Complete Summary

GUIDELINE TITLE

Adjuvant hormonal therapy for stage I endometrial cancer: recommendations.

BIBLIOGRAPHIC SOURCE(S)

Gien L, Kwon J, Oliver T, Fung-Kee-Fung M, Gynecology Cancer Disease Site Group. Adjuvant hormonal therapy for stage 1 endometrial cancer: recommendations. Toronto (ON): Cancer Care Ontario (CCO); 2007 Oct 25. 19 p. (Evidence-based series; no. 4-14). [18 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.

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Stage I endometrial cancer

GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Treatment

CLINICAL SPECIALTY

Obstetrics and Gynecology
Oncology

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

To evaluate the role of hormonal therapy as adjuvant therapy in patients with stage I endometrial cancer

TARGET POPULATION

Women with newly diagnosed stage I endometrial cancer

INTERVENTIONS AND PRACTICES CONSIDERED

Adjuvant hormonal therapy (considered but not recommended)

1. Medroxyprogesterone acetate (MPA)
2. Hydroxyprogesterone caproate (HPC)
3. Tamoxifen
4. Gestonorone
5. Progestagen

MAJOR OUTCOMES CONSIDERED

- Survival
- Recurrence rates
- Adverse events
- Quality of life

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

Literature Search Strategy

The literature was searched using MEDLINE (OVID: 1966 through January 2007), EMBASE (OVID: 1988 through January 2007), the Cochrane Library (OVID: Issue 1, 2007), the Physician Data Query database, the Canadian Medical Association Infobase, and the National Guideline Clearinghouse. In addition, abstracts published in the proceedings of the meetings of the American Society of Clinical Oncology (1997-2006) and the European Society for Medical Oncology (2002-2006) were searched for evidence relevant to this report. Reference lists of related papers and recent review articles were also scanned for additional citations. The literature search of the electronic databases combined disease specific terms (endometrial neoplasms/ or endomet:.ti. and cancer.ti. or neoplasms/ or carcinoma:.ti. or adenocarcinoma:.ti.) with treatment specific terms (antineoplastic agents, hormonal/) for the following study designs: randomized controlled trials, practice guidelines, systematic reviews, and meta-analyses.

Study Selection Criteria

Articles were selected for inclusion in the systematic review of the evidence if they randomized patients with stage I endometrial cancer to adjuvant hormonal therapy versus no adjuvant treatment, or to other forms of hormonal therapy. In order to include trials where the majority of patients had early stage disease, it was decided a priori that trials for inclusion were to report at least 60% of patients with stage I disease or report results separately for patients with stage I disease. At least one of the following outcomes was to be reported: overall survival, disease-free survival, recurrence (local and/or distant), adverse effects, or quality of life. Because of the potential for long-term adverse effects with adjuvant hormonal treatment in this patient population, especially with regard to thromboembolic or cardiovascular events, the rates of non-cancer related deaths were also of interest. It was determined a priori that the search would be expanded to include other study designs if the search of the literature failed to identify sufficient evidence to inform the systematic review.

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.

Articles were excluded from the systematic review of the evidence if they were case reports, letters, editorials, or papers published in a language other than English.

NUMBER OF SOURCE DOCUMENTS

Nine randomized controlled trials and one published data meta-analysis met the specified criteria and were eligible for inclusion in the systematic review of the evidence.

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

Meta-Analysis of Randomized Controlled Trials
Review of Published Meta-Analyses
Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Combining results across trials provides added power for detecting the efficacy of the treatment and improves the reliability or confidence of the point estimate. Ideally, data are pooled using hazard ratios; however, if that method is not possible given the level of reporting of the data, meta-analyses using point in time estimates are conducted. Data are analyzed using the Review Manager 4.2.10 statistical package. Results are expressed as the pooled Hazards ratio (HR) or the Odds ratio (OR) with 95% confidence intervals (CI), where a value less than 1.0 favours the experimental treatment, and a value greater than 1.0 favours control. As part of combining data in a meta-analysis, an assessment of heterogeneity is completed. Clinical heterogeneity is assessed by determining whether the populations, interventions, and outcomes are sufficiently similar to pool data. Statistical heterogeneity is assessed by the Q test, and a p-value of <0.10 is determined to be the level at which heterogeneity would be present. The I^2 statistic quantifies how much heterogeneity can be attributed to chance or to a real effect. If substantial heterogeneity is present, possible clinical and methodological reasons are explored qualitatively. The random effects model is generally chosen over the fixed effects model as the more conservative estimate of effect.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

Nine randomized trials and one published data meta-analysis provide the evidence base for assessing the role of adjuvant hormone therapy in women with stage I endometrial cancer. There are several factors that limit the interpretability of the results, but the greatest limiting factor is that the trials, which span a thirty-year period, generally have inconsistent reporting throughout. This limits the quality assessment of internal validity related to patient and study characteristics, as well as outcomes. There were no quality of life data reported, little data on adverse events or treatment compliance, and limited data on recurrence and survival outcomes, especially concerning data on hazard ratios and time-to-event estimates. There were also differences in patient populations, unexpected findings that were not consistent with the results of similar randomized trials, and noted discrepancies between patients at baseline, despite the randomization process. These limitations affect the external validity of the trials; however, these trials

provide the only randomized data that inform the role of adjuvant hormonal therapy in this patient population.

In spite of the limitations, the evidence was consistent in the direction of effect to indicate that adjuvant hormonal therapy does not confer survival advantages on patients with stage 1 endometrial cancer. Eight of the nine randomized trials failed to detect any differences in survival between treatment and control groups. Although the remaining trial did demonstrate a survival difference, the quality of the trial is subject to criticism because of important differences in baseline characteristics between patient groups, and it is not consistent with the results of the other randomized controlled trials identified. The magnitude of effect is also highly unexpected when one looks at the results of the other similar trials reported. In addition, in two meta-analyses, no survival advantages were detected with adjuvant hormonal therapy.

In seven of the nine randomized trials, recurrence rates were not significantly different between patients in the adjuvant hormonal groups as compared to patients in the control groups. Of the two trials that detected lower recurrence rates in patients in the progestin group, the trial by Urbanski et al. reported more favourable baseline characteristics for patients in the treatment group, and the trial by Quinn reported data on patients at high risk of recurrence. Although the current meta-analysis, as well as the previously published meta-analysis did show a marginal reduction in recurrence rate, this was not statistically significant at the 0.05 level.

Finally, although not consistently reported, the adverse events related to patients in the hormonal groups were generally higher than those in the control groups. Minor side effects were reported to be higher in the treatment groups, though tests of statistical significance were not performed. Non-cancer related deaths were shown to be higher with progestagen in one randomized trial mainly due to cardiovascular or thromboembolic events ($p=0.04$). In contrast, Urbanski et al. reported a 10% non-cancer related death rate in the control group and a 0% rate in the treatment group; an unexpected finding not seen in the other randomized trials. The published data meta-analysis by Martin-Hirsch et al. did not demonstrate a statistically significant difference in the number of non-cancer related deaths.

Given the lack of an overall survival benefit, a marginal decrease in recurrence rates seen mainly in patients at higher risk of recurrence, and the need for treatment regimens that can span years, with possible increases in adverse events, there is currently insufficient evidence to support the use of hormonal therapy as adjuvant treatment for patients with early stage endometrial cancer.

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

Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

The report was reviewed by the Assistant Director of the Program in Evidence-Based Care (PEBC) and the Report Approval Panel (RAP), which consists of two members, including an oncologist, with expertise in clinical and methodology issues.

This report reflects the integration of feedback obtained through the internal review process, with final approval given by the Gynecology Cancer Disease Site Group (DSG) and the Report Approval Panel of the PEBC. The evidence series report was not subjected to formal external review through practitioner feedback, given that adjuvant hormonal therapy for stage 1 cancer is generally not offered to patients in current clinical practice. Practitioners were notified of the results of the evidence series and of the Web publication, and comments were invited. Updates of the report will be conducted as new evidence informing the question of interest emerges.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

The use of hormone therapy is not recommended as adjuvant treatment for patients with stage I endometrial cancer. The available evidence does not demonstrate any benefit with adjuvant hormone therapy.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The recommendations are supported by randomized controlled trials and meta-analyses.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

- One of the nine trials reported a statistically significant survival benefit with adjuvant progestagen when compared with no further treatment. In that trial, the treatment group had a higher number of patients with less myometrial invasion and a lower number of patients with advanced stage disease. These differences in baseline characteristics between randomized groups were

considered to be clinically important. In addition, the results of that trial were not consistent with that of other the trials and the trial was the source of statistical heterogeneity when data were pooled across trials.

- Two of the nine randomized trials detected statistically significant recurrence-free benefits with adjuvant hormone therapy versus no further therapy. In one trial, the difference in rates of recurrence was 16%; however, the methodological concerns of that trial limit its relevance. In the other trial, the difference in rates of recurrence was 5%. In that trial, patients were at a high risk of recurrence. The remaining seven randomized trials did not report any significant differences in recurrence rates between treatment groups.
- The published data meta-analysis identified in the literature detected no statistically significant recurrence-free or overall survival benefits associated with adjuvant hormone therapy when compared to no adjuvant therapy (odds ratio [OR] = 1.05; 95% confidence interval [CI], 0.88-1.24). Those results are consistent with the results of the current published data meta-analysis with an additional two trials included (OR = 1.10; 95% CI, 0.91-1.34).

POTENTIAL HARMS

Not stated

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

Care has been taken in the preparation of the information contained in this report. Nonetheless, any person seeking to apply or consult the report 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 the report content or use or application and disclaims any responsibility for its 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)

Gien L, Kwon J, Oliver T, Fung-Kee-Fung M, Gynecology Cancer Disease Site Group. Adjuvant hormonal therapy for stage 1 endometrial cancer: recommendations. Toronto (ON): Cancer Care Ontario (CCO); 2007 Oct 25. 19 p. (Evidence-based series; no. 4-14). [18 references]

ADAPTATION

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

DATE RELEASED

2007 Oct

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

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

Members of the Gynecology Disease Site Group (DSG) were asked to disclose potential conflict of interest information. No conflicts were reported.

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.

GUIDELINE AVAILABILITY

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

AVAILABILITY OF COMPANION DOCUMENTS

The following is available:

- 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 summary was completed by ECRI Institute on April 8, 2008.

COPYRIGHT STATEMENT

DISCLAIMER

NGC DISCLAIMER

The National Guideline Clearinghouse™ (NGC) does not develop, produce, approve, or endorse the guidelines represented on this site.

All guidelines summarized by NGC and hosted on our site are produced under the auspices of medical specialty societies, relevant professional associations, public or private organizations, other government agencies, health care organizations or plans, and similar entities.

Guidelines represented on the NGC Web site are submitted by guideline developers, and are screened solely to determine that they meet the NGC

Inclusion Criteria which may be found at
http://www.guideline.gov/about/inclusion.aspx .

NGC, AHRQ, and its contractor ECRI Institute make no warranties concerning the content or clinical efficacy or effectiveness of the clinical practice guidelines and related materials represented on this site. Moreover, the views and opinions of developers or authors of guidelines represented on this site do not necessarily state or reflect those of NGC, AHRQ, or its contractor ECRI Institute, and inclusion or hosting of guidelines in NGC may not be used for advertising or commercial endorsement purposes.

Readers with questions regarding guideline content are directed to contact the guideline developer.

Date Modified: 11/3/2008