Provincial Endometrium Cancer Treatment Guidelines

Approved at the Provincial Gyne-Oncology Guideline Meeting
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Clinical practice guidelines have been developed after multi-disciplinary consensus based on best available literature. As the name suggests, these are to be used as a guide only. These guidelines do not replace physician judgment which is based on multiple factors including, but not limited to, the clinical and social scenario, comorbidities, performance status, age, available resources and funding considerations. The Saskatchewan Cancer Agency disclaims all liability for the use of guidelines except as expressly permitted by the Agency. No portion of these guidelines may be copied, displayed for redistribution to third parties for commercial purposes or any non-permitted use without the prior written permission from the Agency.

Recommendations for drug treatment presented in the Agency's guidelines for a cancer site may not reflect provincial cancer drug funding. Please refer to the current Saskatchewan Cancer Agency drug formulary at www.saskcancer.ca for information on cancer drug listing and funding.

Benefits and risk of the proposed treatment should be discussed with patient.

Participating in clinical trials is encouraged when available. Involvement of a multidisciplinary team is strongly recommended.

ENDOMETRIAL CANCER

Contents:

1) Background and Epidemiology

Endometrial cancer is the second most common gynecologic cancer worldwide and the most common gynecologic cancer in Canada (1, 2). Its incidence is on the increase because of increased life expectancy, increased use of Tamoxifen, and increased rates of obesity (3). Obesity increases the risk of endometrial cancer through its effect on circulating estrogen levels. Adipose tissue can convert androgens produced either by the ovaries or by the adrenal glands into estrogen. As a result, obese women have higher levels of estrogen which in turn over stimulates the uterus (3). A woman's body mass index (BMI) can be directly linked to her risk of developing endometrial cancer. A BMI over 25 doubles the risk of cancer and a BMI over 30 triples the risk of cancer (4, 5).

Obesity rates are particularly high in the province of Saskatchewan. According to Statistics Canada 2004, the rate of obesity in Saskatchewan was 32.9% compared to 25.0% in the rest of Canada (2).

Although the prognosis of endometrial cancer is generally good, the increased rate of this Cancer has been associated with a rising death rate. For patients with low-grade early stage disease, the 5 year survival is greater than 80%. For patients with high grade and more advanced disease, the 5 year survival is much worse (6).

There are two categories of endometrial cancer (3). Type I endometrial cancer is characterized by estrogen driven low risk disease. Women with Type I endometrial cancers tend to have grade 1 disease and usually have an excellent prognosis. Risk factors for this type of cancer include use of exogenous estrogens, obesity, and polycystic ovarian syndrome. In contrast, type II endometrial cancers are more often high risk and associated with worse prognosis. This category includes grade 3 endometrial cancers as well as more rare subtypes of endometrial cancer such as clear cell and uterine papillary serous cancers (UPSC). UPSC is a particularly aggressive form of cancer where as many as 50% of women will be found to have metastatic disease at the time of diagnosis (7). Type II endometrial cancer patients often have a family history of other cancers, including colon, endometrial, and ovarian cancer. Type II endometrial cancers are not estrogen driven. Mutations in a p53 tumour suppressor gene have been shown to play a role in this type of endometrial cancer.

Endometrial cancer usually presents in menopausal and post-menopausal women. The incidence peaks at the age of 63. However, 10 to 25% of Endometrial Cancer cases occur in pre-menopausal women and 2-5% in women under the age of 40 (8, 9). Up to 25% of these younger women may have either a synchronous primary ovarian cancer or metastases to the ovaries (10).

2) Risk Factors for Endometrial Cancer

Risk factors for endometrial cancer are summarized in Table 1:

Risk Factor	Relative Risk
Unopposed estrogen replacement	2 to 10
Obesity	10 (and varies with degree of obesity)
Nulliparity	2
Late Menopause (at age over 55)	2.4
Chronic anovulation	3
Diabetes	2.8

HNPCC syndrome	Up to 50% lifetime risk
Tamoxifen use	6 to 8

Ref: 11

3) Diagnosis of Endometrial Cancer

Early detection of Endometrial Cancer is facilitated by the fact that most women will present with irregular vaginal bleeding or post-menopausal bleeding. Diagnosis is generally straight forward and can be made by either office endometrial biopsy or by operative D&C (7). Both procedures are equally effective in the diagnosis of the disease and the sensitivity for both tests is greater than 90% (12, 13).

Office endometrial biopsy has the following advantages over standard D&C:
1. Low cost for the health care system
2. No or little anesthesia needed
3. Less traumatic as it requires no or little cervical dilatation
4. Can be done at the same time as initial consultation

Office endometrial biopsy is not always obtainable in post-menopausal women owing to cervical stenosis (14). In that circumstance, the next diagnostic step is a D&C. If an office endometrial biopsy comes back negative or non-diagnostic and the patient continues to have bleeding, either the office biopsy should be repeated or another diagnostic modality employed (15).

Hysteroscopy is often combined with D&C in the workup of abnormal or post-menopausal bleeding. It may provide additional information regarding benign processes causing bleeding but it has not been shown to increase the yield for diagnosing endometrial cancer and it does increase the cost of initial diagnosis (16).

Ultrasound can help detect increased endometrial thickness which is associated with endometrial hyperplasia and cancer. However, ultrasound for endometrial thickness is not diagnostic for cancer and should not be used in place of office endometrial biopsies. In one review of women with type two endometrial cancers, only 65% had increased endometrial thickness on ultrasound (17). Furthermore, over 80% of asymptomatic women taking Tamoxifen will have increased endometrial thickness, usually caused by endometrial polyps and vacuoles rather then cancer (18).

Women should be investigated for endometrial cancer when they have post-menopausal bleeding. Women who are pre-menopausal should also be investigated for endometrial cancer if they have menorrhagia and other risk factors as listed in table 1. Women who have increased endometrial thickness without bleeding should not be investigated for endometrial cancer (19). There is no evidence to support screening for endometrial cancer among the general population. Women who test positive for the Hereditary Non-Polyposis Colon Cancer gene should undergo screening (20). This topic will be discussed in another guideline.

4) Recommendations

1. Women with post-menopausal bleeding should undergo endometrial biopsy to diagnose or rule out the presence of endometrial cancer. Office endometrial biopsy and biopsy by D&C are equally accurate.
2. Women with menorrhagia and risk factors for endometrial cancer should also undergo endometrial biopsy.

3. Ultrasound should not be used as a diagnostic tool in the evaluation of post-menopausal bleeding or menorrhagia.

5) The Role of Surgery in Endometrial Cancer

Surgery is a fundamental part of the management of endometrial cancer. A SOGC guideline on the topic of surgery in Endometrial Cancer was published as recently as April of 2013 (21). The following will provide a summary of the arguments presented in that guideline. Emphasis will be given to the situation in Saskatchewan.

There are two principle goals of surgery for endometrial cancer. The first is to remove the cancer and the second is to establish extent of disease (staging). While the former may be limited to simple hysterectomy and removal of the ovaries (HBSO), the latter is a much more involved surgery that includes pelvic washings, omental biopsy or complete omentectomy, pelvic lymph node dissection, and para-aortic dissection (21) .

In Canada there is currently no specific guideline regarding extent of surgery for endometrial cancer and patterns of practice vary across the country (22). Whereas there is agreement on the approach to patients with pre-operative high-risk disease (grade 3 and high-risk histological subtypes), there is considerable controversy regarding the surgical management of pre-operative grade 1 and even pre-operative grade 2 disease (23). Approaches to the patient with presumed low risk disease include the following:

1. HBSO and staging of all women
2. HBSO alone without staging
3. HBSO and selective staging based on additional risk factors determined either pre-operatively or intra-operatively

6) Justification for HBOS and Staging Surgery

The GOG protocol 33 published in 1987 demonstrated the need to move from clinical to surgical staging of endometrial cancer (24). In this study, 22% of patients with presumed clinical stage I disease were found to have disease outside the uterus and cervix. Pattern of spread was as follows: 12% had positive peritoneal cytology, 6% had adnexal metastases, 9% has positive pelvic lymph nodes, and 6% had positive para-aortic lymph nodes. Additional extra-uterine metastases, such as spread to omentum, were seen in 6% of patients. In addition, probability of spread was found to correlate highly with final tumour grade. This was particularly noticeable for lymph node involvement. Whereas the risk of nodal spread with grade 1 disease was only 3% for pelvic and 2% for para-aortic, the risk of nodal spread for grade 3 disease was 18% for pelvic and 11% for para-aortic.

Subsequent studies have generally supported these findings. Simply put, a pre-operative clinical exam cannot be relied upon to determine the need for full staging surgery.

Accurate tumour grading is required to determine the best course of action when a patient presents with a pre-operative diagnosis of endometrial cancer. Unfortunately, pre-operative tumour grading is not very reliable. Rates of tumour upgrading following surgery range from 15 to 30% (25-28). In a review of cases from the Saskatoon Health Region, the rate of upgrading of pre-operative grade 1 disease was 29% (29). Thus, it is possible that choosing not to perform full staging surgery on patients with pre-operative grade 1 disease will result in a substantial proportion of patients receiving sub-optimal surgery. A recent review of patients with

'preoperative' 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 (30).

7) Justification for HBSO Without Staging

The majority of patients presenting with endometrial cancer have low risk good prognosis disease (31). In these patients, the risk of finding disseminated disease is quite low. Risk of lymph node metastases is only 2.8% in patients with true (post-operatively confirmed) grade 1 endometrial cancer (22). Recent data suggests that adjuvant treatment recommendations can to a large extent influenced by factor independent of lymph node status i.e. depth of myometrial invasion, lymph vascular space involvement, cervical stromal involvement, final tumour grade, and patient age (31). Therefore, full staging of all patients with endometrial cancer is unnecessary and results in a substantial proportion of patients receiving more surgery than is required for their management (32). A recent Cochrane review of lymphadenectomy in patients with endometrial cancer demonstrated that patients who underwent staging had a substantial increase in surgical morbidity without any survival benefit derived from lymphadenectomy component of the surgery (33).

8) HBSO and Selective Staging

There are three maneuvers that can improve the prediction of the actual risk status in patients with endometrial cancer. These include pre-operative pathology review of endometrial biopsies, pre-operative MRI for determination of depth of myometrial invasion, and intra-operative determination of depth of myometrial invasion. The later can be combined with an intra-operative frozen section to determine depth of myometrial invasion and tumour grade. Formal pathology review of endometrial biopsies can help clarify risk status. Unfortunately, manpower restraints may limit the ability of centres to do perform routine reviews on all patients (34, 35).

Patients with grade 1 disease as a group only have an incidence of lymph node spread of 2.5%. However, those with grade 1 disease and deep myometrial invasion have an incidence of lymph node spread of 12% (36). Pre-operative use of MRI can accurately predict depth of myometrial invasion and can be used to triage patients between HBSO and HBSO with staging (37). A significant advantage of this approach would be that patients found to have less then 50% depth of myometrial invasion could be referred back to general gynecology for their surgery.

Prediction of depth of myometrial invasion by Intra-operative inspection has limited sensitivity. The sensitivity can improve when inspection is combined with a frozen section analysis (38-42). Several centres now manage grade 1 and grade 2 disease using intra-operative frozen section to determine depth of myometrial invasion. Those patients found to have deep myometrial invasion go on to have full staging surgery (43-46).

9) Adequacy of Staging Surgery and Lymph Node Evaluation

The primary purpose of staging surgery in any malignancy is to establish extent of disease. A popular belief is that staging surgery in of itself can improve survival. This has not been proven to be true. In fact, a recent randomized study addressing this question in women with endometrial cancer found that there was no direct survival benefit to patients who underwent lymphadenectomy versus those that did not (46). What staging surgery does provide is an accurate determination of prognosis and information that in turn guides adjuvant treatments designed to improve survival.

Lymphadenectomy is a major component of staging in endometrial cancer. To be accurate, the lymphadenectomy must remove the 'sentinel lymph nodes' or the first lymph nodes receiving lymphatic drainage from that anatomic region. Sentinel lymph node analysis has become a standard method of evaluating lymph node status in melanoma, and breast cancer. It is also proving to be accurate for staging of cervical cancer and early stage vulvar cancer (47-51). Results from initial research into sentinel lymph node mapping for endometrial cancer have been very promising (52-54).

In lieu of sentinel lymph node analysis, the accuracy of lymph node evaluation remains dependent on two factors. The first is whether or not the lymphadenectomy is removing lymph nodes from the correct lymphatic regions. The second is whether or not enough lymph nodes have been moved to capture the metastases to these sites.

Traditional thought on lymphatic spread has been that lymph node metastases occurs first to the pelvic lymph nodes and secondly to para aortic nodes (55). In the landmark GOG protocol 33, the incidence of isolated spread to para-aortic nodes was only 2%. Hence, common practice has been to only perform para-aortic node dissections only in the setting of grade 3 disease or in patients with UPSC or clear cell cancers (56). Recently there has been a shift in this approach towards including more extensive para-aortic lymph node evaluation in all patients with deep myometrial invasion and in any patients with grade 3 or high risk sub-types. This comes in part due to a review out of the Mayo clinic where Mariani et al systematically performed extensive staging on all their patients with endometrial cancer except those with grade 1 and 2 disease that had myometrial invasion ≤ 50% and tumour size ≤ 2cm (45). An adequate para-aortic dissection required removal of lymph nodes up to the renal vessels. The mean number of pelvic lymph nodes removed was 36.5 and the mean number of para-aortic nodes removed was 17.4. Twenty-two percent of patients were found to have lymph node metastases. Of these, 51% had positive nodes in both the pelvic and para-aortic nodes, 33% had only pelvic nodes positive, and 16% had only para-aortic nodes positive. Seventy-seven percent of patients with positive para-aortic nodes had involvement above the level of the IMA. Sentinel lymph node evaluation can help map sites of lymphatic spread and can help determine the need for full lymph node evaluation. Studies of sentinel lymph nodes in endometrial cancer have demonstrated that the most common site of sentinel nodes are at intra-iliac space (the bifurcation of the common iliac artery) and that isolated para-aortic sentinel nodes are rare (52, 53).

Lymph node counts have become a surrogate marker for adequacy of lymph node evaluation in other malignancies such as breast and colon cancer. The American Society of Clinical Oncology (ASCO) and Cancer Care Ontario have recommended that ≥12 lymph nodes be removed during surgical resection of colonic cancers (57). There are currently no specific guidelines on what determines an adequate lymph node evaluation in endometrial cancer. However, recent data has emerged that helps distinguish the need for full lymph node evaluation rather then lymph node sampling.

Several studies have looked at the extent of lymph node evaluation in endometrial cancer (46, 58-61). They found that there was a definite correlation between the extent of lymph node dissection and the likelihood of finding metastatic lymph nodes. They did not demonstrate a direct survival benefit from extensive lymphadenectomy. Detailed summaries of these studies are provided in in Appendix 1.

Summary

Lymph node counts do correlate with the probability of finding metastatic disease. The higher the lymph node count, the greater the probability of identifying spread of disease to these areas. It remains difficult to state exactly how many lymph nodes must be removed for a lymphadenectomy to be adequate. However, removal of less than 10 lymph nodes halves the probability of finding existing stage IIIC disease. Removal of greater than 25 lymph nodes does not substantially increase the probability of finding existing stage IIIC disease.

10) Surgical Approach: Laparoscopy versus Laparotomy

The traditional surgical approach to endometrial cancer has been via laparotomy. Over the past decades, considerable progress has been made in the use of the laparoscopic approach for all types of gynecologic surgery. A Cochrane review comparing laparoscopy with laparotomy in endometrial cancer found no difference in the risk of death from disease or recurrence between the two approaches (HR = 1.14, 95% confidence intervals: 0.62-2.10 and HR = 1.13, 95% confidence interval: 0.9 to 1.42 for overall survival and recurrence free survival respectively). Furthermore, the rate of severe post-operative events was lower in the laparoscopic approach (RR = 0.58, 95% CI: 0.37 to 0.91). Hospital stay was also notably shorter with laparoscopic surgery (62).

11) Advanced Disease

The traditional approach to patients with advanced disease has been to offer palliative treatments (63). However, more recent approaches at surgically debulking patients with advanced endometrial cancer have shown that survival improves when patients are optimally debulked (have the majority of their tumour removed) (63, 64). Recently, 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 (65).

12) Pre-Operative Investigations

There are few indications for extensive pre-operative investigation in patients with an established diagnosis of endometrial cancer. Routine investigations should include a chest X-ray to rule out obvious metastatic disease and routine labs that will establish fitness for surgery.

Pre-operative CT scan may help establish the presence of gross lymphadenopathy but should not be ordered on a routine basis. Magnetic Resonance Imaging (MRI) has been shown to help establish depth of myometrial invasion and spread to the cervix. Pre-operative knowledge of myometrial invasion can be the determinant of whether or not a patient needs full staging surgery versus HBSO. In a meta-analysis of current studies the likelihood ratios for deep myometrial invasion in patients with Grade 1, 2, and 3 endometrial cancers were 13%, 35%, and 54% pre MRI. Likelihood ratios were increased to 60%, 84%, and 92% for positive MRI results and decreased to 1%, 5%, and 10% for negative MRI results (66). The use of MRI to determine need for lymphadenectomy has been shown to be cost effective [67]. A recent review at the University of Saskatchewan found that MRI was 90% sensitive in detecting the presence of deep myometrial invasion and 93% predictive of the absence of deep myometrial invasion (68). Individual centres may wish to use pre-operative MRI as a means of deciding between these two surgical options.

13) Recommendations

1. Patients found to have endometrial caner should be reviewed centrally and referred to a gyne-oncologist for triage, discussion and review at multi-disciplinary tumour board rounds.

2. Most patients with pre-operative grade 1 disease do not require lymphadenectomy. However, pre-operative grading is unreliable. Individual centres should determine their approach to pre-operative low-risk disease.

3. Patients with pre-operative grade 2 and grade 3 disease should undergo HBSO and full staging surgery.
4. Lymph node evaluation should only be considered adequate if a minimum of ten lymph nodes are retrieved. Removal of 2 or 3 external iliac lymph nodes from either side of the pelvis is inadequate for proper decision making.

5. Surgery for endometrial cancer can be carried out by either laparotomy or laparoscopy. The latter should be encouraged because it is associated with decreased surgical morbidity.

6. Patients with advanced disease should be referred to gynecologic oncologists for debulking surgery and subsequent chemotherapy.

14) Adjuvant chemotherapy in Endometrial Cancer

Following surgery, women with endometrial cancer may be advised to have adjuvant radiotherapy, adjuvant chemotherapy, or both. The need for adjuvant treatment is determined by the post-operative risk category in which a patient is placed. Risk categories are determined according to the probability of recurrence. There are four post-operative risk categories: low risk, intermediate risk, high-intermediate risk, and high- risk. These risk categories are defined in Appendix 1.

Studies on adjuvant chemotherapy in high-risk endometrial cancer have to date been quite heterogeneous. Both the populations studied and the treatments given have varied considerably. Kupets et al recently published a summary of these studies. This SOGC guideline from 2013 concluded that the current evidence does not support the routine use of chemotherapy in women with high-risk endometrial cancer (69). However, the review did conclude that the combination of Carboplatin and Paclitaxel should become the chemotherapy protocol of choice. This is because the pooled response rates to this combination ranged from 40 to 63%. The guideline also mentioned that there are two ongoing randomized studies designed to better delineate the role of adjuvant chemotherapy in those patients who have a high risk of recurrence. One of these studies is looking at patients with high-risk stage I disease, while the other looks at patients who have presented with more advanced disease that has been optimally debulked (70,71).

The most recent Cochrane Data Base review on the topic found 5 randomized controlled studies (RCTs) comparing chemotherapy versus no additional treatment in patients who had already received both surgery and radiation. The review also included 4 RCT studies that compared cisplatin based chemotherapy to radiation after surgery for endometrial cancer (72). The pooled number of patients in these studies was 2197. The Hazard Ratio (HR) for overall survival (comparing chemotherapy to no chemotherapy) in this pooled group was 0.74 (95% CI: 0.64-0.89) and the HR for progression free survival was 0.75 95% (CI: 0.64-0.89). The absolute risk reduction gained by the addition of chemotherapy was 4% (95% CI: 1-8%). The number of

women that would need to be treated with chemotherapy in order to prevent one death (the NNT) was 25.

The studies in the Cochrane review were complex and once again heterogeneous. Some aspects of these studies are summarized in Table 2:

The Cochrane review also comments on trials that are currently underway. These trials include the GOG 249, the GOG 258, and the PORTEC III (70, 71, 79).

Table 2: Summary of studies reviewed by Cochrane 2012

Study	Design	Intervention	Population	Outcomes	Bias
NSGO-collaborative Nordic (73)	RCT	Cisplatin & doxorubicin or epirubicin	Initially stage only, then stage II and III included	HR =0.88 (95% CI: 0.63-1.23)	Changes to protocol during study
EORTC 55991 (73)	RTC	Same as NSGO	Same as NSGO	HR = 0.88 (95% CI: 0.63- 1.23)	changes to protocol during study
ManNGO (74)	RTC	doxorubicin & cisplatin versus no additional treatment	advanced stage disease, exclusively endometroid histology	HR = 0.88 (95% CI: 0.63- 1.23)	Actually is pooled results of NSGO and the EORTC 5591
Kouppola et al 2008 (75)	multi-centre RTC	'sandwich regimen of radiation and cisplatin, epirubicin, and cyclophosphamide versus radiation alone	stage IA grade 3, stage IB to IIIa all grades	HR = 0.88 (95% CI: 0.63- 1.23)	
GOG 34 (76)	RTC	Doxorubicin versus no additional treatment except XRT	Women with clinical stage I or occult stage II who after hysterectomy had 'high risk factors' for recurrence	HR = 0.88 (95% CI: 0.63- 1.23)	patients with para-aortic metastases also received para-aortic radiation
GOG 122 (65)	RTC	Doxorubicin and cisplatin for 7 cycles versus whole abdominal radiation	Stage IIIA and up, all histology types	HR = 0.68 (95% CI: 0.51 to 0.89)	Included patients with up to 2 cm of residual disease, XRT dose could be ineffective for that volume
GICOG (77)	RTC	Doxorubicin, cisplatin, & cyclophosphamide (CAP) x 5 cycles versus pelvic XRT	High risk stage IB, to II, grade 3	HR =0.88 (95% CI: 0.63-1.23)	

JGOG 2033 (78)	Multicentre Japanese RTC	CAP versus pelvic radiotherapy	Stage IB to IIIC	HR = 1.07 (95% CI: 0.66 to 1.75)	61% were stage IB, all grades included
GOG 150 (79)	Meta-analysis	Cisplatin & Ifosfamide versus whole body irradiation	Carcinosarcoma, all patients except those with hepatic disease or distant disease spread	HR = 0.79 (95% CI: 0.35 to 1.76)	44% of patients had stage III or IV

15) Recommendations

1. Adjuvant chemotherapy may be considered for both patients with high-risk stage I disease and for patients with more advanced disease. However, the number needed to treat in order to prevent 1 death from recurrence is 25 patients.

2. The chemotherapy protocol of choice is Carboplatin and Paclitaxel. Standard dosing and scheduling are as follows: Carboplatin AUC 5 or 6 and Paclitaxel 175 mg/ m^2 given every 3 weeks for 6 cycles.

3. There are currently three trials underway addressing this topic. Centres may elect to await the results of those trials prior to establishing precise policies on adjuvant chemotherapy in high-risk endometrial cancer.

16) Adjuvant Radiation Treatment for Endometrial Carcinoma

Adjuvant radiation remains an important component of managing endometrial cancer. Approximately a third of women diagnosed with endometrial cancer will receive some form of adjuvant radiation. The past decade has seen an increasing reliance on pathological risk factors to determine the need for and extent of radiation given.

Risk adjusted management is based on the patients age, and pathological factors from the surgery. The pathological factors include tumour grade, histology, depth of myometrial invasion, and presence of lympho-vascular space invasion (LVSI). They also include components of the staging surgery such as lymph node status. These criteria are used to further stratify women into high- and low-intermediate risk groups. This is a heterogeneous group of pts.

There are three basic risk categories used for determining adjuvant treatment. The Intermediate risk category can be further divided into two groups, intermediate risk and high-intermediate risk. The risk categories are summarized in Appendix 2 and the evidence for these risk categories is found in Appendix 3.

- **Low Risk** (High likelihood of being cured without adjuvant therapy): Less than 10% risk of recurrence.

- **Intermediate Risk** (Less likely to be cured by surgery alone and could possibly benefit from post-operative treatment). This group of patients has an increased risk of locoregional relapse in the presence of high risk factors, but overall they are at low risk of distant metastases.) Risk of recurrence 10-29%. NB: High intermediate risk group would have 20-30% of recurrence.

- **High Risk** (Definitely require adjuvant treatment to reduce the risk of recurrence). Greater than 30% risk of recurrence.

Role of adjuvant radiation treatment in low risk group:

Evidence for managing low risk group patients:
There is evidence that patients in this category do not require adjuvant therapy and can be managed by routine follow up. The risk of recurrence is less than 10% and in many situations, less than 5%. Traditional follow up would include a checkup q3 months for one year, then q4 months for one year and then q6months for three years. This protocol has been modified by many centres to just q6month follow up for two years.

See Appendix 4.

Role of adjuvant radiation treatment in intermediate risk group:
The recurrence risk in this group ranges between 10 – 29%. Several studies have defined a high intermediate risk group. Evidence suggests that for the standard intermediate risk group most patients only require vaginal vault radiotherapy. Adjuvant treatment of the high intermediate risk group remains controversial and continues to be researched. Some patients in this category will also be offered pelvic radiotherapy and possibly even chemotherapy. Management needs to be individualized.

See Appendix 5.

Evidence based management for high risk (endometrioid adenocarcinoma) disease management:

- Participate in clinical trial

- Systemic treatment along with Pelvic RT+/-Vault RT

Management of this group of patient remains controversial but always includes adjuvant treatments. Many patients will be offered both chemotherapy and radiotherapy. Existing trials suggest that the combination of both chemo and radiation is superior to just radiation alone. There are on-going studies to clarify this point.

Patients with extra-uterine disease:
Management recommendations would be the same as for the high risk category.

See Appendix 6.

Managing less common histologic subtypes high risk disease:

- Serous adenocarcinoma

- Carcinosarcoma

These tumours have a different more aggressive natural history. There are no large studies to guide decision making. The role of adjuvant RT is controversial. This issue has been addressed in 1 randomized and 2 retrospective analysis.

See Appendix 7

Recommendation summary for high risk sub-types:

Adjuvant treatment should be targeted towards the most probable pattern of recurrence. For example, serous tumour more likely to recur outside of the pelvis and therefore adjuvant treatment should be systemic chemotherapy. For carcinosarcoma, recurrence patterns follow both those of sarcomas and adenocarcinomas. Therefore, adjuvant treatment should include both pelvic radiotherapy and systemic chemotherapy.

- Pelvic RT for MMM
    - Age>60ys, deep myo, cervix involved, high mitotic rate, node positive, post op residual disease(micro or macro)
- Pelvic RT for LMS
    - Controversial however can be considered with micro or macroscopic residual disease in the context of a clinical trial.

Adjuvant radiation treatment recommendations:

The following table is a summary of treatment recommendations:

FIGO stage	Grade		
	I	II	III
IA	Observation	Observation or VB	VB or EBRT with or without VB
IB	VB or EBRT with or without VB	VB or EBRT with or without VB	EBRT with VB
II	EBRT with VB	EBRT with VB	EBRT with VB

- In the previous FIGO staging system (1988), stage IA tumors (limited to the endometrium) could generally be observed; however, VB was considered for grade 3
- EBRT may be omitted in a patient with an adequate negative lymph node dissection; alternatively, EBRT is generally recommended in patients in whom the lymph nodes were not addressed and poor prognosticators were present on pathology

VB: vaginal brachytherapy; **EBRT**: external-beam radiation therapy

Light blue cells low-intermediate risk, *olive cells* intermediate-high risk, *red cells* high risk

☆

Observation is also an option for patients with stage IB, LVSI negative and G I (FIGO) tumour

Referenced from the book “Decision Making in Radiation Oncology”. Author Keyur et al.

Low risk endometrial carcinoma: No adjuvant treatment
Follow –up.

Intermediate risk endometrial carcinoma:

Risk based treatment needs to be provided.

a. Pelvic radiation treatment has proven value in reducing pelvic recurrence and vaginal recurrence. This is based on evidence from well-designed randomized trials.
   Q E I and II-1. See Recommendation B below

b. Vault radiation treatment alone can be offered to this group based on the fact that there is no survival difference between patients treated with pelvic RT and vault RT alone.
   Q E I.

High risk endometrial carcinoma:

Treatment must be individualized depending on the extent of disease.
See recommendation L below

Table 1. 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.[25]

†Recommendations included in these guidelines have been adapted from the Classification of Recommendations criteria described in the Canadian Task Force on Preventive Health Care.[25]

17) References

1. Greenlee RT, Murray T, Bolden S, Wingo PA. Cancer Statistics. CA Cancer J Clin 2000; 50: 7-33.

2. Canadian Cancer Society/National Cancer Institute of Canada. Estimated age-standardized incidence rates for major cancer sites by sex and province, Canada 2005.

3. Bakkum-Gamez JN, Gonzalez-Bosquet J, lack NN, Mariani A, Dowdy SC. Current Issues in the Management of Endometrial Cancer. Mayo Clin Proc. 2008; 83: 97-112

4. Calle EE, Kaaks R. Overweight, obesity and cancer: epidemiological evidence and proposed mechanisms. Nat. Rev Cancer 2004; 4: 579-591.

5. Calle EE, Rodriguez C, Walker-Thurmond K, Thun MJ. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of US adults. N Engl J Med 2003; 348: 1625-1638.

6. Landrum LM, Moore KN, Myers TKN, Lanneau GS, McMeekin S, Walker JL, Gold MA. Stage IVB endometrial cancer: Does applying an ovarian cancer treatment paradigm result in similar outcomes? A case-control analysis. Gynecol Oncol 2009; 112: 337-341.

7. Goff BA, Kato D, Schmidt RA, Ek M, Ferry JA, Muntz HG,et al. Uterine papillary serous carcinoma: patterns of spread. Gynecol Oncol 1994; 54: 264-8.

8. Dorais J, Dodson M, Calvert J, Mize B, Travarelli JM, Jasperson K, Peterson CM, Soisson AP. Fertility-Sparing Management of Endometrial Cancer. Obstetrics and Gynecology Survey 2011; 66: 443-451

9. Renaud MC, Plante M. Medical treatment of endometrial carcinoma for the premenopausal woman wanting to preserve her ability to have children. J Obstet Gynaecol Can 2001;23 (3): 213-9.

10. Walsh C, Holschneider C, Hoang Y, Tieu K, Karlan B, Cass I. Coexisting Ovarian Malignancy in Young Women With Endometrial Cancer. Obstetrics and Gynecology 2005; 106: 693-699

11. Renaud MC, Le T, SOGC-GOC-SCC Policy and Practice Guidelines Committee. Epidemiology and Investigations for Suspected Endometrial Cancer. No. 291, Joint SOGC-GOC-SCC Clinical Practice Guideline, April 2013. J Obstet Gynaecol Can 2013l 35(4 eSuppl C): S1-S9

12. Feldman S. Evaluation of the endometrium for malignant or premalignant disease. Up To Date 2008; 16: 1-12.

13. Leitao Jr MM, Kehoe S, Barakat RR, Alektia K, Gattoc LP, Rabbitt C, Chi DS, Soslow RA, Abu-Rustrum NR. Comparison of D&C and office endometrial biopsy accuracy in patients with FIGO grade 1 endometrial adenocarcinoma. Gynecol Oncol 2009; 113: 105-8.

14. Koss LG, Schrieber K, Oberlander SG, Moukhtar M, Levine HS, Moussouris HF. Screening of asymptomatic women for endometrial cancer. Obstet Gynecol 1981; 57: 681-691.

15. Clark TJ, Mann CH, Shah N, Khan KS, Song F, Gupta JK. Accuracy of outpatient endometrial biopsy in the diagnosis of endometrial cancer: a systematic quantitative review. BJOG 2002; 109: 313-2.

16. Loffer ED. Hysteroscopy with selective endometrial sampling compared with D&C for abnormal uterine bleeding: the value of a negative hysteroscopic view. Obstet Gynecol 1989; 73: 16-20.

17. Wang J et al. Endometrial thickness in women with type II endometrial cancer Wang J et al Gynecol Oncol 101 (2006) 120-125.

18. Lahti E, Blanco G, Kauppila A, Apaja-Sarkkinen M, Taskinen PJ, Laatikainen T. Endometrial changes in postmenopausal breast cancer patients receiving Tamoxifen. Obstet Gynecol 1993; 81; 660-4.

19. Wolfman W; SOGC Clinical Practice Gynaecology Committee. Asymptomatic endometrial thickening. SOGC Clinical Practice Guideline No. 249, October 2010; 32 (10): 990-9

20. Ref: (Kwon JS, Sun CC, Peterson SK, White KG, Daniels MS, Boyd-Rogers SC, Lu KH. Cost-effectiveness Analysis of Prevention Strategies for Gynecologic Cancers in Lynch Syndrome. Cancer 2008; 113: 326-35.

21. Giede C, Le T, Power P, SOGC-GOC-SCC Policy and Practice Guidelines Committee. Epidemiology and Investigations for Suspected Endometrial Cancer. No. 291, Joint SOGC-GOC-SCC Clinical Practice Guideline. J Obstet Gynaecol Can 2013; 35(4 eSuppl A): S1-S8.

22. Kwon SJ, Carey MS, Goldie SJ. Cost-effectiveness Analysis of Treatment Strategies for Stage I and II Endometrial Cancer. J Obstet Gynaecol Can 2007; 29: 131-139.

23. Berek J, Hacker N, editors. Practical gynecologic oncology, fourth ed. Baltimore, MD. Williams and Wilkins 2005. p 403.

24. Creasman WT, Morrow CP, Bundy BN, Homesley HD, Graham JE, Heller PB. Surgical pathological spread patterns of endometrial cancer: a Gynecologic Oncology Group Study. Cancer 1987; 60: 2035-41.

25. Daniel AG, Peters WA. Accuracy of office and operating room curettage in grading of endometrial carcinoma. Obstet Gynecol 1988; 71: 612-4.

26. Obermair A, Geramou M, Gucer F, Denison U, Graf AH, Kapshammer E, et al. Endometrial cancer: accuracy of the finding of well differentiated tumour at dilatation and curettage compared to the findings at subsequent hysterectomy. Int J Gynecol Cancer 1999; 9: 383-6.

27. Frumovitz M, Singh DK, Meyer L, Smith DH, Wertheim I et al. Predictors of final histology in patients with endometrial cancer. Gynecol Oncol 2004; 95: 463-468.

28. Ben-Shachar I, Pavelka J, Cohn DE, Copeland LJ et al. Surgical staging for patients presenting with grade 1 endometrial carcinoma. Obstet Gynecol 2005; 105: 487-93.

29. Giede KC, Yen TW, Pearson RA, Chibbar R. Reliability or pre-operative grading in the operative management of endometrial cancer at the University of Saskatchewan. Abstract 2008

30. Eltabbakh GH, Shamonki J, Mount SL. Surgical stage, final grade, and survival of women with endometrial carcinoma whose preoperative endometrial biopsy shows well-differentiated tumours. Gynecol Oncol 2005; 99: 309-312.

31. Kwon JS, Carey MS, Cook EF, Qui F, Paszat L. Patterns of practice and outcomes in intermediate and high-risk stage I and II endometrial cancer: a population based study. Int J Gynecol Cancer, 17, 433-440.

32. Kwon et al Abstract. Presented at GOC annual review, Vancouver, June 2009

33. May K, Bryant A, Dickinson HO, Kehoe S, Morrison J. Lymphadenectomy for the management of endometrial cancer (Review). The Cochrane Collaboration, The Cochrane Library 2010, Issue 1

34. Leitao MM, Kehoe S, Barakat RR, Alektiar K, Leda P, Gattoe LP et al. Accuracy of preoperative endometrial sampling diagnosis of grade 1 endometrial cancer. Gynecologic Oncology 2008; 111: 244-8.

35. Kwon JS, Francis JA, Qui F, Weir MM, Entler HC. When is a pathology review indicated in endometrial cancer? Obstet Gynecol 2007; 110: 1224-30.

36. Sharma C, Deutsch I, Lewin SN, Burke WM, Qiao Y, Sun X, et al. Lymphadenectomy influences the utilization of adjuvant radiation treatment for endometrial cancer. Am J Obstet Gynecol 2011; 205: 562. E1-9.

37. Frei KA, Kinkel K, Bonel HM, Lu Y, Zaloudek C, Hricak H. Prediction of deep myometrial invasion in patients with endometrial cancer: clinical utility of contrast-enhanced MR. Radiology 2000; 76: 357-61.

38. Franchi M, Ghezzi F, Melpignano M, Chrchi PL, Scarabelli C, Appolloni C, et al. Clinical value of intraoperative gross examination in endometrial cancer. Gynecol Oncol 2000; 76: 357-61.

39. Fanning J, Tsukada Y, Piver MS. Intraoperative frozen section diagnosis of depth of myometrial invasion in endometrial adenocarcinoma. Gynecol Oncol. 1990; 37: 47-50.

40. Malviya VK, Deppe G, Malone JM, Sundareson AS, Lawrence WD. Reliability of frozen section examination in identifying poor prognostic indicators in stage I endometrial adenocarcinoma. Gynecol Oncol 1989; 34: 299-304.

41. Shim JU, Rose PG, Reale FR, Soto H, Take WK, Hunter RE. Accuracy of frozen-section diagnosis at surgery in clinical stage I and II endometrial carcinoma. Am J Obstet Gynecol 1992; 166: 1335-8.

42. Kucera E, Kainz C, Reinthaller A, Sliutz G, Leodolter S, Kucera H, et al. Accuracy of intraoperative frozen-section diagnosis in stage I endometrial adenocarcinoma. Gynecol Obstet Invest 2000; 49: 62-6.

43. Bakkum-Gamez N, Gonzalez-Bosquet J, Laack N, Mariani A, Dowdy SC. Current Issues in the Management of Endometrial Cancer Mayo Clin Proc 2008; 83: 97-112

44. Dowdy SC, Borah BJ, Bakkum-Gamez, Weaver AL, McGree ME, Haas LR, Keeney GL et al. Prospective assessment of survival, morbidity, and cost associated with lymphadenectomy in low-risk endometrial cancer. Gynecol Oncol 2012: 127: 5-10

45. Mariani A, Dowdy SC, Cliby WA, Gostout BS, Jones MB, Wilson TO, Podratz KC. Prospective assessment of lymphatic dissemination in endometrial cancer: A paradigm shift in surgical staging. Gynecol Oncol 2008; 109: 11-18.

46. Panici PB, Basile S, Maneschi F, Lissoni AA, Signorelli M, Scambia G et al. Systemic Pelvic Lymphadenectomy vs. no Lymphadenectomy in Early-Stage Endometrial Carcinoma: Randomized Clinical Trial. J Natl Cancer Inst 2008; 100: 1707-1716.

47. Moore RG, Depasquale SE, Steinhoff MM, Gajewski W, Steller M, Noto R, Falkenberry S. Sentinel node identification and the ability to detect metastatic tumour to inguinal lymph nodes in squamous cell cancer of the vulva. Gynecol Oncol 2003; 89: 475-9.

48. Hampl M, Hantschmann P, Michels W, Hillemanns P. German Study Group. Validation of the accuracy of the sentinel lymph node procedure in patients with vulvar cancer: results of a multicentre study in Germany. Gynecol Oncol 2008; 111: 282-8.

49. Hauspy J, Beiner M, Harley I, Ehrlich L, Rasty G, Covens A. Sentinel lymph node in vulvar cancer. Cancer 2007; 110: 1015-23.

50. Rob L, Strand P, Robova H, Charvat M, Pluta M, Schlegerova D, Hrehorcak M. Study of lymphatic mapping and sentinel node identification in early stage cervical cancer. Gynecol Oncol 2005; 98: 281-8.

51. Frumovitz M, Ramirez PT, Levenback CF. Lymphatic mapping and sentinel lymph node detection in women with cervical cancer. Gynecol Oncol 2008; 110; S17-20.

52. Abu-Rustum NR, Khoury-Collado F, Pandit-Tasker N, Soslow RA, Dao F, Sonoda Y, Levine DA, Brown CL, Chi DS, Barakat RR, Gemignani ML. Sentinel lymph node mapping for grade 1 endometrial cancer: is it the answer to the surgical staging dilemma? Gynecol Oncol 2009; 113: 163-9.

53. Ballester M, Dubernard G, Rouzier R, Barranger E, Darai E. Use of the sentinel node procedure to stage endometrial cancer. Ann Surg Oncol 2008; 15: 1523-9.

54. Kang S, You HJ, Hwang JH, Lim MC, Seo SS, Park SY. Sentinel lymph node biopsy in endometrial cancer: Meta-analysis of 26 studies. Gynecologic Oncology 2011; 123: 522-27.

55. Berek J, Hacker N, editors. Practical gynecologic oncology, fourth ed. Baltimore, MD. Williams and Wilkins 2005. p 404.

56. Berek J, Hacker N, editors. Practical gynecologic oncology, fourth ed. Baltimore, MD. Williams and Wilkins 2005. p 415.

57. http://www.cancercare.on.ca/common/pages/UserFile.aspx?fileId=13954

58. Chan JK, Urban R, Cheung MK, et al. Lymphadenectomy in endometroid uterine cancer staging. How many lymph nodes are enough? A study of 11 443 patients. Cancer 2007; 109: 2454-60.

59. Lutman CV, Havrilesky LJ, Cragun JM et al. Pelvic lymph node count is an important prognostic variable in patients with FIGO stage I an II endometrial carcinoma with high-risk histology. Gynecol Oncol 2006; 102: 92-7

60. Cragun JM, Havrilesky, Calingaert, Synan I, Secord AA, Soper JT, Clarke-Pearson JL, Berchuck A. Retrospective Analysis of Selective Lymphadenectomy in Apparent Early-Stage Endometrial Cancer. Journal of Clinical Oncology 2005; 23: 3668-3675.

61. Abu-Rustum NR, Lasonos A, Zhou Q, Oke E, Soslow RA et al. Is there a therapeutic impact to regional lymphadenectomy in the surgical treatment of endometrial carcinoma? American Journal of Obstetrics & Gynecology 2008; 198: 457 e1-e6.

62. Galaal K, Bryant A, Fisher AD, Al-Khaduri M, Kew F, Lopes AD. Laparoscopy versus Laparotomy for the management of early stage endometrial cancer. The Cochrane Library 2012, issue #9.

63. Landrum LM, Moore KN, Myers TKN, Lanneau GS, McMeekin S, Walker JL, Gold MA. Stage IV endometrial cancer: Does applying an ovarian cancer treatment paradigm result in similar outcomes? A case-control analysis. Gynecol Oncol 2009; 112: 337-341.

64. Bristow RE, Zerbe MJ, Rosenshein NB, Grumbine FC, Montz FJ. Stage IVB Endometrial Cancer: The Role of Cytoreductive Surgery and Determinants of Survival. Gynecol Oncol 2000; 78: 85-91.

65. Randall ME, Filiaci VL, Muss H, Spirtos NM, Mannel RS, Fowler J, Thigpen JT, Benda JA. Randomized Phase III Trial of Whole-Abdominal Irradiation Versus Doxorubicin and Cisplatin Chemotherapy in Advanced Endometrial carcinoma: A Gynecologic Oncology Group Study. J Clin Oncol 2006; 24: 36-44.

66. Frei KA, Kinkel K Bonel HM, Lu Y et al. Prediction of Deep Myometrial Invasion in Patients with Endometrial Cancer: Clinical Utility of Contrast-enhanced MR. Radiology 2000; 216: 444-449.

67. Hardesty LA, Sumkin JH, Nath ME, Edwards RP et al. Use of Preoperative MR Imaging in the Management of Endometrial Carcinoma: Cost Analysis. Radiology 2000; 215: 46-49.

68. Giede et al MRI study [abstract]

69. Kupets R, Le T, SOGC-GOC-SCC Policy and Practice Guidelines Committee. The Role of Adjuvant Therapy in Endometrial Cancer. J of Obstet and Gynaecol Can 2013; 35(4 eSuppl B): S1-S9

70. http://www.cancer.gov/clinicaltrials/ft-GOG-0249. Pelvic Radiation Therapy or Vaginal Implant Radiation Therapy, Paclitaxel, and Carboplatin in Treating Patients With High-Risk Stage I or Stage II Endometrial Cancer. http://clinicaltrials.gov/ct2/show/NCT00807768.

71. GOG 0258 (RTOG 1073 Endorsed). A Randomized Phase III Trial of Cisplatin and Tumour Volume Directed Irradiation Followed by Carboplatin and Paclitaxel vs. Carboplatin and Paclitaxel for Optimally Debulked, Advanced Endometrial Carcinoma. http://www.rtog.org/LinkClick.aspx?fileticket=7aqw-i1bTZ8%3D&tabid=331.

72. Johnson N, Bryant A, Miles T, Hogberg T, Cornes P. Adjuvant chemotherapy for endometrial cancer after hysterectomy ((Review). The Cochrane Colloboration. The Cochrane Library 2012, Issue 3.

73. Kristensen G. A randomized trial of adjuvant treatment with radiation plus chemotherapy versus radiation alone in high risk endometrial carcinoma [EORTC 55991]. http: //groups.eortc.be/gcg/studyprotocols.htm#55991. http:// groups.eortc.be/gcg/studyprotocols.htm#55991.

74. Hogberg T, Signorelli M, Freire de Oliveira C, Fossati R, Lissoni AA, Sorbe B, et al. Sequential adjuvant chemotherapy and radiotherapy in endometrial cancer - Results from two randomised studies. *European Journal of Cancer* 2010;46 (13):2422–31

75. Kuoppala T, Maenpaa J, Tomas E, Puistola U, Salmi T, Grenman S, et al. Surgically staged high-risk endometrial cancer: randomized study of adjuvant radiotherapy alone vs. sequential chemo-radiotherapy. *Gynecol Oncol* 2008; **110(2):190–5.**

76. Morrow CP, Bundy BN, Homesley HD, Creasman WT, Hornback NB, Kurman R, et al. Doxorubicin as an adjuvant following surgery and radiation therapy in patients with high-risk endometrial carcinoma, stage I and occult stage II: A Gynecologic Oncology Group Study. *Gynecologic Oncology* 1990; 36 (2): 166–71.

77. Maggi R, Lissoni A, Spina F, Melpignano M, Zola P, Favalli G, et al. Adjuvant chemotherapy vs. radiotherapy in high-risk endometrial carcinoma: results of a randomised trial. *British Journal of Cancer* 2006;95(3):266–71.

78. Susumu N, Sagae S, Udagawa Y, et al. Randomized phase III trial of pelvic radiotherapy versus cisplatin-based combined chemotherapy in patients with intermediate- and high-risk endometrial cancer: a Japanese Gynecologic Oncology Group study. Gynecol Oncol 2008;108:226-33.

79. CKTO-2006-04ISRCTN14387080, CKTO-PORTEC-3, EU-20664, NCT00411138. Phase III Randomized Study of Concurrent Chemoradiotherapy Followed By Adjuvant Chemotherapy Versus Pelvic Radiotherapy Alone in Patients With High-Risk Stage IB-III Endometrial Carcinoma Alternate Title. Chemotherapy and Radiation Therapy Compared With Radiation Therapy Alone in Treating Patients With High-Risk Stage I, Stage II, or Stage III Endometrial Cancer.

80. Keys HM, Roberts JA, Brunetto VL, et al. A phase III trial of surgery with or without adjunctive external pelvic radiation therapy in intermediate risk endometrial adenocarcinoma: a Gynecologic Oncology Group study. Gynecol Oncol 2004;92:744–51.

81. Creutzberg CL, van utten WLJ, Koper PCM, et al. Surgery and post- operative radiotherapy versus surgery alone for patients with stage-1 endometrial carcinoma: multicentre randomized trial. Lancet 2000;355:1401 – 11.

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