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Review

Endometrial cancer: A review and current management strategies: Part II

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HIGHLIGHTS

- We present adjuvant therapy options for early endometrial cancer.
- We discuss treatment for endometrial cancer including chemotherapy, radiation, and hormones.
- We review fertility sparing options and surveillance for women with endometrial cancer.

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ABSTRACT

Endometrial carcinoma is the most common gynecologic malignancy. A thorough understanding of the epidemiology, pathophysiology, and management strategies for this cancer allows the obstetrician–gynecologist to identify women at increased risk, contribute toward risk reduction, and facilitate early diagnosis. The Society of Gynecologic Oncology's Clinical Practice Committee has reviewed the literature through March of 2014 and created evidence-based practice recommendations for diagnosis and treatment. The level of recommendations used is based on the method used by the U.S. Preventive Services Task Force (A: There is good evidence to support the recommendation, B: There is fair evidence to support the recommendation, C: There is insufficient evidence to support the recommendation; however, the recommendation may be made on other grounds, D: There is fair evidence against the recommendation, E: There is good evidence against the recommendation.). It is not the purpose of this document to provide a complete review of the literature on all aspects of endometrial cancer. This article examines:

- Adjuvant therapy, including radiation, vaginal brachytherapy, and chemotherapy
- Therapy for advanced disease, including chemotherapy and radiation therapy alone and in combination as well as hormone therapy
- Treatment for synchronous endometrial and ovarian cancer
- Fertility-sparing treatment
- Post-treatment patient surveillance
- The role of hormone replacement therapy in the development of endometrial carcinoma
- Novel targeted therapies.

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Contents

The Society of Gynecologic Oncology's ("SGO") Clinical Practice Committee has developed a series of Clinical Documents designed to improve the overall quality of women's cancer care; reduce the use of unnecessary, ineffective, or harmful interventions; and facilitate the optimal treatment of patients, with a goal to maximize the therapeutic benefit and minimize the risk of harm at acceptable cost.

Clinical Documents are intended to be educational devices that provide information to assist health care providers in patient care. This Clinical Document is not a rule and should not be construed as establishing a legal standard of care or as encouraging, advocating, requiring, or discouraging any particular treatment. Clinical Documents are not intended to supplant the judgment of the health care provider with respect to particular patients or special clinical situations. Clinical decisions in any particular case involve a complex analysis of a patient's condition and available courses of action, with the ultimate determination made by the health care provider based on each individual patient's circumstances. Therefore, clinical considerations may lead a provider to take an appropriate course of action that varies from this Document.

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In accordance with CMSS principles, SGO requires that its clinical documents be subject to multiple levels of review, beginning with a review by SGO's full Clinical Practice Committee. After review and approval by the Clinical Practice Committee, Clinical Documents are submitted to the SGO Council, SGO's governing body, which reviewed and approved the Clinical Document for submission to SGO's Journal.

In accordance with those principles, each member of the task force that developed the Clinical Document executed a detailed disclosure statement. None of the members of the task force has a financial relationship or other relationship that conflicts with the writing of this document.

Introduction

Endometrial carcinoma is the most common gynecologic malignancy and will be encountered by almost every gynecologist. A thorough understanding of the epidemiology, pathophysiology, and management strategies for endometrial carcinoma allows the obstetrician–gynecologist to identify women at increased risk, contribute toward risk reduction, and

facilitate early diagnosis of this cancer. The purpose of this document is to continue a review of the risks and benefits of current treatment options and optimize treatment for women with endometrial cancer.

Adjuvant therapy

Selecting appropriate adjuvant therapy for patients with early-stage endometrial cancer is difficult. To date, no level I evidence supports adjuvant therapy of any form in patients with early-stage endometrial cancer when the endpoint is overall 5-year survival. Further complicating the decision process is the fact that "early-stage" endometrial cancer actually comprises two types of patients: those who are comprehensively staged and have received appropriate nodal evaluation and those who are not comprehensively staged.

The most common adjuvant treatment considered for endometrial carcinoma has been radiation therapy; chemotherapy has traditionally been deemed ineffective [2,3]. It is accepted that patients who have FIGO grade 1 or 2 endometrioid carcinomas limited to the inner half of endometrium will not benefit from any additional postsurgical therapies irrespective of comprehensive staging. However, some form of adjuvant therapy has been considered for all others based on evidence from several large studies (Table 1).

Is there a role for adjuvant radiation therapy in patients with stage I or II endometrial cancers?

The value of adjuvant radiation therapy in comprehensively staged patients who have risk factors associated with disease relapse remains unclear. These risk factors include age, tumor grade, presence of lymphovascular invasion, and depth of myometrial invasion. Adjuvant radiation therapy in such patients has been associated with a reduction in locoregional recurrence but no impact on overall survival [4]. This finding is supported by several randomized trials demonstrating that despite improving locoregional control, the use of adjuvant whole pelvic external-beam radiation therapy does not improve disease-specific or overall survival in patients with FIGO 1988 stage I or FIGO 1988 stage IIA endometrial cancer (Table 1) [5–9]. More specifically, although only one trial required comprehensive nodal dissection, the inclusion criteria for each study varied slightly, and some trials required or allowed for vaginal brachytherapy [6–8]. Adjuvant radiation therapy to the pelvis in patients with endometrial carcinoma was shown to reduce the locoregional recurrence rate by approximately 64% but did not have any impact on disease-specific or overall survival [10]. This finding may be due to patients who have not previously been radiated often receiving salvage therapy if they develop recurrences. Further, the survival rate after recurrence has been found to be better in patients who did not receive adjuvant radiation therapy initially compared to those who did [5].

Does vaginal brachytherapy result in similar local control compared to external-beam whole pelvic radiation therapy?

Vaginal brachytherapy has been shown to be equivalent to whole pelvic radiation therapy in achieving local control and providing reasonable disease-specific and overall survival in patients with high-intermediate-risk endometrial cancers [9,11]. These findings apply to all patients regardless of whether they have undergone a comprehensive surgical staging procedure. Vaginal brachytherapy is associated with significantly fewer gastrointestinal toxic effects as well as a better quality of life [9,12].

Is there a role for adjuvant chemotherapy in patients with stage I or II endometrial cancer?

Patients with stage I or II endometrial cancer who are at a higher risk of recurrence based on age, tumor grade, presence of lymphovascular invasion, and depth of myometrial invasion have been identified in large trials [7]. This has led many to consider the use of chemotherapy in such high-intermediate-risk patients despite the lack of any randomized data to support the practice. Two randomized trials have compared adjuvant chemotherapy to whole pelvic radiation therapy in "intermediate"- and "high"-risk endometrial carcinomas (Table 2) [2,3]. These trials did not demonstrate improved survival with chemotherapy compared to radiation. However, it should be noted that the majority of patients in these trials were considered high risk and any firm conclusions are difficult to make. Compared to no further treatment, external-

Table 1
Randomized controlled trials of adjuvant radiation therapy in stage I/II endometrial cancer.

Series	Included cases	LND required	IVRT used	Local recurrence rate		Distant recurrence rate		Disease-specific survival		Overall survival	
				No RT	WPRT	No RT	WPRT	No RT	WPRT	No RT	WPRT
Aalders (1980) [6] No RT arm (N = 277) WPRT arm (N = 263)	Stage I All grades Any invasion Any histology	No	Yes Required Both arms	–	–	–	–	–	–	5-Year 91%	5-Year 89%
PORTEC (2000) [5] No RT arm (N = 360) WPRT arm (N = 354)	IC (grade 1) IB/IC (grade 2) All grade 3 Any histology	No	No	5-Year 13.7%[a]	5-Year 4.2%[a]	5-Year 7%	5-Year 7.9%	5-Year 94%	5-Year 90.8%	5-Year 85%	5-Year 81%
GOG 99 (2004) [7] No RT arm (N = 202) WPRT arm (N = 190)	IB/IC IIA (occult) Any grade Excluded Serous/clear cell	Yes	No	4-Year 7%[a]	4-Year 2%[a]	4-Year 8%	4-Year 5%	4-Year 92%	4-Year 95%	4-Year 86%	4-Year 92%
ASTEC/EN.5 (2009)[b] [8] No RT arm (N = 453) WPRT arm (N = 452)	IA/IB (grade 3) IC/II (all grades) Serous (any) Clear cell (any)	No	Yes Optional Both arms	5-Year 6.1%[a]	5-Year 3.2%[a]	–	–	5-Year 89.9%	5-Year 88.5%	5-Year 83.9%	5-Year 83.5%
PORTEC-2 (2010) [9] WPRT (N = 214) IVRT (N = 213)	Stage IC (grade 1 or 2 and age >60) Stage IB (grade 3 and age >60) Stage IIA except >50% DOI with grade 3 Excluded serous/clear cell histology	No	–	WPRT 5-Year 2.1%	IVRT 5-Year 5.1%	WPRT 5-Year 5.7%	IVRT 5-Year 8.3%	WPRT 5-Year 78%	IVRT 5-Year 83%	WPRT 5-Year 80%	IVRT 5-Year 85%

LND = lymphadenectomy. RT = radiation therapy; WPRT = external beam whole pelvic radiation therapy; IVRT = intravaginal brachytherapy; DOI = depth of invasion; stage is based on FIGO 1988.

[a] Statistically significant difference.

[b] Cases with pelvic nodal metastasis included.

Table 2
Randomized controlled trials assessing chemotherapy in patients with "intermediate"- or "high"-risk endometrial carcinomas.

	Maggi [3]	Susumu [2]
Protocol regimens	RT arm: Pelvic XRT + para-aortic RT if any (+)LNs Chemotherapy arm: CAP q28d × 5 cycles	RT arm: Pelvic XRT +/− Para-aortic RT +/− IVRT Chemotherapy arm: CAP q28d × at least 3 cycles
Included cases	LND optional Excluded serous/clear cell histology FIGO stages: IC (G3) IIA/B (G3) if ≥50% myoinvasion III (any)	LND optional Endometrioid only FIGO stages: IC-IIIC AND >50% myoinvasion <75 years old
N	RT arm: 166 Chemotherapy arm: 174	RT arm: 193 Chemotherapy arm: 192
5-Year PFS	RT arm: 63% Chemotherapy arm: 63%	RT arm: 83.5% Chemotherapy arm: 81.8%
HR (recur)	0.88 (0.63 to 1.23)	1.07 (0.65 to 1.76)
5-Year OS	RT arm: 69% Chemotherapy arm: 66%	RT arm: 85.3% Chemotherapy arm: 86.7%
HR (death)	0.95 (0.66 to 1.36)	0.72 (0.4 to 1.29)

RT = radiation therapy; XRT = external-beam radiation therapy; LN = lymph nodes; CAP = cyclophosphamide, adriamycin, cisplatin; LND = lymphadenectomy; IVRT = intravaginal brachytherapy; PFS = progression-free survival; OS = overall survival; HR = hazard ratio.

beam whole pelvic radiation therapy has no beneficial impact on survival [5–8]. The literature comparing chemotherapy to the whole pelvic radiation therapy in "high"-risk endometrial carcinomas has significant shortcomings and should be interpreted carefully [2,3,13]. The GOG is currently accruing patients with high-intermediate-risk criteria to receive either whole pelvic radiation therapy or chemotherapy with vaginal brachytherapy in a further investigation of the role of adjuvant chemotherapy. The role of adjuvant therapy for patients with clear cell or serous carcinomas of the uterus is also not clear, and the only available data are retrospective.

Recommendations:

- *Adjuvant radiation for certain stage I or II endometrial carcinomas reduces the locoregional recurrence rate but does not affect overall survival (Level of recommendation: A).*
- *Vaginal brachytherapy should be the adjuvant treatment of choice over whole pelvic radiation therapy in patients with early-stage endometrial cancer (Level of recommendation: A).*
- *The use of adjuvant chemotherapy to treat stage I or II endometrial carcinomas is not supported by available evidence (Level of recommendation: C).*

Therapy for advanced stage disease

Advanced-stage endometrial cancer is a heterogeneous disease that may present as pulmonary metastasis, micro- or macroscopic lymph node metastasis, intra-abdominal metastasis, or distant inoperable metastasis. Most investigators consider patients with these different presentations as one group, despite their very different prognoses. Therefore, defining an optimal treatment regimen is difficult.

Is there a role for chemotherapy in patients with advanced endometrial cancer?

The role of chemotherapy has expanded from use as palliation in recurrent or inoperable disease to use for patients following cytoreductive surgery. Although optimal cytoreductive surgery may have a therapeutic benefit [14], patients with metastatic disease, even if resected to microscopic residual disease, have a high risk of recurrence and will benefit from adjuvant treatment. Adjuvant pelvic radiation therapy with or without extended-field radiation in advanced-stage endometrial cancer has been shown to reduce pelvic recurrence significantly. However, failures outside the radiation field limit long-term survival and support the need to explore the use of chemotherapy in adjuvant or salvage treatment of advanced endometrial cancer.

Does chemotherapy alone or in combination with radiation provide better patient outcomes compared with radiation alone in women who have advanced or recurrent endometrial cancer?

The question of whether chemotherapy, radiation, or both improve the outcome for patients with advanced endometrial cancer is difficult to determine. Available data have been collected from studies with different designs, different treatment combinations, and different patient populations. One of the first reports describing patient benefit from combined therapy was in patients with uterine papillary serous carcinoma (UPSC) treated with both adjuvant chemotherapy and radiation [15]. Study results documented an excellent response and improved survival when compared to the typical survival seen in patients with this pathology. Subsequently, multiple studies have shown the benefit of postoperative chemotherapy and vaginal brachytherapy in UPSC [16]. In 2006, the GOG reported a randomized trial comparing whole-abdomen irradiation (WAI) and chemotherapy with doxorubicin and cisplatin in advanced endometrial cancer [13]. The trial demonstrated a survival advantage in the chemotherapy arm despite greater toxicity. The incidence of positive lymph nodes was higher in the chemotherapy arm, further suggesting that chemotherapy may be more effective than whole-abdomen radiation. Another report [17] found a similarly reduced survival for stage III and IV patients who received WAI. In two studies evaluating 42 patients with unresectable stage III or IV disease, the use of radiation after chemotherapy yielded median survivals in excess of 2 years, suggesting a survival benefit from chemotherapy in advanced endometrial cancer [18,19]. More recently, two randomized clinical trials were undertaken to clarify if sequential combination of chemotherapy and radiotherapy improves progression-free survival in high-risk endometrial cancer. The two trials included 534 evaluable patients with operated endometrial cancer, International Federation of Obstetrics and Gynecology (FIGO) stage I–III with no residual tumor, and prognostic factors implying high-risk. Each patient was randomly allocated to adjuvant radiotherapy with or without sequential chemotherapy. In the NSGO/EORTC study, the combined modality treatment was associated with 36% reduction in the risk for relapse or death (hazard ratio (HR) 0.64). The result from the Gynecologic Oncology group at the Mario Negri Institute (MaNGO)-study pointed in the same direction (HR 0.61), but was not significant. The conclusion from the pooled analysis was that the addition of adjuvant chemotherapy to radiation improves progression-free survival in operated endometrial

cancer patients with no residual tumor and a high-risk profile, but does not affect the overall 5-year survival [20].

Do patients with positive para-aortic lymph nodes benefit from adjuvant chemotherapy?

A long-term survival rate of only 50% has consistently been reported in patients with positive para-aortic lymph nodes who received extended-field radiation. To investigate better treatment options, one group of investigators evaluated patients with involved para-aortic lymph nodes treated with chemotherapy followed by pelvic and para-aortic radiation [18]. Patients had a 75% survival rate, an outcome superior to any previous survival rates reported with radiation alone, suggesting that combining chemotherapy with radiation has a therapeutic benefit [18].

What is the role of radiation in the treatment of advanced endometrial cancer?

Radiation is still used for advanced endometrial cancer, but the efficacy is not clear. Multiple studies have shown that it decreases locoregional recurrence, but most studies have not shown a change in overall survival. A retrospective investigation assessed patients with FIGO IIIC disease with pathologically confirmed pelvic nodes and negative para-aortic lymph nodes [21]. Of the 17 patients who met study criteria, 13 had external pelvic radiation therapy alone with or without a vaginal cuff boost. The remaining four patients received whole abdominal radiotherapy. Two patients received systemic and/or hormonal therapy. Although disease-free survival and overall survival (OS) rates were 81% and 72%, respectively, at 5 years, the heterogeneity of the study limits its applicability. A retrospective review of patients with FIGO stage IIIC nonserous, non-clear cell endometrial cancer, all of whom had surgical staging, demonstrated that those receiving radiation had better outcomes than those not receiving radiation [22]. The heterogeneity of the population and treatments, with many patients in the radiation group receiving both radiation and chemotherapy, makes it difficult to conclude that radiation alone is the best treatment for advanced endometrial cancer. A GOG study evaluated the use of WAI in the adjuvant setting for patients with surgically resected stages III and IV disease of all histologic subtypes [23]. The reported survival at 3 years was poor, with an OS of 34.5%. None of the patients with gross residual disease survived, suggesting no curative potential for WAI when given to patients with residual disease following initial cytoreduction.

What is the optimal chemotherapy regimen in advanced endometrial cancer?

Two large randomized studies have compared doxorubicin and cisplatin (AP) with doxorubicin [24,25]. Both studies found that the combination resulted in better response rates but no significant difference in survival. GOG 177 compared paclitaxel, doxorubicin, and cisplatin (TAP) with AP in 273 chemotherapy-naïve women with measurable FIGO stage III–IV or recurrent endometrial carcinoma of any cell type [26]. Response rates as well as OS and progression-free survival (PFS) were significantly better with TAP. However, the TAP combination was toxic, with 39% of patients experiencing grade 2 or 3 peripheral neurotoxicity compared with 5% of patients receiving AP. The most recent GOG study compared TAP to paclitaxel and carboplatin (TC). Although this study is closed to accrual, the results are not mature. Another group reported on the efficacy of adjuvant TC administered to patients who had optimal cytoreduction of stage III and IV endometrial cancer and found a 3-year disease-specific survival rate of 56% [27]. However, treatment was significantly heterogeneous, with 21% of patients receiving external-beam radiation, 10% receiving vaginal brachytherapy, and the remainder receiving individualized treatment [27]. Sixty percent of the patients had UPSC or clear cell carcinoma compared to 25% of the patients on GOG122, and twice as many patients in this study had stage IV disease. Although the investigators concluded that the regimen was active and well tolerated, the heterogeneity in treatment and patients limited the conclusions. Another group of investigators compared patients receiving cisplatin, doxorubicin, and cyclophosphamide (CAP) to those receiving TC in a small retrospective study [28]. The 3-year PFS and OS rates were 50.0% and 75.0%, respectively, in the TC group and 37.5% and 50.0%, respectively, in the CAP group. Although the difference between the two groups was not statistically significant, the difference in toxicity was significant, with those receiving TC having far less toxicity. This group was at high risk for recurrence because most of the patients had residual disease following surgery (87% CAP, 75% TC), and study results suggest that TC has significant activity in advanced endometrial cancer with minimal toxicity. Advanced UPSC is associated with a poor prognosis, and a recent study showed that administration of TC every 3 weeks for 6 cycles showed activity, but most of the patients (73.7%) had tumor recurrence during the follow-up period [29], emphasizing the poor prognosis in advanced UPSC.

Is there a benefit to dose-dense chemotherapy?

Dose-dense chemotherapy has garnered recent interest in gynecologic cancers because this therapy has been reported to improve survival in ovarian cancer [30]. In a study of advanced endometrial cancer, patients were categorized as having gross or microscopic residual disease. Patients received paclitaxel on days 1, 8, and 15 and carboplatin (AUC6) on day 1 for 21-day cycles. Eighty-four percent of the patients were alive without disease in the microscopic disease group after a mean follow-up of 95 months. The group with gross residual disease had a 20% complete response and 66% partial response rate. A second study evaluated the use of paclitaxel and carboplatin (AUC 4) on days 1 and 8 every 3 weeks in patients with recurrent or advanced endometrial cancer [31]. PFS for the advanced cancer group was 10 months. At the time of analysis, 57% of the patients were still alive after a median follow-up of 10 months. The patients were not categorized by residual disease and most had UPSC, which makes the data difficult to interpret. However, these studies suggest that dose-dense TC is a reasonable choice for patients with advanced endometrial cancer and microscopic residual disease.

Is the combination of radiation and chemotherapy better than chemotherapy alone in advanced endometrial cancer?

Radiation appears to provide excellent control of targeted tissues but adds little systemic protection. For this reason, some investigators have suggested that combining chemotherapy and radiation therapy may be optimal in patients without overt disease in the upper abdomen. A study completed in 2004 evaluated patients with stage III/IV endometrial cancer who received 3 cycles of chemotherapy with cisplatin, epidoxorubicin, and cyclophosphamide every 21 days followed by pelvic radiation [32]. Patients with stage IIIA/B disease had a 73% survival rate at 9 years; those with stage IIIC/IV had a 44% survival rate. Despite the promising results, the treatments were heterogeneous, and the optimal regimen is difficult to determine. Nonetheless, the combination of systemic chemotherapy with radiation has a therapeutic benefit.

Multiple studies have examined the sandwich technique that typically consists of 3 cycles of chemotherapy followed by radiation therapy and a subsequent additional 3 cycles of chemotherapy. One study evaluated patients with stage IVB endometrial cancers who underwent cytoreductive surgery followed by adjuvant therapy with platinum-based chemotherapy alone, chemoradiation, or radiation alone [33]. There was no difference in survival among the three groups. Another group reported that radiation followed by chemotherapy shows reasonable efficacy despite 20% of patients not being able to complete the therapy, largely due to hematologic toxicity [34]. This study

compared TAP to AP and found no difference in survival but significantly higher toxicity with TAP. The subgroup of patients with gross residual disease had more than a twofold increase in survival with TAP (37.5% vs. 16%), suggesting that TAP may be more efficacious for patients with residual disease. Geller and associates [35,36] reported the highest survival rate with acceptable toxicity using the combination of carboplatin and docetaxel or paclitaxel sandwiched with field radiation for women with advanced-stage endometrial cancer. The reported overall 5-year survival in the two case series was 79%. In the TC group, the PFS at 1, 3, and 5 years was 100%, 80%, and 74%, respectively, and OS was 100%, 88%, and 79%, respectively. For the 12 patients with endometrioid adenocarcinoma, PFS at 1 year was 100%, at 3 years was 80%, and at 5 years was 70%. A multicenter retrospective study compared three modalities: 1) radiation followed by chemotherapy (3 year PFS/OS = 47%/54%), 2) chemotherapy followed by radiation (3-year PFS/OS = 52%/57%), and 3) chemotherapy followed by radiation and more chemotherapy (3-year PFS/OS = 69%/88%), suggesting that the sandwich technique may be superior to the other two approaches [37]. However, significant design weaknesses of the study limit the ability to conclude reliably that there are significant differences in survival among the three groups. No data in other solid tumors suggest that sandwiching chemotherapy and radiation has any biologic rationale.

Does hormone therapy work for advanced endometrial cancer?

In a phase II GOG study, patients with advanced endometrial cancer were treated with tamoxifen plus alternating weekly cycles of medroxyprogesterone [38]. The response rate was 33%, with a median PFS interval of 3 months and median OS of 13 months. Responses in this study were not only observed in patients with well-differentiated or hormone receptor-positive tumors. The results suggest promising activity for the combination of tamoxifen and medroxyprogesterone acetate in the treatment of advanced or recurrent endometrial cancer, regardless of tumor grade or hormone receptor status.

Recommendations:

- *The use of chemotherapy in the treatment of advanced endometrial cancer improves patient outcomes (Level of recommendation: A).*
- *Chemotherapy and radiation therapy used in combination may offer superior outcomes compared with single-modality treatment (Level of recommendation: B).*
- *In women with gross residual disease, chemotherapy with paclitaxel and carboplatin is as effective as other regimens reported in the literature and has less toxicity (Level of recommendation: B).*

Synchronous endometrial and ovarian carcinoma

Do women with synchronous endometrial and ovarian cancers have worse prognoses?

Women with synchronous tumors of the endometrium and ovary are generally younger than those with either endometrial or ovarian adenocarcinomas. Synchronous tumors tend to be low grade and are often found at an early stage. Synchronous endometrioid tumors are frequently associated with endometriosis and have a better prognosis than other histologic types of carcinoma [39]. A population-based study in the Netherlands sought to identify histologic pathways in the synchronous occurrence [40]. A new primary malignancy in the endometrium was diagnosed in 157 cases (2.9%). The ratio of observed versus expected number of cases of synchronous malignancy in the endometrium was estimated at 3.6 (95% confidence interval [CI]: 2.7–4.7). The mean age at diagnosis of all patients with ovarian cancer was 59.6 years; the 157 women who had new malignancy had an average age of 58.6 years. The histologic subtypes both in the ovary and endometrium were endometrioid when there was a synchronous primary tumor.

Do genetics play a role in synchronous endometrial and ovarian cancers?

In a recent study, 7 out of 102 women (7%) with synchronous endometrial and ovarian cancer had either clinical or molecular criteria suggestive for Lynch syndrome, with most of both tumors having endometrioid histology [41]. The incidence of Lynch syndrome (HNPCC) was low unless there was a family history of HNPCC-associated cancers. Thus, family history is critical in the decision to test for HNPCC; nonetheless, some centers have advocated universal or broadened screening of endometrial cancer patients with algorithms or patient-administered checklists to detect Lynch syndrome [42,43].

Fertility-sparing treatments for endometrial cancer

Up to 30% of patients diagnosed with endometrial cancer are younger than 54 years of age. Approximately 9% of women diagnosed with the disease are younger than age of 44, and 20% are between 45 and 54 years of age [44,45]. Although the common assumption would be that these women would have early-stage, low-grade malignancies, this may not be the case. In a population-based registry (Geneva Cancer Registry), 44 (3.2%) of women with endometrial cancer were 45 years and younger, and only 8 (18%) of these women had stage IA, grade 1 endometrial cancer at the time of final surgical pathology [46]. Therefore, it is imperative to select carefully those women who may be candidates for fertility-sparing approaches to the management of endometrial cancer.

What are the risk factors associated with the development of endometrial cancer in young women?

The most common risk factors for the development of endometrial cancer in young women are increasing BMI, nulliparity, and irregular menstrual cycles [47]. The risk for developing endometrial cancer may be increased by as much as 22-fold in women younger than 45 years of age whose BMIs are greater than 35 [48]. The excessive endogenous estrogen associated with overweight or obesity increases the risk of endometrial carcinoma, but such young women may also have a genetic predisposition to disease development. There is controversy in the literature regarding whether young women with endometrial cancer have an increased rate of HNPCC mutations. Some authors suggest up to a 34% risk in these women, and other investigators argue that this is not the case [47,49]. Considering the discordant data, it is reasonable to triage women by the revised Bethesda criteria to test for microsatellite instability and subsequently the Amsterdam criteria to test for a germline mutation [50].

How should patients considering fertility-sparing options be evaluated?

Fertility-sparing options for the treatment of endometrial cancer do not represent the standard of care, and data on long-term and pregnancy-related outcomes are limited. As previously mentioned, only 18% of endometrial cancer cases in women younger than 45 years of age were stage IA, grade 1 at the time of final pathology [46]. For women who wish to pursue fertility-sparing options, D&C may be better at evaluating the tumor grade. One study showed that only 10% of cases diagnosed by D&C were upgraded at the time of hysterectomy compared with 26% of those diagnosed by endometrial biopsy [51,52]. In addition to grade, depth of myometrial invasion is associated with an elevated risk of extrauterine or nodal metastases. A recent study compared the ability of transvaginal ultrasonography, CT scan, and MRI to predict the depth of myometrial invasion [53]. The accuracy, sensitivity, and specificity of ultrasonography, CT scan, and MRI were 69%/50%/81%, 61%/40%/75%, and 89%/90%/88%, respectively. Accordingly, MRI may be the preferred modality for evaluating the presence of myometrial invasion. Other

Table 3
Factors contributing to ideal candidates for conservative treatment of endometrial cancer.

- A well-differentiated endometrial carcinoma, grade 1
- No myometrial invasion
- No extrauterine involvement (no synchronous ovarian tumor or metastasis, no suspicious retroperitoneal nodes)
- Recommended methods of assessment
  - Dilation and curettage
  - Contrast-enhanced magnetic resonance imaging
  - Office hysteroscopy (optional)
  - Estrogen–progesterone receptor status, molecular prognostic markers such as p53 (optional)
- Laparoscopic staging (optional) or laparoscopic evaluation of adnexal involvement
- Strong desire for sparing fertility
- No contraindications for medical management
- Patient understands and accepts that this is not standard treatment (informed consent)

potentially useful interventions include laparoscopic staging and determination of hormone receptor status [45,54].

Which patients are candidates for fertility-sparing treatment?

Patients with noninvasive, grade 1 endometrial cancers and a reasonable chance of attaining a pregnancy are the ideal candidates for fertility-sparing treatments. Although there is no consensus or established guidelines for selecting patients for these treatments, careful assessment for invasive tumors and metastatic disease is paramount. Table 3 offers an algorithm for identifying appropriate candidate for conservative treatment [55].

What role do progestins play in the fertility-sparing treatment of endometrial cancer?

Progestins have been the mainstay of conservative hormonal treatment for endometrial cancer in both the young woman who wants to preserve fertility and the woman who is deemed to be a poor surgical candidate. The most commonly used progestins are medroxyprogesterone acetate (MPA) and megestrol acetate. Progestin-releasing intrauterine device may also be an acceptable alternative. In a review of 231 cases of fertility-sparing therapy in young women, MPA was used in 50% and megestrol acetate was used in 23% of the patients [55]. Other, less frequently used regimens in this study included other progestins, oral contraceptives, tamoxifen, and medicated intrauterine devices. The overall response rate was 68%, with an overall recurrence rate of 12%. Thirty-two percent of the patients failed to respond to any treatment. The duration of therapy was less than 6 months in 47% (109/231) of patients, 7 to 9 months in 17.3% (40/231), longer than 9 months in 13% (30/231), and not available for the remainder [55].

How long can a patient be treated conservatively before being considered a treatment failure?

The dose, duration, route, and follow-up of progestin therapy have not been well defined. Most available data have been limited to retrospective series. In a phase II prospective study, women 40 years of age and younger with either stage IA or atypical hyperplasia were treated with oral MPA for 26 weeks [56]. Although the complete response rate was 68%, 47% of those who achieved a complete response subsequently had a recurrence. Most investigators recommend definitive surgical management after the completion of childbearing or if conservative options fail. Table 4 offers some guidelines for drug choices, routes, dosages, and durations based on the largest published series.

What are the obstetric outcomes in women who are treated conservatively?

A case series and systematic review of pregnancy after fertility-sparing treatment for endometrial cancer collected data on 50 women and documented 65 deliveries with 77 live births [57]. These pregnancies resulted from both assisted reproductive technologies and spontaneous conceptions. One maternal death was seen due to recurrent disease. Another group reported an overall pregnancy rate of 35.7% (78/218), with approximately 18% of women requiring assisted reproductive technologies [55].

When can ovarian preservation be considered in patients with newly diagnosed endometrial cancer?

Traditionally, bilateral salpingo-oophorectomy (BSO) has been routinely performed in conjunction with hysterectomy when surgically treating women who had endometrial cancer. This recommendation is based on the concept that the ovaries may be sites of occult metastatic disease and oophorectomy may decrease the risk of recurrence or subsequent ovarian cancer. Investigators in a recent study examined 175 women with endometrial cancer who did not undergo BSO [58]. Their median age was 38.5 years, and they were followed for 55 months. The overall survival was 93.3%, with seven patients having recurrent disease. None of the recurrences occurred in women with stage IA disease; all recurrences were seen in women with nonendometrioid histology, deep myometrial invasion, cervical stromal invasion, or inadequate adjuvant therapy. Similarly, an analysis of ovarian preservation at the time of hysterectomy for women with early endometrial cancer using the Surveillance, Epidemiology, and End Results database found no excess deaths associated with ovarian preservation [59]. However, other studies suggest that the risk of a synchronous ovarian malignancy in this patient population is as high as 19% and that BSO should be strongly considered [46,60].

Recommendations:

- *Patients who are considering fertility-sparing treatment should be carefully evaluated with a D&C, MRI, and other diagnostic modalities aimed at detecting advanced or high-risk disease (Level of recommendation: A).*
- *MPA and megestrol acetate are the most commonly used progestins in the fertility sparing treatment of women with early stage endometrial cancer (Level of recommendation: A).*
- *Ovarian conservation at the time of hysterectomy in young women with endometrial cancer is feasible but should be individualized (Level of recommendation: C).*
- *BSO may be appropriate for those women who either have HNPCC or*

Table 4
Options for medical treatment of endometrial cancer.

Author	Number of patients	Treatment	Regression	Relapse	Outcomes	Follow-up (months)
Gotlieb [66]	13	Megestrol/MPA	13/13	6/13	13/13 NED	6 to 358
Imai [67]	15	MPA	15/15	9/15	15/15 NED	10 to 146
Kaku [68]	12	MPA	12/12	5/12	15/15 NED	13 to 90
Niwa [69]	12	MPA	12/12	8/12	12/12 NED	24 to 54
Randall [70]	14	Megestrol/bromocriptine (1)	14/14	5/14	14/14 NED	9 to 78
Ushijima [50]	22	MPA + aspirin	22/22	11/22	21/22 NED	NA

MPA = medroxyprogesterone, NED = no evidence of disease, NA = not available.

a family history worrisome for a genetic cancer predisposition (Level of recommendation: B).

Special considerations

Should surgical staging be completed in all patients who have an incidental diagnosis of endometrial cancer following hysterectomy for another indication?

The need for repeat surgery for the sole purpose of staging in women discovered to have endometrial cancer following hysterectomy needs to be considered carefully. A dedicated study will probably never be performed because of relative rarity of the situation. Comprehensive pathology review is mandatory to retrieve as much information as possible about the uterine features of the cancer. These features include histologic cell type, nuclear and FIGO grade, depth of myometrial invasion, presence of lymphovascular space invasion, and tumor size. If these uterine features include endometrioid histology, grade 1 or 2 tumors, small tumor volume, and superficial myometrial invasion, further intervention may not be indicated because these features are compatible with a low risk of extrauterine disease and recurrence [61,62]. Patients who have intermediate- or high-risk features for extrauterine spread or recurrence, patients with high-risk histologic cell types, and older patients should be considered for comprehensive surgical staging. If the patient is a good candidate for surgery, comprehensive staging can be beneficial either by helping to avoid unnecessary adjuvant therapies or by guiding such therapies [7,61,63].

If a decision is made against surgical staging, how should such women be managed?

If the patient is not a good surgical candidate and has uterine features suggestive of an intermediate to high risk for extrauterine disease or disease recurrence, CT, MRI, or occasionally PET/CT scan along with serum CA125 can evaluate for extrauterine disease. Adjuvant radiation and/or chemotherapy can be administered based on the outcomes of the diagnostic evaluation.

Recommendations:

- *Women found to have endometrial cancer incidentally after hysterectomy should have their risk of extrauterine disease and potential for disease recurrence evaluated based on age, histologic cell type, and uterine tumor features. Individualized treatment plans can be based on the findings (Level of recommendation: C).*

Radiation as primary treatment

Can radiotherapy be used as a primary treatment modality for endometrial cancer?

In patients who cannot undergo hysterectomy or surgical staging following an endometrial cancer diagnosis, primary radiation therapy remains a viable option for locoregional disease control. Several studies have evaluated this special circumstance. The 5-year OS following primary radiation therapy ranges from 39% to 71% [64–66].

How can clinicians optimize the outcome of primary radiation therapy for endometrial cancer?

Advances in modern imaging techniques, such as CT, MRI or PET/CT scan to assess for extrauterine disease, may improve the outcomes of women by allowing administration of adjuvant chemotherapy following completion of radiation therapy. Those women who have been diagnosed with high-risk histology, such as grade 3 endometrioid, clear cell, papillary serous, and carcinosarcoma, should be automatically considered for adjuvant chemotherapy.

Recommendations:

- *Select women diagnosed with endometrial cancer who are unsuitable for surgery can be treated with primary radiation therapy followed by chemotherapy (Level of recommendation: B).*

Surveillance

What is the appropriate follow-up for women after treatment of endometrial cancer?

The aim of surveillance following treatment of endometrial cancer is detection of treatable recurrent disease, thereby enabling cure or improved survival. Unfortunately, the role of surveillance in endometrial cancer has not been evaluated in any prospective trial. Given that most endometrial cancers are early stage when initially diagnosed and treated and that recurrence is often local and curable, a cost-effective surveillance strategy is desirable. A recent review of post-treatment surveillance and diagnosis of recurrence in women with gynecologic cancers sponsored by the SGO provides comprehensive recommendations and should serve as a primary resource for clinicians [67]. Current guidelines of the National Comprehensive Cancer Network (NCCN) recommend physical examination every 3 to 6 months for 2 years and every 6 months or annually thereafter [68]. The SGO review recommends a thorough speculum, pelvic, and rectovaginal examination in addition to elicitation of any new symptoms associated with recurrence, such as vaginal bleeding, pelvic pain, weight loss, or lethargy [67]. The NCCN recommends vaginal cytologic evaluation to aid in the detection of cuff recurrence and annual chest radiograph. The SGO review recommends against these evaluations, noting that most vaginal recurrences are detected with clinical examination alone and that chest radiography is of low utility in detecting asymptomatic recurrence. The SGO review further recommends that radiologic evaluation such as CT scan of the chest, abdomen, and pelvis or PET/CT scans be reserved for assessment in women with suspected recurrent disease.

Recommendations:

- *A thorough speculum, pelvic, and rectovaginal examination in addition to elicitation of any new symptoms associated with a possible recurrence, such as vaginal bleeding, pelvic pain, weight loss, or lethargy, should be completed every 3 to 6 months for 2 years and every 6 months or annually thereafter in patients with endometrial cancer (Level of recommendation: C).*
- *The utility of serum CA125 assessment, vaginal cytology, and chest radiography remains controversial (Level of recommendation: B).*
- *CT scans and PET/CT scans should be used only if there is a suspicion for recurrent disease (Level of recommendation: C).*

Hormone replacement therapy and endometrial cancer

Does hormone replacement therapy increase the risk of developing endometrial carcinoma?

The use of long-cycle estrogen and progestin hormone replacement therapy (HRT) showed a tendency toward an elevated risk of developing endometrial carcinoma both for exposure of less than 5 years (hazard ratio [HR] 1.40; CI 0.82–2.38) and for estimated use of 5 years or more (HR 1.63; CI 1.12–2.38) [69]. For an estimated exposure of more than 10 years, the risk for endometrial cancer was elevated among both users of long-cycle HRT (HR 2.95; CI 2.40–3.62) and sequential HRT (HR 1.38; CI 1.15–1.66). Norethisterone acetate and MPA as parts of HRT did not differ in their endometrial cancer risk. The use of tibolone was associated with no risk for endometrial cancer. The use of sequential and long-cycle HRT is associated with an increased risk of

endometrial cancer, whereas the use of continuous HRT or estradiol plus a levonorgestrel-releasing intrauterine device system shows a decreased risk [69].

A meta-analysis evaluating women taking hormone replacement therapy (HRT) showed that BMI is strongly associated with an increased risk of endometrial cancer [70], with the association becoming stronger at BMIs greater than 27 and being particularly strong in women who have never been exposed to HRT. These findings are consistent with summaries of observational studies estimating that exogenous unopposed estrogen use is associated with a two- to threefold increased risk of postmenopausal endometrial cancer, which is reduced toward that of nonusers in women who use combined estrogen–progesterone preparations. An epidemiologic study in Europe evaluated the risk of endometrial cancer with HRT users versus nonusers. In comparison with those who never used HRT, risk of endometrial cancer was increased among current users of estrogen-only HRT (hazard ratio [HR] = 2.52, 95% CI: 1.77, 3.57), tibolone (HR = 2.96, 95% CI: 1.67, 5.26), and, to a lesser extent, HRT (HR = 1.41, 95% CI: 1.08, 1.83), although risks differed according to regimen and type of progestin used. The association of HRT use and risk was stronger among women who were older, leaner, or had ever smoked cigarettes. The finding of a significantly increased risk of endometrial cancer with estrogen-only HRT and a weaker association with combined HRT supports the hypothesis that progestins have an attenuating effect on endometrial cancer risk [71].

Recommendations:

- *Patients considering the use of HRT should be carefully counseled about the risks and benefits. If the decision is made to initiate treatment, women who have not previously undergone a hysterectomy should be treated with a combined regimen to minimize the risk of developing endometrial cancer (Level of recommendation: A).*

Conflict of interest statement

Mario M. Leitao, Jr, MD is a consultant for Intuitive Surgical. Thomas J. Herzog is a consultant for Merck, Morphotek, and Genentech. All other authors declare no conflicts of interest.

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