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Evidence-based Series 4-10 EDUCATION AND INFORMATION 2013

A Quality Initiative of the
Program in Evidence-based Care (PEBC), Cancer Care Ontario (CCO)

Adjuvant Radiotherapy in Women with Stage I Endometrial Cancer

Members of the Gynecology Cancer Disease Site Group

This Evidence-based Series (EBS) was reviewed in 2013 and put in the Education and Information section by the Gynecology Cancer Disease Site Group (DSG) on August 13 2013. (See Section 4: Document Summary and Review Tool for details.) The PEBC has a formal and standardized process to ensure the currency of each document (PEBC Assessment & Review Protocol).
The reviewed EBS report, which is available on the CCO web site (http://www.cancercare.on.ca), consists of the following four sections:

Section 1: Clinical Practice Guideline (EDUCATION AND INFORMATION)
Section 2: Systematic Review
Section 3: Guideline Development and External Review
Section 4: Guideline Review Summary and Tool

Release Date: August 15, 2013

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Phone: 905-527-4322 ext. 42822 Fax: 905-526-6775 E-mail: ccopgi@mcmaster.ca

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Evidence-based Series #4-10: Version 2: Section 1

Adjuvant Radiotherapy in Women with Stage I Endometrial Cancer: A Clinical Practice Guideline

H. Lukka, A. Chambers, A. Fyles, K. Thephamongkhol, L. Elit, M. Fung-Kee-Fung, J. Kwon, T. Oliver, and members of the Gynecology Cancer Disease Site Group

A Quality Initiative of the
Program in Evidence-based Care (PEBC), Cancer Care Ontario (CCO)

Report Date: March 9, 2006

Education and Information

Questions

What is the role of adjuvant radiotherapy in women with stage I endometrial cancer? Specifically, are there subgroups of patients with stage I endometrial cancer who benefit from adjuvant radiotherapy? If so, which radiotherapy treatment is recommended? Outcomes of interest are survival, pelvic control, ultimate pelvic control, and toxicity.

Target Population

Women with newly diagnosed stage I endometrial cancer who have undergone surgery, either complete surgical staging or total abdominal hysterectomy and bilateral salpingo-oophorectomy. Of interest are outcomes reported by risk of recurrence: low risk (stage IA, IB, grades 1 & 2), intermediate risk (stage IC, grades 1 & 2, or stage IA, IB, grade 3), or high risk (stage IC, grade 3).

Recommendations

There is a lack of consistent well-conducted randomized controlled trial evidence related to the clinical questions. Based on the interpretation of evidence from the available randomized data and expert consensus opinion, the Gynecology Cancer Disease Site Group recommends the following:

- Regardless of surgical staging, adjuvant external beam radiotherapy:
  - is recommended for patients at ***high risk*** of recurrence.
  - is not recommended in patients at ***low risk*** of recurrence,
  - is a reasonable treatment option for patients at ***intermediate risk*** of recurrence,

    - Two randomized trials detected that adjuvant external beam radiotherapy improved pelvic control, but not survival, when compared to no further treatment.
    - In patients with no adjuvant therapy, salvage radiotherapy may be effective upon vaginal recurrence.
    - When considering adjuvant radiotherapy, the potential improvement in pelvic control needs to be weighed against the toxicity of radiotherapy.
    - Radiotherapy was associated with a low incidence of severe acute and late adverse effects; however, many patients experienced mild (grade 1 or 2) side effects. The long-term effects of radiotherapy are unknown at this time.
- There is insufficient evidence to reliably inform the use of intracavitary radiotherapy either alone or in combination with external beam radiotherapy.
    - One randomized trial detected improvements in pelvic control with combined radiotherapy; however, that trial was published in 1980, toxicity was not well reported, and subsequent trials with similar comparisons have not been identified.
    - There were no randomized trials directly comparing external beam radiotherapy alone versus intracavitary treatment alone.
- Complete surgical staging provides additional pathological information and may help guide treatment decisions involving adjuvant therapies.
- With the potential for substantial grade changes upon pathology review, which may influence decisions regarding adjuvant radiotherapy, it may be important for each jurisdiction to establish a level of quality assurance with specific indications for pathology review. However, the extent to which quality assurance can be determined is outside of the scope of this report.

Key Evidence

- No significant differences in disease-free or overall survival were detected between treatment arms in any of the five randomized controlled trials identified in the search of the literature.
- Three trials detected significant improvements in pelvic control with the use of external beam radiotherapy (delivered either alone or in combination with intracavitary radiotherapy).
- No significant differences in distant recurrence were detected between treatment arms in any of the randomized trials.
- One trial reported that upon recurrence, salvage radiotherapy was effective for establishing pelvic control (70% survival rate at 5 years).
- As part of post hoc subgroup analyses, which should be interpreted with caution, three trials reported results according to risk of recurrence. The determination of risk of recurrence was not consistently defined across the trials; however, the magnitude of the reduction of pelvic recurrence with radiotherapy was:
    - for low-risk subgroups, an approximate 2%-5% reduction,
    - for intermediate-risk subgroups, an approximate 5%-10% reduction,
    - for high-risk subgroups, an approximate 15% reduction.

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Contact Information

For further information about this series, please contact **Dr. Michael Fung-Kee-Fung**, Chair, Gynecology Cancer Disease Site Group; Ottawa General Hospital, 501 Smyth Road, Ottawa, Ontario; Telephone: 613-737-8560, FAX: 613-737-8828

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Evidence-based Series #4-10: Section 2

Adjuvant Radiotherapy in Women with Stage I Endometrial Cancer: A Systematic Review

H. Lukka, A. Chambers, A. Fyles, K. Thephamongkhol, L. Elit, M. Fung-Kee-Fung, J. Kwon, T. Oliver, and members of the Gynecology Cancer Disease Site Group

A Quality Initiative of the
Program in Evidence-based Care (PEBC), Cancer Care Ontario (CCO)

Report Date: March 9, 2006

Education and Information

QUESTIONS

What is the role of adjuvant radiotherapy in women with stage I endometrial cancer? Specifically, are there subgroups of patients with stage I endometrial cancer who benefit from adjuvant radiotherapy? If so, which radiotherapy treatment is recommended? Outcomes of interest are survival, pelvic control, ultimate pelvic control, and toxicity.

INTRODUCTION

In 2003, an estimated 3,600 women in Canada were diagnosed with endometrial cancer, 1,400 of those women resided in Ontario (1). Survival and recurrences in women with stage I endometrial cancer vary according to the depth of invasion of the myometrium and tumour grade (2,3) (Table 1).

Women with a low risk of recurrence (grade 1 or 2, < 50% myometrial invasion) do not routinely receive adjuvant radiotherapy; the therapeutic procedure is total abdominal hysterectomy (TAH) with bilateral salpingo-oophorectomy (BSO). The risk of recurrences is low in those patients with or without surgical staging (complete surgical staging includes, in addition to TAH plus BSO, cytology examinations of peritoneal fluid and pelvic and para-aortic lymph node dissections (4). The routine treatment for women at high-risk for recurrence (grade 3, > 50% myometrial invasion) is adjuvant radiotherapy to decrease the risk of pelvic recurrence. However, there is less consensus among the gynecologic oncology community regarding the management of women at an intermediate risk of recurrence (grade 1 or 2, > 50% myometrial invasion or grade 3, < 50% myometrial invasion). Uncertainty surrounds whether radiotherapy improves survival or pelvic control sufficiently to warrant the side effects (including diarrhea, bowel obstructions, bladder volume changes, and vaginal agglutination) in women at an intermediate risk of developing a recurrence.

There are two radiotherapy modalities that have been studied in women with endometrial cancer: external beam radiotherapy (EBRT) for the prevention of pelvic and

vaginal recurrence and intracavitary radiotherapy (ICRT) for the prevention of vaginal recurrence.

The purpose of this systematic review is to identify and analyze the current literature regarding radiotherapy for women with early-stage endometrial cancer; especially those at an intermediate risk of recurrence. It is important to clarify the strengths and weaknesses in the current literature in order to inform best practice with the goal of improving patient survival, local control, or ultimate local control.

Table 1. Risk of recurrence within stage I endometrial cancer.

	Grade 1	Grade 2	Grade 3
Stage IA (limited to endometrium)			
Stage IB (<50% myometrial invasion)			
Stage IC (>50% myometrial invasion)			

Low-risk, risk of recurrence

Intermediate-risk

High-risk, risk of recurrence

METHODS

This systematic review was developed by Cancer Care Ontario's Program in Evidence-based Care (PEBC). Evidence was selected and reviewed by members of the PEBC's Gynecology Cancer Disease Site Group (DSG) and methodologists.

This systematic review is a convenient and up-to-date source of the best available evidence on the role of adjuvant radiotherapy in women with stage I endometrial cancer. The body of evidence in this review is comprised of randomized controlled trial data. That evidence forms the basis of a clinical practice guideline developed by the Gynecology Cancer DSG. The systematic review and companion practice guideline are intended to promote evidence-based practice in Ontario, Canada. The PEBC is editorially independent of Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

Literature Search Strategy

The medical literature was searched using the MEDLINE (Ovid: 1966 to November 2005), EMBASE (Ovid: 1980 to November 2005), and Cochrane Library (Issue 3, 2005) databases. In addition, the Physician Data Query clinical trials database and abstracts published in the conference proceedings from the meetings of the American Society of Clinical Oncology (1997-2005) and the American Society of Therapeutic Radiology and Oncology (1996 to 2004) were searched for reports of new or ongoing trials. The Canadian Medical Association Infobase and the National Guideline Clearinghouse databases were searched for related clinical practice guidelines. Reference lists from relevant articles and reviews were searched for additional trials.

The literature search combined disease specific terms (endometrial neoplasms/ or uterine neoplasms/ or cancer.tw. or malignan:.tw. or tumour.tw. and endometrial.ti.) with treatment specific terms (radiotherapy or adjuvant) with search specific terms for the following study designs and publication types: practice guidelines, systematic reviews, meta-analyses, and randomized controlled trials.

An author of the Post Operative Radiation Therapy in Endometrial Carcinoma (PORTEC) trial (Dr. Creutzberg) was contacted to obtain further information about the trial.

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Inclusion Criteria

Articles were selected for inclusion in the evidence series if they were randomized controlled trials comparing adjuvant radiotherapy to either no adjuvant radiotherapy or to another form of adjuvant radiotherapy in women with early stage endometrial cancer. Specifically, studies were to report data on at least one of the following outcome measures: overall survival, disease-free survival, rate of recurrence (or metastases), ultimate pelvic control, or adverse effects. Ultimate local control refers to the concept that adjuvant radiotherapy is reserved for recurrences and not given to patients at first diagnosis.

In the absence of randomized controlled trials, in order of preference, non-randomized comparative cohort studies, prospective single-cohort studies, and retrospective single-cohort studies were deemed eligible for inclusion. Practice guidelines, meta-analyses, or systematic reviews explicitly based on evidence related to the guideline question were also eligible for inclusion in the systematic review.

Exclusion Criteria

- Case reports, letters, and editorials were not considered.
- Papers published in a language other than English were not considered.

Synthesizing the Evidence

The primary outcomes of interest were survival, local control, and ultimate local control. The outcomes listed depend largely on the study population and intervention. The trials eligible for inclusion in this guideline represent different study populations and modalities of radiotherapy. As a result, the studies examining adjuvant radiotherapy in women with stage I endometrial cancer were deemed too heterogeneous to pool.

RESULTS

Literature Search Results

Five randomized controlled trials (5-9) and four systematic reviews (10-13) evaluating the role of radiotherapy in women with early stage endometrial cancer were identified and included in the review of the evidence. In one trial (6), details on trial characteristics and five-year results were previously published (14,15). For the purposes of this report, only the most recent publication will be referenced (6).

Trial Characteristics

Five randomized trials were identified in the search of the literature. Different staging systems were used by the five trials for the eligibility of patients. Of the three trials that included surgical stage I (Fédération Internationale de Gynécologie Obstétrique [FIGO] 1988) patients (5,6,9), one also included stage IIA and IIB (occult) patients (9). Of the two trials that included clinical stage I (FIGO 1971) patients (7,8), one stated the exclusion of patients with metastases after surgical exploration (7). The study by Piver et al (8), which was also reported previously in 1971 by Graham et al (16), included 3 arms: surgery alone, surgery followed by ICRT or ICRT followed by surgery. For the purposes of this evidence-based series, only the results of the surgery alone and surgery followed by ICRT groups from the most recent publication are reported. Tables 3 and 4 describe the characteristics of the five trials included in the series.

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Table 2. Eligible randomized articles and trial characteristics.

Study	Treatment	# of pts.	Surgical procedure	Staging system	Median follow-up time
GOG 99 2004 (5)	S S + EBRT	202 190	Complete surgical staging [a]	Surgical staging FIGO 1988	68 months
PORTEC 2005 (6)	S S + EBRT	354 360	TAH+BSO peritoneal cytology, biopsy lymph nodes	Surgical staging FIGO 1988	97 months 3 patients lost to follow-up[b]
Aalders 1980 (7)	S + ICRT S + ICRT+EBRT	277 263	TAH+BSO	Clinical staging FIGO 1971 (exclude metastases after surgery)	NR patients followed for 3-10 yrs, no patients were lost to follow-up
Piver 1979 (8)	S S + ICRT	53 49	TAH+BSO	Clinical staging FIGO 1971	NR patients followed for 10 yrs, no patients lost to follow-up
Garzetti 1994 (9)	S + endocrine S + EBRT	17 17	TAH+BSOPLN, PALN	Surgical staging FIGO 1988	NR patients followed for 23 months, no patients were lost to follow-up

Note: # of pts, number of patients; BSO, bilateral salpingo-oophorectomy; EBRT, external beam radiation therapy; FIGO, Fédération Internationale de Gynécologie Obstétrique GOG, Gynecologic Oncology Group; ICRT, intracavitary radiation therapy; NR, not reported; PALN, para-aortic lymphadenectomy; PLN, pelvic lymphadenectomy, PORTEC, Post Operative Radiation Therapy in Endometrial Carcinoma; S, surgery; TAH, total abdominal hysterectomy.

[a] Complete surgical staging included total abdominal hysterectomy, bilateral salpingo-oophorectomy, selective bilateral pelvic and para-aortic lymphadenectomy (removal of suspicious nodes).

[b] Based on data at five years, ten-year data were not available.

Table 3. Eligible randomized articles and trial characteristics.

Study	Treatment	# of pts.	Stage				Myometrial invasion			Grade			Risk[b]		
			IA	IB	IC	II	<50% [a]		≥50% [a]	I	II	III	Low	Intermediate	High
GOG 99 2004 (5)	S S + EBRT	202 190	NA NA	59% 58%	32% 33%	9% 10%	40% 44%	44% 38%	17% 18%	39% 46%	40% 39%	21% 15%	65% [d] 67% [d]		35% [d] 33% [d]
PORTEC 2005 (6)	S S + EBRT	354 360	NA NA	43% 39%	57% 61%	NA NA	43% 39%		57% 61%	19% 21%	70% 69%	11% 10%	32% 29%	68% 71%	NA >1%
Aalders 1980 (7)	S + ICRT S + ICRT+EBRT	277 263	100% 100%			NA NA	66%[c]		34%[c]	11%[c]	55%[c]	34%[c]	49%[c]	32%[c]	18%[c]
Piver 1979 (8)	S S + ICRT	53 49	100% 100%			NA NA	69% [e] 68% [e]		31% [e] 32% [e]	70%[c]	20%[c]	10%[c]	NR NR	NR NR	NR NR
Garzetti 1994 (9)	S + endocrine S + EBRT	17 17	86%[c]			14%[c]	60%[c]		21%[c]	63%[c]	16%[c]	21%[c]	65%[c]	28%[c]	7%[c]

Note: # of pts, number of patients; EBRT, external beam radiation therapy; GOG, Gynecologic Oncology Group; ICRT, intracavitary radiation therapy; NA, not applicable; NR, not reported; PORTEC, Post Operative Radiation Therapy in Endometrial Carcinoma; S, surgery;

[a] In one trial (9) myometrial invasion was reported as <33%, 33-66%, or >66%.

[b] Unless otherwise noted, risk data categorized according to Table 1.

[c] Data were reported for the total treatment population, and not by individual treatment arms.

[d] Patients were categorized as being low-intermediate risk or high-intermediate risk.

[e] Percentages based on 32 patients in the control arm and 38 patients in the treatment arm.

EBRT Versus No Further Treatment

Two randomized trials compared EBRT to no further treatment in women with stage I endometrial cancer (5,6). Table 6 provides a comparison of the two trials. The Gynecologic Oncology Group (GOG) 99 trial (5) reported results for 392 women who had been completely

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surgically staged, including lymphadenectomy between the years of 1987 and 1995. Patients were randomly allocated to receive 50.4 Gy of adjuvant EBRT or to no further treatment. The median follow-up was 68 months, and completeness of follow-up was more than 80%. Two of the three women in the EBRT group who had pelvic recurrences violated the study protocol by refusing radiation therapy. There were limitations of this study in terms of eligibility criteria, final data presented, and subgroup analysis. The purpose of the study was to address the role of EBRT primarily in women with "intermediate" risk endometrial cancer. The study included patients with any degree of myometrial invasion with adenocarcinoma of any grade and no evidence of lymph node involvement with stage IB, IC, IIA (occult), or IIB (occult). The "intermediate" risk patients are not directly comparable to the low-, intermediate-, and high-risk groups in non-surgically staged patients as reported in the PORTEC trial (6), though there is some overlap. While investigators estimated the risk of recurrence to be 20%-25% at five years, in reality the rate of recurrence was 11.2% after 12 years, and the results reported were "estimated at two and four years," despite enrolment between 1987 and 1995 and the study being published in 2004.

The PORTEC trial (6) randomized 714 non-completely staged women with early-stage endometrial cancer, who had undergone TAH plus BSO, peritoneal cytology, and biopsy of any suspicious lymph nodes, to receive either EBRT (46 Gy) or no further treatment. The median follow-up was 97 months, and completeness of follow-up was less than 80%. Initially, the investigators reported that 69% of the women were at intermediate risk of recurrence (i.e., stage IB, grade 3; stage IC, grade 1,2), and the rest were at low risk of recurrence. However, upon pathological review, the investigators reported that 54% of the women were at intermediate risk of recurrence, 27% were at low risk of recurrence, and 19% had unknown pathology. The results reported in this evidence series are based on the revised pathology with a review of the slides of 569 patients. The power to detect significant differences in women at intermediate risk of recurrence between groups is likely diminished with the revised results; however, it is important that the results reflect the true population of patients. The authors of the trial were also contacted in order to obtain further trial information.

Table 4. Comparison of two trials of EBRT versus no further treatment (5,6).

Comparison	GOG 99, 2004 (5)	PORTEC, 2005 (6)
Surgical staging	TAH+BSO, lymphadenectomy	TAH+BSO, biopsy of suspicious nodes
Prognostic factors for recurrence	increasing age depth of myometrial invasion (<33%, 33%-66%, >65%) histological grade presence of lymphovascular invasion	age (<60, 60-70, >70) depth of myometrial invasion (</>50%) histological grade
Definition of risk of recurrence	High intermediate-risk: 1) at least 70 years with one other risk factor; 2) at least 50 years with two other risk factors; 3) any age with all three other risk factors Low intermediate-risk: all other patients	Risk of recurrence not explicitly defined.
# of women included (by stage of disease)	Stage IB: 229 (58%) Stage IC: 126 (33%) Stage II (occult): 37 (9%) Low intermediate-risk for recurrence: 260 (66%) High intermediate-risk for recurrence: 132 (34%)	*After pathology review* Low-risk for recurrence (27%): Stage IB, grade 1: 117 (16%) Stage IB, grade 2: 81 (11%) Intermediate-risk for recurrence (54%): Stage IC, grade 1: 233 (33%) Stage IC, grade 2: 104 (15%) Stage IB, grade 3: 44 (6%)

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		Unknown: 135 (19%)
Radiation therapy dose	50.40Gy (28 fractions of 1.8Gy)	46Gy (2Gy daily fractions 5 days/week)
Median follow-up time	68 months	97 months
Protocol compliance	15 major violations (4%) EBRT group: 12 patients did not receive EBRT Control group: 2 patients received EBRT	21 major violations (3%) EBRT group: 15 patients did not receive EBRT Control group: 6 patients received EBRT

Note: BSO, bilateral salpingo oophorectomy; GOG, Gynecologic Oncology Group; PORTEC, Post Operative Radiation Therapy in Endometrial Carcinoma; TAH, total abdominal hysterectomy.

ICRT+EBRT versus ICRT Alone

In 1980, Aalders et al (7) reported results of the Norwegian Radium Institute trial in which 540 women with endometrial cancer underwent TAH plus BSO and received adjuvant vaginal radium, and then were randomly assigned to either receive external radiation (pelvic field for 4000 cGy) or no further treatment. That trial included patients with stage I disease at any risk of recurrence (low, intermediate, high) and approximately half of the patients entered into the study had intermediate or high-risk disease. Since the study was reported in 1980, with patient accrual occurring during the years of 1968 to 1974, there is concern regarding the applicability of results to current practice as radiotherapy techniques have evolved over the last 25 years.

ICRT versus No Treatment

One small trial by Pivers et al (8) compared adjuvant ICRT to no further treatment in women with endometrial cancer. The results of that trial have been published in two papers from different authors but from the same patient database in the same hospital (7,14). The trial randomized patients to three groups: preoperative ICRT, surgery alone, and adjuvant ICRT; however, for the purposes of this series, only the results from the surgery and adjuvant ICRT arms are presented. Approximately two-thirds of patients had less than 50% myometrial invasion and 70% had grade 1 disease. None of the 102 patients evaluated were lost to follow-up for 10 years. No completed data of toxicity were reported. While the two arms study of the study (surgery and adjuvant ICRT) ask an important question, the small number of patients entered into the study do not allow any definitive conclusions to be drawn. The study also used clinical staging (FIGO 1971), whereas postoperative pathological reporting of hysterectomy specimens is now used to guide treatment decisions following surgery.

EBRT versus Endocrine Treatment

Garzetti et al (9) reported the results of a small immunological study in which 34 women with endometrial cancer underwent TAH+BSO and pelvic and para-aortic lymphadenectomy and were then randomly allocated to EBRT (ranging from 1560 to 5610 cGy) or endocrine treatment. Endocrine treatment consisted of medroxyprogesterone acetate (300 mg/day orally for a week, followed by tamoxifen 30 mg/day orally for a week, consecutively for 18 months). The primary purpose of the trial was to measure immune reactivity in that population; however, some data on local control and survival were also reported. The median follow-up was 23 months, and no patients were lost to follow-up. Compliance for each treatment was not reported.

Study Quality

Important aspects of study quality were examined across the five randomized trials (Table 5). On average, the methodological quality of the larger trials was deemed to be

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adequate. Two trials were not powered to detect statistically significant differences between treatment groups nor were many aspects of study quality reported in the two trials (8,9). Two trials reported that the treatment arm had a worse prognosis than the control arm in terms of myometrial invasion (6,8); however, none of the trials reported a statistical comparison of patient characteristics at baseline. There were important differences in treatment modality, and definitions of risk categorization across the trials. Three trials reported results for subgroups of patients (5-7). None of the studies prospectively designed their subgroup analyses, and none of the subgroup analyses was powered to detect significant differences in survival or recurrence. Results were also not consistently reported for the outcomes of interest across the five trials.

In terms of treatment compliance, in the GOG 99 study (5), there were 20 (5%) compliance violations. Thirteen women in the EBRT group refused any radiation therapy, and five women received less than 90% of the prescribed EBRT dose. Two women in the control group received full-dose radiation therapy. In the PORTEC trial (6), there were 23 (6%) compliance violations in the radiation therapy group (including 15 patients who did not receive any radiation therapy) and eight (2%) compliance violations in the control group (including six patients who received radiation therapy). Other violations were due to treating patients with non-protocol radiation therapy or surgery.

Table 5. Study quality.

Author Year (Ref	# of pts.	Randomization method described	Adequacy of allocation concealment	Balance of baseline factors	Completeness of follow-up >80%	Intention-to-treat analysis [e]	Adequate power	2-sided testing
GOG 99 2004 (5)	392	Yes	NR	Yes	Yes	Yes	Yes	Yes
PORTEC 2000 (6)	714	Yes	Yes	Yes	No	Yes	Yes	Yes
Aalders 1980 (7)	540	No	NR	Yes	Yes	Yes [b]	NR	NR
Piver 1979 (8)	102	No	NR	No [a]	Yes	Yes	NR	NR
Garzetti 1994 (9)	34	No	NR	NR	Yes	Yes	NR	NR

Note: Ref, reference; NR, not reported; vs., versus.

[a] Treatment group has poorer prognostic factors than control group in terms of myometrial invasion (no invasion = 14% vs. 30%, superficial 53 % vs. 42 %, deep 24% vs. 19%); however, those differences were not reported to be statistically significant.

[b] The outcome of total number of patients for death and recurrence rate was reported but only for some patients of each risk group.

[c] Excluded one patient who refused treatment.

[d] Either reported or inferred through the number of patients available for analyses.

Outcomes

Survival and control outcomes reported in the five randomized controlled trials are presented in Table 6.

Table 6. Pelvic recurrence and distant metastases by treatment.

Author Year (Ref)	# of pts	Treatment	Follow-up point (years)	Recurrences				Disease-free survival	Overall survival
				Total # (%)		Vaginal/ Pelvic	Distant		
GOG 99 2004 (5)	202 190	S S + EBRT	5 year	31 13	**15%** **7%** **P≤0.05**	**9%** **2%** **P≤0.05**	6% 5%	NR NR	82% 84%

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PORTEC 2000 (6)	360 354	S S + EBRT	10 year	65 [c] 43 [c]	18%[c] 13%[c]	**14%[d]** **5%[d]** **P<0.001**	4%[c] 8%[c]	NR NR	73%[d] 66%[d]
Aalders 1980 (7)	277 263	S + ICRT S + ICRT +EBRT	5 year	33 32	12% 12%	**7%** **2%** **P<0.01**	5% 10%	NR NR	91% 89%
Piver 1979 (8)[a]	53 49	S S + ICRT	10 year	17 [b]	9% [b]	6% [b]	3% [b]	88% 93%	90% 93%
Garzetti 1994 (9)	17 17	S + endocrine trt. S + EBRT	<2 year	0 0	0% 0%	0% 0%	0% 0%	100% 100%	100% 100%

Note: EBRT, external beam radiation therapy; ICRT, intracavitary radiation therapy; NR, not reported; NS, not statistically significant; S, surgery.

[a] The study by Piver et al (8) included 3 arms: surgery alone, surgery followed by ICRT or ICRT followed by surgery. For the purposes of this practice guideline, where possible, only the results of the surgery alone and surgery followed by ICRT will be reported.

[b] Results were reported on the study population of 189 patients and not separately for each treatment arm.

[c] Data on the complete study population (714 patients) were provided by Dr. C. Creutzberg through personal communication.

[d] Figures are based upon revised pathology review of the slides from 569 patients.

Survival

No significant differences in overall survival were detected between any of the treatment arms of the five randomized controlled trials (5-9). Two trials reported that approximately 50% of all the deaths recorded were due to causes other than endometrial cancer (5,6). One trial (9) reported that disease-free survival and overall survival was 100% for all patients in the study; however, in that small trial, patients were followed for less than two years.

Overall* Control *(Pelvic and Distant)

The total number of recurrences ranged from 0% to 15% across the five randomized trials (5-9). One trial (5) reported a statistically significant improvement in overall control at two years with the use of EBRT when compared with no further treatment (3% versus [vs.] 12%; Relative Hazard 0 .42, p=0.007). The analysis was based upon the estimated two-year cumulative incidence of recurrence. At five years, the actual number of recurrences was 7% with EBRT and 15% for patients with no further treatment ($p \leq 0.05$). The remaining trials did not report any statistically significant differences in overall control between treatment groups (6-9).

Pelvic Control

Three trials reported significant improvements in pelvic control with adjuvant EBRT. In the GOG 99 trial (5), the incidence of recurrence was much less than the anticipated five-year recurrence rate of 20% to 25%. The five-year incidence of pelvic recurrences was 2% in the treatment arm and 9% in the control arm (relative hazard 0.42, 95% confidence interval 0.25 – 0.73, $p \leq 0.05$). In the PORTEC trial (6), at ten years, the rate of pelvic control was significantly improved when compared with patients who received no further treatment (5% vs. 14%, respectively, $p < 0.001$). Aalders et al (7) detected a significant benefit of EBRT combined with ICRT when compared with ICRT alone (1.9% vs. 6.9%, $p<0.01$). Of the two small trials, one did not report separate results between treatment arms (8), and the other reported no pelvic recurrences after 23 months of follow-up.

Distant Control

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No significant differences in distant control were detected between any of the treatment arms of the five randomized controlled trials (5-9). Rates of distant recurrence ranged from 0% to 6% for patients in the control populations, and 0% to 10% for patients in the treatment populations.

Ultimate Local Control

One trial reported data on ultimate pelvic control (6). In that trial, the authors reported that 73% of the pelvic recurrences were isolated vaginal recurrences. Of these patients, with salvage therapy, the five-year survival of patients in the control arm was 70% compared with 38% in the EBRT arm. While salvage therapy was more effective for patients that did not receive adjuvant radiotherapy, there were also more patients with a recurrence in that treatment arm.

Subgroup Analyses

Subgroup information was extracted from three of the randomized trials (5-7) (Table 7). It is important to recognize that none of the trials prospectively designed their subgroup analyses, and none of the subgroup analyses was powered to detect significant differences in survival or recurrence. The determination of risk of recurrence was not consistently defined across the trials; however, the magnitude of the reduction of pelvic recurrence with EBRT was an approximate two% five% reduction for low-risk subgroups, an approximate five% to 10% reduction for intermediate-risk subgroups, and an approximate 15% reduction for high-risk subgroups. The three studies were consistent in reporting differences in pelvic recurrences among women at intermediate to high risk of recurrence in favour of the radiation therapy group over the control group.

In the GOG 99 study (5), patients were categorized as low-intermediate risk and high-intermediate risk. The risk factors used to determine which group the women belonged to were: increasing age, moderate to poor differentiated tumour grade, presence of lymphovascular invasion, and outer-third myometrial invasion. Women in the high-intermediate group (n=132) were: 1) over 70 years old with one other risk factor, 2) over 50 years old with two other risk factors, and 3) any age with three risk factors. All other women were allocated to the low-intermediate group (n=260). Survival appeared to be similar across subgroups regardless of treatment allocation, and in terms of recurrence, 13% of the women in the high-intermediate subgroup who had received radiation therapy had recurrences compared to 29% of the women in the high-intermediate subgroup who did not receive radiation therapy. The GOG 99 study did not separate the recurrences into local and distant.

The PORTEC study (6) analyzed subgroups of women according to age (<60 years, 60-70 years, and >70 years), grade, and myometrial invasion. Patients were deemed at a higher risk of recurrence if they were at least two of the following: ≥ 60 years of age, had grade 3 disease, or ≥ 50% myometrial invasion. Of those patients at a higher risk of recurrence, 5% recurred with radiotherapy, and 23% recurred with no further treatment. When patients were categorized into low and intermediate risk of recurrence using the criteria from Table 1, there were less pelvic recurrences in patients at intermediate-risk with when compared with no further treatment (6% vs. 16%).

Aalders et al (7) reported results according to low, intermediate, and high risk of recurrence. No notable differences between treatment subgroups were reported between treatment groups with the exception of patients who were classified as high risk (grade 3, > 50% myometrial invasion). In that subgroup, 20% of the women at high risk in the control group had pelvic recurrences compared to 5% of the women at high risk in the treatment group.

For Information and Education

Table 7. Local control and survival outcome by risk of recurrence subgroups.

Study Year Ref	# of pts.	Treatment Arms	Point in time - years	Risk [a]	Recurrence			Overall survival
					Total %	Vaginal/ Pelvic	Distant	
GOG 99 2004 (5)	132 128	S S + EBRT	5 year	Low int.[b]	8% 4%	NR NR	NR NR	89% 89%
	70 62	S S + EBRT		High int.[b]	29% 13%	NR NR	NR NR	69% 74%
PORTEC [c] 2000 (6)	106 92	S S + EBRT	10 year	Low	9% 10%	7% 2%	2% 8%	81% 82%
	188 193	S S + EBRT		Int.	22% 15%	16% 6%	6% 9%	85% 82%
	66 69	S S + EBRT		Unknown	21% 9%	19% 5%	2% 4%	85% 69%
Aalders, 1980 (7)	126 131	S + ICRT S + ICRT +EBRT	5 year	Low	6% 9%	4% 2%	2% 7%	98% [d] 93% [d]
	51 32	S + ICRT S + ICRT +EBRT		Int.	14% 18%	10% 9%	4% 9%	92% [d] 87% [d]
	54 45	S + ICRT S + ICRT +EBRT		High	36% 19%	20% 5%	16% 14%	73% [d] 82% [d]

Note: Ref, reference; # of pts, number of patients; MI, myometrial invasion, int, intermediate.

[a] Risk categorized according to Table 1 unless otherwise noted.

[b] Low intermediate-risk = all other patients who are not classified as high intermediate-risk. High intermediate-risk =1) over 70 years old with one other risk factor, 2) over 50 years old with two other risk factors, and 3) any age with three risk factors. Risk factors: increasing age; moderate to poor differentiated tumour grade; presence of lymphovascular invasion; and outer third myometrial invasion.

[c] Subgroup data were provided through personal communication with C. Creutzberg for the PORTEC study (6).

[d] Cancer specific survival, the inverse of deaths from cancer.

Toxicity

The GOG 99 trial (5) reported significantly more hematologic, gastrointestinal, genitourinary, and cutaneous toxicity (all grades) in women who received EBRT compared to women in the control group ($p<0.001$). The most frequently reported grade 3 and 4 toxicities in the EBRT group were gastrointestinal (other than obstruction) (5%), gastrointestinal obstruction (3%), and cutaneous (3%). In the control group, the most frequently reported grade 3 and 4 toxicities were cardiovascular (2%), hematologic (<1%), and cutaneous (<1%).

The PORTEC trial (6) reported that 84 patients in the radiotherapy group (25%) experienced some toxicity; however, only 3% of those patients experienced grade 3 toxicity. Four patients required surgery for small bowel obstructions, and three patients underwent surgery for sigmoid resections.

Aalders et al (7) reported that three patients (2%) in the treatment arm had severe late complications; one patient died from ileal obstruction, adjuvant infection, and fistula formation, and the cause of death of another patient was not clearly defined. The third patient underwent partial bladder resection because of radiation necrosis. Two patients (2%) in the control arm had severe late complications; one patient had rectovaginal fistula, and the other had urethral stricture. Both of those patients were treated successfully. Piver et al (8) reported one rectal reaction and one rectovaginal fistula due to radiotherapy. No other details on adverse events were reported. Garzeti et al reported no significant side effects in patients treated with endocrine therapy, and three out of 17 patients (18%) had intestinal subocclusion felt to be secondary to treatment (previously treated with pelvic and para-aortic RT).

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Table 8. Toxicity data from five randomized trials.

Study	# of pts	Treatment arms	Toxicity (all grades)								# of toxic deaths
			Total adverse events		Hematologic	Gastrointestinal	Gastrointestinal obstruction	Genitourinary	Cutaneous	Fever	
			Grade 1-4	Grade 3-4							
GOG 99	202	S	14%	2%	**10%**	**7%**	8%	**8%**	**7%**	14%	0
2004 (5)	190	S+EBRT	67%	5%	**35%**[a]	**67%**[a]	12%	**30%**[a]	**32%**[a]	17%	2
PORTEC	353	S	3%	0%	NR	<1%	NR	3%	NR	NR	0
2000 (6)	338	S+EBRT	25%	3%	NR	20%	1%	8%	NR	NR	0
Aalders	277	S+ICRT	NR	NR	NR	NR	NR	1%	NR	NR	1
1980 (7)	263	S+ICRT +EBRT	NR	NR	NR	NR	NR	NR	NR	NR	2
Piver	53	S	NR	NR	NR	NR	NR	NR	NR	NR	NR
1979 (8)	49	S+ICRT	NR	NR	NR	NR	NR	4%	NR	NR	NR
Garzetti	17	S+endocrine	NR	NR	NR	NR	NR	NR	NR	NR	NR
1994 (9)	17	S+EBRT	NR	NR	NR	18%	NR	NR	NR	NR	NR

Note: EBRT, external beam radiation therapy; GI, gastrointestinal; GOG, Gynecologic Oncology Group; ICRT, intracavitary radiation therapy; NA, not applicable; NR, not reported; PORTEC, Post Operative Radiation Therapy in Endometrial Carcinoma; RT, radiation therapy; S, surgery.

[a] **Statistically significant at p< 0.05.**

Systematic Reviews

Four systematic reviews meeting the eligibility criteria were identified and included in the review of the evidence. The details of the systematic reviews are described in Table 9. A combination of randomized and non-randomized data was used to inform the conclusions of the systematic reviews, and the randomized trial data were based on the GOG 99, PORTEC, or Alders studies (5-7). Overall, the results of the systematic reviews are consistent with the present evidence series. All concluded that adjuvant radiotherapy significantly improved local control but had no impact on survival outcomes for the patient populations studied. Given the evidence from the randomized trials, the four systematic reviews were unable to reliably inform the efficacy of radiotherapy for patients at intermediate risk of recurrence.

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Table 9. Eligible systematic review articles and article characteristics.

Study	Year& database	# of RCTs	Study population	Type of intervention	Results or recommendation
Einhorn, 1996 (10)	MEDLINE 1983-1993	2	Any stages of endometrial cancer	Any treatments	Benefit of RT in grade 3, stage I-II but timing is questioned.
NHS, 1999 (11)	Searched many databases, hand searched 20 journals	2	Any gynecology cancer	Any treatments	Reduction of rate of pelvic recurrence but no benefit of survival in patients receiving RT.
Look 2002 (12)	CANCERLIT 1975-2001	3	Stage I-II endometrial cancer	Adjuvant RT following surgery	Benefit of RT in local control not survival. Maybe survival benefit in older patients, grade 3 or deep invasion.
Einhorn, 2003 (13)[a]	MEDLINE 1994-2001	2	All stages of endometrial cancer	Any treatments	Reduction of rate of pelvic recurrence but no benefit of survival in high-risk patients receiving RT.

Note: NHS, National Health Service; RCT, randomized controlled trial; RT, radiation therapy.
[a] Review is an update of the paper by Einholm et al (5).

DISCUSSION

It was anticipated that there would be difficulty drawing conclusions due to the limited number of studies, variety of comparisons, small numbers, reporting of analyses, lack of pathology review, and lack of power in subgroup analyses. With the limited data, it is important to highlight the weaknesses of the data, as well as the commonalities, to help inform treating physicians and patients about the role of adjuvant radiotherapy for patients with early-stage endometrial cancer. Only five randomized trials were available for review. Two trials compared similar adjuvant treatment (EBRT vs. no further treatment), with one of the trials including patients who were completely surgically staged and the other trial including patients who were non-surgically staged. All of the trials included a proportion of patients at a low risk of recurrence, a population not generally considered for adjuvant radiotherapy. One trial, upon pathology review, reported that a substantial number of patients were shifted from grade 2 to grade 1, and, as such, 134 patients would not have met the eligibility requirements for participation in that trial. None of the trials was designed to detect statistically significant differences in survival or in subgroup populations.

Despite the noted limitations of the available evidence, patients and clinicians are still faced with treatment decisions regarding adjuvant therapies for early-stage endometrial cancer. In three randomized trials, regardless of surgical staging, the addition of EBRT significantly improved pelvic control, but not survival, when compared with no further treatment or to ICRT alone. While not statistically comparable, the three trials were also consistent in reporting differences in pelvic recurrences among women at intermediate to high risk of recurrence in favour of the radiotherapy group over the control group. In those trials, EBRT was also associated with significant mild adverse effects, as well as a low incidence of significant acute and late adverse effects.

Ultimate pelvic control following salvage radiotherapy was reported in only one of the randomized trials. The benefit of that strategy is that if the ultimate pelvic control rates were found to be definitively equivalent, radiotherapy could be reserved to treat documented recurrences, and fewer women would be exposed to radiotherapy and its adverse effects. Patients may, however, derive a psychological benefit from adjuvant radiotherapy, especially given the significant improvements in pelvic control. While the PORTEC study reported pelvic control and survival after relapse (6), ultimate pelvic control rates according to treatment arm by risk-subgroup based on an intention to treat analyses are not readily available.

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The role of surgical staging is controversial. The advantage of surgical staging is that it selects out patients who may not need adjuvant pelvic radiotherapy (17,18). It is possible that patients with high-grade disease might be spared adjuvant treatment in the absence of metastatic nodal disease after surgical staging—they would likely have received adjuvant treatment had they not undergone surgical staging. The disadvantage of surgical staging is that there are potential risks, such as injury to nerves or blood vessels and the development of lymphocysts (5,17). Furthermore, that procedure requires the expertise of a gynecologic oncologist. Patients may have to wait or travel long distances to a tertiary care centre in order to have that procedure. Finally, there is only one prospective randomized trial that has compared surgical staging to non-surgical staging (i.e., hysterectomy with bilateral salpingo-oophorectomy, no lymphadenectomy) (19). It does not appear that surgical staging confers a survival benefit in early endometrial cancer. Therefore, the decision to offer surgical staging may require consultation with a gynecologic oncologist, and the decision may subsequently have an impact on the decision to offer adjuvant radiotherapy.

The limited information available from the five randomized trials and four systematic reviews highlights the need to conduct well-designed randomized controlled trials evaluating different interventions. Results from such studies would be extremely helpful in clarifying the role of those interventions in patients with stage I endometrial cancer. Unfortunately, no randomized trial has been published comparing adjuvant EBRT to adjuvant ICRT, although a study examining this is currently being conducted (PORTEC2). In the absence of evidence directly comparing EBRT to ICRT, it is not possible to comment on relative efficacy and toxicities of those approaches.

CONCLUSIONS

Overall, the evidence supports that, for patients at a low risk of pelvic recurrence (stage IA, IB, grades 1 & 2), recurrence rates do not warrant the use of adjuvant radiotherapy. In contrast, adjuvant radiotherapy is recommended in high-risk patients (stage IC, grade 3) because of the greater risk of pelvic recurrence. The role of adjuvant radiotherapy for patients at an intermediate risk of recurrence (stage IC, grades 1 & 2, or stage IA, IB, grade 3) requires further study. Based upon the data, however, it is a reasonable treatment option to consider pelvic EBRT in intermediate-risk patients, regardless of surgical staging, to reduce the risk of pelvic recurrence. Patients who choose adjuvant radiotherapy should be made aware of the toxicity and the lack of overall survival benefit associated with adjuvant radiotherapy. Unfortunately, the long-term effects of radiotherapy were not well reported in the randomized trials, and no information on secondary cancers or increased vascular events was reported.

At this time, pelvic EBRT would appear to be the preferred form of radiotherapy, where indicated, as supported by the evidence and because it treats pelvic (including vaginal) microscopic disease. The role of ICRT alone or the addition of ICRT to EBRT needs to be clarified through well-designed randomized controlled trials using modern radiotherapy techniques. Clinical trials are also warranted to further define the role of radiotherapy in subgroups of patients (both surgically staged and non-surgically staged).

ONGOING TRIALS

The Physician Data Query (PDQ) clinical trials database (http://www.cancer.gov/search/clinical_trials/) was searched for reports of new or ongoing trials.

Protocol ID(s)	**Title and details of trial**
CAN-NCIC-EN5	Phase III Randomized Study of Pelvic Radiation Therapy versus Control after

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	Laparoscopically-Assisted Vaginal Hysterectomy or Total Abdominal Hysterectomy in Patients with Intermediate-Risk Stage I Endometrial Cancer. Start date: September 1996. Please note that the databases for the EN5 and ASTEC trials will be combined to form one study.
MRC-ASTEC	Phase III Randomized Study of Lymphadenectomy and Adjuvant External Beam Radiation therapy in Patients with Endometrial Cancer. Start date: March 1999. Please note that the databases for the EN5 and ASTEC trials will be combined to form one study.
RTOG-9905	Phase III Randomized Study of Adjuvant Postoperative Irradiation (pelvic RT 50.4Gy; optional vaginal brachytherapy) with or without Cisplatin/Taxol Chemotherapy Following TAH/BSO for Patients with Endometrial Cancer (stage IC grade 2,3 or stage IIB). This trial was closed as of December 2003.
PORTEC-2	Phase III Randomized Study of Pelvic Radiation Therapy (46Gy) vs. Vault Brachytherapy (HDR, LDR) in Intermediate-risk Stage I Endometrial Cancer (possibly stage IB grade 3, stage IC grade 1,2). Target accrual: 200. Start date: 2002.

FUTURE RESEARCH

The role of ICRT alone or the addition of ICRT to EBRT needs to be clarified through well-designed randomized trials using modern radiotherapy techniques. Clinical trials are also warranted to further define the role of radiotherapy in subgroups of patients (both surgically staged and non-surgically staged).

CONFLICT OF INTEREST

No potential conflicts of interest were declared.

JOURNAL REFERENCE

A systematic review based on this guideline has been published in the peer-reviewed journal *Gynecologic Oncology*:

(http://www.elsevier.com/wps/find/journaldescription.cws_home/622840/description#description)

- Lukka H, Chambers A, Fyles A, Thephamongkhol K, Fung-Kee-Fung M, Elit L, et al. Adjuvant radiotherapy in women with stage I endometrial cancer: a systematic review. Gynecol Oncol. 2006 Aug;102(2):361-8. doi:10.1016/j.ygyno.2006.03.008. Epub 2006 May 2.

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For a complete list of the Gynecology Cancer DSG members and the Practice Guidelines Coordinating Committee group members, please visit the CCO Web site at http://www.cancercare.on.ca/

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Contact Information

For further information about this series, please contact **Dr. Michael Fung Kee Fung**, Chair, Gynecology Cancer Disease Site Group; Ottawa General Hospital,501 Smyth Road, Ottawa, Ontario;
Telephone: 613-737-8560, FAX: 613-737-8828

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Evidence-based Series #4-10: Section 3

Adjuvant Radiation Therapy in Women with Stage I Endometrial Cancer: Guideline Development and External Review - Methods and Results

H. Lukka, A. Chambers, A. Fyles, K. Thephamongkhol, L. Elit, M. Fung-Kee-Fung, J. Kwon, T. Oliver, and members of the Gynecology Cancer Disease Site Group

A Quality Initiative of the
Program in Evidence-based Care (PEBC), Cancer Care Ontario (CCO)

Report Date: March 9, 2006

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THE PROGRAM IN EVIDENCE-BASED CARE

The Program in Evidence-based Care (PEBC) is an initiative of the Ontario provincial cancer system, Cancer Care Ontario (CCO) (1). The PEBC mandate is to improve the lives of Ontarians affected by cancer, through the development, dissemination, implementation, and evaluation of evidence-based products designed to facilitate clinical, planning, and policy decisions about cancer care.

The PEBC supports a network of disease-specific panels, called Disease Site Groups (DSGs) and Guideline Development Groups (GDGs), mandated to develop the PEBC products. These panels are comprised of clinicians, other health care providers, methodologists, and community representatives from across the province.

The PEBC is well known for producing evidence-based practice guideline reports, using the methods of the Practice Guidelines Development Cycle (1,2). The PEBC reports consist of a comprehensive systematic review of the clinical evidence on a specific cancer care topic, an interpretation of and consensus agreement on that evidence by our DSGs and GDGs, the resulting clinical recommendations, and an external review by Ontario clinicians in the province for whom the topic is relevant. The PEBC has a formal standardized process to ensure the currency of each clinical practice guideline report, through the routine periodic review and evaluation of the scientific literature and, where appropriate, the integration of that literature with the original clinical practice guideline information.

The Evidence-based Series: A New Look to the PEBC Practice Guidelines

Each Evidence-based Series is comprised of three sections.

- *Section 1: Clinical* Practice Guideline. This section contains the clinical recommendations derived from a systematic review of the clinical and scientific literature and its interpretation by the DSG or GDG involved and a formalized external review by Ontario practitioners.
- Section 2: Systematic Review. This section presents the comprehensive systematic review of the clinical and scientific research on the topic and the conclusions reached by the DSG or GDG.
- Section 3: Guideline Development and External Review: Methods and Results. This section summarizes the guideline development process and the results of the formal external review by Ontario practitioners of the draft version of the clinical practice guideline and systematic review.

DEVELOPMENT OF THIS EVIDENCE-BASED SERIES

Development and Internal Review

This evidence-based series was developed by the Gynecology Cancer DSG of CCO's PEBC. The series is a convenient and up-to-date source of the best available evidence on the role of adjuvant radiotherapy in women with stage I endometrial cancer, developed through systematic review, evidence synthesis, and input from practitioners in Ontario.

External Review by Ontario Clinicians

Following review and discussion of sections 1 and 2 of this evidence-based series, the Gynecology Cancer DSG circulated the clinical practice guideline and systematic review to clinicians in Ontario for review and feedback. Box 1 summarizes the draft clinical recommendations and supporting evidence developed by the panel.

BOX 1:
DRAFT RECOMMENDATIONS (approved for external review October 8, 2004)

Target Population

- The recommendations apply to women newly diagnosed with early stage endometrial cancer who have undergone surgery and either complete surgical staging or total abdominal hysterectomy and bilateral salpingo-oophorectomy.

Draft Recommendations

- Adjuvant radiation therapy is not recommended in patients at low risk (stage IA, IB, grades 1 & 2) of recurrence, regardless of surgical staging.
- When considering adjuvant radiation therapy, the benefits need to be weighed against the toxicity of radiation therapy.
- Adjuvant external beam radiation therapy is a reasonable consideration for patients with stage IA and IB, grade 3 and stage IC disease, regardless of surgical staging, to manage the risk of local recurrence.
- All patients should have their pathology from surgery reviewed by an expert pathologist before a decision is made regarding adjuvant radiation therapy.
- The absence of RCTs comparing adjuvant EBRT alone to adjuvant ICRT alone prevents any comment on the efficacy and relative toxicities of these approaches.
- There is insufficient evidence to support or refute the use of ICRT in addition to pelvic EBRT in terms of survival or local control.

Qualifying Statements

- Complete surgical staging provides additional pathological information and may help

guide treatment decisions involving adjuvant therapies.

- The recommendation regarding consider adjuvant EBRT for patients with stage IA and IB, grade 3 and stage IC disease is based on the results from two RCTs that found that adjuvant pelvic EBRT improves local control compared to no treatment.

Practitioner Feedback

Based on the evidence and the draft recommendations presented above, feedback was sought from Ontario clinicians.

Methods

Practitioner feedback was obtained through a mailed survey of 47 practitioners in Ontario (18 radiation oncologists, 15 surgeons, and 14 gynecologists). The survey consisted of items evaluating the methods, results, and interpretive summary used to inform the draft recommendations and whether the draft recommendations above should be approved as a practice guideline. Written comments were invited. The practitioner feedback survey was mailed out on October 8, 2004. Follow-up reminders were sent at two weeks (post card) and four weeks (complete package mailed again). The Gynecology Cancer DSG reviewed the results of the survey.

Results

Thirteen responses were received, of the 47 surveys sent (27.7% response rate). Responses include returned completed surveys as well as phone, fax, and email responses. Of the practitioners who responded, nine indicated that the report was relevant to their clinical practice and completed the survey. Key results of the practitioner feedback survey are summarized in Table 9.

Table 9. Practitioner responses to eight items on the practitioner feedback survey.

Item	Number (%)		
	Strongly agree or agree	**Neither agree nor disagree**	**Strongly disagree or disagree**
The rationale for developing a clinical practice guideline, as stated in the "*Choice of Topic*" section of the report, is clear.	8 (88.9%)	1 (11.1%)	-
There is a need for a clinical practice guideline on this topic.	7 (87.5%)	-	1 (12.5%)
The literature search is relevant and complete.	6 (75.0%)	2 (25.0%)	-
The results of the trials described in the report are interpreted according to my understanding of the data.	7 (87.5%)	1 (12.5%)	-
The draft recommendations in this report are clear.	7 (87.5%)	1 (12.5%)	-
I agree with the draft recommendations as stated.	7 (87.5%)	1 (12.5%)	-
This report should be approved as a practice guideline.	5 (71.4%)	2 (28.6%)	-
If this report were to become a practice guideline, how likely would you be to make use of it in your own practice?	**Very likely or likely**	**Unsure**	**Not at all likely or unlikely**
	6 (85.7%)	1 (14.3%)	-

Summary of Written Comments

Three respondents (33.3%) provided written comments; two respondents requested revisions to the guideline, and one practitioner made positive comments on the utility of a guideline on this topic.

- One practitioner requested that an in-depth discussion on survival in patients at an intermediate or high risk of recurrence be added. The practitioner commented that, with

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the small number of patients available for analysis, the guideline should emphasize the lack of evidence regarding improved survival benefits in intermediate- or high-risk patients treated with adjuvant radiation.
- One practitioner commented that, in the GOG trial (9) of adjuvant ERBT versus no further treatment, the morbidity from ERBT was quite high. The practitioner questioned whether patients with total pelvic lymphadenectomies who are node negative would be better served with ICRT (which may confirm similar therapeutic results with lower morbidity).

Modifications/Actions

In response to the written comments, the following modifications/actions were taken by the DSG:

- Regardless of risk, adjuvant radiation therapy did not confer a statistically significant survival advantage for patients in any of the randomized trials. None of the studies was powered adequately to detect significant survival differences. However, two randomized trials did detect statistically and clinically significant differences in pelvic recurrence rates with EBRT. The improvement in pelvic recurrence warrants a discussion of adjuvant EBRT for patients at intermediate risk of recurrence provided the risk of recurrence includes a discussion of the benefits of EBRT as well as a discussion of toxicity. Adjuvant EBRT would be recommended for patients in the high-risk category. To address the practitioner's concerns, the recommendations were revised to improve clarity concerning the level of evidence used to inform the recommendation of the DSG.
- The gastrointestinal morbidity (≥ grade 3) of EBRT in patients who underwent nodal dissection in the GOG study was two out of 202 (1%) in the no-radiotherapy arm compared to 15 out of 190 (8%) with radiotherapy. In that study, most of the pelvic recurrences in the no-radiotherapy group were vaginal. Vaginal recurrences were 14 out of 202 (7%), and there were five out of 202 (2%) pelvic non-vaginal recurrences. ICRT has been commented to prevent vaginal recurrence with a lower morbidity, and would appear to be an attractive treatment option in the scenario where nodal dissection is performed. However, there is an absence of randomized controlled trials comparing adjuvant EBRT alone to adjuvant intracavitary treatment alone. In light of that, no definite recommendation for ICRT in this scenario can be made.

Report Approval Panel

The evidence series was circulated to the two members of the Report Approval Panel and the Guidelines Coordinator of the PEBC. Feedback was provided by the Panel and the Coordinator and is summarized below. The feedback was reviewed by the Gynecology Cancer DSG and modifications were made to the series in response (see modifications below).

Summary of Written Comments with Modifications/Actions Taken by the Gynecology Cancer DSG

- The wording of the first two recommendations was found to be confusing, and it was requested that they be revised to improve clarity. It was also suggested that the qualifying statement regarding the value of surgical staging may warrant a recommendation unto itself.
  - *The recommendations were revised and reorganized to improve clarity. The recommendations were also clearly linked to the available evidence used to inform the Gynecology Cancer DSG.*
- It was suggested, but not required, that the evidence be presented according to the questions and recommendations rather than by study.
  - *To improve clarity, evidence was reorganized by outcome.*

Education and Information

- The concept and importance of ultimate control was not well explained in the document.
  - *A section on ultimate control was added to the Results section.*
- There was confusion around the PORTEC study with the reporting of published and unpublished data, the statistical calculations of the unpublished data by the Gynecology Cancer DSG, and the reporting of different values in the text and in the tables.
  - *All data, especially evidence from the PORTEC trial, was re-examined and reported in a consistent manner throughout the text.*
- It was suggested that all of the subgroup data be reported in a separate section that clearly indicates all of the data that was based upon subgroup populations.
  - *The reporting of subgroup analyses and unpublished data was reduced substantively and was reported in a separate section.*
- The table of subgroup results was confusing, and the results do not seem to be consistent with the overall results presented in the previous table. It is also unclear why the level of detail and calculations were provided for patients at intermediate risk and not for the patients at low risk. Given the importance of the PORTEC trial, it was suggested that the methods and reporting be re-analyzed and reported in a consistent manner.
  - *Tables and text were reviewed for accuracy and were re-formatted in an effort to improve clarity and consistency.*
- In the Discussion section, under the first question, the GOC trial was not included and was reported in a separate section. Given that both speak to the issue, it would be helpful to integrate that study into the discussion.
  - *The discussion section was revised with evidence integrated by outcomes rather than by trial.*
- The recommendations are principally derived from three trials. Two trials (Piver and Garzelli) have sample sizes that are insufficient to detect important differences. As pooling of data has not been performed (and thus the ability of these trials to provide additive benefit is not possible), those trials do not add meaningful contributions to the analysis of the problem. Rather than detailing those trials, the authors should consider simply stating that the trials were underpowered.
  - *While there was very little emphasis placed on the two smaller trials, the trials were included in an effort to be thorough and to help inform the role of adjuvant radiotherapy in this patient population.*
- Of related importance is the statement on page 12 that ICRT was associated with a 'non statistically associated benefit of…'. It is more correct to indicate that a 'benefit could not be detected'.
  - *The statement was revised to improve clarity.*
- As one reads through the Guideline, it becomes apparent that the well-written conclusions of the abstract are moreso informed by evidence than directly based on the evidence. The DSG has then done substantial interpretation in order to reach their conclusions that therapy should be based on histologic/stage risk stratification. This process leading to these recommendations should be more explicitly stated. Examples of where the DSG has not adequately indicated that their conclusions are based on substantial interpretation, rather than directly form evidence, include:
  - *Results by histologic/stage risk group do not appear to have been reported in the GOG study.*
  - *Only two of the trials reported the histologic/stage risk group baseline features of the randomized groups.*
  - *Additional results are reported for risk subgroups that take into account factors other than histology and stage. For one of the trials, those data have not been reported but instead obtained as unpublished data. This makes for very complicated reporting.*

Education Not Information

- *The trials did not prospectively identify histologic/staging risk subgroups for their analyses. The document does not state whether the randomization process of any of the trials was stratified by histology/stage.*
- *The determination of histology/stage risk categorization appears to be associated with substantial observer variation (perhaps based on expertise, as suggested by the DSG). The degree of uncertainty expressed calls into question the feasibility of using histologic/stage stratification for treatment planning.*

Overall, the limitations described above are not to refute the DSG's attempt to justify treatment recommendations based on histologic/stage risk categorization but rather to indicate that there is a need to be more explicit about how these recommendations were derived.

- *Statements were added to the recommendations, clarifying the level of evidence used to inform the conclusions derived by the Gynecology Cancer DSG.*

- With respect to ICRT, the DSG needs to give good reason why it is not concluding that there are insufficient data to justify this therapy, as opposed to stating 'justify or refute'. According to their interpretation that reducing pelvic recurrences is a policy-determining outcome measure, one of the trials failed to detect a difference in that outcome (the trial was underpowered) and the second trial (Alders) was not designed to test that intervention; instead it was designed to test the addition of EBRT to ICRT versus ICRT alone (note that the nature of that trial is misstated on page 3 of the abstract, bullet number ii). In that comparison, EBRT was associated with a superior outcome with respect to pelvic recurrences. As there is a 'default position' that EBRT is efficacious with respect to that outcome measure, the data appear to warrant a statement that the evidence is 'insufficient' to support use of ICRT at this time. Is the DSG not stating this because of data of some other type (Phase II?) that moderate their conclusions?
  - *The recommendation was revised to reflect that there was insufficient evidence in which to inform a recommendation. Two supporting bullet points were also added, detailing why there was insufficient evidence to inform the role of ICRT.*
- The justification for not pooling the results of the GOG and PORTEC studies appears inadequate. The trials appear to be well done and have assessed similar populations and similar interventions, and both had as their primary analysis the results of all patients (not subsets). This appears to be an ideal opportunity to pool data.
  - *While there are important subtle differences between the data from the GOG 99 and PORTEC studies, pooling data would be feasible; however, the authors felt that adding pooled data for recurrence or survival would do little to inform the clinical questions, especially with regard to patients at an intermediate risk of recurrence.*
- The reporting of the systematic reviews raises questions for the reader regarding what studies were included. It appears that all would fail to include the GOG study, and potentially only 2 would include the PORTEC study. The low reliance placed on those reviews by the DSG appears reasonable, but the specifics of these reasons are understated.
  - *Further detail of the evidence used to inform the results of the systematic reviews was added to the Outcomes section.*
- The document would benefit from a more explicit statement regarding how clinicians should value the outcome measure of freedom from pelvic recurrence versus overall survival. While the details of that balance may be well known to experts, a brief synopsis of that balance may be beneficial for others who will read this document.
  - *A statement regarding the trade off between greater pelvic control but less effective salvage resulting in similar survival outcomes was added to the Discussion.*

Education and Information

- In summary, EBRT reduces pelvic recurrences but does not appear to affect overall survival, and most patients appear to die from other causes. That situation invites some statement of the longer term risks (late effects) of radiation therapy. In addition, it would be worthwhile to comment whether there are secondary cancers or vascular (aorto-femoral) risks to EBRT?
    - *Unfortunately, the long-terms effects of radiotherapy were not well reported in the randomized trial,s and no information on secondary cancers or increased vascular events was reported. A comment to that effect was added to the Conclusions.*
- The use of the term 'salvage' therapy should be reconsidered. Other terms such as 'subsequent' or 'subsequent-line' therapy are preferred.
    - *Because the term `salvage' is the common phraseology for the treatment of patients who recur, to avoid confusion, it was felt that the use of the term was appropriate.*
- The DSG appears to have been overly critical in Table 5, where they indicate by point 'd' that there is an imbalance in a baseline characteristic of the two randomized groups.
    - The authors agree that a difference of 4% in depth of myometrial invasion between treatment arms does not constitute a concern when comparing patient baseline characteristics. The table was revised to indicate that baseline characteristics were similar between treatment groups.

Through the Practitioner Feedback and Report Approval Panel process, there have been significant modifications to the draft evidence series. The Gynecology Cancer DSG believes that the current iteration satisfies the criterion for internal PEBC approval and is appropriate for publication in a peer-reviewed journal.

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Contact Information

For further information about this series, please contact **Dr. Michael Fung-Kee-Fung**, Chair, Gynecology Cancer Disease Site Group; Ottawa General Hospital,501 Smyth Road, Ottawa, Ontario;
Telephone: 613-737-8560, FAX: 613-737-8828

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Phone: 905-525-9140, ext. 22055 Fax: 905-522-7681

Education and Information

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Education and Information

Ontario
Cancer Care Ontario
Action Cancer Ontario

Evidence-based Series 4-10 Version 2: Section 4

A Quality Initiative of the
Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

Adjuvant Radiotherapy in Women with Stage I Endometrial Cancer

Guideline Summary Review

A. Fyles, C. Agbassi and Members of the Gynecology Cancer Disease Site Group

The 2004 guideline recommendations are

ARCHIVED

This means that the recommendations will no longer be maintained but may still be useful for academic or other information purposes.

Review Date: August, 2013

The original version of this guidance document was released by Cancer Care Ontario's Program in Evidence-based Care in 2006. In September 2011, this document was assessed in accordance with the PEBC Document Assessment and Review Protocol and was determined to require a review. As part of the review, a PEBC methodologist conducted an updated search of the literature. A clinical expert (AF) reviewed and interpreted the new eligible evidence and proposed the existing recommendations could be archived. The Gynecology Cancer Disease Site Group (DSG) archived the recommendations found in Section 1 (Clinical Practice Guideline) in August 2013.

DOCUMENT ASSESSMENT AND REVIEW RESULTS

Questions Considered

What is the role of adjuvant radiotherapy in women with stage I endometrial cancer? Specifically, are there subgroups of patients with stage I endometrial cancer who benefit from adjuvant radiotherapy? If so, which radiotherapy treatment is recommended? Outcomes of interest are survival, pelvic control, ultimate pelvic control and toxicity.

Education and Information

Literature Search and New Evidence

The new search (November 2005 to April 2013) yielded 11 new full text publications of three retrospective studies, two RCTs and two metanalysis that compared adjuvant radiotherapy to either no adjuvant radiotherapy or to another form of adjuvant radiotherapy. An additional search for ongoing studies on Clinicaltrials.gov yielded no potentially relevant ongoing RCT. Brief results of these searches are shown in the Document Review Tool.

Impact on Guidelines and Its Recommendations

The new data contradicts existing recommendations; EBRT is no longer recommended for intermediate risk groups. Therefore, the Gynecology Cancer DSG ARCHIVED the 2006 recommendations on adjuvant radiotherapy in Women with Stage I Endometrial Cancer.

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Cancer Care Ontario
Action Cancer Ontario

Document Review Tool

Number and title of document under review	**4-10 Adjuvant Radiotherapy in Women with Stage I Endometrial Cancer**
Current Report Date	**March 9, 2006**
Clinical Expert	**Dr. Anthony Fyles**
Research Coordinator	**Chika Agbassi**
Assessment Date	**Sept 2011**
Approval Date and Review Outcome (once completed)	August 13 2013 [ARCHIVED]

Original Question(s):
What is the role of adjuvant radiotherapy in women with stage I endometrial cancer? Specifically, are there subgroups of patients with stage I endometrial cancer who benefit from adjuvant radiotherapy? If so, which radiotherapy treatment is recommended? Outcomes of interest are survival, pelvic control, ultimate pelvic control and toxicity.

Target Population:
Women with newly diagnosed stage I endometrial cancer who have undergone surgery, either complete surgical staging or total abdominal hysterectomy and bilateral salpingo-oophorectomy. Of interest are outcomes reported by risk of recurrence: low-risk (stage IA, IB, grades 1 & 2), intermediate-risk (stage IC, grades 1 & 2, or stage IA, IB, grade 3), or high-risk (stage IC, grade 3).

Study Selection Criteria:

Inclusion Criteria

Articles were selected for inclusion in the evidence series if they were randomized controlled trials (RCTs) comparing adjuvant radiotherapy to either no adjuvant radiotherapy or to another form of adjuvant radiotherapy in women with early stage endometrial cancer. Specifically, studies were to report data on at least one of the following outcome measures: overall survival, disease-free survival, rate of recurrence (or metastases), ultimate pelvic control, or adverse effects. Ultimate local control refers to the concept that adjuvant radiotherapy is reserved for recurrences and not given to patients at first diagnosis.

In the absence of randomized controlled trials, in order of preference, non-randomized comparative cohort studies, prospective single-cohort studies, and retrospective single-cohort studies were deemed eligible for inclusion. Practice guidelines, meta-analyses, or systematic reviews explicitly based on evidence related to the guideline question were also eligible for inclusion in the systematic review.

Exclusion Criteria

- Case reports, letters, and editorials were not considered.
- Papers published in a language other than English were not considered.

Search Details:

- November 2005 to April 2013 (Medline week 3 and Embase week 33)
- November 2005 to April 2013 (ASCO Annual Meeting)
- November 2005 to April 2013 (Clinical trial.gov)

Education and Information

Brief Summary/Discussion of New Evidence:

Of 269 total hits from Medline + Embase and one hit from ASCO conference abstract searches, 11 references representing three retrospective studies, two RCTs and two meta-analysis were found. One RCT was included in the existing guideline (row highlighted in grey in the Table).

Interventions	type / Name of Study (med F/U)	Population (n)	Outcomes	Brief results	References
Post-op EBRT (40-46Gy in 20-25 dfr) vs. observation	Pooled analysis of 2RCTs: ASTEC & EN.5 (58mos)	Intermediate and low risk Stage 1A &1B(G3) 1C	OS	There was no difference in OS between arms.	The ASTEC/EN.5 Study group writing committee 2009
Postop EBRT (40-46Gy in 20-25 dfr) vs. observation	Meta- analysis of 4RCTs		OS	There was no difference in OS between arms but pelvic EBRT significantly reduced locoregional recurrence with a RR of 0.28 (95% CI 0.17-0.44) p<0.00001	Kong A. et al 2007
Pelvic EBRT (46Gy with 2Gy dfr) vs. No additional treatment	PORTEC-1 (13.3yrs)	TAH-BSO Stage 1C & 1B (n=351 patients confirmed to be alive out of the 0riginal 714)	HRQL	Locoregenal recurrence rates were 5.8% for EBRT against 15.5% for NAT (p<0.001). EBRT significantly increased the rates of urinary incontinence, diarrhea and fecal leakage (P=0.01) There was no difference in OS between arms	Nout RA. et al 2011
EBRT (46Gy in 23 dfr) vs. VBT (21Gy high-dose or 30Gy low-dose in 3dfr)	PORTEC-2 (65mos)	High and intermediate risk Stage 1BG3-2A (n=427)	QoL, LRR OS, DFS	There was no significant difference in OS, DFS and LRR between the two groups. VBT patients reported better social functioning (p=0.005) and lower symptoms scores for diarrhea, and fecal leakage (p=0.001) compared to EBRT	Nout RA. et al 2012 Nout RA. et al 2010 Nout RA. et al 2009
Post-op RT	(64mos)	Mean Age= 59yrs Stage I-III (n=157)	OS, DSF	OS at two and five years are 95% and 84%. 86% remained disease free	Korcum A. et al 2010
Adjuvant RT vs No RT	(5yrs)	Stage 1 UCCC Med Age =68yrs (n=25)	OS, DFS	There was no difference in DFS between the two arms	Rauh-Hain JA. et al 2009
Adjuvant RT (4,500-5040cGy in 25-28 dfr) vs No RT	(422mos)	(n=40)	QoL	The global overall QoL in the RT arm significantly improved with increased time from diagnosis. Bowel symptoms were significantly increased in patients treated with RT.	Tien Le et al 2008
Pelvic EBRT vs Vaginal BT	(55mos)	Stage IA & II (n= 78)	DFS	There was no difference in DFS between the two arms	Lin L. et al 2007
Adjuvant RT	(5yrs)	Stage IC & II (n=3664)	DSS	Adjuvant RT significantly improved the DSS rate When compared with no treatment, (89.9% vs 87.8%) p=0.04. However this improvement	Parthasarathy A. et al 2007

BT= Brachytherapy; dfr= daily fraction; DFS= disease free survival; DSS= Disease specific survival; EBRT= External beam radiotherapy; HRQL= Health related quality of life; LRR= Locoregional relapse; mos= months; n= number recruited; TAH-BSO= Total abdominal hysterectomy and bilateral salpingoopherectomy; OS= overall survival; QoL= Quality of life; UCCC= uterine clear cell cancer; yr=years; VBT= Vaginal Brachytherapy

Instructions. Instructions. For each document, please respond YES or NO to all the questions below. Provide an explanation of each answer as necessary.

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1. Does any of the newly identified evidence, on initial review, contradict the current recommendations, such that the current recommendations may cause harm or lead to unnecessary or improper treatment if followed?	Yes, EBRT is no longer recommended for intermediate risk groups as PORTEC 2 has shown equivalent outcome and reduced toxicity with brachytherapy alone
2. On initial review, a. Does the newly identified evidence support the existing recommendations? b. Do the current recommendations cover all relevant subjects addressed by the .evidence, such that no new recommendations are necessary?	NO NO
3. Is there a good reason (e.g., new stronger evidence will be published soon, changes to current recommendations are trivial or address very limited situations) to postpone updating the guideline? Answer Yes or No, and explain if necessary:	No
4. Do the PEBC and the DSG/GDG responsible for this document have the resources available to write a full update of this document within the next year?	Not applicable

Review Outcome	ARCHIVED
DSG/GDG Approval Date	August 13 2013
DSG/GDG Commentary	

Clinical Expert Interest Declaration:
No potential conflict of interest was declared by the clinical expert.

New References Identified

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Archived Information

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Literature Search Strategy:

Medline

1. exp endometrial neoplasms/
2. (cancer? or carcinoma? or neoplasm? or tumo?r).tw.
3. (endometr? or uter?).tw.
4. 2 and 3
5. 1 or 4
6. exp Radiotherapy, Adjuvant/
7. 5 and 6
8. (200511$ or 2006$ or 2007$ or 2008$ or 2009$ or 2010$ or 2011$ or 2012$ or "201304").ed.
9. 7 and 8
10. limit 9 to humans

Embase

1. exp endometrial neoplasms/
2. (cancer? or carcinoma? or neoplasm? or tumo?r).tw.
3. (endometr? or uter?).tw.

Education and Information

4. 2 and 3
5. 1 or 4
6. exp adjuvant/
7. exp radiotherapy/
8. 6 and 7
9. 5 and 8
10. (200543$ or 2006$ or 2007$ or 2008$ or 2009$ or 2010$ or 2011$ or 2012$ or "201317").ew.
11. 9 and 10
12. limit 11 to human

ASCO – searched http://www.asco.org/ascov2/Meetings/Abstracts with keywords: (Adjuvant radiotherapy) AND (endometrial cancer)
Clinicaltrials.gov – searched http://clinicaltrials.gov/ct2/home with keywords: (Adjuvant radiotherapy) AND (endometrial cancer)

OUTCOMES DEFINITION

1. **ARCHIVED** – An archived document is a document that will no longer be tracked or updated but may still be useful for academic or other informational purposes. The document is moved to a separate section of our website, each page is watermarked with the word "ARCHIVED".

2. **ENDORSED** – An endorsed document is a document that the DSG/GDG has reviewed for currency and relevance and determined to be still useful as guidance for clinical decision making. A document may be endorsed because the DSG/GDG feels the current recommendations and evidence are sufficient, or it may be endorsed after a literature search uncovers no evidence that would alter the recommendations in any important way.

3. **DELAY** – A delay means that there is reason to believe new, important evidence will be released within the next year that should be considered before taking further action.

4. **UPDATE** – An Update means that the DSG/GDG recognizes that there is new evidence that makes changes to the existing recommendations in the guideline necessary but these changes are more involved and significant than can be accomplished through the Document Assessment and Review process. The DSG/GDG will rewrite the guideline at the earliest opportunity to reflect this new evidence. Until that time, the document will still be available as its existing recommendations are still of some use in clinical decision making.

Education and Information