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REVIEW ARTICLE

Cancer Endometrium: An Update

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ABSTRACT

Endometrial cancer is the most common gynecological cancer in developed countries and second most common in developing countries. Its incidence is increasing in postmenopausal women. Factors related to chronic estrogen exposure are associated with a higher incidence. Abnormal uterine bleeding is the cardinal symptom. All women with suspected endometrial cancer require transvaginal ultrasonography and most will undergo endometrial biopsy; more sophisticated radiological examinations are required for preoperative staging. The general approach for treatment of endometrial cancer is hysterectomy, bilateral salpingo-oophorectomy, abdominopelvic washings, lymph node evaluation and maximal surgical cytoreduction for those with advanced disease. Postoperative adjuvant therapy [vaginal brachytherapy, external beam radiation therapy (RT), chemotherapy] may be recommended depending on the estimated risk of recurrence. Individual patient characteristics and surgical as well as pathologic staging are the main factors that are used for postsurgical risk stratification, which in turn, directs the selection of adjuvant treatment.

Keywords: Endometrial cancer, Update, Bilateral salpingo-oophrectomy, Radiotherapy, Chemotherapy.

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INTRODUCTION

Uterine cancer is the most common gynecologic malignancy in developed countries, with an incidence of 12.9 per 100,000 women and a mortality rate of 2.4 per 100,000. In developing countries, it is the second most common gynecologic malignancy (cervical cancer is more common), with an incidence of 5.9 per 100,000 and a mortality rate of 1.7 per 100,000.[1,2]

Cure is possible and the overall 5 years survival rate for all stages is currently around 80%.

RISK FACTORS

The precise cause of endometrial cancer is unknown. Excessive exposure to estrogen is the primary risk factor for developing endometrial cancer (Table 1).

CLINICAL PRESENTATION

Endometrial cancer is classically present with postmenopausal bleeding. In the perimenopausal age group, it presents with abnormal uterine bleeding.[3,4] Pain, vaginal discharge and pyometra are rarer symptoms and tend to be secondary to advanced cancer.

Drug history (hormone replacement therapy, oral contraceptive pill, tamoxifen), gynecological history (early menarche/late menopause, known endometrial hyperplasia, parity) or medical and surgical history (obesity, treatment for breast cancer, diabetes mellitus, hypothyroidism, hypertension, and Lynch-type syndrome) may be relevant.

PRETREATMENT EVALUATION

Prior to treatment, a complete general physical and pelvic examination should be performed. Presence of extrauterine masses, ascites; potential sites of nodal metastases (supraclavicular) should also be examined.[3]

Two investigations—transvaginal ultrasound and endometrial biopsy are mandatory in women with suspected endometrial cancer. Transvaginal ultrasound showing endometrial thickness greater than 5 mm raises a high suspicion for malignancy in postmenopausal bleeding.[5] A definitive diagnosis by endometrial biopsy is obtained.

CA-125 is a clinically useful test for predicting extrauterine spread of endometrial carcinoma and a value >40 units/ml

Table 1: Risk factors for endometrial cancer

Estrogen-related factors	*Other risk factors*
• Starting monthly periods before age 12 • Starting menopause later in life • Never giving birth or a history of infertility • Using tamoxifen (to treat breast cancer and/or reduce the likelihood of developing breast cancer in women at increased risk) • Having estrogen replacement therapy (adding progesterone lessens this risk) • Estrogen secreting tumors (granulosa or thecal cell tumors of ovary) • Polycystic ovarian disease	• Increasing age—the risk of endometrial cancers increases as a woman ages. More than half of all endometrial cancers are diagnosed in women in the 50- to 69-year age group. • Having hereditary nonpolyposis colon cancer (HNPCC) or having it in your family • Diabetes • Ovarian diseases, such as polycystic ovaries • Overweight or obesity • Diet high in animal fat • Family history of endometrial cancer • History of breast or ovarian cancer • Prior pelvic radiation therapy • Hypertension • Physical inactivity • Immunodeficiency

have a 78% sensitivity and 81% specificity for lymph node metastases.[6]

Contrast-enhanced magnetic resonance imaging (MRI) appears to be the best radiographic modality for detecting myometrial invasion or cervical involvement when compared with nonenhanced MRI, ultrasound or computed tomography (CT).[7,8]

Lymph nodes (pelvic and para-aortic) should be assessed intraoperatively and biopsy or removal of enlarged nodes should be done.

A chest radiograph should be performed as part of the initial assessment.

HISTOPATHOLOGICAL SUBTYPES

Endometrial cancer can been divided into two major types (Table 2). Type 1 cancers (80-90%), are usually estrogen dependent endometrioid adenocarcinomas having a good prognosis. Type 2 tumors usually present late, behave more aggressively, and carry a poor prognosis. They are not estrogen driven and the risk of relapse and metastasis is high.[9] Within this category, the commonest histological types are uterine papillary serous carcinoma and clear cell carcinoma.[10]

INITIAL TREATMENT

The initial treatment is primary surgery, but in few cases it may be primary radiotherapy which will be discussed later.

Primary Surgery

Total extrafascial hysterectomy with bilateral salpingo-oophorectomy with pelvic and para-aortic lymph node dissection is the standard staging procedure for endometrial carcinoma.[11]

Most surgeons record results of peritoneal cytology, but these are not part of new FIGO staging. Cytoreduction often is performed when metastases are evident. An omentectomy is frequently done for patients with serous or clear cell histology.

One of the most important prognostic factor is the presence of extrauterine disease, particularly pelvic and para-aortic lymph node metastases. The approach to lymph node assessment is controversial, particularly in women presumed to have early stage disease. The rate of nodal spread varies from 3 to 5% in well-differentiated superficially invasive tumors to as high as 20% in poorly differentiated deeply invasive disease.[12-14]

There is ongoing controversy over whether pelvic and para-aortic node sampling or complete LND should be performed.[15-18] Women who do not undergo at least sampling of pelvic and para-aortic lymph nodes at the time of surgery are incompletely surgically staged.

Sentinel lymph node biopsy for endometrial carcinoma is still investigational.[19]

Surgery can be open, via laparotomy or laparoscopic. Two extensive meta-analyses and a quantitative review showed no significant difference in terms of recurrence and survival among these two surgical options.[20-22]

We suggest complete pelvic LND and extended para-aortic node dissection rather than selective nodal sampling. Given the importance of lymph node involvement to staging and treatment decisions, lymph node assessment is best performed by experienced surgeons, such as gynecologic oncologists.

STAGING

The old and new FIGO staging are enumerated in Table 3.

PROGNOSIS

The prognosis of endometrial cancer is primarily determined by disease stage and histology. A stratification of 5-year survival outcomes using the newer 2010 FIGO/AJCC TNM staging criteria is shown in Table 4. [23]

PROGNOSTIC FACTORS

The major pathologic factors that are associated with an increased risk of extrauterine spread and recurrence are high grade (grade 3), greater depth of myometrial invasion and tumor extension beyond the uterine fundus (e.g. lower uterine segment, cervix, adnexa or pelvis).[13,24-28]

Some additional risk factors, not encompassed by the current staging system,[9,12] are histologic type (clear cell and uterine papillary serous), involvement of lymphovascular spaces large tumor (>2 cm in diameter, controversial) and positive peritoneal cytology.[29,30] Although the presence of positive peritoneal washings was previously an indicator of T3a disease, in recent staging system, it is no longer used. [31]

Older age has been associated with higher rates of clinical failure. The reason may be that women over the age of 65 have

Table 2: WHO/International society of gynecological pathology classification

Type 1	*Type 2*
Endometrioid adenocarcinoma With squamous differentiation Villoglandular Secretory With ciliated cells	Papillary serous adenocarcinoma Clear cell adenocarcinoma Mucinous adenocarcinoma Undifferentiated carcinoma Mixed carcinoma *Other types* Uterine carcinosarcoma Uterine sarcomas • Stromal sarcomas (in the supporting connective tissue of the endometrium) • Leiomyosarcomas (in the myometrium or muscular wall of the uterus)

Table 3: Old and new FIGO staging

Old FIGO staging		*New FIGO staging (2010)*	
IA	Tumor limited to endometrium	IA	No or <50% of the myometrium
IB	Invasion to <50% of the myometrium	IB	Invasion >50% of the myometrium
IC	Invasion to >50% of the myometrium		
IIA	Endocervical glandular involvement only	II	Tumor invades cervical stroma but does not extend beyond the uterus
IIB	Cervical stromal invasion	IIIA	Tumor invades serosa of the corpus uteri and/or adnexae
IIIA	Tumor invades serosa and/or adnexa and/or positive peritoneal cytology		
IIIB	Vaginal metastases	IIIB	Vaginal and/or parametrial involvement
IIIC	Metastases of pelvic and/or para-aortic lymph nodes	IIIC1	Positive pelvic lymph nodes
		IIIC2	Positive para-aortic lymph nodes with or without pelvic nodes
IVA	Tumor invasion of bladder and/or bowel mucosa	IVA	Tumor invasion of bladder and/or bowel mucosa
IVB	Distant metastases including intra-abdominal and/or inguinal lymph nodes	IVB	Distant metastases including intra-abdominal and/or inguinal lymph nodes

Table 4: Prognosis of endometrial cancer

Stages	*Prognosis (%)*
Stage IA	89.6
Stage IB	77.6
Stage II	73.5
Stage IIIA	56.3
Stage IIIB	36.2
Stage IIIC1	57
Stage C2	49.4
Stage IVA	22
Stage IVB	21.1

more frequent deep myometrial invasion, high tumor grade and advanced tumor stage or less aggressive therapy due to poor functional status could also account for some of the poor outcomes seen in older patients.[32-34]

Black women have a consistently poorer outcome than do Caucasians.[35,36]

RISK STRATIFICATION

Patients can be stratified into treatment groups based upon the estimated risk of disease recurrence.[37] The risk stratification scheme is as follows:

Low risk: Low-risk disease includes comprehensively staged endometrioid cancers that are confined to the endometrium (stage IA) grade 1 or 2.

Intermediate risk: Confined to the uterus but invade the myometrium or demonstrate occult cervical stromal invasion. Thus, they include some patients with stage IA disease, all patients with stage IB disease, and a subset of those with stage II disease. These groups have a higher risk of recurrence than do patients confined to the endometrium. They are further stratified into low-intermediate-risk and high-intermediate risk according to age and presence of certain adverse prognostic factors like outer one-third myometrial invasion, grade 2 or 3 differentiation and presence of lymphovascular invasion.

The high intermediate risk population includes patients of any age with all three adverse prognostic factors, patients who are 50 to 69 with two adverse prognostic factors and patients who are 70 or older with any one of the adverse prognostic factors. Other intermediate risk patients are considered to be at low intermediate risk.

High risk: Includes gross involvement of the cervix (a subset of stage II disease), stage III or IV disease (regardless of grade) and papillary serous or clear cell uterine tumors. These histologies have a greater propensity for lymphovascular and upper abdominal spread and are associated with a worse outcome than endometrioid adenocarcinomas.

POSTOPERATIVE ADJUVANT THERAPY

Postsurgical adjuvant treatment recommendations for women with stages I or II endometrial cancer are based upon the estimated risk of recurrent disease, which correspond to the low-risk, low-intermediate, high-intermediate and high-risk categories as defined above.

Low-risk and low-intermediate-risk Disease

In general, this group has local relapse rates are 5% or less.[24,25,27,28,37]

Given the low risk of pelvic nodal involvement, pelvic RT should particularly be avoided, since it would only expose these women to toxicity without benefit.[38]

Women with low-intermediate-risk disease are also at a relatively low risk of recurrence. Although there is not high quality evidence to suggest that radiation is less effective in this group as compared to those with high-intermediate-risk disease the overall probability of recurrence argues for observation as a reasonable choice.[37,39]

There is no evidence that adjuvant systemic chemotherapy after primary surgery significantly decreases the risk of recurrent disease or death from low-risk or low-intermediate-risk endometrial cancer.[40,41]

Hysterectomy with evaluation of the pelvic and para-aortic lymph nodes, provides adequate treatment for women with low-risk endometrioid endometrial cancer who have no adverse risk factors.

We recommend for women with low-risk endometrioid endometrial cancer that is confined to the endometrium,

adjuvant therapy is not indicated. For resected low-intermediate-risk disease, observation or vaginal brachytherapy are both acceptable postsurgical options. The main benefit of vaginal brachytherapy is to reduce local recurrence rates.

High-intermediate-risk Disease

Women with high-intermediate-risk disease benefit the most from postoperative adjuvant RT, and we recommend it to those patients with the intent of reducing the frequency of local recurrence. Guidelines from the NCCN, which are endorsed by the American Brachytherapy Society (ABS), recommend consideration of adjuvant RT for most of these patients, but they also list observation as an option, at least for patients with stage I disease. [42, 43]

Because of the higher risk of nodal metastases compared to women with low-risk disease, the surgical treatment of choice is an extrafascial total abdominal hysterectomy with bilateral salpingo-oophorectomy (TAH-BSO) with pelvic and para-aortic lymph node dissection.

For women with high-intermediate-risk uterine cancer, we recommend adjuvant RT to reduce the risk of a local recurrence. For most patients, we recommend vaginal brachytherapy rather than pelvic RT, because locoregional control can be achieved with a more favorable short-term and long-term toxicity profile.

High-risk Disease

Adjuvant therapy is recommended for all women with high-risk disease. At most institutions, adjuvant RT is recommended to patients with high-risk organ-confined disease (i.e. gross cervical involvement) and chemotherapy for women with advanced extrauterine disease.

The optimal RT approach for women with organ-confined high-risk disease is controversial. In some centers such patients undergo whole pelvic RT while in others receive vaginal brachytherapy. Both approaches have been associated with excellent pelvic control and survival rates. [44-46]

Intermediate-risk and Organ-confined High-risk Disease

Benefit of Adjuvant RT

Five large prospective phase III trials have been conducted evaluating the role of adjuvant pelvic RT in women with early stage endometrial cancer.[15,37,39,47-49] GOG and PORTEC trial concluded that adjuvant pelvic RT significantly reduces rates of local recurrence (58-70%) but does not prolong survival.

A concern with the routine use of adjuvant RT is the risk of treatment-related toxicity. Early gastrointestinal (GI) side effects may occur in up to 60% of women receiving pelvic RT.[50,51] Severe, grade 3 to 4 GI complications developed in 8% of irradiated women in the GOG 99 trial.[37]

Perhaps more concerning, late toxicity is also increased. An early report of the PORTEC trial indicated that grade 3 or 4 GI toxicity at 5 years was only 3% in the radiotherapy arm (compared to zero in the control group).[39] However, with longer (median 13 years) follow-up, patients treated with EBRT reported significant higher rates of urinary incontinence, diarrhea and fecal leakage, leading to more limitations in daily activities and a significantly more frequent use of incontinence materials (43 *vs* 15%).

Post-hoc analysis of several trials identified clinicopathologic factors like age to further refine prognostic stratification.[15,37,39] The authors concluded that patients under the age of 60 with otherwise intermediate-risk disease did not need postoperative RT.

Retrospective analyses from the SEER and National Cancer databases provide indirect support for the benefit of adjuvant RT in early-stage endometrial cancer with adverse pathologic features.[27,52-57]

Pelvic Irradiation vs Vaginal Brachytherapy

Vaginal brachytherapy was directly compared to pelvic EBRT in the randomized PORTEC-2 trial.[50] At a median follow-up of 45 months, there were no significant differences in total locoregional (vaginal plus pelvic; 5.1 *vs* 2.6% for brachytherapy and pelvic EBRT respectively), vaginal (1.8 *vs* 1.6%) or pelvic recurrence rates. There were also no differences in the rates of distant metastases, 5-year disease-free and overall survival (85 *vs* 80%). Vaginal brachytherapy was associated with significantly lower rates of treatment-related diarrhea and other bowel symptoms.

Thus, brachytherapy appears to be the preferred strategy for women with high-intermediate-risk disease.

The combined use of pelvic RT plus vaginal brachytherapy should be discouraged, since it increases the risk of toxicity, without improving pelvic control.[58,59] One possible exception to this general principle may be patients with cervical stromal invasion (stage II disease).[60]

Chemotherapy vs RT for Intermediate-risk Disease

The efficacy of chemotherapy as an alternative to RT is unclear. In a Japanese trial at a median follow-up of approximately 60 months, there were no significant differences between the groups in terms of 5-year progression-free survival (PFS, 84 *vs* 82 for RT and chemotherapy respectively) or overall survival (85 *vs* 87%). The authors concluded that adjuvant chemotherapy was a useful alternative to RT for intermediate-risk endometrial cancer.[61]

Gynecologic oncology group (GOG) trial 122 showed that adjuvant chemotherapy significantly improved outcomes as compared to whole abdominal RT (WART) in women with stage III and IV disease.[32]

For women with intermediate-risk disease, the available data indicate that adjuvant pelvic RT decreases the likelihood of a local recurrence, but has no beneficial impact on survival, and it is associated with long-term urinary and bowel symptoms and impaired quality of life. The decision whether to irradiate an individual patient should rest on a careful assessment of the benefits and risks of treating (and of not treating).

Vaginal brachytherapy is preferred as it provides comparable reduction in local recurrence rates as does pelvic

EBRT, with less toxicity, and a shorter duration of treatment. Adjuvant pelvic RT in intermediate-risk disease should be given, if complete surgical staging has not been performed.

There is no apparent benefit to combined pelvic RT plus vaginal brachytherapy for completely surgically staged women with intermediate-risk disease.

Regardless of whether adjuvant RT is administered, close follow-up is indicated to maximize the likelihood of successful salvage for those who recur locally.

Women with grade 3 endometrioid cancers and deep myometrial invasion are at the highest risk for disease persistence or recurrence, particularly if they also have lymphovascular space invasion. Like patients with nonendometrioid histology uterine cancer (i.e. papillary serous and clear cell uterine cancers), they have a poor prognosis with postoperative pelvic RT alone and are often considered for adjuvant chemotherapy.

Advanced Extrauterine Disease

Benefit of Radiation Therapy

There is no consensus as to the optimal RT approach for women with high-risk extrauterine disease. Patients whose disease is limited to the pelvis typically undergo pelvic RT with or without vaginal brachytherapy, analogous to those with high-risk organ-confined disease.

WART was advocated mainly for women with positive peritoneal cytology due to concerns for extrapelvic relapses. However, this approach has waned in view of reports questioning the prognostic significance of positive cytology in the absence of other adverse features.[62]

Women whose disease is limited to adnexal or uterine serosal involvement (stage IIIA) have also been treated with WART at some centers due to concerns over abdominal relapse.[63] However, equivalent favorable results are reported with pelvic RT alone.[64-66]

Considerable attention has been focused on the use of adjuvant RT in patients with node-positive (stage IIIC) endometrial cancer.[67-71]

Although, long-term relapse-free survival (RFS, and therefore, possibly cure) is reported in women with positive para-aortic nodes who receive extended field RT patients with isolated pelvic nodal involvement represent a relatively favorable group.[67,68]

Benefit of Chemotherapy

Three randomized trials directly comparing chemotherapy *vs* RT in women with high-risk disease have concluded that results with chemotherapy are at least as good as with RT, and one trial suggests superior outcomes.[61,63,72]

GOG 122 showed at a median follow-up of 74 months, there was a statistically significant 29% reduction in disease progression with chemotherapy relative to WART and a significant 32% improvement in 5 years overall survival that favored chemotherapy. The pelvic recurrence rate was slightly higher in the chemotherapy-treated patients (18 *vs* 13%).[72]

Japanese randomized trial at a median follow-up of approximately 60 months showed no significant differences in PFS (84 *vs* 82%) or 5-year overall survival (OS) (85 *vs* 87%). [61]

Also in an Italian trial, at a median follow-up of 96 months, there were no significant differences between the two groups in PFS (63% both groups) or 5-year OS (69% *vs* 66%).

Combined Chemotherapy and RT

Adjuvant chemotherapy alone may not provide sufficient locoregional control for women with advanced stage disease. Interest is increasing in a combined approach of chemotherapy plus RT. At least three randomized trials are available with conflicting results.[73-75]

In a multi-institutional Nordic trial, the preliminary report at a median follow-up of 3.5 years reveals a significant 38% reduction in progression associated with combined therapy relative to RT alone, which translated into a 5-year PFS 83 *vs* 74%. There was a statistically nonsignificant trend toward better overall survival in the chemotherapy group (HR for death, 0.65; 5-year OS, 82 *vs* 74%).

A pooled analysis included data from this trial and another previously unpublished trial (ILIADE-III) of pelvic RT alone or plus chemotherapy showed significantly improved PFS (HR for progression, 0.63; 95% CI, 0.41-0.99). In this study, there was a nonstatistically significant trend toward improvement in OS (HR for death, 0.69; 95%, CI 0.46-1.03).

In contrast to these results, the addition of chemotherapy to adjuvant RT failed to improve either OS or recurrence rates in a trial in which 156 patients with high-risk disease were randomly assigned to adjuvant RT only or combined with three courses of cisplatin, epirubicin and cyclophosphamide.[76] Although current interest in WART is limited to select centers, this approach is under evaluation in combination with either concomitant (GOG 9907) or sequential (GOG 9908) chemotherapy.

Choice of Chemotherapy Regimen and Duration

The optimal chemotherapy regimen is unclear. While GOG 122 used doxorubicin plus cisplatin for eight cycles, the TAP regimen (cisplatin 50 mg/m^2 on day 1 plus doxorubicin 45 mg/m^2 on day 1 and paclitaxel 160 mg/m^2 on day 2, which requires hematopoietic growth factor support) is preferred by some. It provides a significant survival advantage over doxorubicin/cisplatin alone in women with advanced or recurrent endometrial cancer.[77]

Guidelines from the NCCN consider either regimen acceptable.[42]

We recommend six to eight courses of chemotherapy given without interruption. Chemotherapy may be followed by RT in order to maximize local control for patients at elevated risk of pelvic failure. Although the best regimen has not been defined, acceptable options include TAP (paclitaxel plus doxorubicin and cisplatin), cisplatin plus doxorubicin or carboplatin plus paclitaxel.

A specific area of uncertainty is the optimal sequencing of treatment when both chemotherapy and RT are given (i.e. chemotherapy first followed by RT, RT first, followed by chemotherapy or a 'sandwich' technique of three cycles of chemotherapy followed by RT, then three additional cycles of chemotherapy.

Hormone Therapy

Adjuvant progestin therapy after primary surgery is not effective and not recommended for any disease stage.[78-80] Its role will be discussed later in the advanced stage of metastatic disease of endometrial cancer.

TREATMENT OF WOMEN WITH INCOMPLETE SURGICAL STAGING

Women who do not undergo evaluation (either sampling or removal) of pelvic and para-aortic lymph nodes at the time of surgery are referred to as being incompletely surgically staged.

Reoperation for staging in those with grade 3 tumors and/or deep myometrial invasion should be considered for certain patients. Restaging surgery may obviate the need for adjuvant pelvic RT in patients who are found not to have nodal metastases, or it may identify women who have more advanced disease, for whom postoperative adjuvant chemotherapy is recommended.

The benefit of adjuvant pelvic RT in women with incomplete surgical staging was directly addressed in the PORTEC study.[39] The 5-year risk of pelvic failure was significantly lower after RT (4 *vs* 14%), but treatment-related complications were significantly more (26 *vs* 4%). [81]

We recommend adjuvant RT to decrease the risk of local recurrence for women with intermediate-risk disease who do not undergo full surgical staging, despite the lack of a survival benefit. For women without cervical involvement, pelvic RT alone is associated with excellent pelvic control rates; we consider adding vaginal brachytherapy only if there is cervical stromal invasion.

Reoperation should be considered for certain patients (i.e., grade 3 tumor or deep myometrial invasion). Restaging surgery may obviate the need for adjuvant pelvic RT in patients without nodal metastases, or it may identify women with more advanced disease, for whom adjuvant chemotherapy is recommended.

PRIMARY RT FOR POOR SURGICAL CANDIDATES

Stage I disease not good candidates for surgery due to significant comorbid conditions, primary RT may be preferable to surgery.

The 5-year PFS rates for clinical stage I grade 1, 2 and 3 tumors were 94, 92 and 78%, respectively, among women who received combined intracavitary and external beam RT.[82] These results are comparable to those expected following TAH-BSO.

Surgical risk assessment should be individualized, since it is unclear whether disease-specific survival rates are comparable to women undergoing surgical staging and treatment.

POST-TREATMENT FOLLOW-UP

Post-treatment follow-up includes surveillance as described in Table 5.

Table 5: Follow-up of treated patients of endometrial cancer

- Physical examination every 3 to 6 months for 2 years, then every 6 months or annually
- Vaginal cytology every 6 months for 2 years, then annually
- Patient education regarding symptoms
- Optional measurement of serum CA-125 at each visit
- Annual chest X-ray
- CT/MRI only as clinically indicated
- Genetic counseling for patients with a significant family

TREATMENT OF RECURRENT DISEASE

Treatment options for recurrent disease include RT, surgery, hormone therapy and cytotoxic chemotherapy.

Retrospective reports suggest that surgical resection enhances long-term recurrence-free survival in selected patients who recur locally with no retroperitoneal lymph nodes involvement or disease extension to the pelvic sidewall. Outcomes are most favorable in patients with an isolated vaginal recurrence who are able to undergo complete resection.[83-86] In it is usually followed by chemotherapy and/or radiation therapy.

Isolated central pelvic recurrence may be considered for pelvic exenteration, though it is associated with a high operative morbidity.[87] Five-year survival rates after pelvic exenteration are 20 to 45%.[87-89]

RT is more commonly offered to isolated vaginal or pelvic recurrence, with surgery reserved for RT failures in women who are with comorbidities, such as obesity, diabetes and hypertension. Five-year survival rates are 50%.[86,90-93]

We suggest that women with recurrent endometrial cancer may be treated for palliation or cure, depending on the site of disease relapse and prior treatment. For the majority of women with a pelvic recurrence, radical RT rather than surgery, particularly if they have not been previously irradiated should be the option. We suggest reserving surgical salvage for women who are good surgical candidates (medically and surgically) who have an isolated vaginal recurrence in a previously irradiated field that can be completely surgically resected.

Women with recurrent papillary serous or clear cell endometrial cancer are rarely cured. We suggest that these women should be treated with paclitaxel and carboplatin, the same regimen as used for advanced epithelial ovarian cancer.

TREATMENT OF METASTATIC DISEASE

Systemic therapy is most often used for women with metastatic disease. The most common sites of distant spread are liver and lungs.

Hormone therapy is a particularly attractive option for the treatment of advanced endometrial cancer because it is well-tolerated and lacks the usual toxicities associated with cytotoxic chemotherapy. Among 15 to 30% women respond to hormone therapy, most frequently in low-grade, hormone receptor-positive tumors.[94] While most remissions are partial, and relatively brief in duration, some patients may remain progression-free for extended periods of time (>2 years).[95] Oral progestin (e.g. megestrol acetate 160 to 320 mg daily) is the agent of choice.

Tamoxifen is effective in women with advanced endometrial cancer, with response rates of 30 to 35%.[96,97] As with progestin therapy, low-grade, hormone receptor-positive cancers are more likely to respond to tamoxifen than are high-grade, hormone receptor-negative tumors.

In a randomized trial comparing tamoxifen *vs* progestins in stage III or IV disease, objective response rates were similar (35 and 46% for tamoxifen and medroxyprogesterone respectively).[98]

Although, response rates for various combination regimens that include doxorubicin and/or a platinum-type drug (i.e. cisplatin plus doxorubicin with or without cyclophosphamide, cyclophosphamide plus doxorubicin, carboplatin plus pegylated liposomal doxorubicin) are slightly higher than with monotherapy (ranging from 36 to 67%), PFS durations are only 4 to 8 months.[99-101]

GOG trial 177 and French trial revealed better response rates, PFS and OS in paclitaxel-based regimens while another GOG trial[85] failed to show better outcome in all these paramenters.[77,102,103]

Systemic therapy can provide meaningful palliation for patients with advanced disease that is not amenable to local therapy. We recommend initial progestin therapy for women with progesterone receptor (PR)-positive tumors. Oral megestrol acetate is recommended to the doses of 160 mg daily.

Because of the low rate of response to progestins in women with PR-negative tumors, we suggest initial chemotherapy rather than hormone therapy. The best regimen for first-line chemotherapy has not been established. Reasonable choices for systemic therapy of endometrioid tumors include TAP (paclitaxel plus doxorubicin and cisplatin) or paclitaxel plus carboplatin. If bone marrow tolerance is compromised by prior RT, cisplatin may be a better choice as it is less myelo-suppressive than carboplatin.

Cytoreductive surgery could also be considered in women with distant metastases involving the pelvic sidewall or beyond that can be optimally cytoreduced. These patients will also require additional chemotherapy or RT after surgery depending on the site of recurrence.

FUTURE APPROACHES—TARGETING BIOLOGIC THERAPIES FOR TREATING ENDOMETRIAL CARCINOMA

Endometrial carcinomas have expressed EGFR (49%) and HER-2/neu (59%). These results raise the potential for future therapeutic strategies targeting these with monoclonal antibodies like trastuzumab (anti-HER2 monoclonal antibody) or lapatinib (tyrosine kinase inhibitor that affects both EGFR and HER2 receptors). Success using herceptin for recurrent or metastatic disease has only appeared in case reports and is not a standard practice.[104]

CONCLUSION

Majority of the cases of endometrial cancers are cured in the initial stage of presentation but some women will require additional therapy. The role of radiotherapy and chemotherapy is now being widely accepted to improve the outcomes in these cohort of patients. Further research work is needed to define better treatment options for those who require additional therapy because of locally advanced, recurrent or metastatic disease after one line of treatment.

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