal regions at risk (internal iliac, external iliac, obturator nodes, and presacral nodes if the cervix is involved). If they are at risk for disease involvement, the common iliac and para-aortic nodes may be included in the target volume as well. Historically, pelvic EBRT was delivered using 2D or 3D conformal radiation techniques covered these regions; however, recent level I evidence demonstrated improved toxicities and quality of life using pelvic IMRT in the postoperative setting for gynecologic cancers compared to 3D conformal radiation (Klopp et al. 2016). Consensus guidelines for IMRT target delineation serve as a
good reference for contouring target volumes when using IMRT and are utilized in current clinical trials (Small et al. 2008).

**EBRT Dose:** The majority of the trials for endometrial cancer utilize a dose of 45–50.4Gy in 1.8–2Gy fractions, both when delivering radiation alone and with the addition of chemotherapy in the treatment of advanced disease (Aalders et al. 1980; Creutzberg et al. 2000; Greven et al. 2006; Keys et al. 2004; Nout et al. 2010). For close margins, adnexal or parametrial involvement, or gross residual disease, a boost dose can be considered. There is little data on the use of altered fractionation in the treatment of endometrial cancer and is not routinely used outside of clinical trials.

**EBRT Technique:** Historically, adjuvant pelvic radiation was delivered using conventional, 2D- or 3D-conformal radiation techniques, treating an area as shown in Fig. 1 with the borders described in Table 5. However, this treatment carried the risk of GI and GU toxicity, especially due to the small bowel that falls into the pelvis after hysterectomy, with late GI complications of up to 20–25% (Creutzberg et al. 2001). With the advent of IMRT, multiple dosimetric and clinical studies demonstrated the feasibility of pelvic IMRT in the postoperative setting for gynecologic cancers, with lower rates of GI and hematologic toxicities (Brixey et al. 2002; Mundt et al. 2003). Small, et al. formed an expert consensus guideline for the target volumes in the treatment of postoperative gynecologic malignancies. This atlas was used in RTOG 1203 (TIME-C), a randomized trial comparing 3D CRT to IMRT, aimed at evaluating toxicities (Small et al. 2008). Results showed

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**Table 5** Historic borders used for pelvic radiation therapy in the 2D and 3D era

| Borders used for pelvic radiation in the 2D and 3D era |
|------------------------------------------------------|
| **Superior**                                        |
| L5/S1 border (PORTEC) or L4/L5 border (GOG)          |
| **Inferior**                                        |
| Upper half of the vaginal canal or lowest extent of obturator foramen |
| **Anterior**                                        |
| Anterior edge of pubic symphysis                    |
| **Posterior**                                       |
| Posterior to body of S3                            |
| **Lateral**                                         |
| 2 cm lateral to pelvic brim                        |

PORTEC = Postoperative Radiation Therapy in Endometrial Cancer; GOG = Gynecologic Oncology Group; L/S = lumbar and sacral vertebrae, numbered respectively

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**Fig. 1** Example of standard AP and lateral fields used for pelvic radiation for postoperative endometrial cancer
significantly improved acute GI toxicity and better patient reported quality of life in the IMRT arm compared to the historic 3D conformal arm (Klopp et al. 2016).

**Vaginal Brachytherapy**

Vaginal brachytherapy is delivered via a vaginal cylinder, which can be single or multicatheter applicator. The appropriate size cylinder should be selected for the patient so that there is circumferential contact with the vaginal mucosa with minimal motion. There are little data regarding the standard VBT dose, although one study demonstrated a higher toxicity rate with increasing dose per fraction when using HDR brachytherapy (Sorbe et al. 2005). Less commonly, LDR BT is used, often to a dose of 30 Gy to 0.5 cm depth, as was used on PORTEC-2 (Nout et al. 2010). HDR brachytherapy monotherapy are variable, but doses typically range from 3–6 fractions of 4–7 Gy prescribed to either the vaginal cuff surface or 5 mm depth, and 2–3 fractions of 5–6 Gy for a vaginal cuff boost following pelvic EBRT (Harkenrider et al. 2016). Whether used as a boost or as monotherapy, typically the proximal 3–5 cm or approximately one-quarter to two-thirds of the vagina is treated, as was performed in multiple randomized trials (Creutzberg et al. 2000; Keys et al. 2004; Nout et al. 2010; Sorbe et al. 2005). The American Brachytherapy Task Force recently published a comprehensive review of the literature and consensus recommendations, which can serve as a guide when deciding on vaginal cuff brachytherapy planning (Harkenrider et al. 2017).

**Outcomes and Prognosis**

Despite the high prevalence of endometrial cancer, it ranks sixth in cancer deaths in women and accounts for 4% of all cancer deaths (Siegel et al. 2018). This overall good prognosis is due to early intervention and effective treatment. Individual risk factors, both patient and tumor specific, as discussed above are both predictive of the extent of disease at diagnosis, as well as for disease recurrence. These include older patient age, tumor stage, extent of myometrial involvement, tumor histology, grade, tumor size, location, and presence of LVSI. Type II endometrial carcinomas, including clear cell and serous carcinoma are generally more aggressive than type I endometrioid carcinomas and have a propensity to present at a more advanced stage and have a greater risk of metastases.

Additionally, these poor histologic subtypes have lower 5 year OS of 50–60% compared to 83% for endometrioid type. FIGO stage is an important prognostic factor predictive of overall survival, with an estimated 5 year OS rate ranging from 15–20% for FIGO stage IV disease to around 90% for FIGO stage I disease (Creasman et al. 2003). The risk of locoregional recurrence and distant metastases depend on an individual’s risk factors and the treatment given, as described above. For early stage, high risk (stage IB/grade 3 and stage II) and locally advanced endometrial cancer, the Hogberg analysis demonstrated improved PFS and OS with combination sequential chemoradiation following surgical resection (Hogberg et al. 2010). A phase II trial of concurrent chemoradiation followed by adjuvant chemotherapy in high risk stage I–III disease patients demonstrated a 4 year OS of 85%; however, in the stage III patients, it was between 72% and 77%, demonstrating the important prognostic and predictive effect of FIGO stage (Greven et al. 2006). De Boer et al. recently reported the results of PORTEC 3, a phase 3 trial comparing pelvic radiation alone to concurrent chemoradiation followed by adjuvant carboplatin/paclitaxel chemotherapy in high risk endometrial cancer patients. The addition of concurrent and adjuvant chemotherapy to pelvic radiation lead to a borderline statistically significant improved 5 year failure free survival (78.5% vs. 68.9%, $p = 0.078$), with no statistically improvement in overall survival (81.8% vs. 76.7%, $p = 0.18$). However, there was a significant benefit for patients with stage III endometrial cancer, with a failure free survival of 69.3% vs. 58% in the radiation alone arm ($p = 0.03$) (de Boer et al. 2017). Further results from ongoing trials looking at further aggressive adjuvant therapy to improve disease
outcomes in patients with locally advanced and high-risk endometrial cancer are eagerly awaited.

Vaginal brachytherapy is an effective modality to reduce the risk of vaginal recurrence with minimal toxicity for those at risk with low risk of non-vaginal cuff pelvic disease. EBRT should be considered for early stage high-risk patients. For patients with locally advanced disease, there are mixed data about the optimal adjuvant therapy. There is data to support (1) combined modality therapy with EBRT and concurrent and adjuvant chemotherapy or (2) chemotherapy alone. Early use of EBRT reduces locoregional failures but at the expense of increased distant metastases which may be due to delay or reduced doses of chemotherapy (Matei et al. 2017). Early use of chemotherapy reduces distant metastases but at the expense of increased distant metastases which may be due to delay or reduced doses of chemotherapy. In the meantime, competing risks of failure should be weighed to guide recommendation of adjuvant therapy and proper sequencing. Advanced techniques of surgery and radiotherapy continue to improve associated treatment-related toxicity profiles. The type of surgery, use of lymph node dissection, and recommendation of adjuvant radiotherapy and chemotherapy should all be performed with combined decision-making including the patient to optimize the risks and benefits.

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