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The Role of Surgery in Endometrial Cancer

This clinical practice guideline has been prepared by the SOGC-GOC-SCC Policy and Practice Guidelines Committee, reviewed by the SOGC Clinical Practice Gynaecology Committee and approved by the Executive and Council of the Society of Gynecologic Oncology of Canada and the Executive and Council of the Society of Obstetricians and Gynaecologists of Canada.

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Abstract

Objective: To review current practice and make recommendations for the management and treatment of endometrial cancer.

Outcomes: This guideline makes recommendations with respect to extended surgical staging, which provides important prognostic information and aids in determining the need for adjuvant treatments.

Evidence: Published literature was retrieved through searches of PubMed, CINAHL, and The Cochrane Library, using appropriate controlled vocabulary (e.g., endometrial neoplasms) and key words (e.g., endometrium cancer, endometrial carcinoma). Results were restricted to systematic reviews, randomized control trials/controlled clinical trials, and observational studies. There were no date or language restrictions. Searches were updated on a regular basis and incorporated in the guideline to December 31, 2011. Grey (unpublished) literature was identified through searching the websites of health technology assessment and health technology assessment-related agencies, clinical practice guideline collections, clinical trial registries, national and international medical specialty societies, and recent conference abstracts

Benefits, harms, and costs: This guideline reviews the benefit of extended surgical staging compared with the potential harm of a limited surgery in grade 2 and 3 disease.

Values: The quality of evidence is rated and recommendations are made using the criteria described by the Canadian Task Force on Preventive Health Care (Table).

SUMMARY STATEMENTS

Low-risk disease (grade 1 adenocarcinoma on biopsy)

1. In low-risk disease, there is no evidence that lymphadenectomy improves survival in grade 1 adenocarcinoma. (I)
2. Endometrial cancer requires a coordinated multidisciplinary team approach for management. (III)
3. The purpose of lymphadenectomy is to guide adjuvant therapy that may affect survival in high-risk populations or prevent treatments that may result in unnecessary toxicity. (III)

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Key Words: Endometrial cancer, lymphadenectomy, surgical staging, sentinel nodes for endometrial cancer

Key to evidence statements and grading of recommendations, using the ranking of the Canadian Task Force on Preventive Health Care

Quality of evidence assessment*	Classification of recommendations†
I: Evidence obtained from at least one properly randomized controlled trial	A. There is good evidence to recommend the clinical preventive action
II-1: Evidence from well-designed controlled trials without randomization	B. There is fair evidence to recommend the clinical preventive action
II-2: Evidence from well-designed cohort (prospective or retrospective) or case–control studies, preferably from more than one centre or research group	C. The existing evidence is conflicting and does not allow to make a recommendation for or against use of the clinical preventive action; however, other factors may influence decision-making
II-3: Evidence obtained from comparisons between times or places with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of treatment with penicillin in the 1940s) could also be included in this category	D. There is fair evidence to recommend against the clinical preventive action
	E. There is good evidence to recommend against the clinical preventive action
III: Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees	L. There is insufficient evidence (in quantity or quality) to make a recommendation; however, other factors may influence decision-making

*The quality of evidence reported in these guidelines has been adapted from The Evaluation of Evidence criteria described in the Canadian Task Force on Preventive Health Care.[60]

†Recommendations included in these guidelines have been adapted from the Classification of Recommendations criteria described in the Canadian Task Force on Preventive Health Care.[60]

Extent of lymph node evaluation

4. Decisions regarding adjuvant therapy in endometrial cancer are dependent on both histopathologic risk factors for recurrences post-hysterectomy and the status of retroperitoneal lymph nodes when lymphadenectomy is performed. (III)

RECOMMENDATIONS

Low-risk disease

1. Surgery may be limited to hysterectomy and bilateral salpingo-oophorectomy as an acceptable alternative to staging patients with grade 1 disease. However, relying on preoperative tumour grading will underestimate high-risk status in a proportion of patients and may subject these women to either second surgery or a more liberal use of external beam adjuvant radiation. (III-B)
2. Additional risk assessment can include preoperative or intraoperative evaluation of depth of myometrial invasion. For final histopathological stage and grade, regional multidisciplinary teams should come to consensus on the use of prognostic factors to guide adjuvant therapy. (III-B)

High-risk disease (grade 2 or 3 adenocarcinoma / clear cell / papillary serous on biopsy)

3. Consideration should be given to performing pelvic and/or para-aortic lymphadenectomies in patients with preoperative grade 2 and 3 disease to facilitate accurate planning of adjuvant therapy, which is often required postoperatively. The survival benefit of lymphadenectomy in this specific group of patients has not been studied. (II-2B)
4. Patients with high-risk histological subtypes of endometrial cancer such as clear cell and papillary serous adenocarcinomas should receive full staging surgery that includes pelvic and/or para-aortic lymphadenectomy and omentectomy. (II-2B)
5. A coordinated multidisciplinary team approach should be used for management of high-risk endometrial cancer. (III-B)
6. Regional multidisciplinary teams should come to local consensus on the use of prognostic factors to guide adjuvant therapy. (III-B)
7. Performing lymphadenectomy on the basis of palpation for "bulky" nodes is inaccurate and should not be done. (II-2E)

Advanced disease

8. Patients presenting with advanced disease should be referred to gynaecologic oncologists at a regional cancer centre for treatment planning. (II-2B)

ABBREVIATIONS

HBSO	hysterectomy and bilateral salpingo-oophorectomy
SEER	Surveillance, Epidemiology and End Results
SLN	sentinel lymph node

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INTRODUCTION

Surgery is a fundamental part of the management of endometrial cancer. The two principal goals of the surgery are (1) removal of the cancer, and (2) accurate documentation of the extent of disease (staging). While the former may be limited to simple hysterectomy and removal of the ovaries, the latter is much more involved and includes pelvic washings, omental biopsy or complete omentectomy, pelvic lymph node dissection, and para-aortic lymph node dissection.

In Canada, there is no guideline regarding extent of surgery for endometrial cancer, and patterns of practice vary across the country.[1]

In 1988, the International Federation of Gynecology and Obstetrics recommended that endometrial cancer be staged surgically. Controversy arose over what precisely constitutes an adequate staging procedure in endometrial cancer. A wide range of surgical procedures have been offered to patients, from simple hysterectomy and bilateral salpingo-oophorectomy to HBSO with omentectomy, and retroperitoneal nodal evaluation that includes both pelvic and para-aortic lymph node dissection.[2] The 2009 revision of the FIGO staging recommendations further separates patients with pelvic nodal involvement (IIIC1) and para-aortic nodal metastasis (IIIC2), emphasizing the differences in prognosis between these two groups.[3]

Currently in Canada, there are 2 commonly recommended options for surgical management of endometrial cancer patients: (1) limited surgery including a total hysterectomy and bilateral salpingo-oophorectomy, and (2) comprehensive surgical staging consisting of HBSO and surgical pathologic evaluation of retroperitoneal lymph nodes including pelvic and/or para-aortic regions, together with omentectomy in certain types of endometrial cancer. Individual centres and local disease site groups should determine treatment policies that are based on their own experience with accuracy of preoperative grading, availability and accessibility of preoperative MRI to determine depth of myometrial invasion, and ability to carry out intraoperative assessment of depth of myometrial invasion.

LIMITED SURGERY (HBSO) IN ENDOMETRIAL CANCER

The majority of patients with endometrial cancer present with early stage disease and have a good prognosis.[4] The likelihood of nodal metastasis in these patients is low. The risk of lymph node metastases in patients with confirmed grade 1 adenocarcinoma after hysterectomy has been reported to be approximately 2.8%.[1] A Canadian retrospective case series suggested that adjuvant treatment recommendations could, to a large extent, be based on pathologic factors from the hysterectomy specimen independent of lymph node status.[5] These factors included depth of myometrial invasion, lymph vascular space involvement, cervical stromal involvement, final tumour grade, and patient age. Knowledge of nodal status was not a significant predictor of survival in this study. The authors concluded that surgical nodal evaluation in endometrial cancer is unnecessary and potentially results in a substantial proportion of patients being surgically overtreated. In addition, the risks of pelvic lymph node dissection should be taken into account.

Two recent prospective randomized trials have also demonstrated that lymphadenectomy offers no survival benefit in the management of endometrial cancer.[6,7] The ASTEC trial randomized 1408 patients with endometrial cancer (all grades included) to either HBSO with washings and removal of grossly enlarged lymph nodes or HBSO and complete surgical staging that included pelvic, but not para-aortic, lymphadenectomy.[6] Adherence to the study protocol was good, but 45% of patients randomized to the lymphadenectomy arm had lymph node counts of less than 10. The 5-year overall survival was 80% in the group that had full staging, and 81% in the group that had HBSO. Results were further confounded in the second part of the study, which randomized patients to receive pelvic radiation therapy regardless of their surgical-pathological findings. In 2008, Panici et al. looked at the value of lymphadenectomy in patient survival by conducting a prospective randomized trial of HBSO versus HBSO and lymph node dissection in patients with endometrial cancer.[7] The protocol required that at least 20 pelvic lymph nodes be removed to be considered adequate evaluation in the lymphadenectomy arm. At a median follow-up of 48 months, the hazard ratio for death (lymphadenectomy vs. no lymphadenectomy arm) was 1.1 (95% CI 0.7 to 1.71; $P = 0.50$). The 5-year disease-free and overall survival rates were 81% versus 85.9% and 81.7% versus 90% with no significant differences between the two arms.

Proponents of limited surgery also believe that patients found to have higher uterine pathologic risk factors for recurrence after their hysterectomy can be further managed by additional staging surgery to guide subsequent adjuvant therapies or by a more liberal use of adjuvant radiotherapy or chemotherapy.[8] If the strategy of limited surgery including a total hysterectomy and bilateral salpingo-oophorectomy is chosen, patients should be informed that a second staging surgery might be recommended to accurately define the risk of recurrence and guide subsequent treatment planning, because knowledge of nodal status has been shown to affect recommendations regarding the need for further adjuvant radiation therapy.[9]

SURGICAL STAGING IN ENDOMETRIAL CANCER

Gynecologic Oncology Group Protocol 33, a prospective surgical pathological study published in 1987, clearly demonstrated the limitation of clinical assignment of stage compared with surgical-pathological evaluations.[10]

In this study, 22% of patients with clinical stage I uterine cancer were found to have metastatic extra-uterine disease. Pattern of spread was carefully documented and showed that 12% had positive peritoneal cytology, 6% had adnexal metastases, 9% had positive pelvic lymph nodes, and 6% had positive para-aortic lymph nodes. In addition, omental involvements were seen in 6% of patients. The probability of finding metastatic disease was strongly correlated with final tumour grade, using the hysterectomy specimens. This was particularly important for lymph node involvement, as the risk of nodal spread with grade 1 disease was 3% for pelvic and 2% for para-aortic, while the risk of nodal spread for grade 3 disease was 18% for pelvic and 11% for para-aortic nodes.

Tumour grade is an important predictive factor for metastatic disease in endometrial cancer. Unfortunately, the correlation between preoperative tumour grading, based on either endometrial biopsy or uterine curettage specimen, and final tumour grade after hysterectomy is only modest. The discordance rate can range from 15% to 30%.[11–14] In a large population-based Ontario study, the concordance rate between preoperative and postoperative diagnosis of grade 1, 2, and 3 tumours was only 73%, 52%, and 53%, respectively.[8] A recent review of patients with a preoperative diagnosis of grade 1 disease found that 4% of patients had lymph node metastases, 10% had disease beyond the uterus, and 25% had other high-risk features that can influence subsequent adjuvant treatment planning.[15] Given these significant discrepancies, preoperative tumour grades cannot be used to reliably stratify the risk for the presence of extra-uterine metastasis and guide the need for surgical staging.

Staging surgery that includes accurate documentation of nodal status can assist in subsequent treatment planning. In the past, adjuvant radiation therapy was given to as many as 40% of patients with endometrial cancer.[16] However, 3 randomized trials demonstrated that in patients with postoperative low- or intermediate-risk endometrial cancer, adjuvant pelvic radiation did not improve survival.[17–19] A 2011 analysis of the SEER database demonstrated that patients who have had a lymphadenectomy are less likely to receive pelvic radiotherapy.[9]

Staging patients with endometrial cancer also allows selection of patients who may benefit from vaginal vault radiotherapy. Several studies have demonstrated that vaginal vault relapse can be controlled as effectively with vault brachytherapy alone as with pelvic radiotherapy.[19–22] The most recent of these studies, the PORTEC-2 trial, randomized women who were intermediate- to high-risk for recurrence to either external beam radiotherapy or vaginal vault high-dose radiotherapy. Rates of vaginal vault relapse and overall survival were the same in the 2 groups, and toxicities were much lower in the brachytherapy group.[22]

Knowledge about lymph node status can also help guide decision-making regarding the need for adjuvant chemotherapy. Patients with lymph node-positive endometrial cancer (stage IIIC) may have improved survival with the addition of postoperative chemotherapy.[23]

PREOPERATIVE RISK ASSESSMENTS FOR NODAL INVOLVEMENT IN ENDOMETRIAL CANCER

Currently, the most commonly used determinant of preoperative risk status for metastatic disease is tumour grade assigned on an endometrial biopsy. However, as discussed above, preoperative grading is frequently different from the final grade determined from a more complete pathologic evaluation of the hysterectomy specimen.[10–13] A formalized pathology review by gynaecologic pathologists can lead to an improvement in the accuracy of preoperative grading.[24,25] but because of current human resource constraints, it may not be feasible at all Canadian centres. Another frequently used determinant of potential for metastatic disease is depth of myometrial invasion by the tumour. Myometrial invasion is closely correlated to tumour grade. The incidence of deep myometrial invasion for grades 1, 2, and 3 is 13%, 35%, and 54%, respectively.[26] The incidence of lymph node metastases in patients with grade 1 disease who have deep myometrial invasion is approximately 10%.[9] Depth of myometrial invasion is difficult to determine preoperatively, but MRI has been shown to be the most sensitive imaging modality.[26] Intraoperative gross inspection of the uterus with or without a frozen section has a varying degree of sensitivity for determination of risk for lymph node metastasis.[27–31] Several centres have adopted management protocols that incorporate intraoperative evaluation of depth of myometrial invasion for patients with grade 1 and 2 endometrial cancer.[7,32,33] In these protocols, patients found to have deep myometrial invasion go on to have the full staging surgery.

EXTENT OF LYMPH NODE EVALUATION IN ENDOMETRIAL CANCER

The principle of lymph node evaluation in any malignancy is to establish extent of disease. Precise knowledge of the extent of disease allows accurate determination of prognosis and helps guide decisions about the need for adjuvant therapies.

There are two factors that determine the accuracy of lymph node evaluations. The first is having a clear understanding of lymph node drainage patterns to evaluate lymph node areas to which the disease typically spreads. The second is maximizing the probability that the removed nodes are an accurate reflection of the status of the regional nodal basin.

LYMPHADENECTOMY BASED ON CLINICAL ASSESSMENTS

It has long been recognized that lymph node palpation is an inaccurate method of determining which patients require lymph node evaluation.[34] Fewer than 30% of lymph node metastases are identified through palpation, and nearly one half of lymph node metastases are in lymph nodes measuring less than 1 cm.[35–37] Panici et al. found that when patients underwent a formal lymphadenectomy, 4 times as many were found to have lymph node metastases than when lymph node evaluation was based on palpation.[7]

LYMPH NODE COUNT IN ENDOMETRIAL CANCER

Lymph node counts have become a marker for adequacy of lymph node evaluation in a variety of solid tumour disease sites. For example, the American Society of Clinical Oncology and Cancer Care Ontario have recommended that ≥ 12 lymph nodes be removed during surgical resection of colonic cancers.[38,39] Lymph node counts have been associated with increased survival in gastric, bladder, lung, esophageal, pancreatic, and breast cancers. The association between improved survival and higher lymph node counts is attributed to stage migration and better selection of patients who might benefit from adjuvant treatments.[40] At present, there are no recommendations on the use of nodal counts in assessing the quality of nodal dissections in endometrial cancer.

To date, recommendations regarding lymph node counts in endometrial cancer have not been reflective of the probability of finding disease. The Gynecologic Oncology Group Surgical Procedures Manual suggests that a minimum of 10 lymph nodes be retrieved for evaluation. This is based on their recommendation that at least 1 lymph node be removed from each node-bearing region in the pelvis and para-aortic area.[41]

Recently, several studies have directly or indirectly looked at the relationship between lymph node counts and the probability of finding metastases in endometrial cancer. Two retrospective reviews found that patients had improved survival when at least 10 to 12 lymph nodes were removed during lymphadenectomy.[42,43] The improved survival was likely due to stage migration (better identification of patients with stage IIIC disease).

The largest study looking at lymph node counts was a review of 11 443 endometrial cancer cases recorded in the SEER database between 1990 and 2001.[44] Of the 11 443 patients, 638 (5.6%) had positive lymph nodes. Lymph node counts were analyzed categorically as follows: up to 5 nodes, up to 10, up to 20, up to 25, and more than 25 nodes. The percentage of patients with positive nodes identified per category was 27%, 46%, 74%, 85%, and 100% respectively. A logistic regression model with a baseline category of 1 to 5 lymph nodes determined that the retrieval of 21 to 25 lymph nodes provided the greatest incremental gain in identification of positive lymph nodes (OR 1.45; 95% CI 1.08 to 1.94; $P < 0.01$). Removing more than 25 lymph nodes did not significantly increase the probability of detecting at least 1 positive node. A 2008 Italian trial randomized patients with intermediate- and high-risk endometrial cancer to either HBSO or HBSO with lymph node dissection.[7] The primary outcome was a comparison of overall survival between the 2 groups. The protocol required that at least 20 lymph nodes be removed for a lymphadenectomy to be considered adequate. Lymphadenectomies were carried out in the control arm of the study only if grossly enlarged lymph nodes were identified by palpation. Although there was no survival benefit in the lymphadenectomy arm of the study, statistically, more patients in this arm were found to have stage IIIC disease (13.3% vs. 3.2% in the HBSO group; 95% CI 5.3% to 14.9%; $P < 0.001$).

Many centres use lymph node counts as a way of ensuring adequacy of lymph node assessment. In their randomized study, Panici et al. required a count of 20 lymph nodes from the pelvis for a pelvic lymphadenectomy to be deemed adequate.[7] At the Mayo clinic, Mariani et al. found the mean lymph node count of their surgical group to be 36 for the pelvis. This number was then used to determine the adequacy of lymphadenectomies performed by individual surgeons.[34]

Lymph node counts provide a surrogate way of measuring the adequacy of a lymph node dissection but do not necessarily show that the dissection was carried out in all the relevant lymph node regions. A recent review comparing the number of lymph nodes removed with the nodal regions sampled found that the latter was more reflective of lymph node involvement.[45]

SENTINEL LYMPH NODES IN ENDOMETRIAL CANCER

The lymphatic drainage of the uterus is complex, with several anatomical areas at risk for metastases. The sentinel lymph node is defined as the first node in the lymphatic

basin that receives the lymphatic flow. If the SLN is negative for metastatic disease, other nodes are expected to be free of disease. The advantage of a sentinel node biopsy is lower morbidity than full lymphadenectomy and the potential for improved diagnostic accuracy. SLN biopsy has revolutionized treatment of breast cancer and melanoma, and its accuracy in early stage vulvar and cervical cancers has been very encouraging.[46–50]

At present, the role of SLN biopsy in endometrial cancer is less clearly defined than in breast cancer, melanoma, or early stage vulvar and cervical cancers. Optimal timing of injection, best site of injection and the most appropriate tracer material are still being actively investigated. Identifying the SLN in endometrial cancer has recently been well described, with detection rates ranging from 69% to 87%.[51–55] Oonk et al. recently reviewed studies published in English, and in the 8 trials they reviewed, detection rates were 40% to 87%.[56] There were no false negatives in any of those trials, yet there was significant heterogeneity in terms of the sites injected and tracers used. Ballester et al. have completed a prospective trial that used both blue dye and radioactive tracer injected into the cervix. At least 1 sentinel node was found in 111 of 125 patients. Nineteen of the 111 (17%) were found to have lymph node metastases. The negative predictive value and sensitivity for detecting these metastases through sentinel lymph node biopsy were 97% and 84% respectively.[57] In summary, sentinel node evaluation is a promising technique that deserves further evaluation in the management of endometrial cancers.

ADVANCED STAGE ENDOMETRIAL CANCER

The traditional approach to patients with advanced disease has been to offer palliative treatments.[58] However, more recent approaches of surgically debulking patients with advanced endometrial cancer have shown improved survival when patients are optimally debulked.[58,59] In 2006, Randall et al. demonstrated improved survival in patients with advanced disease who were optimally debulked to less than 2 cm residual disease when they subsequently received aggressive chemotherapy.[23]

SUMMARY STATEMENTS

Low-risk disease (grade 1 adenocarcinoma on biopsy)

1. In low-risk disease, there is no evidence that lymphadenectomy improves survival in grade 1 adenocarcinoma. (I)
2. Endometrial cancer requires a coordinated multi-disciplinary team approach for management. (III)
3. The purpose of lymphadenectomy is to guide adjuvant therapy that may affect survival in high-risk populations or prevent treatments that may result in unnecessary toxicity. (III)

Extent of lymph node evaluation

4. Decisions regarding adjuvant therapy in endometrial cancer are dependent on both histopathologic risk factors for recurrences post-hysterectomy and the status of retroperitoneal lymph nodes when lymphadenectomy is performed. (III)

RECOMMENDATIONS

Low-risk disease

1. Surgery may be limited to hysterectomy and bilateral salpingo-oophorectomy as an acceptable alternative to staging patients with grade 1 disease. However, relying on preoperative tumour grading will underestimate high-risk status in a proportion of patients and may subject these women to either second surgery or a more liberal use of external beam adjuvant radiation. (III-B)
2. Additional risk assessment can include preoperative or intraoperative evaluation of depth of myometrial invasion. For final histopathological stage and grade, regional multidisciplinary teams should come to consensus on the use of prognostic factors to guide adjuvant therapy. (III-B)

High-risk disease (grade 2 or 3 adenocarcinoma / clear cell / papillary serous on biopsy)

3. Consideration should be given to performing pelvic and/or para-aortic lymphadenectomies in patients with preoperative grade 2 and 3 disease to facilitate accurate planning of adjuvant therapy, which is often required postoperatively. The survival benefit of lymphadenectomy in this specific group of patients has not been studied. (II-2B)
4. Patients with high-risk histological subtypes of endometrial cancer such as clear cell and papillary serous adenocarcinomas should receive full staging surgery that includes pelvic and/or para-aortic lymphadenectomy and omentectomy. (II-2B)
5. A coordinated multidisciplinary team approach should be used for management of high-risk endometrial cancer. (III-B)
6. Regional multidisciplinary teams should come to local consensus on the use of prognostic factors to guide adjuvant therapy. (III-B)
7. Performing lymphadenectomy on the basis of palpation for "bulky" nodes is inaccurate and should not be done. (II-2E)

Advanced disease

8. Patients presenting with advanced disease should be referred to gynaecologic oncologists at a regional cancer centre for treatment planning. (II-2B)

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