No. 290, April 2013

The Role of Adjuvant Therapy in Endometrial Cancer

This clinical practice guideline has been prepared by the SOGC-GOC-SCC Policy and Practice Guidelines 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.

PRINCIPAL AUTHORS

Rachel Kupets, MD, Toronto ON

Tien Le, MD, Ottawa ON

SOGC-GOC-SCC POLICY AND PRACTICE GUIDELINES COMMITTEE

Tien Le, MD (Chair), Ottawa ON

James Bentley, MB ChB, Halifax NS

Scott Farrell, MD, Halifax NS

Michel P. Fortier, MD, Quebec QC

Christopher Giede, MD, Saskatoon SK

Rachel Kupets, MD, Toronto ON

Marie Plante, MD, Quebec QC

Patti Power, MD, St. John's NL

Marie-Claude Renaud, MD, Quebec QC

Alexandra Schepansky, MD, Edmonton AB

Vyta Senikas, MD, Ottawa ON

SPECIAL CONTRIBUTORS

Janice Kwon, MD, Vancouver BC

Michel Préfontaine, MD, London ON

Isabelle Germain, MD, Quebec QC

Robert Pearcey, MD, Edmonton AB

David D'Souza, MD, London ON

Mary Senterman, MD, Ottawa ON

Paul Hoskins, MD, Vancouver BC

Disclosure statements have been received from all contributors.

The literature searches and bibliographic support for this guideline were undertaken by Becky Skidmore, Medical Research Analyst, Society of Obstetricians and Gynaecologists of Canada.

Abstract

Objective: To review the evidence relating to the use of adjuvant therapy after surgical treatment for endometrial cancer.

Options: Women with endometrial cancer can be given the option of receiving adjuvant radiotherapy and/or chemotherapy according to pathologic findings at time of surgery.

Outcomes: The outcomes measured are postoperative progression-free and overall survival in endometrial cancer patients.

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 Grey (unpublished) literature was identified through searching the websites of health technology assessment and health technology assessment-related agencies, clinical practice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.

Values: The quality of evidence was rated using the criteria described in the Report of the Canadian Task Force on Preventive Health Care (Table 1).

Benefits, harms, and costs: This guideline is intended to help standardize postoperative treatment of endometrial cancer and minimize undertreatment and overtreatment.

Validation: The guideline was reviewed for accuracy by content experts in pathology, radiation oncology, and medical oncology. Guideline content was also compared with relevant documents from the American Congress of Obstetricians and Gynecologists.

J Obstet Gynaecol Can 2013;35(4 eSuppl B):S1–S9

Key Words: Endometrial cancer, radiation therapy, chemotherapy

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]

SUMMARY STATEMENTS

Stage I Intermediate-Risk Endometrial Cancers

External beam pelvic radiotherapy

1. Pelvic radiation has been shown to reduce local recurrence in low- to intermediate-risk endometrial carcinoma. (II-1)
2. Pelvic radiation has been shown to reduce local pelvic and vaginal recurrences in intermediate- to high-risk endometrial carcinoma. (II-1)

Vaginal brachytherapy

3. Vaginal brachytherapy alone in the treatment of women with intermediate- to high-risk endometrial cancer has been shown to have outcomes in local control and overall survival that are similar to those of pelvic radiotherapy in a well-defined intermediate- to high-risk group. (I)
4. Vaginal brachytherapy has the same outcome as external beam radiotherapy with respect to overall survival in the defined intermediate- to high-risk group. (I)

Chemotherapy

5. Chemotherapy has not been well studied in stage I intermediate- to high-risk endometrial cancers. There is no strong evidence for or against chemotherapy in this population at present. The benefits of chemotherapy in addition to adjuvant radiotherapy specifically in surgically stage I patients with high-risk features are not clearly defined. (III)

Expectant Management

6. Patients in the intermediate-risk category who are managed expectantly have a higher recurrence rate than those who are treated, although there has not been a lack of survival benefit demonstrated. Patients who are managed expectantly report higher scores in quality of life studies because of less gastrointestinal toxicity. (II-3)

Advanced Stage (II to IV) Endometrial Cancer

7. Chemotherapy with cisplatin and doxorubicin or carboplatin and paclitaxel has demonstrated efficacy in advanced uterine cancer in published phase III studies. (II-2)

RECOMMENDATIONS

Stage I Low-Risk Endometrial Cancers

1. As risk for recurrent disease is low in this patient group, no further treatment should be given after definitive surgery. Regular follow-up should be performed to monitor for signs and symptoms of recurrences. (II-1B)

Advanced Stage (II to IV) Endometrial Cancer

2. Treatment of these patients should be tailored according to disease distribution and local treatment practices. (II-2C)

ABBREVIATIONS

GOG Gynecologic Oncology Group

PORTEC Postoperative Radiation Therapy for Endometrial Carcinoma

The abstract of this document was previously published in:

J Obstet Gynaecol Can 2013;35(4):375–376

INTRODUCTION

Clinically significant prognostic indicators in patients with endometrial cancer are FIGO stage, histopathologic tumour type, tumour grade, depth of myometrial invasion, extent of lymph vascular space involvement, and patient age.[1] These factors form the basis for subsequent treatment planning and follow-up.

In 2009, the FIGO staging system for endometrial carcinoma was revised. All studies discussed in this document used the 1988 staging classification. Recommendations are based on existing literature using the 1988 FIGO staging classification (Appendix 1).

Published studies have frequently categorized stage I endometrial cancer patients as low-risk, intermediate-risk, and high-risk for recurrence on the basis of surgical pathologic findings. Recommendations for adjuvant therapy are based on the estimated risk for disease recurrence.

Although the exact definition of risk for patients with stage I disease varies between studies, the ***low-risk*** group is generally defined as pathologic stage IA, grade 1 and 2 endometrioid adenocarcinoma, with no or minimal myometrial invasion. The 5-year risk of recurrence for patients in this low-risk category is between 2% and 10%.[1]

The stage I ***intermediate-risk*** group has been defined differently in various randomized trials as shown in Table 2. Generally speaking, this includes patients with grade 1 or 2 adenocarcinoma with more than 50% invasion or grade 3 tumours with superficial invasion and the presence of extensive lymph vascular space invasion in the uterine specimen. Being age 60 or over is also a risk factor. The 5-year risk of recurrence for patients in this group is as high as 20% to 25%.[1–5]

The ***high-risk*** group includes all patients with deep cervical stromal involvement or stages III and IV disease, including all aggressive histologies such as serous or clear cell.[1] Treatment options for advanced stage endometrial cancer (stage II with deep cervical stromal invasion to 4 cm) should be individualized and may include chemotherapy, radiotherapy, or a combination of both. The 5-year risk of recurrence for patients in this risk group is between 30% and 65%. The 5-year survival rate for this group is up to 58% for stage III and up to 15% for stage IV.[6–9]

TREATMENT OPTIONS FOR MANAGEMENT OF LOW-RISK STAGE I ENDOMETRIAL ADENOCARCINOMA

As risk for recurrent disease is low in this patient group, no further treatment is recommended. A regular follow-up plan should be recommended to monitor for signs and symptoms of recurrences (Appendix 2).

TREATMENT OPTIONS FOR MANAGEMENT OF STAGE I INTERMEDIATE-RISK ENDOMETRIAL ADENOCARCINOMA

Eight randomized trials have been published that address mainly treatment strategies for patients with low- and intermediate-risk uterine cancer (Table 2). Treatment options considered for low- and intermediate-risk endometrial cancer included observation alone, vaginal brachytherapy, pelvic radiation, both modalities together, chemotherapy alone, and chemotherapy and radiation therapy together.

SURVIVAL OUTCOMES FOR STAGE I INTERMEDIATE- AND HIGH-RISK ENDOMETRIAL CANCER

The summary of clinical outcomes from the randomized trials is shown in Table 3.

Available randomized trials do not indicate a survival advantage to adjuvant pelvic radiation in intermediate-risk endometrial cancer patients, staged or unstaged. Seven of the published randomized trials did not have a positive finding regarding overall survival for any of the treatment options investigated in the management of intermediate-risk uterine carcinoma.[2–5,10–12] There were significant differences, however, with respect to recurrence rates in the studies that compared pelvic radiotherapy with observation or vaginal brachytherapy, favouring the radiation arm. A recent meta-analysis and Cochrane Review determined that pelvic external beam radiotherapy reduced locoregional recurrence by 72% (RR 0.28) with an absolute risk reduction of 6%. The number needed to treat to prevent 1 locoregional recurrence is 16.7 patients. The reduction in locoregional recurrence did not reduce the risk of distant recurrence or death from endometrial cancer.[13] The study by Högberg et al.[14] included stage IA to IC grades 2 to 3, and stage II and III patients. They were randomized between pelvic radiotherapy and pelvic radiotherapy plus chemotherapy with doxorubicin and cisplatin or paclitaxel and carboplatin according to the preference of the treating physicians. The combined analysis indicated a survival benefit with a 36% reduction in the risk for relapse or death.

The major criticism of the Högberg et al. study is that it combines 2 cohorts that have heterogeneous patient populations at different disease stages, making it difficult to determine at which risk level patients benefited most from additional chemotherapy. Furthermore, the chemotherapy regimen used was chosen in a non-randomized fashion.

Table 2. Randomized studies in the adjuvant treatment of intermediate risk endometrial cancer

Author	Patients, n	Study population	Control arm	Intervention arm	Surgical treatment
Aalders et al.[4]	540	Stage I adenocarcinoma	Vaginal brachytherapy	Vaginal brachytherapy plus pelvic radiation	TAH/BSO
Creutzberg et al.[15]	715	Stage IC G1, IB, C G2 IAG3	Observation	Pelvic radiation	TAH/BSO
Keys et al.[5]	448	IB/IC/II All node negative	Observation	Pelvic radiation	TAH/BSO pelvic and aortic node dissection
Susumu et al.[11]	385	IC-IIIC Stage IC/II made up 75% of study population	Pelvic radiation	Chemotherapy with CAP	TAH/BSO pelvic and aortic node dissection
Kuoppala et al.[10]	159	IA/B G3 IC-IIIA GI,2,3	Pelvic radiation	Pelvic radiation plus 3 cycles of CAP	TAH/BSO pelvic node dissection
Blake et al.[12] ASTEC/EN5	905	IA/B G3 IC G1,2,3, serous, clear cell ± positive pelvic nodes	Observation (50% received brachytherapy)	Pelvic radiation	TAH/BSO ± pelvic node dissection
Nout et al.[2] PORTEC -2	427	Age ≥ 60 + stage IC grade I or 2 or IB grade 3 Or stage IIA any age	External beam radiotherapy	Vaginal brachytherapy	TAH/BSO
Högberg et al.[14] /NSGO-EC-9501/ EORTC-5591	540	Stage I, no residual postoperative tumour, later amendment to add occult stage II, stage IIIA (cytology) and IIIC, pelvic nodes only (237 patients)	Pelvic radiotherapy Brachytherapy optional	4 cycles of doxorubicin/cisplatin or paclitaxel/ carboplatin (MD choice) and pelvic radiation Brachytherapy optional	TAH/BSO Lymphadenectomy optional

TAH: total abdominal hysterectomy; BSO: bilateral salpingo-oopherectomy; CAP: cyclophosphamide-doxorubicin-cisplatin; ASTEC-EN5: Adjuvant external beam radiotherapy in the treatment of endometrial cancer; NSGO-EC: Nordic Society for Gynecological Oncology-Endometrial Cancer; EORTC: European Organisation for Research and Treatment of Cancer

Subgroup analyses performed in some studies have hypothesized that some high-risk categories of patients may be at increased risk of poor outcome and may benefit from adjuvant treatment, although subgroup analyses are hypothesis-generating only and should not form the basis for treatment recommendation.

The study by Aalders et al. found that a high-risk subgroup of stage I endometrial cancer patients with grade 3 disease infiltrating greater than 50% of the myometrium may benefit from adjuvant radiation. In this subgroup of patients who received pelvic radiotherapy, pelvic relapses were decreased from 20% to 4.4% with a 10% absolute survival advantage.[4]

The PORTEC study identified a high- to intermediate-risk group defined as patients over 60 years of age with stage IC, grade 1 to 2 tumours or patients with stage IB, grade 3 tumours. The rate of locoregional recurrence in this group of patients was 19% without radiotherapy, and was reduced to 5% with radiotherapy.[3] An 8-year follow-up study of PORTEC found that the majority of locoregional recurrences were located in the vagina, primarily at the vault. An 89% complete remission was obtained with treatment consisting primarily of external beam and brachytherapy treatment. The 3-year survival after vaginal relapse was 73%. The 5-year survival after vaginal relapse was 65% in the control arm compared with 43% in the radiation arm.[15] The results of the PORTEC-2 study indicate that vaginal brachytherapy had the same outcome as external beam radiotherapy regarding overall survival in the defined high- to intermediate-risk group.[2] The study also indicated that gastrointestinal toxicity was significantly reduced in the vaginal brachytherapy arm compared with the external beam radiotherapy arm of 13% versus 54%, resulting in an improved quality of life score in the vault brachytherapy arm.[16]

The GOG 99 study published by Keys et al. addressed node negative endometrial cancer treatment. This study determined that the 2-year cumulative incidence of recurrence was 12% in the no-treatment arm and 3% in the radiation arm.[5] The treatment difference was most noted in the intermediate- to high-risk group in GOG 99, which was defined as:

Table 3. Outcomes of studies in adjuvant treatment of intermediate risk endometrial cancer

Author	Local recurrence control arm, %	Local recurrence intervention arm, %	Overall survival control arm, %	Overall survival intervention arm, %
Aalders et al.[4]	6.9	1.9	91	89 (NS)
Creutzberg et al.[3]	14	4	85	81 (NS)
Keys et al.[5]	12, IHR 26	3, IHR 6	86	92 (NS)
Susumu et al.[11]			85	86 (NS)
Kuoppala et al.[10]			85	82
Blake et al.[12] ASTEC/EN5			84	84 (NS)
Nout et al.[2] PORTEC-2	1.6 vaginal recurrence 2.1 locoregional recurrence	1.8 vaginal recurrence 5.1 locoregional recurrence	79.6	84.8 (NS)
Högberg et al.[14]			72	79 HR 0.64 (95% CI 0.41 to 0.99) *P* = 0.04

NS: not significant; IHR: intermediate- to high-risk; ASTEC/EN5: Adjuvant external beam radiotherapy in the treatment of endometrial cancer

1. Patients who are age 70 or older and any ***1*** of the following risk factors:
   – Tumour grade 2 or 3
   – Outer third myometrial invasion
   – Presence of lymphovascular space involvement.
2. Patients 50 years of age or older and any ***2*** of the risk factors described above.
3. Patients of any age and all ***3*** factors described above.

The high- to intermediate-risk group had a cumulative incidence of recurrence of 26% in the no-treatment arm versus 6% in the radiation arm. Overall survival was not affected, with a 4-year survival of 86% in the observation arm versus 92% in the radiation arm ($P = 0.557$).[5]

The meta-analysis and Cochrane Review also found a trend to improved survival with the addition of radiation in patients with at least 2 risk factors (age, lymphovascular space involvement) including grade 3 and stage IC disease. A subgroup analysis that combined the results from the studies by Aalders et al.[4] and Keys et al.[5] found a trend towards reduction of death from endometrial carcinoma. The relative risk of death from endometrial cancer was 0.65 (95% CI 0.38 to 1.14, $P = 0.13$).[13]

In summary, randomized trials have not indicated a survival advantage with adjuvant pelvic radiation in the intermediate- to high-risk patient group. Subgroup analysis is suggestive of a potential overall survival benefit from locoregional radiotherapy. Vaginal brachytherapy alone in the treatment of women with intermediate- to high-risk endometrial cancer has been shown to have an outcome in local control and overall survival similar to that of pelvic radiotherapy in a well-defined intermediate- to high-risk group.

TREATMENT OPTIONS FOR ADVANCED STAGE (II TO IV)/HIGH-RISK ENDOMETRIAL CANCER

Various combinations of surgery, chemotherapy, and radiotherapy have been studied for the treatment of advanced stage or high-risk endometrial cancer in view of the relatively high likelihood of recurrences after surgery. Commonly used chemotherapeutic agents include doxorubicin, cisplatin, and paclitaxel. External beam radiotherapy and whole abdominal therapy have also been evaluated. A summary of current published randomized trials in patients with advanced stage, high-risk endometrial cancer is shown in Table 4. The corresponding survival outcomes of these randomized studies are shown in Table 5. There is no clearly identified superior treatment regimen showing significant survival advantage in patients with advanced and metastatic disease, with the exception of a single study comparing doxorubicin and cisplatin with doxorubicin and cisplatin and paclitaxel that reported a 3-month survival benefit.[18] A combination regimen of cisplatin and doxorubicin has demonstrated improved response rates. Chemotherapy appears to offer a survival benefit over whole abdominal radiation in stage III disease, although there has been some criticism of the dose of radiation used.[9]

Many centres use a multimodality treatment with chemotherapy and radiation in advanced stage disease. Clinical trial involvement should be encouraged for this group of patients.

Table 4. Randomized studies in treatment of high risk/advanced stage endometrial cancer

Author/year	Patients, n	Study population	Control arm	Intervention arm
Fleming et al.[17]	317	Advanced uterine carcinoma	Cisplatin and doxorubicin and pelvic radiation n = 157	24 hour paclitaxel and doxorubicin and GCSF and pelvic radiation n = 160
Fleming et al.[18]	263	Advanced uterine carcinoma	Doxorubicin/cisplatin	Doxorubicin/paclitaxel/ cisplatin
Thigpen et al.[8]	281	Stage III/IV; recurrent disease	Doxorubicin	Doxorubicin and cisplatin
Maggi et al.[7]	345	ICG3; IIG3 > 50% myometrial invasion; stage III	External beam pelvic radiation	Cisplatin and doxorubicin and cyclophosphamide for 5 cycles
Randall et al.[9]	422	Stage III/IV; ≤ 2 cm residual disease	Whole abdominal radiation n = 202	Doxorubicin and cisplatin n = 194
Högberg et al.[14] MaNGO ILIADE-III	157	IIB, IIIA-C Exclude serous and clear cell	Pelvic radiation	Cisplatin and doxorubicin plus pelvic radiation

GCSF: granulocyte-colony stimulating factor; MaNGO: Mario Negri Institute

TRENDS IN CHEMOTHERAPY OPTIONS FOR ADVANCED UTERINE CANCER

Because of the safety and efficacy of carboplatin and paclitaxel in the management of other gynaecologic malignancies, there is an interest in using this regimen as first-line treatment in patients with advanced endometrial cancer. Six phase II studies have been published of previously untreated patients with advanced disease with overall response rates ranging from 40% to 63%.[19–24]

The Gynecologic Oncology Group has 2 ongoing phase III studies addressing the question of first-line carboplatin and paclitaxel treatment:

1. GOG 249: Phase III study of pelvic radiation therapy versus vaginal cuff brachytherapy followed by paclitaxel and/or carboplatin chemotherapy in patients with high-risk early stage endometrial cancer.

2. GOG 258: Randomized phase III trial of cisplatin and tumour volume directed irradiation followed by carboplatin and paclitaxel versus carboplatin and paclitaxel for optimally debulked advanced endometrial cancer.

SUMMARY

Adjuvant therapy should be designed according to patient's physical status, disease stage, and surgical-pathologic findings to estimate risk of recurrence. Appropriate use of adjuvant radiotherapy and/or chemotherapy after surgery can improve local control and progression-free survival.

SUMMARY STATEMENTS

Stage I Intermediate-Risk Endometrial Cancers

External beam pelvic radiotherapy

1. Pelvic radiation has been shown to reduce local recurrence in low- to intermediate-risk endometrial carcinoma. (II-1)
2. Pelvic radiation has been shown to reduce local pelvic and vaginal recurrences in intermediate- to high-risk endometrial carcinoma. (II-1)

Vaginal brachytherapy

3. Vaginal brachytherapy alone in the treatment of women with intermediate- to high-risk endometrial cancer has been shown to have outcomes in local control and overall survival that are similar to those of pelvic radiotherapy in a well-defined intermediate- to high-risk group. (I)
4. Vaginal brachytherapy has the same outcome as external beam radiotherapy with respect to overall survival in the defined intermediate- to high-risk group. (I)

Chemotherapy

5. Chemotherapy has not been well studied in stage I intermediate- to high-risk endometrial cancers. There is no strong evidence for or against chemotherapy in this population at present. The benefits of chemotherapy in addition to adjuvant radiotherapy specifically in surgically stage I patients with high-risk features are not clearly defined. (III)

Expectant Management

6. Patients in the intermediate-risk category who are managed expectantly have a higher recurrence rate than those who are treated, although there has

Table 5. Outcomes of studies in the treatment of high risk/advanced stage endometrial cancer

Author	Survival Control Arm	Survival Intervention Arm	*P*
Fleming et al.[17]	7.2 months median PFS 12.6 months median OS	6 months median PFS 13.6 months median OS	NS
Fleming et al.[18]	12.3 months	15.3 months	< 0.05
Thigpen et al.[8]	25% response rate 3.8 months median PFS 9.2 months median OS	42% response rate 5.7 months median PFS 9.0 months median OS	0.004 NS NS
Maggi et al.[7]	78% 3 yr OS 69% 5 yr OS 62% 7 yr OS	76% 3 yr OS 66% 5 yr OS 62% 7 yr OS	 NS
Randall et al.[9]	42% 5 yr predicted survival	Stage adjusted death hazard ratio favours AP 0.68 (95% CI 0.52 to 0.89) 55% 5 yr predicted survival	< 0.01
Homesley et al.[6]	62% 3 year recurrence free	64% 3 year recurrence free subgroup analysis—50% reduction in risk of recurrence or death among people without gross residual disease	NS
Högberg et al.[14] MaNGO ILIADE-III	61%	74%	0.10 HR 0.61 (95% CI 0.33 to 1.12)

PFS: progression-free survival; OS: overall survival; MaNGO: Mario Negri Institute

not been a lack of survival benefit demonstrated. Patients who are managed expectantly report higher scores in quality of life studies because of less gastrointestinal toxicity. (II-3)

Advanced Stage (II to IV) Endometrial Cancer

7. Chemotherapy with cisplatin and doxorubicin or carboplatin and paclitaxel has demonstrated efficacy in advanced uterine cancer in published phase III studies. (II-2)

RECOMMENDATIONS

Stage I Low-Risk Endometrial Cancers

1. As risk for recurrent disease is low in this patient group, no further treatment should be given after definitive surgery. Regular follow-up should be performed to monitor for signs and symptoms of recurrences. (II-1B)

Advanced Stage (II to IV) Endometrial Cancer

2. Treatment of these patients should be tailored according to disease distribution and local treatment practices. (II-2C)

REFERENCES

1. Fakiris AJ, Randall ME. Endometrial carcinoma: the current role of adjuvant radiation. J Obstet Gynaecol 2009;29:81–9.
2. Nout RA, Smit VT, Putter H, Jürgenliemk-Schulz IM, Jobsen JJ, Lutgens LC, et al.; PORTEC Study Group. Vaginal brachytherapy versus pelvic external beam radiotherapy for patients with endometrial cancer of high-intermediate risk (PORTEC-2): an open-label, non-inferiority, randomised trial. Lancet 2010;375:816–23.
3. Creutzberg CL, van Putten WL, Koper PC, Lybeert ML, Jobsen JJ, Wárlám-Rodenhuis CC, et al. Surgery and postoperative radiotherapy versus surgery alone for patients with stage-1 endometrial carcinoma: multicentre randomised trial. PORTEC Study Group. Post Operative Radiation Therapy in Endometrial Carcinoma. Lancet 2000;355:1404–11.
4. Aalders J, Abeler V, Kolstad P, Onsrud M. Postoperative external irradiation and prognostic parameters in stage I endometrial carcinoma: clinical and histopathologic study of 540 patients. Obstet Gynecol 1980;56:419–27.
5. Keys HM, Roberts JA, Brunetto VL, Zaino RJ, Spirtos NM, Bloss JD, et al.; Gynecologic Oncology Group. 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.
6. Homesley HD, Filiaci V, Gibbons SK, Long HJ, Cella D, Spirtos NM, et al. A randomized phase III trial in advanced endometrial carcinoma of surgery and volume directed radiation followed by cisplatin and doxorubicin with or without paclitaxel: A Gynecologic Oncology Group study. Gynecol Oncol 2009;112(3):543–52.
7. 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. Br J Cancer 2006;95:266–71.
8. Thigpen JT, Brady MF, Homesley HD, Malfetano J, DuBeshter B, Burger RA, et al. Phase III trial of doxorubicin with or without cisplatin in advanced endometrial carcinoma: a gynecologic oncology group study. J Clin Oncol 2004;22:3902–8.
9. Randall ME, Filiaci VL, Muss H, Spirtos NM, Mannel RS, Fowler J, et al.; Gynecologic Oncology Group Study. 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.

10. Kuoppala T, Mäenpää 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;110:190–5.

11. Susumu N, Sagae S, Udagawa Y, Niwa K, Kuramoto H, Satoh S, et al.; Japanese Gynecologic Oncology Group. 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.

12. ASTEC/EN.5 Study Group, Blake P, Swart AM, Orton J, Kitchener H, Whelan T, Lukka H, et al. Adjuvant external beam radiotherapy in the treatment of endometrial cancer (MRC ASTEC and NCIC CTG EN.5 randomised trials): pooled trial results, systematic review, and meta-analysis. Lancet 2009;373:137–46.

13. Kong A, Johnson N, Cornes P, Simera I, Collingwood M, Williams C, et al. Adjuvant radiotherapy for stage I endometrial cancer. Cochrane Database Syst Rev 2007:CD003916.

14. Högberg T, Signorelli M, de Oliveira CF, Fossati R, Lissoni AA, Sorbe B, et al. Sequential adjuvant chemotherapy and radiotherapy in endometrial cancer—results from two randomised studies. Eur J Cancer 2010;46(13):2422–31. doi: 10.1016/j.ejca.2010.06.002.

15. Creutzberg CL, van Putten WL, Koper PC, Lybeert ML, Jobsen JJ, Wárlám-Rodenhuis CC, et al.; PORTEC Study Group. Survival after relapse in patients with endometrial cancer: results from a randomized trial. Gynecol Oncol 2003;89:201–9.

16. Nout RA, Putter H, Jürgenliemk-Schulz IM, Jobsen JJ, Lutgens LC, van der Steen-Banasik EM, et al. Quality of life after pelvic radiotherapy or vaginal brachytherapy for endometrial cancer: first results of the randomized PORTEC-2 trial. J Clin Oncol 2009;27:3547–56.

17. Fleming GF, Filiaci VL, Bentley RC, Herzog T, Sorosky J, Vaccarello L, et al. Phase III randomized trial of doxorubicin + cisplatin versus doxorubicin + 24-h paclitaxel + filgrastim in endometrial carcinoma: a Gynecologic Oncology Group study. Ann Oncol 2004;15(8):1173–8.

18. Fleming GF, Brunetto VL, Cella D, Look KY, Reid GC, Munkarah AR, et al. Phase III trial of doxorubicin plus cisplatin with or without paclitaxel plus filgrastim in advanced endometrial carcinoma: a Gynecologic Oncology Group Study. J Clin Oncol 2004;22:2159–66.

19. Price FV, Edwards RP, Kelley JL, Kunschner AJ, Hart LA. A trial of outpatient paclitaxel and carboplatin for advanced, recurrent, and histologic high-risk endometrial carcinoma: preliminary report. Semin Oncol 1997;24:S15–78-S15–82.

20. Hoskins PJ, Swenerton KD, Pike JA, Wong F, Lim P, Acquino-Parsons C, et al. Paclitaxel and carboplatin, alone or with irradiation, in advanced or recurrent endometrial cancer: a phase II study. J Clin Oncol 2001;19:4048–53.

21. Scudder SA, Liu PY, Wilczynski SP, Smith HO, Jiang C, Hallum AV 3rd, et al.; Southwest Oncology Group. Paclitaxel and carboplatin with amifostine in advanced, recurrent, or refractory endometrial adenocarcinoma: a phase II study of the Southwest Oncology Group. Gynecol Oncol 2005;96:610–5.

22. Sovak MA, Dupont J, Hensley ML, Ishill N, Gerst S, Abu-Rustum N, et al. Paclitaxel and carboplatin in the treatment of advanced or recurrent endometrial cancer: a large retrospective study. Int J Gynecol Cancer 2007;17:197–203.

23. Pectasides D, Xiros N, Papaxoinis G, Pectasides E, Sykiotis C, Koumarianou A, et al. Carboplatin and paclitaxel in advanced or metastatic endometrial cancer. Gynecol Oncol 2008;109:250–4.

24. Nomura H, Aoki D, Takahashi F, Watanabe Y, Konishi I, Jobo T, et al. Randomized phase II study comparing docetaxel plus cisplatin, docetaxel plus carboplatin, and paclitaxel plus carboplatin in patients with advanced or recurrent endometrial carcinoma: a Japanese Gynecologic Oncology Group study (JGOG2041). Ann Oncol 2011;22:636–42.

25. Woolf SH, Battista RN, Angerson GM, Logan AG, Eel W. Canadian Task Force on Preventive Health Care. New grades for recommendations from the Canadian Task Force on Preventive Health Care. CMAJ 2003;169:207–8.

APPENDIX 1. FIGO STAGING ENDOMETRIAL CARCINOMA

In 2009, the FIGO staging system was revised. The above mentioned studies were based upon the older FIGO staging system. Both staging systems are included in this paper for ease of reference.

1988 FIGO Staging Endometrial Carcinoma	
Stage Ia	Tumor limited to the endometrium
Stage Ib	Invasion to less than half of the myometrium
Stage Ic	Invasion equal to or more than half of the myometrium
Stage IIa	Endocervical glandular involvement only
Stage IIb	Cervical stromal invasion
Stage IIIa	Tumor invades the serosa of the corpus uteri and/or adnexae and/or positive cytological findings
Stage IIIb	Vaginal metastases
Stage IIIc	Metastases to pelvic and/or para-aortic lymph nodes
Stage IVa	Tumor invasion of bladder and/or bowel mucosa
Stage lVb	Distant metastases, including intraabdominal metastasis and/or inguinal lymph nodes
2009 FIGO Staging Endometrial Carcinoma	
IA	Tumour confined to the uterus, less than 50 % myometrial invasion
IB	Tumour confined to the uterus, more than 50% myometrial invasion
II	Cervical stromal invasion, but not beyond uterus
IIIA	Tumour invades serosa or adnexa
IIIB	Vaginal and/or parametrial involvement
IIIC1	Pelvic node involvement
IIIC2	Para-aortic lymph node involvement and/or pelvic lymph node involvement
IVA	Tumour invasion bladder and/or bowel mucosa
IVB	Distant metastases including abdominal metastases and/or inguinal lymph nodes

APPENDIX 2. FOLLOW-UP AFTER PRIMARY THERAPY FOR ENDOMETRIAL CANCER

Adapted from the Program in Evidence Based Care, Cancer Care Ontario, Provincial Gynecology Cancer Disease Site Group

Women who have had potentially curative treatment are divided into 2 categories:

1. Low risk of recurrence: stage IA, IB grade 1 or 2.
2. Higher risk of recurrence: Stage IA, IB grade 3, stage IC, advanced stage.

Recommendations

1. Patients should be counselled regarding signs and symptoms of potential recurrence including vaginal bleeding, discharge, detection of a mass, abdominal distension, abdominal or pelvic pain, fatigue, diarrhea, nausea and/or vomiting, persistent cough, swelling, and weight loss.
2. Patients at low risk should have a complete history taken and pelvic-rectal examination performed semi-annually or annually for the first 2 years and annually for the next 2 years.
3. Patients at high risk should have a complete history taken and pelvic-rectal examination performed every 3 to 6 months for the first 3 years and semi-annually for the next 2 years.
4. Patients should be followed by a health care professional who is knowledgeable about the natural history of the disease and who is comfortable performing a vaginal examination.
5. After 5 years of follow-up, patients can return to regular annual screening.

Follow-up with Pap smear, abdominal ultrasound, CT scan, or CA 125 is NOT recommended.