Current Recommendations and Recent Progress in Endometrial Cancer

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Abstract: Endometrial cancer is the most common gynecologic cancer in the United States, and its incidence is rising. Although there have been significant recent advances in our understanding of endometrial cancer biology, many aspects of treatment remain mired in controversy, including the role of surgical lymph node assessment and the selection of patients for adjuvant radiation or chemotherapy. For the subset of women with microsatellite-instable, metastatic disease, anti–programmed cell death protein 1 immunotherapy (pembrolizumab) is now approved by the US Food and Drug Administration, and numerous trials are attempting to build on this early success. **CA Cancer J Clin 2019;69:258-279. © 2019 American Cancer Society.**

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Introduction

Endometrial cancer incidence in the United States has been rapidly rising in recent years. It has been suggested that this increase is due in part to declining rates of hysterectomy for benign causes.[1] In 2013, there were an estimated 49,560 cases and 8190 deaths from uterine cancer cancer[2]; by 2018, there were an estimated 63,230 new cases and 11,350 deaths,[3] making uterine cancer the fourth most common cancer in women and the fifth most common cause of cancer death in the United States.[4] Five-year, age-adjusted survival for uterine cancer has not improved recently; it was estimated in the US Surveillance, Epidemiology, and End Results (SEER) database at 83.18% in 2015 and at 81.81% in 1985.[5] Substantial racial disparities in endometrial cancer exist, with an estimated 5-year relative survival (all stages and subtypes included) in 2018 of 84% for white women and 62% for black women.[6]

These disparities have been attributed to an increased incidence of tumors with advanced stage, high grade, and aggressive histology along with decreased use of surgery for black women.[7] Adjuvant treatment recommendations for this cancer remain complicated and controversial, and there are relatively few treatment options for metastatic disease. Trials in this disease, which is associated with older age and with obesity, have been challenged by comorbidities and toxicity. However, large strides in our understanding of the biology of endometrial cancer have been made, and modern clinical trials are targeting biologic subsets rather than treating all the disparate histologic types as one disease, which is likely to improve therapies in the near future. For example, recognition of a subset (microsatellite-instable tumors) that is particularly sensitive to immunotherapy should dramatically improve outcomes for that group.

Genetic Predisposition

About 3% of endometrial cancers occur in women who have an autosomal dominant hereditary predisposition to cancer known as Lynch syndrome. This most

commonly results from germline mutations in 1 of the mismatch repair (MMR) proteins (mutL homolog 1 [*MLH1*], mutS homolog 2 [*MSH2*], *MSH6*, or PMS1 homolog 2 [*PMS2*]) or epithelial cell adhesion molecule (*EPCAM*) (regulator of *MSH2*). Patients with Lynch syndrome are at an increased lifetime risk of multiple cancers, including colorectal, endometrial, ovarian, and gastric. Less commonly, they may also have cancers of the small bowel, transitional cell cancer of the genitourinary tract, pancreatic carcinoma, sebaceous adenomas, and glioblastoma multiforme. Colon and endometrial cancers are the most common malignancies in Lynch syndrome and occur at about equal frequency (range, 40%-60%). In 2014, the Society of Gynecologic Oncology released a clinical practice statement recommending systematic screening for Lynch syndrome in all women with newly diagnosed endometrial cancer. If this is done with immunohistochemistry analysis (IHC) for loss of expression for the MMR proteins (rather than polymerase chain reaction [PCR]-based microsatellite instability [MSI] analysis), it must be realized that a proportion of endometrial cancers have loss of expression of MLH1 caused by sporadic promoter methylation, and *MLH1* methylation analysis should be applied to all tumors with loss of MLH1 expression to determine whether the loss is a result of a germline mutation or not.[8]

Prognostic Factors

Although incident endometrial cancers are increasing, the majority of patients diagnosed have early-stage disease with a good prognosis after surgery alone.[3] It has been difficult to reliably identify the patients with early-stage disease who are at the highest risk for recurrence and apply effective, individualized adjuvant therapies while at the same time avoiding overtreatment with accompanying short-term and long-term toxicities. The use of predictive biomarkers (eg, p53 or L1 cell adhesion molecule [L1CAM]) is very promising but remains investigational (ClinicalTrials.gov identifier NCT03469674).

Currently, nearly all risk stratification systems in endometrial cancer use a composite of stage (including depth of myometrial invasion [MMI] and involvement of lymph nodes), histology, and grade.[9,10] Genomic factors are not yet in standard clinical use for the assessment of prognosis.

A categorization of endometrial cancer subtypes was proposed by Bokhman in 1983.[11] That system proposed 2 broad types of endometrial cancer and was widely adopted as a framework for refining prognosis and for establishing different treatment approaches that reflect the disparate biologic behaviors of cancers within each of these groups. Type I cancers (70%) are mediated primarily by the sequelae of obesity and are associated with excess endometrial cell proliferation. Accordingly, patients with type I endometrial cancer are frequently afflicted with hyperestrogenism, hyperlipidemia, diabetes, and anovulatory uterine bleeding; all of these conditions are associated with the metabolic syndrome, which has been identified as an independent risk factor for the development of endometrial cancer.[12] Histologically, type I tumors are predominantly well-differentiated to moderately differentiated endometrioid tumors, and at least 90% express moderate to high levels of the estrogen receptor.[13] Type II endometrial cancers, in contrast, are not associated with hyperestrogenemia or endometrial hyperplasia, often arise in nonobese women, and are not associated with metabolic or endocrine disorders. Histologically, type II tumors are poorly differentiated, most commonly serous, clear cell, or carcinosarcoma subtypes. They are clinically aggressive and are associated with a higher stage at initial presentation and a higher risk of recurrence. Premalignant forms differ for each type: endometrial intraepithelial neoplasia is associated with type I cancers, and endometrial intraepithelial carcinoma is associated with type II cancers.[14]

Endometrioid histology is the most common form of carcinoma of the endometrium, comprising 75% to 80% of cases.[15] Serous and clear cell cancers make up about 10% and 4%, respectively (Fig. 1). These latter are more likely to present at an advanced stage and to have a worse prognosis at any given stage than grade 1 or 2 endometrioid tumors of similar stage. Seventy percent of serous carcinomas will have already spread outside the uterus at the time of presentation, and intraperitoneal disease is frequently present even in the absence of MMI.[16]

Unfortunately, histomorphologic assessment of endometrial cancer has poor reproducibility, particularly among high-grade carcinomas,[17,18] and mixed histology is not infrequent. Numerous adjunctive, single-marker assays involving IHC-based, fluorescence in situ hybridization–based, and/or PCR-based mutation analyses have been used in combination with morphologic assessment to distinguish among endometrial carcinoma subtypes and potentially help predict biologic behavior. Notable among them are IHC expression markers, such as p53, phosphatase and tensin homolog (PTEN), estrogen receptor (ER), p16, Napsin A/HNF-1B, and AT-rich interaction domain-containing protein 1A (ARID1A).[19-21] Mutational assays that can help include *p53*, *PTEN*, phosphoinositide 3-kinase (PIK3) catalytic subunit α (*PIK3CA*), PIK3 regulatory subunit 1 (*PIK3R1*), fibroblast growth factor receptor 2 (*FGFR2*), *ARID1A*, catenin β1 (*CTNNB1*), Kirsten rat sarcoma viral oncogene homolog (*KRAS*), and protein phosphatase 2 scaffold subunit Aα (*PPP2R1A*). No single marker is sensitive and specific enough to reliably define a histotype[22] and, although numerous panels have been proposed that improve histologic interobserver agreement, the specific elements of such a panel are not universally agreed upon.

The most comprehensive molecular study of endometrial cancer to date was accomplished through The Cancer Genome Atlas (TCGA)[4] funded by the National Cancer Institute. The endometrial carcinoma report published in 2013 integrated whole-genome sequencing, exome sequencing, MSI assays, copy number analyses, and proteomics to classify 373 endometrial cancers (307 endometrioid, 53 serous, and 13 mixed histology cases) into 4 clusters, 3 of which were almost exclusively of endometrioid morphology: 1) ultramutated/polymerase ε (*POLE*)–mutated (7%); 2) hypermutated/MSI (MSI-H) (30%); 3) copy number–low (microsatellite stable [MSS]) (65%); and 4) copy number–high (predominantly serous histology; 26%). Progression-free survival (PFS) correlates with cluster, with POLE tumors doing the best and copy number–high tumors doing the worst.

POLE-mutated tumors are frequently of high-grade endometrioid histology and are characterized by few copy number alterations. They are negative for MSI but exhibit extremely high mutational rates 10 times the rate in the MSI-H group, and 100 times the rate in the copy number–low/MSS group). Importantly, despite the proportion of *POLE*-mutated tumors noted with high-grade morphology, their prognosis is significantly better than that in the other 3 groups.[21] Commonly mutated genes within the POLE subset are *PTEN* (94%), *PIK3R1* (65%), *PIK3CA* (71%), F-box and WD repeat domain-containing 7 (*FBXW7*) (82%), *KRAS* (53%), and *POLE* (100%).

MSI-H/hypermutated tumors include Lynch syndrome cancers as well as tumors that have loss of MMR through hypermethylation of one of the MMR proteins and comprise approximately 25% to 30% of endometrial carcinomas. They have a high mutation frequency which is approximately 6-fold greater than that seen in MSS (copy number–low) or copy number–high tumors. Alterations in the receptor tyrosine kinase (*RTK*)/rat sarcoma (*RAS*)/*B-catenin* and *PTEN*/*PI3K* signaling pathways are relatively common, with notable mutations identified in *PTEN* (88%), *PIK3CA* (55%), *PIK3R1* (40%), *KRAS* (38%), *CTNNB1* (19%), and *FGFR2* (16%).

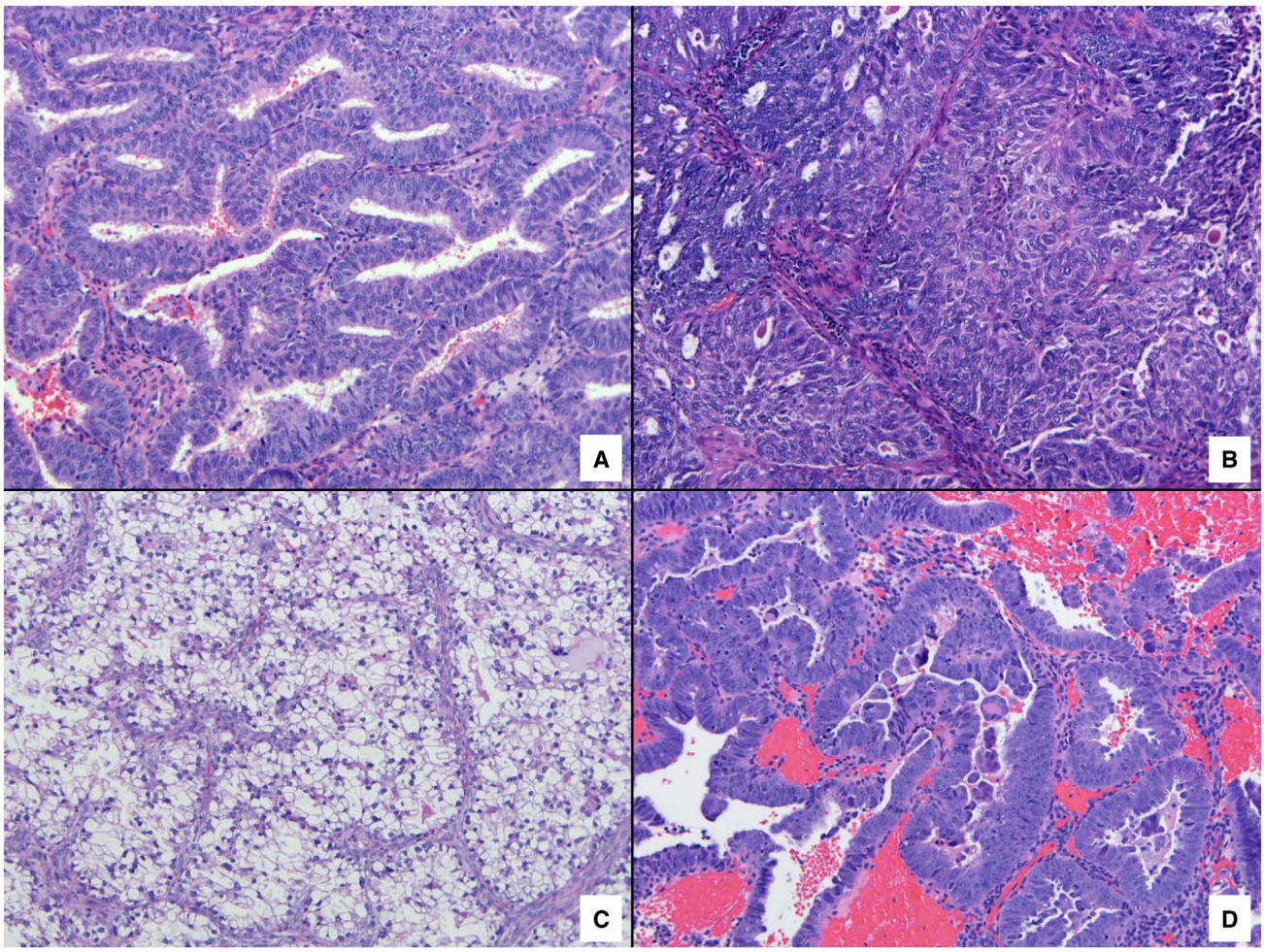

FIGURE 1. Histologic Subtypes of Endometrial Cancer. Photomicrographs show (A) endometrial endometrioid carcinoma (International Federation of Gynecology and Obstetrics [FIGO] grade 1), (B) endometrial endometrioid carcinoma (FIGO grade 3), (C) endometrial clear cell carcinoma, and (D) endometrial serous carcinoma (A-D: H & E, original magnification ×20).

MSS or copy number–low tumors comprise the majority (65%) of endometrial cancers. They exhibit low mutational frequency. *KRAS*/B-*catenin* and *PTEN/PI3K* pathway alterations are common, including mutations in *PTEN* (77%), *PIK3CA* (53%), *CTNNB1* (53%), *PIK3R1*, *KRAS* (15%), *FGFR2* (11%), and sex-determining region Y-box 17 (*SOX17*) (8%). Increased progesterone receptor expression was noted in the copy number–low group, suggesting potential responsiveness to progestin therapy. Notable in this cluster were mutually exclusive mutations in *CTNNB1*, *KRAS*, and *SOX17*, all of which play an important role in activated B-catenin persistence.

Copy number–high (serous-like) tumors comprised 26% of endometrial cancers. They have low mutational frequency and are predominantly of serous histology, although up to 35% of morphologically classic, high-grade endometrioid carcinomas also fall within the copy number–high cluster. Of note, *ERBB2* is focally amplified with protein overexpression in 25% of serous or serous-like tumors, suggesting a potential role for human epidermal growth factor receptor 2 (HER2)–targeted therapy (for HER2-targeted therapies, see Anti–HER2 Therapy, below).[23]

Although some molecular alterations were relatively unique to individual clusters (*POLE* and *FBXW7*, *POLE*; *p53* and *RPL22*, copy number–low), alterations in the *PTEN/PI3K* and *RTK/KRAS/B-catenin* pathways were common to multiple TCGA clusters (POLE, MSI, and MSS). Among single mutations, those commonly shared across clusters were loss-of-function *PTEN* and *ARID1A* mutations (POLE, MSI, and MSS), missense *PIK3CA* mutations (all clusters), as well as truncating *PIK3R1* mutations (POLE, MSI, and MSS).

The original TCGA study excluded clear cell carcinomas and carcinosarcomas. These represent only about 5% of endometrial cancer cases each but are responsible for a disproportionate number of deaths because of their aggressive biology.[24,25] For example, uterine carcinosarcoma accounts for 16% of all deaths caused by a uterine malignancy.[26]

In 2017, TCGA published a molecular characterization of 57 uterine carcinosarcoma cases using the same integrated technique described for the characterization of endometrial carcinoma in 2013.[24] Two of 57 cases (4%) were MSI-H. One POLE tumor was identified. Twelve cases (22%) were endometrioid-like, and 43 (78%, including tumors in all 10 of the patients who presented with stage IV disease) were serous-like. Ninety-one percent of cases had *TP53* mutations, and >62% had mutations in 1 or more PI3K pathway genes (*PIK3CA,* 35%; *PTEN*, 19%; *PIK3R1*, 11%). However, unlike most other endometrial cancers in which *PTEN* and *TP53* mutations are mutually exclusive, 73% of *PTEN*-mutated tumors also had *TP53* mutations. Greater than 75% of cases had mutations in *FBXW7*, amplification of cyclin 31 (*CCNE1*), or retinoblastoma 1 (*RB1*) loss, suggesting dysregulated cell cycle function. *ARID1A*, which includes an SWI/SNF epigenetic chromatin remodeler that has been implicated in many tumor types, was also frequently altered. Of note, no *BRCA1* promoter methylation or somatic mutations were found in any tumors.

De Lair et all performed a histopathologic review and massive parallel sequencing of 32 pure endometrial clear cell carcinomas. The authors found that these represented a histologically and genetically heterogeneous group of tumors with various outcomes; all molecular subtypes represented in the TCGA analysis of serous and endometrioid tumors were found. Two were ultramutated and harbored *POLE* mutations. Among *POLE* wild-type clear cell carcinomas, 46% showed *p53* mutations. *PIK3CA*, *PP2R1*, *FBXW7*, *ARID1A*, and *SPOP* genes were also frequently mutated. Eighteen percent and 11% had *CCNE* and *HER2* amplification, respectively.[25]

Because of the potential improvement in prognostic categorization that might be realized by clinical implementation of the categories reported in the TCGA analysis, several groups have proposed simplified algorithms based on the TCGA data set for use in clinical settings. The 2 best described and validated algorithms are the "Leiden" and the Proactive Molecular Risk Classified for Endometrial Cancer (PRoMise) algorithms.[27,28] Both strategies use sequential, dichotomous triaging assays to categorize tumors into 1 of 4 groups analogous to those described in TCGA analyses. In both systems, surrogate assays for p53 status are used to identify TCGA copy number–high tumors, and MMR IHC is used as a surrogate to identify MSI status. The 2 systems differ with respect to the order in which component assays are performed as well as the assay technologies used to for categorization (ie, P53 status based on IHC vs mutational analyses). The PRoMise molecular classifier has recently been validated in a larger, population-based case series with good results.[29]

Therapy-Surgery

Endometrial cancer is usually treated primarily with surgery, and surgical staging has been part of the initial management of endometrial cancer for both the prognostic stratification and the identification of patients who may benefit from chemotherapy or radiation therapy (RT). Total extrafascial hysterectomy with removal of the uterus and cervix, along with bilateral salpingo-oophorectomy (BSO), is standard. This can be done by minimally invasive or open approaches. Lymph node assessment with removal of suspicious-appearing lymph nodes at a minimum is recommended. Gross extrauterine

TABLE 1. Proportion of Patients Undergoing Surgical Staging for Clinical Stage I Endometrial Cancer With Pelvic and Para-Aortic Lymph Node Metastases According to Tumor Grade and Depth of Invasion: Gynecologic Oncology Group Trial 33[a]

		PERCENTAGE OF PELVIC/PARA-AORTIC LYMPH NODE METASTASES BY DEPTH OF MYOMETRIAL INVASION			
HISTOLOGIC GRADE	NO. OF PATIENTS	NONE	INNER ONE-THIRD	MIDDLE ONE-THIRD	OUTER ONE-THIRD
1	180	0/0	3/1	0/5	11/6
2	288	3/3	5/4	9/0	19/14
3	153	0/0	9/4	4/0	34/24

[a]Adapted from: Creasman WT, Morrow CP, Bundy BN, Homesley HD, Graham JE, Heller PB. Surgical pathologic spread patterns of endometrial cancer. A Gynecologic Oncology Group study. *Cancer.* 1987;60(8 suppl):2035-2041.[40]

disease should be biopsied and removed wherever possible. Peritoneal cytology is performed at the provider's discretion, although it was taken out of the surgical staging system in 2009, and it has been hypothesized that positive cytology sometimes results from uterine manipulation,[30] especially in minimally invasive surgery. Omentectomy is usually included for clear cell, serous, and sometimes carcinosarcoma histologies given an increased risk of advanced-stage disease at diagnosis and relatively low morbidity with the procedure, although the risk of microscopic involvement in the absence of visible macroscopic disease is low.[31-33]

Oophorectomy is usually included to identify micrometastases in the ovary and to decrease circulating estrogen production, which could theoretically promote proliferation of metastatic cells outside of the uterus.[34] However, it has not been demonstrated that ovarian preservation worsens overall survival (OS) in young women (aged <50 years) with low-grade, early-stage endometrioid endometrial cancer based on SEER population data.[35] In fact, ovarian preservation was associated with improved OS and a decreased risk of cardiovascular death in this population. Ovarian preservation helps to mitigate the vasomotor symptoms and the cardiovascular and bone density risks associated with BSO, and it also may allow for more fertility options for young women. This approach may be considered in select patients who are well counseled and do not have Lynch syndrome. Conservative therapy with progestin therapy is beyond the scope of this review but may be appropriate for some patients, either because they have minimal, low-grade disease and desire fertility preservation or because they have comorbidities making surgery unacceptably morbid. Gunderson et al published a review of 45 series including 391 women with grade 1 adenocarcinoma or complex, atypical, endometrial hyperplasia (median age, 31.7 years) who were treated with progestin therapy. A durable complete response was noted in 53.2% (65.8% with hyperplasia and 48.2% with carcinoma; $P = .002$; median follow-up, 39 months). During the respective study periods, 41.2% of those with hyperplasia and 34.8% with a history of carcinoma became pregnant, and 117 live births were reported.[36]

Surgical staging of endometrial cancer has historically included complete pelvic and para-aortic lymphadenectomy. The National Comprehensive Cancer Network recommends "lymph node assessment" for apparent uterine-confined disease, a term that reflects the range of practice patterns and controversy regarding the extent and approach to lymphadenectomy in the staging of endometrial cancer.[37] According to the National Comprehensive Cancer Network, lymph node assessment "includes evaluation of the nodal basins that drain the uterus, and often comprises a pelvic nodal dissection with or without para-aortic nodal dissection."[37] European Society for Medical Oncology guidelines do not recommend lymphadenectomy (to include systematic removal of pelvic and para-aortic nodes up to the level of the renal veins) for low-risk, grade 1 or 2 disease and state that it "can be considered" with sentinel lymph node dissection as an option for MMI >50% for grade 3, and recommend it for grade 3 MMI >50% and for all stages of nonendometrioid histology.[38]

The Gynecologic Oncology Group (GOG) *Surgical Procedures Manual* defines a staging lymphadenectomy as the bilateral removal of all nodal tissue with skeletonization of all vessels from the mid-portion of the common iliac vessels superiorly to the circumflex iliac vein inferiorly, from the mid-psoas laterally to the ureters medially, including the obturator fossa. The para-aortic dissection extends from here to the level of the inferior mesenteric artery (IMA).[39] At a minimum, visible, or suspicious-appearing, or palpable nodes should be removed, and unresectable nodes should be marked with clips for potential RT planning.

Lymphadenectomy: Pro

The role of lymphadenectomy was established in a landmark GOG study, GOG 33, in 1987.[40] In GOG 33, patients with apparent uterine-confined disease underwent surgical staging, including pelvic and para-aortic lymph node dissection. The incidence of lymph node involvement was correlated with tumor grade and depth

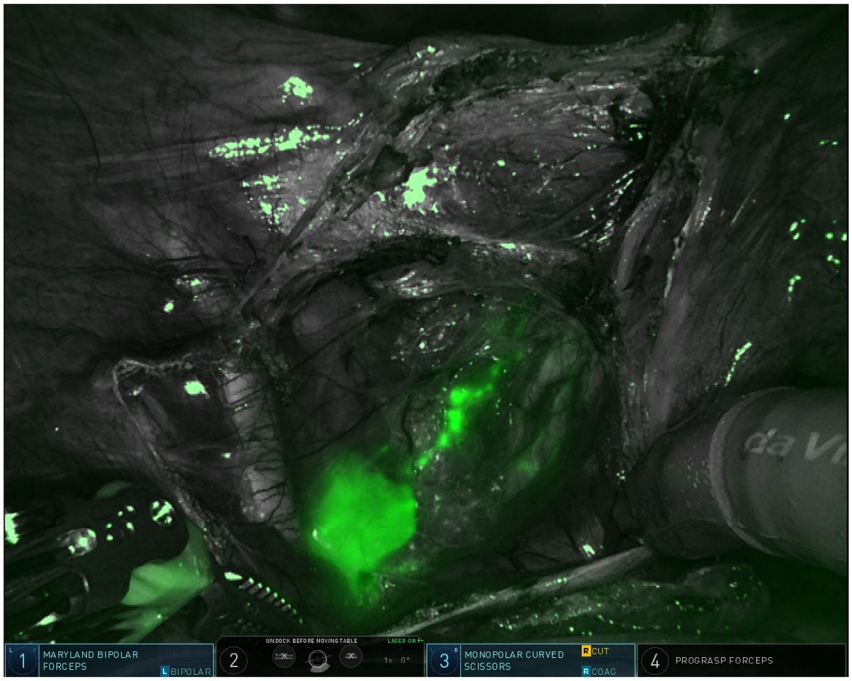

FIGURE 2. Sentinel Lymph Node. The robotic appearance of a sentinel lymph node lying just medial to the external iliac vessels is revealed using the Firefly technology (used with da Vinci® Surgical System, Intuitive Surgical) after the injection of indocyanine green. Some finer lymph channels leading to the node can also be seen.

of invasion in thirds (Table 1).[40] This study served as the foundation for the initial 1988 International Federation of Gynecology and Obstetrics (FIGO) endometrial cancer staging system.

Some retrospective reviews suggested a therapeutic effect of lymphadenectomy. In patients with poorly differentiated endometrial cancer, removal of >11 pelvic lymph nodes was associated with improved OS and PFS compared with removal of <11 pelvic lymph nodes.[41] A similar effect was also seen in patients with high-risk histologies, including clear cell, papillary serous, and grade 3 endometrioid.[42] A large, retrospective cohort analysis also demonstrated a survival benefit associated with pelvic and para-aortic lymphadenectomy in patients with intermediate-risk and high-risk disease, but not in those with low-risk disease.[43] Patients with intermediate-risk or high-risk disease who underwent para-aortic plus pelvic lymphadenectomy also experienced an improved disease-specific survival compared with those who had pelvic lymphadenectomy only (8-year disease-free survival [DFS], 84% vs 69%) and a lower risk of death (hazard ratio [HR], 0.44; $P < .0001$). Population data (SEER) have also demonstrated a survival advantage associated with more extensive lymphadenectomy in high-risk, but not low-risk, endometrial cancer.[44]

Role of para-aortic lymphadenectomy

Assessment of para-aortic nodes remains another controversial area of management in endometrial cancer. Because the drainage pattern from the uterus is often to the pelvic lymph nodes and then the para-aortic beds, and it is usually the case that metastatic disease is found in the pelvic nodes before the para-aortic ones, some have advocated for the omission of para-aortic lymphadenectomy in patients with low-risk to moderate-risk disease.[45] Para-aortic lymphadenectomy can be particularly challenging in the morbidly obese patient, and injury to the inferior vena cava during para-aortic dissection can be life-threatening. Patients with node-positive disease in any basin will often receive adjuvant chemotherapy, which may eradiate microscopic disease in other nodal basins that may not be known based on surgical findings. Thus, the argument can be made that the important thing is to identify patients with any nodal disease, and, if that information can be relatively accurately gauged with a pelvic dissection alone, then it may be adequate in some circumstances.

The risk of isolated para-aortic lymph node metastases in the absence of pelvic nodal metastases depends on tumor grade, histology, location of the tumor, and the presence of lymphovascular space invasion (LVSI).[46] Evaluation of a prospectively collected database of 1453 patients with endometrioid endometrial cancer identified no patients with isolated para-aortic lymph node recurrence who had grade 1 disease at the time of diagnosis. Evaluation of patients who underwent a pelvic and para-aortic lymphadenectomy with ≥8 pelvic lymph nodes and had at least 1 para-aortic lymph node removed identified isolated para-aortic disease in 1.8% of patients, and in only 1% of patients with grade 1 disease.[47]

Lymphadenectomy: Con

Two large, randomized trials have failed to show a survival benefit associated with lymphadenectomy. The UK Medical Research Council-A Study in the Treatment of Endometrial Cancer (MRC-ASTEC) trial was a large study with double randomization to answer the questions: 1) does pelvic lymphadenectomy improve survival; and 2) does adjuvant external-beam RT (EBRT) improve survival in patients with intermediate-risk and high-risk, early-stage endometrial cancer? A total of 1408 patients with clinical stage I disease were randomly assigned to either standard surgery, in which lymph nodes were palpated and removed if suspicious, or pelvic lymphadenectomy. All patients also underwent hysterectomy and BSO. Patients with intermediate-risk or high-risk disease, including those with positive nodes, were randomized to EBRT or no further therapy. In the lymphadenectomy group, 8% of patients had no lymph nodes removed, and 35% of patients had <10 nodes removed. In the standard surgery arm, only 5% of patients had nodes sampled (median count, 2). The use of EBRT was similar between the 2 groups. OS was similar between the 2 groups, and no survival benefit was seen with lymphadenectomy.[48] Limitations of the ASTEC trial include that the number of lymph nodes removed was low, and systematic para-aortic nodal dissection was not performed.

Another prospective trial also evaluated the role of lymphadenectomy. A total of 514 patients with preoperative clinical stage I endometrial cancer were randomized to pelvic lymphadenectomy or no systemic lymphadenectomy (clinically enlarged nodes removed). Adjuvant therapy was at the discretion of the treating physician. Patients in the lymphadenectomy group had a median of 26 lymph nodes removed. Although patients who underwent staging lymphadenectomy were more likely to have nodal disease detected, 5-year OS and DFS were not statistically different between the 2 groups.[49] Adjuvant treatment also was not significantly different between the 2 arms, suggesting either that, although more node-positive patients were identified and likely treated in the lymphadenectomy arm, the number was too small to affect outcomes overall (13.3% with surgically staged IIIC disease in the lymphadenectomy arm vs 3.2% in the no-lymphadenectomy arm) or that patients who were perceived to be at high risk but were not staged may have been treated regardless.

Individualized Lymphadenectomy

Decisions regarding the extent of staging lymphadenectomy vary by provider and institution. As the risk of lymph node involvement increases with tumor grade, high-risk histology, and depth of invasion, many surgeons open the uterus after hysterectomy and individualize the extent of staging based on intraoperative uterine risk factors. Both frozen-section and gross evaluation strategies are used, and strategies often vary by provider and institution. A recent meta-analysis of 6387 women undergoing intraoperative evaluation of hysterectomy specimens compared intraoperative gross evaluation with intraoperative frozen section. Sensitivity was higher for frozen section compared with gross evaluation (85% vs 71%; $P = .0008$) as was specificity (97% vs 91%; $P = .0021$).[50] Although frozen section can take significantly longer (from 20 minutes to greater than an hour in some instances), final pathology is upgraded from preoperative endometrial biopsy or curettage specimen in >23% of patients undergoing hysterectomy, and this discrepancy may incorrectly influence a decision about staging lymphadenectomy.[51] Frozen section is not perfect, with one study reporting accuracy of 88% for depth of MMI and 84% for grade, and clinically relevant upstaging from frozen section to final pathology in 18% of patients, although other studies have shown higher concordance.[52,53] On the basis of this, some have advocated for staging lymphadenectomy in all patients.

A series of evaluations of patients with endometrioid endometrial cancer have generated the "Mayo criteria." Retrospective evaluation of patients with grade 1 and 2 disease and <50% MMI found positive pelvic lymph nodes in only 5% of patients. This was followed by a prospective evaluation. The investigators then omitted the use of lymphadenectomy starting in 2004 for patients who met the following criteria: grade 1 or 2 endometrioid histology, MMI ≤50%, and tumor diameter ≤2 cm.[54] All others underwent lymphadenectomy up to the renal vessels. Nodal basins were separately evaluated, including the para-aortic nodes above and below the IMA. Twenty-seven percent of the cohort was able to forgo a lymphadenectomy. Of the 209 at-risk patients with endometrioid tumors who underwent a lymphadenectomy, lymph node metastases were identified in 34 (16%). Isolated para-aortic lymph node involvement was found in 6 patients (19%). Of all patients who had para-aortic lymph nodes involved, including those with non-endometrioid histology, 77% had disease above the IMA, and 60% had negative ipsilateral nodes below the IMA.[54] This is clinically noteworthy, because many providers limit their dissection to the level of the IMA in concordance with the GOG staging manual. Of note, this study was performed before the era of routine minimally invasive surgery, and it is notable that a higher para-aortic dissection with minimally invasive techniques becomes increasingly difficult with increasing body mass index, especially with central obesity.

These "Mayo criteria" were applied to a large group of prospectively treated patients undergoing minimally invasive versus open surgery for clinically early-stage endometrial cancer. Nodal disease was found in only 0.8% of patients who met the Mayo criteria. In those for whom

staging would have been indicated, the incidence of lymph node metastases was 10.7%, roughly that of the risk of lymphedema associated with the procedure in some studies. In the entire study cohort, para-aortic lymph node involvement was identified in 38% of those with pelvic lymph node involvement but in only 2.3% of patients with negative pelvic lymph nodes.[46]

In summary, whereas decision making is variable among surgeons and depends to some extent on the individual surgical risk factors of the patient, commonly used criteria for performing lymph node dissection in the United States are:

- Tumor size >2 cm; *or*
- Grade 3 endometrioid, serous, or clear cell histology; *or*
- Depth of MMI >50%.

Sentinel Lymph Node Evaluation

Sentinel lymph node procedures are rapidly gaining popularity in the treatment of endometrial cancer (Fig. 2). The use of this approach lagged behind other disease sites because of both the difficulty in identifying a reliable marker dye and the controversy about technique. Cervical injection has now been associated with the highest rate of sentinel lymph node detection.[55] An early (n = 125) prospective trial done in Europe (the Sentinel Node Procedure and Endometrial Cancer [SENTI-ENDO] study) demonstrated an increase in the use of adjuvant RT and chemotherapy and no difference in recurrence-free survival for patients with a sentinel lymph node identified; however, the study had limited power, and limited complete pelvic and para-aortic staging was performed.[56]

A recent prospective cohort study (the Fluorescence Imaging for Robotic Endometrial Sentinel Lymph Node Biopsy [FIRES] trial) evaluated test characteristics of sentinel lymph node biopsy in patients with clinical stage I disease of any histology.[57] Surgeons were required to have demonstrated competency with the procedure, in which 0.5 mg of indocyanine green was injected superficially and deep into the cervical stroma at the 3 and 9 o'clock positions for a total of 1 mg. A full pelvic lymphadenectomy was performed in all patients, and para-aortic dissection was performed in 74% at the discretion of the surgeon. Information about the location of the mapped sentinel lymph node was collected. Sentinel lymph nodes were processed separately using a sentinel lymph node protocol. At least 1 sentinel lymph node was found in 86% of patients, and bilateral mapping occurred successfully in 52% of patients. Sentinel lymph nodes mapped to the external iliac region in 38%, the obturator in 25%, the internal iliac in 10%, the inframesenteric para-aortic region in 10%, the presacral region in 3%, and the supramesenteric/infrarenal posteroanterior region in 1%. The study was stopped early for efficacy, because 97% of patients had disease correctly identified in their sentinel lymph nodes. Six patients (17%) had isolated disease detected in sentinel lymph nodes outside of a standard dissection field (presacral, internal iliac), suggesting a therapeutic benefit to the procedure. The sentinel lymph node was the most distal node affected in 80% of patients. The false-negative rate was 3%, with 1 false-negative finding identified in a patient with prior back surgery violating the retroperitoneum who should not have been eligible for the study. However, this patient did have serous cancer—histology at higher risk for lymph node metastases, including isolated para-aortic metastases—raising the question of whether the procedure is appropriate for high-risk histologies.

Surgical Approach

Recent advances in minimally invasive surgery have led to shorter hospital stays, less pain, and faster recovery for patients.[58] Moreover, minimally invasive surgery in endometrial cancer has been associated with equal to improved quality of life, less blood loss, and similar cancer-related outcomes, although it may be accompanied by longer operative times.

The Laparoscopic Approach to Cancer of the Endometrium (LACE) trial evaluated outcomes and quality of life in 332 patients who underwent laparoscopic (TLH) versus open (TAH) hysterectomy for stage I endometrial cancer. Quality of life was improved across all domains except for emotional and social well-being for up to 6 months after surgery, which was the last time point evaluated.[59] Although operating time was longer for TLH compared with TAH (138 vs 109 minutes; $P = .001$), intraoperative complications were similar, and postoperative grade 3 and 4 adverse events were more likely in the TAH group (23.2% vs 11.6%; $P = .004$).[59] DFS was similar between the 2 groups.[60]

A 2012 Cochrane Database systematic review evaluated 8 trials that included 3644 women undergoing laparoscopic versus open hysterectomy for endometrial cancer. No significant difference was seen in the risk of death or recurrence. Blood loss was lower in patients undergoing laparoscopy in an evaluable subset of patients with this variable reported, and severe postoperative adverse events were also lower in the minimally invasive group.[61]

The GOG also demonstrated noninferiority of laparoscopy compared with laparotomy in the landmark randomized LAP2 trial. Patients were randomized 2:1 to laparoscopic versus open hysterectomy, BSO, and pelvic and para-aortic lymphadenectomy. Conversion to open surgery occurred in 25.8% of patients, with the most common reason being poor visualization, although this trial was done as minimally invasive surgery was just gaining popularity, and surgeons were likely still in the learning curve. Operative time was longer for laparoscopy (204 vs 130 minutes),

although intraoperative complications were similar, and fewer moderate-to-severe postoperative adverse events were seen in the laparoscopy group (14% vs 21%; $P < .0001$). Patients undergoing laparoscopy were slightly less likely to have a para-aortic lymphadenectomy performed (6.8% vs 3.2%; $P = .0002$). Full staging with pelvic and para-aortic lymphadenectomy was done in 95.8% of patients undergoing open surgery and 91.5% of patients undergoing laparoscopy.[62] The median node count was excellent and was similar between the 2 groups (17-18 pelvic nodes, 7 para-aortic nodes), and 9% of both groups had lymph node metastases identified, suggesting similar efficacy in staging when done. Quality of life was better in the laparoscopy group at 6 weeks, although it was not statistically different between the 2 groups at 6 months other than in the domain of body image.[63] The 3-year recurrence rate was 11.2% in the TLH group versus 10.2% with laparotomy. Five-year OS was not different between the 2 groups, although the study fell just short of meeting the noninferiority endpoint for recurrence-free survival (HR, 1.14 for laparoscopy; 90% to 95% CI, −1.28 to 4.0).[64]

Practically, although outcomes have been shown to be relatively similar between the 2 groups, it can be difficult to perform a high para-aortic dissection laparoscopically. Minimally invasive surgery should be reserved for providers who are competent in the technique. In addition, the uterus should be removed intact and not morcellated, which sometimes requires at a least a mini-laparotomy for specimen removal.

Robotic surgery is now more commonly performed than laparoscopic surgery for endometrial cancer in many centers. Robotic surgery is more costly, although the increased dexterity of the wristed instruments may improve complex dissection techniques, such as para-aortic lymphadenectomy, radical hysterectomy, and surgery in the morbidly obese.[65,66] Compared with standard laparoscopy and open surgery, robotic surgery is associated with less blood loss than the other 2 approaches, although the operative time is similar to that for laparoscopy (both take longer than open surgery). Conversion to open rates were lower and para-aortic lymph node counts were higher with robotic surgery compared with regular laparoscopy, although neither comparison was significant.[67] Single-site laparoscopy has also been reported.[68] Vaginal hysterectomy is usually not preferred because it does not allow the surgeon the ability to visibly inspect the abdominal cavity for metastatic disease and can make complete removal of the tubes and ovaries challenging. This approach is reasonable for sick patients with comorbidities that may preclude Trendelenburg positioning, pneumoperitoneum, and general anesthesia, which are necessary for laparoscopic or robotic surgery. Perioperative complications are relatively low, and disease-specific survival is reasonable using vaginal hysterectomy in some series, although the data are limited.[69]

Surgery When Cervical Involvement Is Present

Surgery for endometrial cancer when the cervix is grossly involved has traditionally been a radical hysterectomy. This had been based on the assumption that the pattern of spread when cervical involvement is present is similar to the pattern of spread of a primary cervical cancer, and parametrial involvement has been demonstrated in 11.5% of patients with cervical involvement from endometrial cancer.[70,71] Moreover, it can be difficult to distinguish primary endometrial cancer from cervical cancer, for which radical hysterectomy is standard. However, cervical involvement does not necessarily predict parametrial involvement; LVSI may be a stronger predictor.[72]

Some (but not all) retrospective studies have suggested a survival advantage associated with radical hysterectomy for endometrial cancer with involvement of the cervix.[73,74] The type of hysterectomy (simple vs modified vs radical) was not an independent prognostic factor associated with recurrence or survival in a pooled analysis of Japanese patients who had endometrial cancer with suspected gross cervical involvement at diagnosis.[75] Because risk factors for endometrial cancer, such as diabetes and obesity, also are risk factors for surgical complications, the increased risks of radical surgery need to be considered. Postoperative RT has also been identified as an independent predictor of recurrence and survival.[76] In one large, recent SEER analysis, RT was shown to improve survival for patients with stage II endometrial cancer, whereas radical hysterectomy was not associated with prognosis.[77] Patients with cervical involvement are also more likely to have nodal or other metastatic disease that will result in adjuvant therapy regardless of the type of hysterectomy performed. Most patients with stage II endometrial cancer go on to receive adjuvant RT to the pelvis and/or vaginal cuff. Thus, many advocate for performing a simple hysterectomy (the uterus and cervix are removed, but the structures surrounding the uterus are left intact) and using RT postoperatively to decrease the risk of locoregional recurrence. Radical hysterectomy (including removal of at least part of the parametria and division of the uterine vessels lateral to the uterus) should still be considered for patients with bulky cervical involvement if simple hysterectomy would "cut through" the tumor. Preoperative RT can also be considered in this situation.[78]

Cytoreduction Surgery for Advanced or Recurrent Disease

Although the majority of patients with endometrial cancer are diagnosed at an early stage, from 10% to 15% will present with advanced-stage disease, and their prognosis

is poor. When disease is primarily intraperitoneal, management is often extrapolated from that of ovarian cancer. Cytoreduction to <2 cm has also been correlated with survival, with the maximum benefit in patients who can be reduced to no visible disease remaining.[79-81] A recent meta-analysis of cohorts of patients undergoing cytoreductive surgery for advanced or recurrent endometrial cancer demonstrated an association between optimal tumor debulking and survival. A 10% increase in the percentage of patients undergoing complete (vs incomplete) cytoreduction was associated with a 9.3-month improvement in OS for the cohort.[82] Thus the goal whenever possible should be cytoreduction to no gross residual disease.

For patients who are not candidates for optimal cytoreduction, neoadjuvant chemotherapy may be considered before interval surgery. Several studies have demonstrated the utility of this approach, often in patients with serous histology because the pattern of disease spread is similar to that of ovarian cancer, in which the use of neoadjuvant chemotherapy is well described. In some cohorts, neoadjuvant chemotherapy has resulted in decreased operative time and hospital stay without worsening OS.[83,84]

Adjuvant Therapy

Radiation Therapy

Comprehensive guidelines were issued by the American Society for Radiation Oncology in 2013 and endorsed by the American Society for Clinical Oncology in 2014.[85]

Although postoperative RT can significantly reduce the risk of local recurrence, randomized prospective trials in general have not demonstrated an OS benefit in early-stage endometrial cancer. Most of the trials have not been powered for OS, and the competing risks of death are high in this elderly population, but this lack of OS benefit has contributed to the ongoing debate regarding the choice of adjuvant treatment. Adjuvant therapy to the whole pelvis can be associated with toxicities, including urinary incontinence and fecal leakage, which may have a long-lasting impact on quality of life.[86] One meta-analysis found that low-risk patients who had either one-third or less MMI or middle one-third invasion with grade 1 or 2 disease, had significantly worse survival with the use of EBRT with an odds ratio for OS of 0.71.[87]

Adjuvant treatment should be omitted for patients of sufficiently low risk (see Low-risk disease, below). For higher risk patients with early-stage disease, vaginal brachytherapy (VBT) offers good local control at the vaginal cuff with less toxicity compared with EBRT, although without full coverage of the pelvis. Locally advanced patients are generally treated with EBRT to include nodal regions at risk. The decision for adjuvant RT and specific techniques used (VBT and/or EBRT) can be controversial and often rests on a physician's assessment of individual clinicopathologic features, whether lymph node sampling was performed, and the use of chemotherapy.

Low-risk disease

Low-risk disease, generally defined as low-grade disease limited to the endometrium or with limited MMI, is typically managed with surgery alone with good outcomes. Low-grade disease limited to the endometrium has an extremely low risk of nodal metastases.[40] These patients have very good rates of local control of 96.9%, even with no additional therapy.[88]

Intermediate-risk disease

Intermediate-risk disease is described by a wide body of literature, including at least 6 randomized trials.[89-94] Intermediate risk is typically defined as having any MMI, up to occult stage II disease, or grade 2 or 3 disease. A subgroup of high-intermediate risk (HIR) has also been defined by the GOG and the Post-Operative Radiation Therapy in Endometrial Cancer (PORTEC) group. The PORTEC definition includes those with 2 of the following: age older than 60 years, grade 3 disease, or ≥50% MMI. Alternatively, the GOG defines HIR based on age and the number of risk factors (grade 2-3, the presence of LVSI, or outer one-third MMI): patients aged at least 70 years must have 1 risk factor, those aged at least 50 years must have 2 risk factors, and those younger than 50 years must have all 3 risk factors. Various clinical trial inclusion criteria and practice patterns regarding surgical lymph node sampling make it difficult to reach an integrated therapy recommendation that is consistent with all available data.

The benefit of adjuvant RT for HIR tumors was demonstrated in GOG 99[89] and PORTEC-1.[91] GOG 99 included patients with stage I and II intermediate-risk adenocarcinoma treated with surgical resection and selective pelvic and para-aortic lymph node dissection who were randomized to observation versus EBRT (50.4 grays [Gy]). EBRT was associated with a decreased risk of recurrence overall, but, on subset analysis, it was the patients with HIR disease who experienced the greatest benefit from therapy, whereas there was no statistically significant reduction in recurrence risk for others. Absolute risk reduction was nearly 20% at 24 months (26% vs 6% relative hazard, 0.42; 95% CI, 0.21-0.83) for HIR tumors compared with only a 4% absolute risk reduction for low-intermediate risk tumors. Most recurrences occurred within 18 months of initial therapy. Overall, 4-year OS (92% for RT vs 86% for observation; $P = .557$) and distant relapse as the initial event (5.3% vs 6.4%, respectively) were not significantly different. However, GOG 99 was not formally powered to detect an OS

advantage. PORTEC-1 also demonstrated improved rates of locoregional failure after 46 Gy of adjuvant EBRT was compared with no additional therapy after hysterectomy, with 71% of recurrences in the no additional therapy arm occurring in the vagina. Similar to GOG 99, long-term follow-up revealed locoregional recurrence rates of >20% with no additional treatment versus 5% after EBRT in the HIR group (at 15-year follow-up: HR, 3.31 [95% CI, 1.73-6.35]; $P = .0003$).[91] Survival figures, both overall and disease-specific, were numerically lower with EBRT (52% vs 60% for overall survival at 15 years), but this did not reach statistical significance. In comparing these outcomes, it should be noted that in the PORTEC-1 trial routine lymphadenectomy was not performed; suspicious lymph nodes were biopsied. On GOG 99, selective bilateral pelvic and para-aortic lymphadenectomy with the removal of any enlarged or suspicious nodes was required. The improvement in locoregional recurrence rates and the associated lack of benefit in OS was confirmed by a meta-analysis of PORTEC-1, GOG 99, and 2 other trials.[95]

On the basis of available evidence, patients with early-stage, high-grade disease, >50% MMI, and the presence of LVSI or advanced age should generally receive some form of adjuvant RT unless there is a contraindication.[85] Patients with early-stage endometrioid carcinoma who do not meet these criteria can generally be managed with surgery alone. A nuanced approached may often be used to determine the relative importance of clinicopathologic risk features, noting that many factors, such as age and LVSI, may lie on a continuous spectrum. For instance, locoregional control is progressively worse for focal to increasingly diffuse LVSI.[96] As such, the decision regarding adjuvant therapy is often not based on the binary presence or absence of specific features.

Radiation techniques. The tendency for failures to be at the vaginal cuff in HIR patients suggested that VBT might be a sufficient, and less toxic, regimen for adjuvant therapy. VBT was randomized directly against EBRT in PORTEC-2 for HIR patients.[92] No difference in locoregional control or survival was noted. Rates of pelvic failure were overall low, although they were slightly increased in patients who received VBT (3.8% vs 0.5%; $P = .02$). Notably, acute gastrointestinal (GI) toxicity was decreased with VBT versus EBRT.[86] Those who received VBT also reported better social functioning and reduced GI symptoms in long-term follow-up. There was no difference in sexual functioning between the 2 regimens, although both groups were below the normal population.[97] A Cochrane meta-analysis showed no significant difference in survival with the use of EBRT in HIR patients.[87] These data may be interpreted to suggest that most HIR patients can be treated with adjuvant VBT.

In PORTEC-2, deeply invasive grade 3 disease was excluded. These tumors are often considered to be high risk and are generally treated with EBRT, particularly in situations in which lymphadenectomy has not been performed, as it was not routinely performed in PORTEC-2. In an older study by Aalders et al, patients with stage I disease were given postoperative VBT (60 Gy) with or without EBRT to 40 Gy; the subset of patients with deeply invasive, grade 3 disease experienced decreased cancer deaths with the addition of EBRT (27% vs 18%; no P value provided) as well as improved locoregional control.[90] It should be noted that these patients, however, did not have surgical nodal staging, and the added benefit of EBRT to locoregional control in the setting of lymph node sampling and modern imaging may be less pronounced. An analysis of patients actually enrolled on PORTEC-2 revealed that, after central pathology review, the vast majority of patients had grade 1 disease (78%); in addition, <10% had LVSI.[92] Therefore, some radiation oncologists may hesitate to apply the results of the study to all patients who fit the trial's original eligibility criteria. In practice, those with high-grade disease and/or deep MMI or those with risk factors such as extensive LVSI may be considered for treatment using EBRT. An integrated clinicopathologic and molecular risk profile was able to separate the HIR patients from PORTEC-1 and PORTEC-2 into 3 separate groups: favorable, intermediate, and unfavorable.[98] The ongoing PORTEC-4a trial for women with HIR disease (ClinicalTrials.gov identifier NCT03469674) randomly assigns patients to a standard arm of VBT or an experimental arm consisting of observation, VBT, or EBRT, depending on the risk profile.

In general, patients with stage I intermediate-risk disease often are not treated with both VBT and EBRT. A Swedish study[99] showed a small absolute 5-year locoregional recurrence benefit from EBRT plus VBT over VBT alone (1.5% vs 5%; $P = .01$), but with no OS or cancer-specific survival benefit. It is also unclear whether the addition of VBT to EBRT has any clinically significant benefit over EBRT alone because the vaginal control rates for EBRT alone are excellent.[14]

The benefit to combining VBT with EBRT in stage II disease has not been specifically studied in randomized trials. An increased risk of vaginal recurrence seems possible for cases of cervical stromal involvement, which may be addressed with a brachytherapy boost after EBRT. However, there is no high-quality evidence to support or refute this practice. Given the low added toxicity to a brachytherapy boost, a brachytherapy boost may be appropriate in patients perceived to be at highest risk for vaginal cuff failure: those who have stage II and III disease with close or positive margins.[100] The American Brachytherapy Society has published guidelines for radiation oncologists pertaining to the use of VBT.[101]

High-risk disease

The term "high-risk endometrial cancers" typically includes those with stage III disease or any stage with a high-risk histology (clear cell and serous carcinoma). As noted above, many practitioners also include deeply invasive, high-grade stage I endometrioid carcinomas within this group because of their worse prognosis compared with other early-stage types of disease. These patients were excluded from randomization on the intermediate-risk PORTEC trials[102] and are now included in many high-risk trials (see below). Clear cell and serous carcinoma tumors also have higher recurrence rates, even at earlier stages of presentation, and are similarly included in high-risk trials. Unfortunately, these trials have not been powered to separately examine clear cell and serous tumors, which have different biology from each other as well as from lower grade endometrioid cancers.

Older studies (Table 2)[103-106] examined the utility of adjuvant RT versus chemotherapy in this group of patients,[103,105,106] with results generally demonstrating equivalent survival and disease outcomes. Other prospective studies, as discussed below (Table 3),[10,104,107] have combined both adjuvant treatment modalities in an effort to optimize both locoregional and distant control. Various sequencing approaches have been studied, including concurrent, sequential, and sandwich, consisting of RT administered between chemotherapy cycles, and it is unclear whether one approach is superior to the others.[108] In the most recent 2 large, cooperative group, randomized trials, chemoradiation (CRT) was administered with concurrent cisplatin followed by adjuvant carboplatin and paclitaxel.

RT techniques. The RT technique generally used in high-risk, stage III, endometrial cancers is EBRT (either using 3-dimensional, conformal RT or intensity-modulated RT [IMRT]) directed to the pelvis, inclusive of the vaginal cuff, parametria, and lymphatics at risk (with consideration of coverage of the para-aortic lymph nodes) given the high risk of pelvic nodal disease and recurrence risk in this population. Those with deeply invasive, high-grade, early-stage endometrioid adenocarcinoma are also typically managed with whole pelvic RT based on older studies demonstrating improved locoregional control and even potentially survival compared with brachytherapy alone. For those with high-risk, early-stage serous or clear cell carcinoma, VBT is often used in conjunction with adjuvant chemotherapy based initially on retrospective data and, more recently, on preliminary results from GOG 249 suggesting equivalent outcomes to whole pelvic RT alone (see below).

Recent advances in EBRT techniques include the use of highly conformal techniques (such as IMRT) that allow for greater normal tissue sparing. Radiation Therapy Oncology Group 1203 (TIME-C; ClinicalTrials.gov identifier NCT01672892) is a randomized trial of standard RT techniques versus IMRT in the postoperative setting for patients with either cervical or endometrial cancer; preliminary results suggest that IMRT is associated with improved acute GI and genitourinary toxicity using a variety of patient-reported measures.[109] The reported time point was at 5 weeks after the initiation of RT, at the expected peak of RT-related toxicity; longer follow-up is needed to determine whether IMRT is

TABLE 2. Phase 3 Trials of Adjuvant Chemotherapy[a] Versus Radiotherapy

STUDY	POPULATION	TREATMENT	CONTROL	OUTCOME
Susumu 2008[103] (N = 475)	Intermediate-high risk, stage IC-IIIC	Chemotherapy (CAP): cyclophosphamide (333 mg/m^2), doxorubicin (40 mg/m^2), + cisplatin (50 mg/m^2) every 4 wk × 3 or more cycles	RT: pelvic EBRT + para-aortic (6%) and/or VBT (3%)	5-y PFS: 81.8% vs 83.5% (NS); 5-y OS: 86.7% vs 85.3% (NS); HIR: 89.7% vs 83.8%; LIR: NS; high risk, NS
GOG 249: Randall 2017[104] (N = 527)	HIR and stage I/II serous and clear cell	Chemotherapy (VBT/CT): VBT, carboplatin (AUC 6) + paclitaxel (175 mg/m^2) every 3 wk × 3 cycles	RT: pelvic EBRT + VBT (if stage II, or serous, or clear cell)	RFS: 82% vs 82% (NS); 5-y OS: 88% vs 91%; vaginal recurrence: 2.5% vs 2.5%; distant recurrence: 18% vs 18%
GOG 122: Randall 2006[105] (N = 278)	High risk, stage III/IV	Chemotherapy (AP): doxorubicin (60 mg/m^2) + cisplatin (50 mg/m^2) every 3 wk × 8 cycles*	RT: whole abdominal radiation	5-y PFS: 50% vs 38%[a]; 5-y OS: 55% vs 42%[a]
Maggi 2006[106] (N = 345)	Intermediate-high risk, stage IC-III	Chemotherapy (CAP): cyclophosphamide (600 mg/m^2), doxorubicin (45 mg/m^2), + cisplatin (50 mg/m^2) every 4 wk × 5 cycles	RT: pelvic EBRT	5-y OS: 66% vs 69% (NS)

Abbreviations: AUC, area under the curve; EBRT, external-beam radiotherapy; GOG, Gynecologic Oncology Group; HIR, high-intermediate risk; LIR, low-intermediate risk; NS, not significant; OS, overall survival; PFS, progression-free survival; RT, radiotherapy; VBT, vaginal brachytherapy.
[a]Patients received chemotherapy with or without vaginal brachytherapy.
*Final cycle single agent cisplatin.

TABLE 3. Adjuvant Chemoradiotherapy Versus Radiotherapy or Chemotherapy Alone

STUDY	POPULATION	TREATMENT	CONTROL	OUTCOME
MaNGO/ILIADE III + NSGO-9501/EORTC-55991: Hogberg 2010[107] (N = 540)	Intermediate-high risk, stage I-III	Chemoradiation (sequential), varied: most received doxorubicin + cisplatin × 3-4 cycles followed by EBRT	RT: pelvic EBRT with VBT prescribed for cervical stromal involvement	PFS (pooled): HR, 0.63 (95% CI, 0.44-0.89)[a]; OS (pooled): HR, 0.69 (95% CI, 0.46-1.03 [NS])
GOG 258: Matei 2017[111] (N = 813)	High risk, stage III/IV	Chemoradiation (combined): cisplatin (50 mg/m^2 on d 1 and d 29) + EBRT followed by carboplatin (AUC 5*) + paclitaxel (175 mg/m^2) every 3 wk × 4 cycles	Chemotherapy: carboplatin (AUC 6) + paclitaxel (175 mg/m^2) every 3 wk × 6 cycles	RFS: HR, 0.9 (95% CI, 0.74-1.10 [NS]); 5-y OS (prelim): 70% vs 73% (NS)
PORTEC-3: de Boer 2018[10] (N = 686)	High risk, stage III/IV	Chemoradiation (combined): cisplatin (50 mg/m^2 on d 1 and d 29) + EBRT followed by carboplatin (AUC 5) + paclitaxel (175 mg/m^2) every 3 wk × 4 cycles	RT: pelvic EBRT	RFS: HR, 75.5% vs 68.6%[a]; 5-y OS: 81.8% vs 76.7% (NS)

Abbreviations: AUC, area under the curve; EBRT, external-beam radiotherapy; EORTC, European Organization for Research and Treatment of Cancer; GOG, Gynecologic Oncology Group; HR, hazard ratio; MaNGO/ILIADE III, Mario Negri Institute Gynecologic Oncology Group ILIADE III trial; NS, not significant; NSGO, Nordic Society for Gynecologic Oncology; OS, overall survival; PFS, progression-free survival; PORTEC-3, third Post Operative Radiation Therapy in Endometrial Cancer trial; prelim, preliminary; RFS, recurrence-free survival; RT, radiotherapy; VBT, vaginal brachytherapy.
[a]Significant.
*Escalated to AUC 6 in subsequent cycles as tolerated.

also associated with improved late toxicity measures. The PARCER trial (Postoperative Adjuvant Conventional Radiation Versus Image-Guided IMRT for Reducing Late Bowel Toxicity in Cervical Cancer; ClinicalTrials.gov identifier NCT01279135) from India is also accruing patients for randomization to either a postoperative standard RT technique versus IMRT, although this is only in patients with cervical cancer. An interim analysis reported no different in acute GI toxicity using physician-reported outcomes.[110] An important difference in the patient populations of these 2 trials include rates of concurrent chemotherapy use (88% in PARCER vs 25% in TIME-C), which may have a considerable effect on toxicity measures. Although longer follow-up is needed and the impact of concurrent chemotherapy should be further explored, the use of advanced RT techniques may improve treatment-related toxicity in those patients who require adjuvant EBRT for endometrial cancers.

In summary, low-risk disease, including low-grade tumors confined to the endometrium or with limited MMI, is typically managed with surgery alone and no RT.

Intermediate-risk disease is usually treated with at least VBT, with EBRT sometimes used for HIR disease. High-grade, deeply invasive disease is usually treated with EBRT. Most clear cell and serous tumors are usually treated with at least VBT. In general, RT will decrease the risk of locoregional recurrence but has not been shown to have an impact on OS.

Chemotherapy

Firm data on which patients derive true benefit from chemotherapy and which regimen/duration of therapy is preferable are sparse. In general, data support the use of chemotherapy for serous tumors and for stage III or higher tumors of any histology. Carboplatin and paclitaxel is the most commonly used regimen.

High-intermediate–risk disease

Only a few trials have investigated the use of chemotherapy in what would generally be classified as high-risk or intermediate-risk disease, and its use in this setting remains controversial. In the phase 3 trial in Japan,[103] patients with FIGO 1988 stage IC through IIIC endometrioid histology endometrial cancer with >50% MMI were randomized postoperatively to adjuvant chemotherapy versus pelvic RT. The chemotherapy arm consisted of cyclophosphamide (333 mg/m^2), doxorubicin (40 mg/m^2), and cisplatin (50 mg/m^2) (so-called CAP chemotherapy) given every 4 weeks for 3 or more courses. Patients in the RT arm received pelvic RT with optional para-aortic boost (5.7% of cases) and VBT (3.1%). The study did not achieve its primary endpoint of a 13% improvement in OS with CAP versus EBRT (5-year OS in the CAP vs pelvic EBRT groups: 86.7% vs 85.3%, respectively; P = .462) but in an unplanned subgroup analysis, patients who met HIR criteria (for this study, FIGO 1988 stage II or IIIA [positive cytology] or FIGO 1988 stage IC aged >70 years or with grade 3 tumors) had improved OS and PFS with CAP compared with EBRT (CAP, 89.7% vs 73.6%; and EBRT, 83.8% vs 66.2%; P = .006). There was no difference in OS or PFS for low-intermediate–risk groups or high-risk subgroups.

A more recent GOG study, which to date has been reported only in abstract form, also investigated whether chemotherapy was superior to RT in patients with early-stage disease who had risk factors for recurrence.[104] On

GOG 249, patients with HIR or high-risk early-stage disease were randomized to VBT followed by 3 cycles of adjuvant chemotherapy versus pelvic EBRT. Here, HIR was defined as FIGO 2009 stage I endometrioid histology with the following risk factors: grade 2 to 3, invasion into the outer one-half of the myometrium, or LVSI. Patients of any age with 3 risk factors, of age >50 years with 2 risk factors, or of age >70 years with 1 risk factor were eligible. Patients with FIGO 2009 stage II endometrioid histology and stage I and II serous or clear cell histology (considered high risk) were also included. Lymphadenectomy was not required but was performed in 89% of patients. In the RT arm, women were treated with EBRT using a 3-dimensional–conformational approach or IMRT approach, and VBT was prescribed for stage II cancer or any clear cell or serous histology. In the chemotherapy arm, all patients received VBT by high dose rate or low dose rate approaches followed by 3 cycles of carboplatin (area under the curve 6) and paclitaxel (175 mg/m^2) on day 1 of every 21-day cycle. Of the 527 patients treated, most had FIGO 2009 stage I disease (75%) and tumors of endometrioid histology (75%); 15% of tumors were serous and 5% were of clear cell histology. Recurrence-free survival was 82% in both treatment arms, with no statistical difference in vaginal recurrence, distant recurrence, or OS (2.5%, 18%, and 91%, respectively, in the control EBRT arm, and 2.5%, 18%, and 88%, respectively, in the VBT/C arm). There was no evidence of treatment heterogeneity with respect to stage, histology, performance status, or lymphadenectomy on recurrence-free survival and OS. There was an increased incidence of pelvic or para-aortic recurrence in the VBT/C arm compared with the pelvic RT arm (9% v 4%).

GOG 249 was not powered for analyses of histologic subtypes. In the United States, pelvic RT is often used for higher risk tumors of endometrioid histology, while chemotherapy is favored for serous tumors because of their proclivity for distant spread. Considerable uncertainty exists about clear cell cancers, as they are rarer than the other 2 tumor types but, by analogy with ovarian cancer, suspected to be less chemotherapy sensitive. Questions include whether 3 cycles of chemotherapy are sufficient, and the ongoing ENGOT-EN2-DGCG trial (ClinicalTrials.gov identifier NCT01244789) compares observation (VBT allowed) with 6 cycles of chemotherapy in surgically staged N0 tumors that are stage I grade 3, stage II, or stage I and II nonendometrioid histology.

High-risk disease

GOG 122 compared chemotherapy with adjuvant RT in 396 patients with advanced endometrial cancer.[105] Patients with stage III or stage IV endometrial cancer with less than 2 cm residual disease after primary surgery were eligible, and approximately 25% of patients had serous or clear cell histology. The chemotherapy arm consisted of doxorubicin plus cisplatin for 7 cycles followed by 1 additional cycle of cisplatin (AP regimen). Patients in the RT arm received whole abdominal RT (WAI). Although fewer patients completed the assigned therapy in the chemotherapy arm (63% in AP vs 84% in WAI), patients in the chemotherapy arm had significantly longer PFS (5-year PFS, 50% vs 38%; stage-adjusted HR, 0.71 [95% CI, 0.55-0.91]; $P < .01$) and OS (5-year OS, 55% vs 42%; stage-adjusted HR, 0.68 [95% CI, 0.92-0.89]; $P < .01$). There was no evidence of treatment heterogeneity in exploratory subgroup analyses including histology, age, stage, and presence of residual disease. Although both WAI and AP chemotherapy are infrequently used today, this study documents the benefits of chemotherapy for advanced disease.

Poor outcomes in all arms in the advanced-stage trials led to interest in combining the modalities.

Addition of chemotherapy to RT

The Nordic Society for Gynecologic Oncology (NSGO)-9501/European Organization for Research and Treatment of Cancer (EORTC)-55991 and Mario Negri Gynecologic Oncology Group (MaNGO)/ILIADE-III studies investigated the sequential administration of EBRT before or after chemotherapy compared with EBRT alone.[109] In the EORTC study, chemotherapy consisted of either 4 cycles of doxorubicin (50 mg/m^2) plus cisplatin (50 mg/m^2; the AP regimen), doxorubicin plus carboplatin, epirubicin plus cisplatin, epirubicin plus paclitaxel, or carboplatin plus paclitaxel. Use of VBT was a stratification factor. In the MaNGO study, chemotherapy consisted of doxorubicin (60 mg/m^2) plus cisplatin (50 mg/m^2) every 3 weeks for 3 cycles. VBT was prescribed for cervical stromal involvement. Lymph node assessment was optional in both studies. The studies were designed to detect a difference in PFS, with OS as a secondary endpoint. In the pooled analysis, PFS was significantly increased in the sequential CRT arm compared with pelvic RT alone (HR, 0.63 [95% CI, 0.44-0.89]; $P = .009$). There was no difference in OS, although there appeared to be a trend toward improvement with multimodality therapy (HR, 0.69 [95% CI, 0.46-1.03]; $P = .07$). There was a significant reduction in cancer-specific survival with combination therapy (HR, 0.55 [95% CI 0.35-0.88]; $P = .01$).

A concurrent approach has also been investigated. Two randomized phase 3 trials explored a concurrent combined approach compared with chemotherapy alone (GOG 258) or EBRT alone (PORTEC-3). The PORTEC-3 study randomized women with high-risk endometrial cancer to pelvic RT with or without nodal RT alone or pelvic RT with or without nodal RT with 2 doses of cisplatin (50 mg/m^2)

followed by 4 cycles of carboplatin and paclitaxel.[10] There was no difference in 5-year OS (81.8% with CRT vs 76.7% with RT alone; $P = .11$), but the use of chemotherapy did significantly improve 5-year failure-free survival (FFS) (75.5% vs 68.6%; $P = .022$). Interestingly, OS differences only appeared to emerge after about 3 years. In subgroup analysis, women with stage III disease had 78.7% 5-year OS and 69.3% FFS rate with CRT versus 69.8% for OS and 58% for FFS with RT alone ($P = .074$ and $P = .014$, respectively). For women with serous carcinoma (n = 105) CRT yielded a FFS of 58% versus 48% ($P = .11$) with EBRT alone.

In GOG 258 (ClinicalTrials.gov NCT00942357), 813 patients with mostly stage III through IVa disease were randomized to receive either CRT, consisting of 2 doses of cisplatin plus volume-directed RT followed by 4 cycles of carboplatin and paclitaxel, or 6 cycles of carboplatin and paclitaxel with no RT.[111] Results have been reported only in abstract form. The majority of patients had FIGO 2009 stage IIIC disease (approximately 70%), and 80% had tumors of endometrioid histology. About 50% of women in the CRT arm received VBT in addition to pelvic EBRT. Whereas vaginal recurrences (7% vs 3%: HR, 0.36 [95% CI, 0.16-0.82]) and pelvic/para-aortic recurrences (21% vs 10%: HR, 0.43 [95% CI, 0.28-0.66]) were more frequent in the chemotherapy arm, distant recurrences were more frequent in the CRT arm (28% vs 21%: HR, 1.37 [95% CI, 1.00-1.86]). There was no difference in recurrence-free survival (CRT vs chemotherapy: HR, 0.9 [95% CI, 0.74-1.1]). At the time of reporting, 5-year OS data were maturing; however, preliminary estimates showed that 5-year OS was similar (73% in the chemotherapy arm and 70% in the CRT arm).

In summary, adjuvant chemotherapy is generally used for women with stage III disease and, although evidence is lacking, is often used for any stage of serous cancer.

Therapy for Recurrent or Metastatic Disease

Median survival for metastatic/recurrent endometrial cancer is short, on the order of 12 to 15 months for women with measurable disease (Table 4).[112-116] For the majority of women, initial therapy for unresectable recurrent/metastatic disease will be chemotherapy with carboplatin and paclitaxel. For those with potentially endocrine-sensitive tumors, a trial of endocrine therapy, usually progestin-based, is appropriate.

Endocrine Therapy

Patients with lower grade, ER-positive disease are the most likely to derive benefit from endocrine therapy. Although several older randomized studies showed no benefit from the use of progestins in the adjuvant setting, they can be useful in the front-line treatment of metastatic disease.

Commonly used regimens include progestins alone and progestins alternating with tamoxifen. In chemotherapy-naive patients, the use of progestins alternating with tamoxifen in biomarker-unselected patients has produced response rates from 27% to 33%.[117] In an analysis of GOG 119, a single-arm, phase 2 trial of megestrol acetate alternating with tamoxifen, Singh et al found that ERα expression

TABLE 4. First-Line Recurrent and Metastatic Disease

STUDY	POPULATION	EXPERIMENTAL ARM	CONTROL ARM	OUTCOME
GOG 177: Fleming 2004[112] (N = 263)	Advanced/recurrent	TAP: doxorubicin (45 mg/m^2), paclitaxel (160 mg/m^2), + cisplatin (50 mg/m^2)* every 3 wk × 7 cycles	AP: doxorubicin (60 mg/m^2) + cisplatin (50 mg/m^2) every 3 wk × 7 cycles	ORR: 57% vs 34%[a]; PFS: 8.3 vs 5.3 mo[a]; OS: 15.3 vs 12.3 mo[a]
GOG 209: Miller 2012[113] (N = 1381)	Advanced/recurrent	CT: carboplatin (AUC 5 or 6) + paclitaxel (135** or 175 mg/m^2) every 3 wk × 7 cycles	TAP: doxorubicin (45 mg/m^2), paclitaxel (160 mg/m^2), + cisplatin (50 mg/m^2)* every 3 wk × 7 cycles	ORR: 51% vs NR; PFS: 14 vs 14 mo (HR, 1.03); OS: 32 vs 38 mo (HR, 1.01); CT noninferior to TAP
GOG 3007: Slomovitz 2018[114] (N = 74)	Advanced/recurrent	Everolimus/letrozole (EL) or megestrol acetate/tamoxifen (MT)	NA	ORR (chemo-naive): EL: 53%; MT: 43%
Fader 2018[115] (N = 61; 100 planned)	Advanced/recurrent, HER2-positive, serous	CT + trastuzumab: carboplatin (AUC 5), paclitaxel (175 mg/m^2), + trastuzumab (6 mg/kg)	CT: carboplatin (AUC 5) + paclitaxel (175 mg/m^2)	ORR: 44% vs 75% (NS); CBR: 100% vs 87.5% (NS); PFS: 8 vs 12.6 mo (first line, 9.3 vs 17.9 mo); OS: NR
GOG 86P: Aghajanian 2018[116] (N = 349)	Advanced/recurrent	CT + bevacizumab: carboplatin, paclitaxel, + bevacizumab	Historical control (GOG 209)	ORR: 60% vs 51% (NS); PFS: NR; OS: HR, 0.71 (95% CI, 0.55-0.91)[a]

Abbreviations: AUC, area under the curve; CBR, clinical benefit rate; chemo-naive, chemotherapy-naive; GOG, Gynecologic Oncology Group; HER2, human epidermal receptor 2; HR, hazard ratio; NA, not applicable; NR, not reported; NS, not significant; ORR, overall objective response rate; OS, overall survival; PFS, progression-free survival.
[a]Significant.
*Required filgrastim support.
**Lower doses for prior pelvic RT.

was the strongest determinant of response to treatment, whereas PRα and PRβ did not correlate with response.[118]

Cytotoxic Chemotherapy

Most women with metastatic endometrial cancer will be candidates for chemotherapy. Chemotherapy trials have primarily focused on 3 active groups of agents: anthracyclines, platinum agents, and taxanes. GOG 177 randomly assigned 263 previously untreated patients with unresectable stage III, stage IV, or recurrent endometrial cancer receive to doxorubicin and cisplatin (AP) versus paclitaxel, doxorubicin, and cisplatin (TAP).[112] TAP was superior to AP in terms of response rate (57% vs 34%; $P < .01$), PFS (83 vs 5.3 months; $P < .01$), and OS (15.3 vs 12.3 months; $P = .037$). This was the first trial to show a survival benefit from the use of chemotherapy for women with advanced endometrial cancer. Subsequently, in an attempt to reduce toxicity, the combination of carboplatin and paclitaxel was compared with TAP in front-line disease in the GOG 209 trial. In that study of 1381 women, which has only been reported in abstract form, carboplatin and paclitaxel was noninferior to TAP with equivalent OS in both groups (HR, 1.01).[113] Carboplatin and paclitaxel was better tolerated than TAP and has become the first-line choice of chemotherapy for metastatic or recurrent disease.

For women who have received prior adjuvant carboplatin and paclitaxel, retreatment with the same regimen may be appropriate if there has been a substantial length of time since the prior chemotherapy. One publication suggests that response rates to second-line, platinum-based therapy for patients who have endometrial cancer with platinum-free intervals <6 months, from 6 to 12 months, from 12 to 13 months, and >24 months were 25%, 38%, 61%, and 65%, respectively.[119] However, response rates to any agent in the setting of progression on first-line therapy are poor. There is currently no single standard of care. It has been contended that doxorubicin, based on its activity in chemotherapy-naive patients (response rates, 17%-25%),[120,121] ought to be used. However, doxorubicin has not performed well in the setting of prior carboplatin and paclitaxel, with one retrospective review noting no responses among 17 patients treated with adjuvant carboplatin and paclitaxel and then doxorubicin at the time of recurrence.[122] One phase 3 trial (n = 496) in women with recurrent disease who received 1 to 2 total prior chemotherapy regimens tested ixabepilone against a control treatment of either doxorubicin or paclitaxel (paclitaxel was used only for women who had received prior doxorubicin, which represented 19% of the control group). The median PFS in the control arm was only 4.0 months (95% CI. 2.7-4.3 months), and the response rate was 15.7% for those with measurable disease. Ixabepilone performed no better, with a median PFS of 3.4 months (95% CI, 2.8-4.2 months; HR for progression, 1.0 [95% CI, 0.8-1.3]) and a response rate of 15.2%.[123] Various other cytotoxic agents have been tested, including liposomal doxorubicin, topotecan, pemetrexed, and gemcitabine, all with response rates from 4% to 12%.[117]

Anti–HER2 Therapy

A recent report noted a 16% rate of *HER2* amplification as well as a smaller number of *HER2* mutations in a series of 197 advanced/metastatic endometrial cancers.[124] Rates are highest in serous and clear cell tumors. However, a benefit to anti–*HER2* therapy has been difficult to demonstrate in this tumor type. A phase 2 study of single-agent trastuzumab that included 18 women with metastatic, *HER2*-amplified tumors reported no results.[125] A basket trial performed in heavily pretreated patients published no responses to the combination of pertuzumab plus trastuzumab among 7 women with *HER2*-amplified or overexpressing (3+) tumors.[126] Reasons hypothesized for the difficulty in demonstrating the activity of anti–HER2 agents in endometrial cancer include the selection of heavily pretreated patients, the activation of pathways that may confer resistance to trastuzumab (eg, PI3K-Akt), and high levels of HER2 extracellular domain shedding.[127] Immunoconjugates may bypass some of these issues, and a patient with *HER2*-amplified serous carcinoma has been reported to have a complete response to trastuzumab emtansine.[124]

There is also a suggestion of promise for trastuzumab in the front-line setting. Fader et al randomized women with primary stage III and IV or recurrent HER2-positive (defined as 2+ or 3+ overexpression and confirmed amplification by fluorescence in situ hybridization) serous endometrial cancer to receive either carboplatin and paclitaxel or carboplatin, paclitaxel, and trastuzumab.[115] Although only 61 patients were randomized, the study closed early because of slow accrual, and there was an improvement in PFS from 8 to 12.6 months with the addition of trastuzumab ($P = .005$). In the subgroup with primary advanced disease, the median PFS improved from 9.3 to 17.9 months ($P = .013$).

Immunotherapy

POLE-mutated and MSI endometrial cancers are associated with high numbers of tumor-infiltrating lymphocytes and high neoantigen loads, which suggest they would respond well to immunotherapy, in particular programmed cell death protein 1 (PD-1)/programmed death-ligand 1 (PD-L1) checkpoint inhibitors.[128,129]

Le et al evaluated pembrolizumab in a phase 2 trial of MMR-deficient tumors (determined either by PCR or IHC) regardless of origin.[129,130] All participants had received at least one prior therapy and had evidence of

progressive disease before enrollment. Fifteen patients with endometrial cancer were included. Three patients (20%) had a complete response, and 5 (33%) had a partial response.

Pembrolizumab (anti–PD-1 monoclonal antibody) has since received US Food and Drug Administration (FDA) accelerated approval for patients with MSI or MMR-deficient solid tumors, including endometrial cancers, that have progressed after prior treatment and who have no satisfactory alternative treatment options. Responses are often long-lasting. In the FDA approval, it was noted that, across all MSI tumor types, among patients who responded to pembrolizumab, 78% had responses that lasted for at least 6 months.

Unfortunately, the majority of endometrioid (72%) and serous (98%) cases belong to the copy number–low or copy number–high groups, which lack evidence of MSI.

However, responses may sometimes be seen in endometrial cancers that are not MSI or POLE-mutated. The endometrial cancer cohort of the KEYNOTE-28 study (pembrolizumab) selected tumors for PD-L1 expression.[131] Forty-eight percent of endometrial tumors screened had PD-L1 expression. Twenty-four patients, most of whom had received numerous prior chemotherapy regimens, were enrolled. The objective response rate was 13%, and 3 patients achieved a partial response. Responses appeared to be durable, with 2 patients remaining on treatment at the time of reporting. One responder had an MSS but ultra-mutated tumor, one had MSS disease, and one had disease of unknown MSS status; the one patient with known MSI disease had a best response of progressive disease. Although MSS endometrial cancers will occasionally respond to immunotherapy, we do not yet have biomarkers to select who these responders will be. Current trials in MSS endometrial cancers are focusing on enhancing the activity of immune checkpoint inhibitors by combining them with other agents, such as upfront with chemotherapy, with poly(ADP-ribose) polymerase (PARP) inhibitors, or with antiangiogenic drugs. Combinations with other immunotherapeutic agents and RT are also of interest. Representative, ongoing, large studies include the following. The phase 3 AtTEnd trial (ClinicalTrials.gov identifier NCT03603184) is a double-blind, placebo-controlled study. Patients with metastatic or inoperable uterine carcinoma or carcinosarcoma are randomized to either carboplatin and paclitaxel plus placebo or carboplatin, paclitaxel, and atezolizumab (a PD-L1 inhibitor), with placebo or atezolizumab continued until progression. The KEYNOTE-775 (ClinicalTrials.gov identifier NCT03517449) is an open-label, randomized trial of lenvatinib (a vascular endothelial growth factor [VEGF] receptor tyrosine kinase inhibitor) plus pembrolizumab versus treatment of physician's choice of doxorubicin or paclitaxel in advanced endometrial cancer (1-2 prior regimens).

Future Directions

The US National Cancer Institute convened an endometrial cancer clinical trials planning meeting in January 2016. Angiogenesis, DNA repair, and AKT serine/threonine kinase 1 were among the pathways prioritized for further investigation.[132]

Antiangiogenic Therapy

Antiangiogenic agents consistently have some activity in the treatment of endometrial cancer. Bevacizumab yielded a response rate of 14% and a 6-month PFS rate of 40% in women who received 1 to 2 prior cytotoxic regimens for endometrial cancer, which compares favorably with any other second-line regimen.[133] In the randomized phase 2 GOG 86P trial, the addition of bevacizumab to front-line carboplatin and paclitaxel therapy did not improve PFS compared with historical controls, although it did increase OS (HR, 0.71 [95% CI, 0.55-0.91]).[116] Conversely, a randomized phase 2 Italian trial (MITO END-2) reported a significant increase in PFS from 8.7 to 13 months with the addition of bevacizumab to upfront carboplatin and paclitaxel chemotherapy, although these results have not been published in full.[134] However, at this time, no antiangiogenic agents are FDA-approved for endometrial cancer.

Poly(ADP-Ribose) Polymerase Inhibitors

It has been hypothesized that PARP inhibitors will have activity in endometrial cancer, based partly on the frequency of *ARID1A* mutations in this disease. ARID1A deficiency impairs homologous recombination DNA repair, which is associated with PARP sensitivity.[135] There are data suggesting sensitivity to PARP inhibition in endometrial cancer cell lines and mouse models.[136] One ongoing, randomized, phase 2 study, NRG Oncology trial NRG-GY012 (ClinicalTrials.gov identifier NCT03660826) compares single-agent olaparib (a PARP inhibitor) with single-agent cediranib (an oral tyrosine kinase inhibitor targeting VEGF receptor [VEGFR], platelet-derived growth factor receptors [PDGFRs], and FGFR) and with the combination of both agents in women who have metastatic/recurrent endometrial cancer.

The PI3K/mTOR/Akt Pathway

Both *PTEN* and *PIK3CA* mutations are exceedingly common in endometrial cancer. Given the proven efficacy of an everolimus (mammalian target of rapamycin [mTOR] inhibitor) plus letrozole (aromatase inhibitor) regimen in breast cancer, this regimen has also been explored in endometrial cancer. GOG 3007, which has been reported in abstract form only, enrolled patients with recurrent endometrial cancer and no or one prior systemic regimens

to receive either regimen (everolimus and letrozole or megestrol and tamoxifen).[114] In the intention-to-treat population, 24% of patients treated with everolimus and letrozole and 22% of patients treated with alternating megestrol acetate and tamoxifen had a response, with a PFS of 6.4 versus 3.8 months. In chemotherapy-naive patients, 53% of patients treated with everolimus and letrozole and 43% of those treated with megestrol acetate and tamoxifen had Response Evaluation Criteria in Solid Tumors (RECIST) responses. Endometrioid histology appeared to be predictive of response. Responses could be durable; 17 patients continued on treatment at the time of reporting.

However, no advantage was found from the addition of the mTOR inhibitor temsirolimus to standard carboplatin and paclitaxel chemotherapy,[116] and multiple trials of single-agent rapamycin-analog mTOR inhibitors in advanced or recurrent disease have shown only modest activity (<25% response rates even in the setting of chemotherapy-naive disease), and no association between activity and *PTEN* or *PIK3CA* alterations has been observed. One report noted significantly increased PFS and response rates in 3 patients whose tumors had *AKT1* mutations.[137]

Trials of newer generation agents targeting this pathway continue, but to date they have produced only low response rates and have been plagued by toxicity, including hyperglycemia, rash, and diarrhea.[138]

Conclusions

Endometrial cancer is increasingly recognized as several biologically different tumor types. For early-stage disease, current practice is surgery followed by RT and/or chemotherapy, guided primarily by standard histopathologic parameters. Ongoing trials, such as PORTEC IV, are attempting to validate the incorporation of newer genomic prognosticators to decrease both overtreatment and undertreatment. Advanced disease is currently not curable, and chemotherapy remains the mainstay of therapy for most patients; new directions include antiangiogenic therapy combinations and the use of PARP inhibitors. The recent advances in immunotherapy have opened options for women with the MSI subset of tumors, and current trials are attempting to expand the benefits of immune checkpoint inhibition to a wider group of patients with endometrial cancer. ■

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