Endometrial Cancer

GYNE/ONC Practice Guideline

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This guideline is a statement of consensus of the Gynecologic Oncology Disease Site Team regarding their views of currently accepted approaches to treatment. It is not intended to replace the independent medical judgment of the physician in the context of individual clinical circumstances to determine any patient’s care or treatment.
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**Background & Incidence**

Endometrial cancer is the most common gynaecologic malignancy. One in 42 Canadian women is affected by endometrial cancer; one in 175 is expected to die from it. It is the fourth most common cancer and the eighth leading cancer causing death among Canadian women. The peak age range at diagnosis is between 60 and 79 years, the average age at diagnosis is 63 years.

Canadian Cancer Statistics for 2010, estimate that there will be 4,500 new cases of endometrial cancer with 790 deaths. Survival is dependent on stage of cancer at initial presentation; early stage disease has a 5-year survival rate of 83% and advanced stage disease, a survival rate of 26%. Unfortunately, the incidence of endometrial cancer is increasing over time in Canada, currently to 19 cases per 100,000 women per year.

The risk of endometrial cancer increases when the balance of female hormones shifts toward relatively more estrogens. Because fat tissue can change some hormones into estrogens, being overweight increases a women’s risk by two to threefold. Associated with obesity, high dietary fat, diabetes and hypertension convey an increased risk of endometrial cancer as well.

**Clinical Assessment of a Patient with Suspected Endometrial Cancer**

Most patients with endometrial carcinoma present with abnormal vaginal bleeding, commonly in the post-menopausal period.

At a primary care level testing and procedures that a patient should undergo prior to referral are:
- History & physical
- Blood work (CBC, Chemistry, INR/PTT)
- Endometrial biopsy or referral to gynaecologist for biopsy

Diagnosis can often be made by an outpatient endometrial biopsy although there is a false negative rate of approximately 10%. A non-diagnostic endometrial biopsy in a symptomatic patient warrants curettage under anaesthesia. An alternative approach, in patients considered high risk for anaesthesia, would be an ultrasound to measure endometrial thickness. When cervix involvement is suspected, cervical biopsy and/or MRI should be considered. Cervical cytology should be assessed.

When clinical symptoms, physical findings or laboratory findings suggest advanced disease, additional investigations that may be carried out at the discretion of the specialist to rule out extra uterine involvement are:
- Abdominal/pelvic ultrasound and/or CT/MRI
- Cystoscopy and/or sigmoidoscopy
- CA125 assay
Referral to a Gynecologic Oncologist:

Patients with clinical stage I, grade 1 (on endometrial biopsy) disease should be managed in the community/by a general gynecologist unless there are extenuating circumstances (ie. suspicion of metastatic disease, medical co-morbidities, excessive surgical risk)

Referral are commonly made for the following scenarios:

- If preoperative histology such as Grade 2 or 3, papillary serous, clear cell or carcinosarcoma is found, suggestive of a greater risk of extra uterine spread
- If final pathology reveals an unexpected endometrial cancer following a hysterectomy for other reasons
- If there is evidence of cervical or extra uterine disease
- If pelvic washings contain malignant cells
- For diagnosis or suspicion of recurrent disease
- For consideration of non-surgical treatment

Surgical Treatment and Surgical Staging

The standard treatment for the majority of patients with endometrial cancer is simple hysterectomy, bilateral salpingo-oophorectomy with or without surgical staging.

As discussed above, patients with clinical stage I, grade 1 disease can be managed in the community unless there are extenuating circumstances.

Patients with grade 2 or grade 3 endometrioid adenocarcinoma or high risk histology, that is clear cell or papillary serous adenocarcinoma, on endometrial biopsy or curettage are commonly referred to gynecologic oncology. In cases where it may alter management, pathology review should be at LHSC. If the grade or histological type is confirmed, the rationale for and against, and the risks and benefits of surgical staging and lymphadenectomy should be discussed by the gynecologic oncologist during the preoperative consultation and documented.

The following points should be discussed with the patient. The risk of pelvic lymph node metastases will be in the range of 5% to 34%, and half of that for para-aortic lymph nodes. If lymph nodes are positive for metastatic cancer then systemic therapy may result in a modest improvement in survival.
If the lymph nodes are negative for metastases, chemotherapy and external beam radiation therapy may be safely omitted, unless the patient is a candidate for, and elects to participate in a clinical trial of adjuvant therapy based on uterine risk factors. Negative lymph nodes do not guarantee a cure, however the likelihood of recurrence is much lower. Conversely patients with low risk features in the uterus, who would otherwise not be considered for adjuvant treatment, may benefit from adjuvant treatment, including chemotherapy, if a lymphadenectomy showed evidence of metastatic disease. Pelvic lymphadenectomy is associated with a 2% to 3% risk of chronic unremitting lymphedema in the lower extremities. With this information as part of the informed consent, patients should be given the opportunity to participate in the decision as to whether or not they would like to proceed with staging lymphadenectomy.

Surgical staging should include resection of pelvic nodes along the external iliac artery from the common iliac artery bifurcation to the circumflex iliac vein, along the internal iliac artery and obturator fossa. The dissection should aim to sample a minimum of 11 pelvic lymph nodes. If there is grade 3 disease, clear cell or papillary serous histology, gross adnexal involvement or grossly positive pelvic nodes, the para-aortic or pre-caval nodes should be sampled. Staging should include biopsy of any suspicious peritoneal lesion and omentectomy or omental biopsy for high-risk histological types.

**Surgery for advanced endometrial cancer**

In patients with clinical stage II disease where the cervix is clinically involved by non bulky tumour, the options include a radical hysterectomy, bilateral salpingo-oophorectomy, with pelvic and para-aortic lymphadenectomy if the patient is a suitable surgical candidate. Alternatively the patient may be treated with a simple hysterectomy, bilateral salpingo-oophorectomy and staging, with decision for adjuvant treatment based on final pathology. If the patient has bulky cervical disease, preoperative radiation therapy followed by a simple hysterectomy and bilateral salpingo-oophorectomy is an alternative option. However it is acknowledged that this approach does not evaluate the status of lymph nodes and will generally result in chemotherapy being omitted.

If there is stage III disease based on vaginal metastases, treatment should be individualized based on the size and location of vaginal metastases between primary surgery and preoperative irradiation followed by surgery. If there is advanced intra-abdominal tumour at surgery, with extension to the ovaries, omentum, peritoneal surfaces, or gastrointestinal tract, an effort at surgical cytoreduction or debulking should be attempted and individualized to the extent that in can be safely performed.
Management of clinically advanced endometrial cancer

Patients who present with clinical evidence of disease extending beyond the uterus (into the cervix, parametria, abdomen, or elsewhere) require special, individualized consideration. Systemic therapy, radical radiotherapy, and surgery (radical hysterectomy, debulking surgery or clearing hysterectomy) may all be appropriate. These patients should be initially assessed in a tertiary referral center for access to expertise in all three disciplines. A multidisciplinary approach to decision-making should occur and be documented.

Surgical approach to hysterectomy in endometrial carcinoma:

The standard approach to total hysterectomy and bilateral salpingo-oophorectomy for endometrial cancer has been by laparotomy through a midline incision. The alternative approach by minimally invasive surgery has the potential to reduce hospital stay and patient morbidity, and shorten the recovery time. When feasible, laparoscopically assisted bilateral salpingo-oophorectomy and vaginal hysterectomy, and if appropriate staging lymphadenectomy should be considered and discussed with the patient. There is ample evidence that the oncologic outcome of patients treated with minimally invasive surgery is equivalent to those managed with laparotomy. In selected cases of morbid obesity or severely compromised cardiorespiratory impairment, where the risks of a laparotomy are substantial, and with specific patient counseling, a vaginal approach to hysterectomy and bilateral salpingo-oophorectomy, with the possibility that the ovaries and fallopian tubes may not be removed, can be considered. The risk of metastases to the ovaries/fallopian tubes in endometrial carcinoma is in the realm of 3%. If the patient accepts this risk and a vaginal hysterectomy is feasible, then this approach may be undertaken.

Radiation Therapy

The use of adjuvant radiotherapy for women with endometrial cancer is based on the estimated risk of recurrent disease and is one of the most controversial areas in gynecologic oncology. The risk of local failure is determined from pathologic assessment of the hysterectomy specimen. This takes into account the depth of invasion in the uterus (endometrium alone, inner half or outer half of myometrium), involvement of the cervical stroma and margins (vaginal, parametrical). The primary information in decision-making for radiotherapy obtained by surgical staging over hysterectomy alone is the status of lymph nodes. Without this information, an estimate is made of there being occult disease in pelvic lymph nodes and the benefits of adding external beam radiation.
Individual FIGO staging can contain patients whose diseases are associated with vastly different patterns of failure and prognosis. Recent changes in the FIGO system have also changed the staging classification significantly.

Characteristics such as age, histologic grade, lymphovascular space invasion, tumour volume, and extent of surgical staging are also used in part to determine subgroup risk classifications to tailor our management for these individuals.

**No Radiation Therapy**

The risk of pelvic recurrence in patients with grade 1 or 2 endometrial cancer, without myometrial invasion is very low (2-10%), with <5% risk of lymph node involvement. Adjuvant RT (either external beam or brachytherapy) is therefore not warranted in patients having these pathologic features. Low intermediate risk disease can be defined as endometrioid histology, with no LVSI and confined to the endometrium or less than 50% myometrial invasion AND grade 1 or 2 histology. These patients have a low risk of relapse, and a high chance of cure without any further therapy. Balancing the risk/benefit ratio of treatment, adjuvant therapy is not warranted in this patient group.

**Brachytherapy**

A group of patients with high intermediate risk (HIR) disease has been identified by different investigators based on criteria that differ slightly from one group to another. A commonly used classification uses three high risk factors: grade 3, outer one third myometrial invasion, and lymphovascular space invasion. HIR includes patients age 70 and above with one risk factor, age 50 and above with two risk factors, and any age with three risk factors. Patients with HIR disease should be considered candidates for vaginal brachytherapy rather than external beam radiation therapy based on risk of recurrence and toxicity. Vaginal brachytherapy (VB) alone is a reasonable choice for most patients with uterine confined endometrial cancer who are deemed candidates for adjuvant radiotherapy. These would include those in the low and high intermediate risk groups for which observation is not sufficient.

**External Beam Radiation without or without Brachytherapy (no Chemotherapy)**

Several randomized control trials have shown that in a selected group of patients with early endometrial cancer, the addition of pelvic EBRT after surgery reduces the rate of loco regional recurrence without an overall survival benefit.
This approach has been associated with an increase in gastro-intestinal toxicity and a decreased quality of life. In patients who have negative surgical staging, adjuvant external beam radiation therapy may still be considered if there are high risk prognostic factors (e.g. deep invasion, high grade, LVSI and/or suboptimal lymph node sampling).

Surgically staged women aged 70 or more with one above risk factor, aged 50 or more with two risk factors and any age with three risk factors may benefit from EBRT. Published studies do not address the treatment of all Stage I and II patients. This includes unstaged patients; stage IIB, stage IC (grade 1 or 2) with LVSI and surgically staged patients IC or II who are less than 50 years of age. We favour the use of adjuvant RT for such patients, which may consist of EBRT and/or VB. There is also a judgment required whether an adequate staging procedure has been done or what to do in cases where the presence of multifocal LVSI raises the risk of recurrence despite negative nodes sampled.

**Using Brachytherapy with External Beam Radiation**

There is not much data available in the literature to support the use of combined VB with pelvic EBRT. Yet there is a rationale to use this approach. In most of clinical trials assessing the value of adjuvant pelvic radiation (EBRT only) for patients with endometrial cancer, the dose was in the range of 50 Gy. An alternative strategy is to limit the dose of external beam radiation to 45 Gy to minimize gastro-intestinal toxicity and to combine to the external beam radiation with VB for those patients deemed at risk for vaginal recurrence (e.g. deep myometrial invasion, cervical stromal involvement).

**Radiation Integrated with Chemotherapy**

A multidisciplinary team discussion is helpful in deciding on the post-operative management of patients with endometrial cancer in cases where evidence is inconclusive. Enrolment in clinical trials when available is recommended. We define “locally advanced” as meaning Stage III and IVa disease (FIGO 2009 Uterine Cancer Staging) irrespective of histology. The following section refers to adjuvant therapy for women who have undergone a hysterectomy, bilateral salpingo-oophorectomy, and a surgical staging procedure (which generally includes pelvic and para-aortic nodal sampling, omental biopsy and selected biopsies of suspicious areas and peritoneal washings) and are diagnosed with stage III or IVA disease. Adjuvant radiotherapy has been used alone historically (pelvic, extended field or whole abdomen) and is associated with high rates of distant failure and death in this patient group. However, there are select patients treated with limited nodal disease who have been cured with radiotherapy alone. With obvious room for improvement, chemotherapy has been increasingly used in the adjuvant setting.
Given the favourable side effect profile and response rates with carboplatin and paclitaxel chemotherapy from use in ovarian cancer, this combination has become the most common choice for locally advanced endometrial cancer. With adjuvant pelvic radiation alone, pelvic control rates are reasonable, but the problem is upper abdominal and distant failures. Chemotherapy is thought to better address the issue of disease in these sites. However, pelvic failure rates remain significant with chemotherapy alone. Therefore, multimodality treatment with chemotherapy and radiation may offer an advantage with better pelvic disease control if toxicity is acceptable.

Whole abdomen radiation has generally fallen out of favor. “Involved field” radiotherapy, where radiation is given to areas of known disease can provide good disease control rates in select patients. However when used routinely alone in all Stage III/IV patients, upper abdominal and distant failure become an issue. Radiotherapy should be delivered to sites of suspected microscopic or gross disease often described as the Clinical Target Volume (CTV) or Gross Tumour Volume (GTV). Vaginal cuff brachytherapy treats a very small volume of tissue (generally the upper vagina and extending less than 1cm beyond the mucosal surface). In order to adequately treat a proper CTV, external beam radiation is usually required. The defined treatment volume will depend on several factors, including the extent of the surgical procedure, distribution of disease and patient factors. Treatment volumes may range from "limited" pelvic field, whole pelvis or extended fields that include a portion of the para-aortic nodes. External beam doses are in the range of 4500-5040 cGy using 180-200 cGy daily fractions. Vaginal cuff brachytherapy is often used in combination with external beam.

Systemic Therapy as Adjuvant Therapy for Resected Endometrial Cancer

The use of combination therapy has theoretical advantages in cases of resected advanced endometrial cancer. There are both published and ongoing studies of combinations of chemotherapy and radiation. In resected stage III and IV disease, where there is no macroscopic residuum after surgery, cisplatin / doxorubicin chemotherapy was associated with a survival advantage over whole abdominal radiation, but with a high pelvic recurrence rate in the chemotherapy arm. This has led many to advocate for combined chemotherapy and radiotherapy in high-risk endometrial cancer. Several studies compared radiation alone to radiation and chemotherapy. In addition to a negative study, one study did show a progression-free survival benefit of approximately 7% in favor of chemotherapy and radiation over radiation alone for high-risk patients with stage I-III endometrial cancer.
Given the uncertainties on what is the optimal treatment for these groups of patients, enrollment of patients is encouraged to help answer these important study questions, currently PORTEC 3 or EN7 at this institution. PORTEC-3 is seeking to answer the question of whether the addition of carboplatin and paclitaxel sequentially, as well as the addition of concurrent cisplatin with radiotherapy, improves survival in high-risk resected endometrial cancer.

Given the suggestion in the literature that chemotherapy may confer a small but statistically significant survival benefit, our current standard involves giving sequential therapy in a so-called “sandwich” approach to treat patients with high-risk endometrial cancer (high-risk histology, stage III). This includes: four cycles of carboplatin (AUC6)/ paclitaxel (175mg /m^2), followed by 45Gy EBRT +/- brachytherapy (5Gy x 3), followed by two further cycles of carboplatin / paclitaxel (if tolerated). The advantage to this approach is even if a patient declines treatment after radiation, she has received a reasonable amount of chemotherapy. Adjuvant chemotherapy with carboplatin and paclitaxel is recommended for papillary serous and clear cell histologies, with the exception of stage IA disease.

We generally consider carcinosarcomas a high-risk histology and consider resected patients with this disease for adjuvant chemotherapy and radiotherapy. Randomized evidence exists to suggest a survival advantage to adjuvant chemotherapy for patients with resected stage I-IV, treated with three cycles of cisplatin / ifosfamide. Again, carboplatin / paclitaxel appear active in this disease, and have replaced ifosfamide-containing regimens by most practitioners.

**Systemic Therapy for Metastatic, Unresectable or Recurrent Endometrial Cancer**

Disseminated metastatic disease, or isolated but unresectable disease, can be treated with palliative intent using various systemic agents.

**Hormonal Therapy**

- Megestrol acetate
- Medroxyprogesterone acetate
- Tamoxifen
- Aromatase inhibitors (e.g. Letrozole)

No dose or type of hormonal therapy has been proven superior to any other.

Main predictors of benefit from hormonal therapy include: low grade disease, long disease-free interval, location and extent of extra pelvic metastatic disease.
Chemotherapy
Combination chemotherapy is preferred over monotherapy in fit patients with good performance status, as combination therapy has been shown to be more efficacious than single agents. However, combination chemotherapy is associated with greater side-effects.

The ideal regimen to be used as adjuvant therapy in endometrial cancer is not clear based on available evidence. For advanced disease, the regimen with highest activity is cisplatin, paclitaxel and doxorubicin. This regimen is toxic, requires prophylactic filgrastim, and is impractical for most patients. Carboplatin / paclitaxel is a well-tolerated regimen and those who treat gynecologic cancer have extensive experience with this regimen from use in ovarian cancer. The standard regimen is carboplatin dosed at an AUC of 5 or 6 plus paclitaxel 175 mg / m². Acceptable alternatives include the following:

- Cisplatin / doxorubicin
- Cisplatin / doxorubicin / paclitaxel / G-CSF
- Cisplatin
- Carboplatin
- Doxorubicin
- Liposomal doxorubicin
- Gemcitabine
- Paclitaxel
- Ifosfamide

Response rates to 2nd line (salvage) chemotherapy after failure of first-line chemotherapy for metastatic disease is poor. Any of the above agents, or hormonal therapy, would be reasonable in this situation, although best supportive care or enrolment in a clinical trial exploring an investigational agent are preferred.

Monitoring & Follow-up
There is no evidence (even in high-risk patients) that follow-up for asymptomatic patients leads to improved survival. Most recurrences are initially detected by patients due to symptoms rather than findings on clinical exam at follow-up visits. Furthermore there is no evidence for the routine use of investigations in this group.
The traditional purpose of regular routine follow-up is to help determine the need for and timing of further treatment. In addition it is recognized that important goals of follow-up are to provide continuous education, psycho-emotional support and reassurance. This follow-up should be consistent and created with the patient’s quality of life at the forefront of consideration. Wherever possible, opportunity for follow-up should be made available in their own community, with the understanding that expeditious referral back to the specialist center will be made at the first sign of symptomatic recurrence.

For some patients follow-up visits may provoke anxiety, worry and fear. The follow-up strategy needs to be individualized based on each patient’s specific needs.

There is a lack of literature regarding optimal frequency of follow-up. We suggest the following for patients:

- Clinic visit with physical exam and patient education regarding symptoms every 3-6 months for 2 years, then at 6 month to 1 year intervals
- Imaging as clinically indicated based on signs and symptoms

Patients with bleeding (vaginal, bladder, or rectal), decreased appetite, weight loss, pain (pelvis, abdomen, hips, or back), cough, shortness of breath, and swelling (abdomen or legs) should seek prompt evaluation and not delay until next scheduled appointment.

When follow-up is at the cancer centre and multiple specialists are involved, visits should alternate between physicians to avoid close repeat examinations, if appropriate.

**Palliative Care**
For patients who have documented evidence of disease progression and who have had a critical point of care conversation, consideration should be given to a referral for Palliative Care. This provides the opportunity to maximize symptom management, explore local resources, and to begin advance care planning for the future, even while active treatment is being implemented.

**Genetic Counselling**
Hereditary Non-Polyposis Colon Cancer (HNPCC) or Lynch syndrome is caused by a mutation in the mismatch repair (MMR) genes. It is an inherited disorder which increases an individual’s chance of developing not only colon cancer, but other types of cancer, including endometrial cancer. Those with HNPCC have an 80% lifetime risk of developing colon cancer, and more specifically, women with HNPCC have a 20-60% lifetime risk of developing endometrial cancer.
Obtaining a detailed family history at the time of initial consultation is extremely important for a genetics referral to be considered. Genetic counseling is an assessment of cancer risk based on personal and family medical history. Individuals with a family history of cancer in multiple family members, cancer diagnosed before 50 years of age in the individual or another family member, or a known cancer syndrome, such as breast and ovarian or colon may be referred to genetics.

Genetic counseling can provide information to help individuals manage their risk for cancer, and their eligibility for genetic testing. Genetic testing is done to determine an individual’s predisposition to cancer and helps the genetics team to advise on the proper screening and preventative methods for each individual.

**Individuals to Consider for Genetic Counselling**
Gene mutations associated with familial colon cancer may also increase the risk for developing endometrial cancer.
A genetic test for cancer predisposition is a blood test that shows whether an individual has inherited a gene mutation that increases the risk for certain cancers. Individuals diagnosed with endometrial cancer and with a personal or family history of breast, ovarian or colon cancer, who meets published criteria, should be referred to a genetic counselor to discuss cancer risks and clarify eligibility for genetic testing. Women with known HNPCC (Hereditary Non Polyposis Colon Cancer) mutation should be evaluated and counseled for prophylactic hysterectomy after completion of childbearing.

Genetic counseling is an assessment of cancer risk based on personal and family medical history. Genetic counseling can provide information to help individuals manage their risk for cancer, whether or not they have genetic testing. It also determines a person’s eligibility for a blood test for genetic testing to determine cancer predisposition, and helps the genetic team advise on the proper screening and preventive methods for each individual.

**Appendix 1**

**STAGE INFORMATION**
A hysterectomy is required to determine the degree of myometrial invasion. The following surgical staging has been adopted by the International Federation of Gynecology and Obstetrics (FIGO) and by the American Joint Committee on Cancer (AJCC): [16-19]

**Stage I**
Stage I* endometrial cancer is carcinoma confined to the corpus uteri.
   - Stage IA: no or less than half myometrial invasion
   - Stage IB: invasion equal to or more than half of the myometrium
Stage II
Stage II* endometrial cancer involves the corpus and the cervix, but has not extended outside the uterus.
   Stage II: Tumor invades cervical stroma, but does not extend beyond the uterus**

Stage III
Stage IIIA: tumor invades serosa of the corpus uteri and/or adnexa#
Stage IIIB: vaginal and/or parametrial involvement#
Stage IIIC: Metastases to pelvic and/or para-aortic lymph nodes#
   IIIC1: positive pelvic nodes
   IIIC2: positive para-aortic lymph nodes +/- positive pelvic lymph nodes

Stage IV
Stage IV* endometrial cancer involves the bladder or bowel mucosa or has metastasized to distant sites.
   Stage IVA: tumor invasion of bladder and/or bowel mucosa
   Stage IVB: distant metastases, including intra-abdominal and/or inguinal lymph nodes

* Either G1, G2, or G3
** (Endocervical glandular involvement only should be considered as Stage I and no longer as Stage II)
#Positive cytology has to be reported separately without changing stage
Resources


42. Eltabbakh GH, Piver MS, Hempling RE et al.


