

ENDOMETRIAL CANCER

Effective Date: November 2015

The recommendations contained in this guideline are a consensus of the Alberta Provincial Gynecologic Oncology Tumour Team and are a synthesis of currently accepted approaches to management, derived from a review of relevant scientific literature. Clinicians applying these guidelines should, in consultation with the patient, use independent medical judgment in the context of individual clinical circumstances to direct care.

BACKGROUND

Endometrial cancer is the fourth most common cancer in women in North America and the most common cancer of the female genital tract. It accounts for 50% of all new gynecologic cancers and 7% of all cancers in women, with an annual incidence of 23.3 per 100,000 women in developed countries.¹ In Alberta, there were 529 cases of cancer of the uterus and 87 deaths in 2012.² The majority (75-85%) of cases are in women over the age of 50 years, with 95% of cases in women over the age of 45 years.¹ The peak incidence is at the age of 55–65 years.³ Over 80% of cases are early stage.

There are several histological types of endometrial cancer. These include (1) endometrioid and variants, such as ciliated cell carcinoma, secretory adenocarcinoma, villoglandular, and carcinoma with squamous and mucinous differentiation, accounting for 75-80% (endometrioid carcinomas are graded based on the extent of solid non-squamous component into grade 1-3) (2) mixed accounting for 10% (3) uterine serous, accounting for <10%; (4) dedifferentiated and undifferentiated carcinoma (1%), (5) clear cell, accounting for 4%; (6) squamous cell, accounting for <1%.^{4,5} Staging of endometrial cancer is based on the Federation Internationale de Gynecologie et d'Obstetrique (FIGO).^{6,7} A detailed description of this staging system can be found in the Appendix A.

The reasons for the staging system are summarized as follows:⁸

- *Stage IA* cannot always be reliably distinguished
- *Stage IA and IB* are poorly defined pathologically and may not differ prognostically (5-year survival for endometrioid carcinomas: 90%)
- *Stage IIIA* alone is heterogeneous; positive cytology is rare but with small effect⁹ (5-year survival: 85%); adnexae/uterine serosa is more significant (5-year survival: 63.4%)
- *Stage IIIB* vaginal metastasis/parametria have a poor prognosis but are rare (5-year survival: 38.8%)
- *Stage IIIC* (5-year survival: 51.1%)
- *Stage IIIC1* pelvic nodes significant (5-year survival: 70%)
- *Stage IIIC2* para-aortic nodes significantly worse (5-year survival: 30%); grossly positive nodes, capsule involvement and desmoplasia are associated with a worse prognosis
- *Stage IV* (5-year survival: 20-26%)

GUIDELINE QUESTIONS

- Is chemotherapy following surgery in women diagnosed with endometrial cancer, at various stages and grades and in certain histotypes more effective than surgery alone in preventing recurrence and/or improving progression free survival?
- Is radiation therapy following surgery in women diagnosed with endometrial cancer, at various stages and grades and in certain histotypes more effective than surgery alone in preventing recurrence and/or improving progression free survival?
- Is hormone therapy following surgery in women diagnosed with endometrial cancer, at various stages and grades and in certain histotypes more effective than surgery alone in preventing recurrence and/or improving progression free survival?

DEVELOPMENT AND REVISION HISTORY

This guideline was reviewed and endorsed by the Alberta Provincial Gynecologic Oncology Tumour Team. Members of the Alberta Provincial Gynecologic Oncology Tumour Team include gynecologic oncologists, radiation oncologists, medical oncologists, pathologists, nurses, and pharmacists. Evidence was selected and reviewed by a working group comprised of members from the Alberta Provincial Gynecologic Oncology Tumour Team and a Knowledge Management Specialist from the Guideline Resource Unit. A detailed description of the methodology followed during the guideline development process can be found in the [Guideline Resource Unit Handbook](#).

This guideline was originally developed in September, 2009. This guideline was revised in December 2009, August 2011, April 2012, October 2013, and November 2015.

SEARCH STRATEGY

Entries to the Medline, EMBASE, and Cochrane databases and clinical practice guideline databases were searched for evidence relevant to this topic. Search terms originally included: endometrial OR endometrium AND cancer OR carcinoma OR adenocarcinoma OR carcinosarcoma AND (1) chemotherapy OR carboplatin OR Taxol; or (2) brachytherapy OR radiotherapy OR radiation; or (3) progestagens OR megestrol OR Megace OR hormone; or (4) oophorectomy OR lymphadenectomy OR hysterectomy OR surgery. The literature was reviewed prior to each update, using the search terms: endometrial OR endometrium AND cancer OR carcinoma OR adenocarcinoma OR carcinosarcoma. A total of 46, 13, and 11 studies were included in the 2011, 2012, and 2013 reviews, respectively. The 2015 update focused on imaging, sentinel lymph node mapping and screening for Lynch syndrome and retrieved a total of 33 studies were included from a search of the Medline database. Following a review of the evidence by the Alberta Gynecologic Oncology Team, relevant literature was added to the discussion section.

In addition, the National Guidelines Clearinghouse database was searched and other guideline developers for existing guidelines. The following guidelines were reviewed and information included where relevant: the National Comprehensive Cancer Network (NCCN) guidelines,¹⁰ the European Society for Medical Oncology (ESMO) guidelines,¹¹ the BC Cancer Agency (BCCA) guidelines,¹² Cancer Care Ontario (CCO) Program in Evidence-Based Care guidelines,^{13,14} the Society of Gynecologic Oncology of Canada, Society of Obstetricians and Gynaecologists of Canada and Society of Canadian Colposcopy (SOG-GOC-SCC),¹⁵ the Society of Gynecologic Oncology (SGO),^{16,17} the American College of Radiology,¹⁸ and the Mallorca group.¹⁹

TARGET POPULATION

The recommendations outlined in this guideline apply to women with endometrial cancer, including uterine carcinosarcoma. This guideline does not cover leiomyosarcoma and endometrial stromal sarcoma, which should be staged as uterine sarcomas. For recommendations on the management of uterine sarcomas, please refer to the Alberta Health Services guideline, [Uterine Sarcoma](#).

RECOMMENDATIONS

The following recommendations were considered when developing the recommendations: NCCN, ESMO, BCCA, and CCO, as per FIGO Staging (2010).

I. Lynch Syndrome Screening

Lynch syndrome screening is recommended for all patients with newly diagnosed endometrial carcinoma. This syndrome is caused by germline mutations in DNA mismatch repair (MMR) genes. These mutations are disruptive, leading to absence of MMR protein expression and genetic instability. MMR protein immunohistochemistry (IHC) and/or microsatellite instability (MSI) analyses are screening tests to identify individuals at risk for Lynch syndrome. MSI analysis identifies high-frequency instability in microsatellite markers. In Alberta, high MSI results should prompt IHC testing. Immunohistochemistry involves analysis of MLH1, PMS2, MSH2, and MSH6 protein expression.^{*} For cases with absent MLH1/PMS2, MLH1 hypermethylation testing is necessary, as hypermethylation suggests a somatic event and genetic referral is not required. For all other abnormal findings genetic referral is necessary, namely, absence of MLH1/PMS2 without MLH1 hypermethylation, and absence of PMS2, MSH2, or MSH6. Patients with significant personal or family history suggestive of hereditary cancer syndromes should be considered for genetic referral regardless of normal screening studies.

II. Surgery

All patients should be referred to a gynecologic oncologist for comprehensive continuing care as they are trained to decide and provide appropriate individualized treatment. Additionally, a full staging procedure with minimally invasive surgery can be offered with evidence to suggest that high volume centers have better long-term outcomes.¹⁷

A pathology review should be performed by a pathologist with experience in gynecologic pathology. Preoperative imaging is not recommended for all patients. However, imaging may be considered if clinically indicated, for example, patients suspected to have extrauterine disease.

As the majority of patients are diagnosed with grade 1 endometrioid carcinomas and have an early stage, the standard treatment is a hysterectomy with bilateral salpingo-oophorectomy with or without lymph node dissection. Para-aortic lymphadenectomy is recommended for those patients with high risk histologies, such as grade 3 endometrioid carcinomas. Many patients with endometrioid carcinoma are upstaged based on final histology^{20,21} and therefore consideration may also be given to para-aortic lymphadenectomy for patients with grade 2 endometrioid carcinomas.

Endometrial serous, clear cell carcinomas, and carcinosarcomas of the uterus require a comprehensive staging procedure which includes a hysterectomy, bilateral salpingo-oophorectomy, pelvic and para-aortic lymph node dissection, and an omentectomy.¹⁴ Consideration should be given to an appendectomy in endometrial serous and clear cell carcinomas.

For clinically obvious cervix involvement consideration can be given to a radical hysterectomy, bilateral salpingo-oophorectomy with lymphadenectomy, OR preoperative radiotherapy followed by a simple

^{*} If your lab reports MSH6 and PMS2 present, this infers that all four proteins are normal in expression.

hysterectomy with bilateral salpingo-oophorectomy. For **medically unfit patients**, where surgery is not an option, treatment may include radiotherapy alone or with hormonal therapy and/or chemotherapy.

There is insufficient evidence to recommend routine sentinel lymph node biopsy for patients with endometrial cancer.

III. Adjuvant Treatment for Completely Surgically Staged Endometrioid Carcinoma (as per FIGO, 2010)

Stage IA

The majority (70%) of Stage 1A patients will present with a grade 1 or 2 tumours, while about 30% will present with a grade 3 tumour. Treatment can vary, depending on the presence of adverse risk factors. These include positive lymphovascular invasion, tumour size, and age > 65 years.

- Grade 1: observe/no adjuvant treatment
- Grade 2: observe/no adjuvant treatment or vaginal vault brachytherapy can be considered if patient has LVSI or based on patient age
- Grade 3: vaginal brachytherapy if adverse risk factors are present (30% of stage 1A grade 3 patients)

Stage IB

Approximately 30% of all patients with endometrial cancer will present with a stage IB.

- Grade 1/2: vaginal vault brachytherapy can be offered
- Grade 3: vaginal vault brachytherapy +/- whole pelvic radiation therapy (consideration of chemotherapy to be discussed in a multidisciplinary setting)

Stage II

Approximately 10% of all patients with endometrial cancer will present with a stage II tumour. For clinically obvious cervix involvement, consider a radical hysterectomy, bilateral salpingo-oophorectomy with lymphadenectomy, OR preoperative radiotherapy followed by a simple hysterectomy with bilateral salpingo-oophorectomy. In the case of stage II disease where pre-operative radiotherapy is given, intracavitary radiotherapy is usually given in addition to EBRT.

Postoperative management:

- Grade 1/2: Options include
 - Observe/no treatment if radical hysterectomy, bilateral salpingo-oophorectomy (BSO), and pelvic lymphadenectomy done; otherwise, treat with pelvic radiotherapy plus vaginal brachytherapy
- Grade 3: Options include:
 - if radical hysterectomy, bilateral salpingo-oophorectomy (BSO), and pelvic lymphadenectomy done, consider vaginal brachytherapy
 - Treat with pelvic radiotherapy plus vaginal brachytherapy

Stage III

Approximately 20% of all patients with endometrial cancer will present with a stage III tumour.

Stage IIIA and IIIB

- Grades 1/2/3: Options include
 - Chemotherapy +/- radiotherapy +/- hormone therapy
 - OR Adjuvant radiotherapy +/- chemotherapy +/- hormone therapy
 - OR Pelvic radiotherapy +/- vaginal brachytherapy

Stage IIIC1 and stage IIIC2

- Grades 1/2/3: Options include
 - Chemotherapy +/- external beam radiotherapy +/- vaginal brachytherapy +/- hormone therapy

Stage IV

Approximately 10% of all patients with endometrial cancer will present with a stage IV tumour.

Stage IVA

Options include:

- Chemotherapy +/- hormone therapy +/- pelvic external beam radiotherapy
- Participation in clinical trials is strongly encouraged

Stage IVB

Options include:

- Chemotherapy +/- hormone therapy +/- consideration of palliative radiotherapy
- Participation in clinical trials is strongly encouraged

Positive cytology (for completely staged patients with no other extrauterine disease)

Grades 1/2/3: Options include:

- Observe or consider vaginal brachytherapy or pelvic RT +/- vaginal brachytherapy +/- chemotherapy if there are other prognostic factors

Recommended Chemotherapy

Four to six cycles of carboplatin (AUC 5) with paclitaxel at 175 mg/m². In the case of hypersensitivity to paclitaxel, docetaxel at 75 mg/m² should be considered.

Recommended Hormone Therapy

The recommended medications are Medroxyprogesterone (Provera) 200-400 mg daily or Megestrol (Megace) 160 mg daily.

VI. Adjuvant Treatment for Surgically Staged High Risk Histotypes Including Endometrial Serous, Clear Cell, Dedifferentiated/undifferentiated Carcinomas and Carcinosarcomas

Stage IA

Options, at the discretion of the gynecologic oncologist and the patient include:

- Observation alone
- Vaginal brachytherapy
- Chemotherapy +/- RT

Stage IB, Stage II

Options include:

- Chemotherapy +/- RT

Stage III, Stage IV (adequately debulked)

Options include:

- Chemotherapy +/- RT

Recommended Chemotherapy

Six cycles of carboplatin (AUC 5) with paclitaxel at 175 mg/m². In the case of hypersensitivity to paclitaxel, docetaxel at 75 mg/m² should be considered.

V. Adjuvant Treatment for Incompletely Surgically Staged Patients

A CT scan of the chest, abdomen and pelvis is recommended.

Consider reoperating for surgical staging.

Stage IB

- Grades 1/2: Options include
 - If radiologic imaging is negative, treat with vaginal brachytherapy +/- pelvic radiotherapy
 - If radiologic imaging is positive, surgically restage and then treat as for completely surgically staged patients (as above)
- Grade 3: Options include
 - If radiologic imaging is negative, treat with pelvic radiotherapy and vaginal brachytherapy +/- para-aortic radiotherapy. For Grade 3 tumours, chemotherapy may be added.
 - If radiologic imaging is positive, consider surgical restaging; treat with pelvic radiotherapy +/- vaginal brachytherapy.

Stage II

Options include

- If radiologic imaging is negative, treat with pelvic radiotherapy and vaginal brachytherapy +/- para-aortic radiotherapy. For Grade 3 tumours, chemotherapy may be added.
- If radiologic imaging is positive, treat with pelvic radiotherapy +/- vaginal brachytherapy +/- chemotherapy.

VI. Therapy for Relapsed Patients

The recurrence rate for endometrial cancer is approximately 20%. The majority (70%) of recurrences will be confined to the pelvis (endometrioid type more common), while the remaining (30%) will be extrapelvic recurrences (high risk histotypes more common).

- Consider enrolment in a clinical trial if available
- For pelvic recurrences, if no prior radiotherapy has been given to site of recurrence, then treat with external beam radiotherapy plus brachytherapy or surgical exploration of the pelvis plus resection, with post-operative radiation therapy (PORT)
- For extrapelvic recurrences, treat with chemotherapy +/- hormone therapy +/- radiotherapy; if prior radiotherapy has been given to the site of recurrence, one of the following can be considered:
 - Surgical exploration of the pelvis plus resection, with or without PORT
 - Hormone therapy
 - Chemotherapy

- For isolated metastases, consider resection with or without radiotherapy. If the tumor is unresectable or if there is further recurrence, then treat as disseminated metastases (see below).
- For disseminated metastases, if asymptomatic or low grade, treat with hormone therapy then chemotherapy. If symptomatic or Grade 2/3, or large volume, then treat with chemotherapy and/or palliative radiotherapy.

VII. Follow Up and Surveillance

The following suggestions for follow-up of women without evidence of disease after primary potentially curative treatment for any stage of endometrial cancer have been modified from the ACOG²² and CCO²³ follow-up guidelines.

- Patient counseling on potential recurrence symptoms could include discussion of:
 - unexplained vaginal bleeding or discharge
 - detection of a mass
 - abdominal distension
 - persistent pain, especially in the abdomen or pelvic region
 - fatigue
 - diarrhea, nausea or vomiting
 - persistent cough
 - swelling
 - weight loss
- Follow-up by the treating gynecologic oncologist, general gynecologist, or general practitioner could be based on the risk of recurrence. The majority of recurrences are symptomatic and occur within 5 years. A general examination, including complete history, speculum, and a pelvic-rectal examination, could be performed as follows:
 - Low-risk patients (i.e., stage IA or IB, grade 1 or 2): every 6 months during years 1 through 3, then once yearly during years 4 and 5.
 - High-risk patients (i.e., stage IA or IB, grade 3, or stage II or higher): every 4 months during years 1 through 3, then every 6 months during years 4 and 5.
- Patients who are symptomatic should undergo appropriate investigations to rule out recurrence, as many local recurrences are potentially curable with additional therapy.

DISCUSSION

Treatment of endometrial carcinoma should be managed by a gynecologist oncologist and is based on staging and histological type. It is recognized that the reproducibility of histological type for high-risk histologies is limited among pathologists.^{24,25} Review by a pathologist with subspecialty interest in gynecological pathology is recommended. The use of immunohistochemical markers such as p53 to support endometrial serous and Napsin A to support clear cell carcinoma may be indicated in appropriate cases. It is also important to note that many patients are upstaged after final histology. Retrospective analyses have found between 13% to 30% of patients are upstaged from preoperative biopsy.^{20,21}

The SGO recommends that gynecologic oncologists be involved in the complete care of patients with endometrial carcinoma as their expertise allows for comprehensive and cost-effective care.¹⁷ In particular,

the SGO highlights that gynecologic oncologist “involvement enhances the preoperative and intraoperative decision process, allowing for completion of any necessary procedure (comprehensive staging or debulking), and facilitates the decision regarding the need for additional therapy.”¹⁷ There is conflicting evidence on the usefulness of imaging for all patients. The American College of Radiation (2014) states that cross-sectional imaging is a complementary tool to surgical evaluation and can play a role in pretreatment assessment.¹⁸ The Canadian SOG-GOC-SCC guideline recommends that CT and MRI scans not be routinely used, except in specific clinical cases for high-grade tumours or if there is a clinical suspicion of extrauterine disease.¹⁶ The NCCN also recommends limited use of pretreatment imaging.²⁶ In addition to the accuracy of imaging the cost must also be considered. There is limited research specifically investigating the utility of CT scans for endometrial cancer. Basnal and colleagues²⁷ examined 250 abdominal-pelvis CT scans of patients with adenocarcinomas of the uterus in the United States and found that CT imaging altered management in 4% of cases. Imaging was significantly more likely to alter management in those patients with high-risk histologies such as endometrial serous and clear cell tumors (11%) and sarcomas (13%). They reported a cost of \$17,622 to alter management of one patient.

Carcinoma

In early stage carcinoma, post-operative radiotherapy has been shown to reduce vaginal and pelvic recurrences, but not distant metastases, thereby yielding no differences in 15-year survival between radiotherapy and observation alone;²⁸ however, patients with poorly differentiated tumours that infiltrate more than half the myometrial thickness were found to benefit from additional radiotherapy.²⁹ In fact, subsequent studies have also shown benefit, in terms of recurrence and survival outcomes, from radiotherapy among early stage high risk patients.³⁰⁻³² However, a recent meta-analysis of data from the ASTEC and EN.5 trials comparing adjuvant radiotherapy with observation alone in early stage intermediate and high risk patients confirmed no benefit of radiotherapy in terms of overall survival (hazard ratio 1.04; 95% CI 0.84-1.29).³³

In the absence of data to clearly show an advantage of post-operative radiotherapy over chemotherapy in patients with high-risk disease,³⁴ efforts have shifted towards a combined modality approach, combining chemotherapy with radiotherapy. The PORTEC-3 trial was designed to compare concurrent radiation and adjuvant chemotherapy with pelvic radiation alone in high risk and advanced stage endometrial carcinoma. Results of this study are awaited.

A combination of carboplatin with paclitaxel is the recommended protocol for systemic therapy in endometrial cancer. This is based on results showing better efficacy and less toxicity compared to other regimens, including cisplatin/doxorubicin, cisplatin/doxorubicin/paclitaxel, ifosamide/paclitaxel, carboplatin, carboplatin/paclitaxel, cisplatin alone, doxorubicin alone, paclitaxel alone, cisplatin/ifosamide (for carcinosarcoma), and ifosamide alone (for carcinosarcoma).³⁵⁻⁴² Hoskins et al.⁴³ had initially shown that a combination of carboplatin with paclitaxel was effective and less toxic than other combination chemotherapy regimes in advanced and recurrent endometrial cancers. Subsequently, a meta-analysis by Humber et al.⁴⁴ in 2007 concluded that combination chemotherapy was superior to single agent chemotherapy, with the addition of anthracyclines and taxanes to cisplatin giving the best response. Many studies since then have shown the superiority of carboplatin with paclitaxel, both in response and toxicity profile.⁴⁵⁻⁵⁰ Results from GOG 209 a randomized phase III trial of doxorubicin/cisplatin/paclitaxel and G-CSF vs. carboplatin/paclitaxel in patients with stage III and IV or recurrent endometrial cancer are awaited.

Martin-Hirsch et al.⁵¹ carried out a meta-analysis of six randomized control trials (4,350 patients) and concluded that progestins alone were not efficacious in the adjuvant setting. Subsequent studies have also failed to demonstrate efficacy with adjuvant hormone therapy alone.⁵²⁻⁵⁴ Furthermore, combination

therapy (e.g. megestrol and tamoxifen) has not shown better results than megestrol alone: response rate of 19% versus 20% and median survival time of 8.6 versus 12.0 months, respectively.⁵⁵

Carcinosarcomas

There is growing evidence to suggest that carcinosarcomas (malignant mixed mesodermal tumours or MMMT) arise through a transdifferentiation of a uterine carcinoma into a sarcoma. Hence, in the 2010 FIGO staging, they are now staged with endometrial carcinoma.^{7,8} They are rare tumours that account for 1% of female genital cancers and 3% of uterine cancers. Carcinosarcomas are highly aggressive tumours, with a 5-year survival rate of about 20% overall; between five and ten percent have a history of pelvic radiotherapy with a risk of 0.17 per 1000 women on long term tamoxifen. The recurrence rate for patients with stage I and II disease is 50% with metastasis to the pelvic and para-aortic lymph nodes and omentum being the most common.^{56,57}

National guidance supports a treatment approach consisting of surgery (i.e. surgical staging, total hysterectomy plus bilateral salpingo-oophorectomy with pelvic and para-aortic lymphadenectomy, cytology, omenectomy, and maximal tumour debulking for the advanced carcinosarcomas) and adjuvant therapy.¹⁰ Lymph node involvement will be found in 14-38% of carcinosarcoma patients undergoing lymphadenectomy and lymphadenectomy has been shown to provide significant survival benefit.⁵⁷

Depending on the stage of disease, adjuvant therapy may include chemotherapy and/or whole abdominopelvic radiotherapy with or without brachytherapy.^{10,58} The majority of evidence for the role of radiotherapy is from non-randomized controlled trials (RCTs). However, there have been two RCTs: EORTC 55874 and GOG 150. EORTC 55874 compared post-operative radiation and observation alone in 'high grade' sarcomas. Pelvic radiotherapy (51 Gy in 28 fractions over 5 weeks) improved local control (61 vs. 47%) but provided no survival benefit. There was, however, an increased rate of distant first relapse.⁵⁹ GOG 150 compared whole abdominal radiotherapy with cisplatin/ifosfamide chemotherapy in stage I-IV optimally debulked patients. Vaginal recurrences were more frequent in the chemotherapy arm, while abdominal recurrences were more common in the radiotherapy arm. Having adjusted for stage, cell type, and age, the death rate was 30% lower for the chemotherapy arm.⁶⁰

Chemotherapy drugs have included single agent cisplatin, carboplatin, ifosfamide, doxorubicin, and paclitaxel.¹⁰ Combination therapy has included treatment with cisplatin and ifosfamide with or without doxorubicin, and carboplatin and paclitaxel.¹⁰ As yet there is no convincing evidence that adjuvant chemotherapy can improve progression free survival (PFS) and overall survival (OS) in patients with early stage disease.

Ifosamide combination therapy has demonstrated efficacy both with cisplatin (54% overall response rate; 52% overall survival rate at 84 months)^{61,62} and with paclitaxel (45% response rate overall)⁶³ in patients with advanced, persistent, or recurrent uterine carcinosarcoma. Other regimens that have shown promising results include: carboplatin and paclitaxel alone or alternated with carboplatin and doxorubicin (overall response rate 62-67%; median progression-free survival 5.5-12.0 months)⁶⁴⁻⁶⁶ Hoskins et al. reported a 60% response rate using a combination of carboplatin and paclitaxel.⁴⁷ Median PFS was 16 months with a median 12 month PFS for recurrences. Importantly, the decrease in toxicity and convenience of administration was superior to the combination of cisplatin and ifosfamide. Other regimens that have demonstrated limited efficacy in carcinosarcoma include gemcitabine and paclitaxel, imatinib mesylate, sorafenib, docetaxel alone, topotecan, and paclitaxel alone.⁶⁷⁻⁷²

Sentinel lymph nodes

There is a lack of evidence for the evaluation of sentinel lymph nodes. A meta-analysis conducted by Ansari et al.⁷³ combined results from 51 studies and found a pooled detection rate of 77.8% and pooled sensitivity of 89%. They note that sentinel lymph node mapping appears feasible for patients with endometrial cancer, but will not consider this procedure safe until larger studies evaluating the false negative rates and factors influencing sensitivity are conducted. Another meta-analysis performed by Kang et al.⁷⁴ found a similar detection rate of 78% and sensitivity of 93% in 26 studies, however, they caution the interpretation of the results because of significant small study effects.

Lynch syndrome screening

Lynch syndrome is an inherited cancer syndrome caused by autosomal dominant mutations in genes encoding DNA mismatch repair (MMR) proteins. Women with Lynch syndrome are at risk of endometrial, colorectal, and other Lynch syndrome-associated cancers.⁷⁵ Their first-degree relatives (parents, siblings, and children) are at a 50% risk of also having Lynch syndrome.⁷⁵ Identifying individuals with Lynch syndrome allows for increased screening and earlier detection of cancer. Universal screening of endometrial tumours for Lynch syndrome via IHC and/or MSI analysis has been recommended by the SGO.¹⁷ Screening has also been shown to be cost-effective.^{76,77} However, there is no evidence to recommend IHC and/or MSI analysis over each other or both.⁷⁵

GLOSSARY OF ABBREVIATIONS

Acronym	Description
BCCA	BC Cancer Agency
BSO	bilateral salpingo-oophorectomy
EBRT	external beam radiotherapy
ESMO	European Society for Medical Oncology
FIGO	Federation Internationale de Gynecologie et d'Obstetrique
HR	hazard ratio
IHC	immunohistochemistry
LVSI	lymphovascular space involvement
OS	overall survival
MSI	microsatellite instability
MMR	Mismatched repair
NCCN	National Comprehensive Cancer Network
PFS	progression free survival
PORT	post-operative radiation therapy
RCT	randomized controlled trial
RT	radiotherapy
SOGC-GOC-SCC	Society of Gynecologic Oncology of Canada , Society of Obstetricians and Gynaecologists of Canada and Society of Canadian Colposcopy
SGO	Society of Gynecologic Oncology
WAI	Whole-abdominal irradiation
WPR	Whole pelvic radiation

DISSEMINATION

- Present the guideline at the local and provincial tumour team meetings and weekly rounds.
- Post the guideline on the Alberta Health Services website.
- Send an electronic notification of the new guideline to all members of CancerControl Alberta.

MAINTENANCE

A formal review of the guideline will be conducted at the Annual Provincial Meeting in 2017. If critical new evidence is brought forward before that time, however, the guideline working group members will revise and update the document accordingly.

CONFLICT OF INTEREST

Participation of members of the Alberta Provincial Gynecologic Oncology Team in the development of this guideline has been voluntary and the authors have not been remunerated for their contributions. There was no direct industry involvement in the development or dissemination of this guideline. CancerControl Alberta recognizes that although industry support of research, education and other areas is necessary in order to advance patient care, such support may lead to potential conflicts of interest. Some members of the Alberta Provincial Gynecologic Oncology Team are involved in research funded by industry or have other such potential conflicts of interest. However the developers of this guideline are satisfied it was developed in an unbiased manner.

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APPENDIX A

Staging of endometrial cancer is based on the Federation Internationale de Gynecologie et d'Obstetrique (FIGO) 2010:

Stage I* Tumor confined to the corpus uteri

- IA* No or less than half myometrial invasion
- IB* Invasion equal to or more than half of the myometrium

Stage II* Tumor invades cervical stroma, but does not extend beyond the uterus**

Stage III* Local and/or regional spread of the tumor

- IIIA* Tumor invades the serosa of the corpus uteri and/or adnexae*
- IIIB* Vaginal and/or parametrial involvement*
- IIIC* Metastases to pelvic and/or para-aortic lymph nodes*
 - IIIC1* Positive pelvic nodes
 - IIIC2* Positive para-aortic lymph nodes with or without positive pelvic lymph nodes

Stage IV* Tumor invades bladder and/or bowel mucosa, and/or distant metastases

- IVA* Tumor invasion of bladder and/or bowel mucosa
- IVB* Distant metastases, including intra-abdominal metastases 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 the stage

Endometrial cancer can be grouped with regard to the degree of differentiation of the adenocarcinoma, as follows:

- G1: no more than 5% of a nonsquamous or nonmorular solid growth pattern.
- G2: 6% to 50% of a nonsquamous or nonmorular solid growth pattern.
- G3: greater than 50% of a nonsquamous or nonmorular solid growth pattern.