Complete Summary

GUIDELINE TITLE

Adjuvant radiotherapy in women with stage I endometrial cancer: a clinical practice guideline.

BIBLIOGRAPHIC SOURCE(S)

Lukka H, Chambers A, Fyles A, Thephamongkhol K, Elit L, Fung-Kee-Fung M, Kwon J, Oliver T, Gynecology Cancer Disease Site Group. Adjuvant radiotherapy in women with stage I endometrial cancer: a clinical practice guideline. Toronto (ON): Cancer Care Ontario (CCO); 2006 Mar 9. 24 p. (Evidence-based series; no. 4-10). [21 references]

GUIDELINE STATUS

This is the current release of the guideline.

The EVIDENCE-BASED SERIES report, initially the full original Guideline, over time will expand to contain new information emerging from their reviewing and updating activities.

Please visit the Cancer Care Ontario Web site for details on any new evidence that has emerged and implications to the guidelines.

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SCOPE

DISEASE/CONDITION(S)

Stage I endometrial cancer

GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Treatment

CLINICAL SPECIALTY

Obstetrics and Gynecology
Oncology
Radiation Oncology

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

- To evaluate the role of adjuvant radiotherapy in women with stage I endometrial cancer
- Specifically, to evaluate whether there are subgroups of patients with stage I endometrial cancer who benefit from adjuvant radiotherapy, and if so, which radiotherapy treatment is recommended

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).

INTERVENTIONS AND PRACTICES CONSIDERED

Adjuvant external beam radiotherapy (EBRT)

Intracavitary radiotherapy (ICRT) was considered but not specifically recommended.

MAJOR OUTCOMES CONSIDERED

- Survival
- Pelvic control
- Ultimate pelvic control
- Toxicity

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

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 to 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 was contacted to obtain further information about the trial.

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.

NUMBER OF SOURCE DOCUMENTS

Five randomized controlled trials and four systemic reviews were reviewed.

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Expert Consensus (Committee)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE 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.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

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 (external bean radiotherapy [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 intracavitary radiotherapy (ICRT) alone.

While not statistically comparable, the 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 Post Operative Radiation Therapy in Endometrial Carcinoma (PORTEC) study reported pelvic control and survival after relapse, ultimate pelvic control rates according to treatment arm by risk-subgroup based on an intention to treat analyses are not readily available.

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. 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. 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). 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.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Following review and discussion of sections 1 and 2 of this evidence-based series, the Gynecology Cancer Disease Site Group (DSG) circulated the clinical practice guideline and systematic review to clinicians in Ontario for review and feedback.

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 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.

Report Approval Panel

The evidence series was circulated to the two members of the Report Approval Panel and the Guidelines Coordinator of the Program in Evidence-Based Care (PEBC). Feedback was provided by the Panel and the Coordinator and is summarized in the original guideline document. The feedback was reviewed by the Gynecology Cancer DSG and modifications were made to the series in response.

The guideline reflects the integration of feedback obtained through the external review process with final approval given by the Gynecology Cancer DSG and the Report Approval Panel of the Program in Evidence-based Care.

RECOMMENDATIONS

MAJOR 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.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The recommendations are supported by randomized controlled trials and systemic reviews.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

- Three trials detected significant improvements in pelvic control with the use of external beam radiotherapy (delivered either alone or in combination with intracavitary radiotherapy).
- 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

POTENTIAL HARMS

Refer to the original guideline document for common toxicities and other adverse events reported in the trials reviewed.

QUALIFYING STATEMENTS

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Care has been taken in the preparation of the information contained in this document. Nonetheless, any person seeking to apply or consult the evidence-based series is expected to use independent medical judgment in the context of individual clinical circumstances or seek out the supervision of a qualified clinician. Cancer Care Ontario makes no representation or guarantees of any kind whatsoever regarding their content or use or application and disclaims any for their application or use in any way.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Lukka H, Chambers A, Fyles A, Thephamongkhol K, Elit L, Fung-Kee-Fung M, Kwon J, Oliver T, Gynecology Cancer Disease Site Group. Adjuvant radiotherapy in women with stage I endometrial cancer: a clinical practice guideline. Toronto (ON): Cancer Care Ontario (CCO); 2006 Mar 9. 24 p. (Evidence-based series; no. 4-10). [21 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2006 Mar 9

GUIDELINE DEVELOPER(S)

Program in Evidence-based Care - State/Local Government Agency [Non-U.S.]

GUIDELINE DEVELOPER COMMENT

The Program in Evidence-based Care (PEBC) is a Province of Ontario initiative sponsored by Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

SOURCE(S) OF FUNDING

Cancer Care Ontario
Ontario Ministry of Health and Long-Term Care

GUIDELINE COMMITTEE

Provincial Gynecology Cancer Disease Site Group

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

For a current list of past and present members, please see the Cancer Care Ontario Web site.

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

No potential conflicts of interest were declared.

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GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from the Cancer Care Ontario Web site.

AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- Adjuvant radiotherapy in women with stage I endometrial cancer: a clinical practice guideline. Summary. Toronto (ON): Cancer Care Ontario (CCO), 2006 Mar 9. Various p. (Practice guideline; no. 4-10). Electronic copies: Available in Portable Document Format (PDF) from the Cancer Care Ontario Web site.
- Browman GP, Levine MN, Mohide EA, Hayward RSA, Pritchard KI, Gafni A, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. J Clin Oncol 1995;13(2):502-12.

PATIENT RESOURCES

None available

NGC STATUS

This NGC summary was completed by ECRI on June 9, 2006. The information was verified by the guideline developer on June 26, 2006.

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