Evidence-based Series 4-14 EDUCATION AND INFORMATION 2015

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

Adjuvant Hormonal Therapy for Stage I Endometrial Cancer

L. Gien, J. Kwon, T. Oliver, M. Fung-Kee-Fung, and the Gynecology Cancer Disease Site Group

Report Date: October 25, 2007

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This EBS consists of the following 3 sections

Section 1: Recommendations
Section 2: Evidentiary Base
Section 3: Guideline Development and External Review-Methods and Results

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Adjuvant Hormonal Therapy for Stage I Endometrial Cancer: Recommendations

L. Gien, J. Kwon, T. Oliver, M. Fung-Kee-Fung, and the Gynecology Cancer Disease Site Group

A Quality Initiative of the
Program in Evidence-based Care (PEBC), Cancer Care Ontario (CCO)
Developed by the Gynecology Cancer Disease Site Group

Report Date: October 25, 2007

QUESTIONS
What is the role of hormonal therapy as adjuvant therapy in patients with stage I endometrial cancer? Outcomes of interest include survival, recurrence rates, adverse events, and quality of life.

TARGET POPULATION
Women with newly diagnosed stage I endometrial cancer.

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.

KEY EVIDENCE
Nine randomized trials and one published data meta-analysis comparing adjuvant hormone therapy to no adjuvant therapy in women with stage I endometrial cancer comprised the evidence base.

• 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).

RELATED GUIDELINES
Program in Evidence-based Care Evidence-based Series:
- #4-9: Follow-up for Endometrial Cancer
- #4-10: Postoperative Radiation Therapy for Early Stage Endometrial Cancer

Contact Information
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Funding
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Evidence-based Series 4-14: Section 2

Adjuvant Hormonal Therapy for Stage I Endometrial Cancer:
Evidentiary Base

L. Gien, J. Kwon, T. Oliver, M. Fung-Kee-Fung, and the Gynecology Cancer Disease Site Group

A Quality Initiative of the
Program in Evidence-based Care (PEBC), Cancer Care Ontario (CCO)
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QUESTION
What is the role of adjuvant hormonal therapy in patients with stage I endometrial cancer? Outcomes of interest include overall survival, recurrence rates, adverse events, and quality of life.

INTRODUCTION
Endometrial cancer is the most common gynecologic cancer in Canada (1). Each year approximately 3900 women are diagnosed with endometrial cancer in Canada, and 1550 of those are in the province of Ontario (1). Approximately 75% of patients present with stage I disease, which is confined to the uterus (2). Primary surgical treatment for patients with stage I endometrial cancer typically consists of a total abdominal hysterectomy with bilateral salpingo-oophorectomy or complete surgical staging, which involves abdominal hysterectomy, bilateral salpingo-oophorectomy, pelvic and/or para-aortic node dissection or sampling, peritoneal cytology, omentectomy, and peritoneal biopsies (3).

For patients with stage I endometrial cancer, there is little consensus on the role of adjuvant treatment. There is currently evidence to support the role of adjuvant pelvic radiotherapy in stage I endometrial cancer to decrease the risk of recurrence for higher-risk patients (stage IC, grade 3), and perhaps for patients at an intermediate risk of recurrence (stage IC, grades 1, 2, or stage IA, IB, grade 3), but not for patients at a lower risk of recurrence (stage IA, IB, grades 1, 2) (4). Although the use of hormonal therapy has been established in advanced disease (5), there is less agreement on the role of adjuvant hormone therapy in early stage disease.

The objective of this evidence series is to review the existing literature on the role of hormone therapy as adjuvant therapy in patients with stage I endometrial cancer.

METHODS
The evidence-based series (EBS) reports developed by Cancer Care Ontario’s Program in Evidence-Based Care (PEBC) use the methods of the Practice Guidelines Development Cycle (6). For this project, the core methodology used to develop the evidentiary base was the
systematic review. Evidence was selected and reviewed by two members of the PEBC Gynecology Cancer DSG and one methodologist.

This systematic review is a convenient and up-to-date source of the best available evidence on adjuvant hormonal therapy in patients with stage I endometrial cancer. The body of evidence in this review is primarily comprised of randomized controlled trial data. That evidence forms the basis of the recommendations developed by the Gynecology Cancer DSG in Section 1 of this report. The systematic review and companion recommendations are intended to promote evidence-based practice in Ontario, Canada. The PEBC is supported by the Ontario Ministry of Health and Long-Term Care through Cancer Care Ontario. All work produced by the PEBC is editorially independent from its funding source.

**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 endometrial.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.

**Synthesizing 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\(^1\) 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.

**RESULTS**

**Literature Search Results**

Nine randomized controlled trials (7-15) and one published data meta-analysis (16) on adjuvant hormone therapy for patients with stage I endometrial cancer met the specified criteria and were deemed eligible for inclusion in the systematic review of the evidence. Since a sufficient number of randomized controlled trials were identified, the search was not expanded to include other study designs.

In the nine trials, patients were randomized to either adjuvant progestagen therapy or to a control group with no adjuvant therapy (7-15). In seven trials, patients in the control group received no further treatment (7-13), and in two trials, patients in the control group received a placebo control. One trial also included a third group of patients randomized to receive tamoxifen (7).

**Study Quality**

Only two of the nine randomized trials specifically described the randomization process (7,12); however, an additional two trials (10,15) were multicentred investigations that reported centralized randomization procedures. Thus, while not specifically reported, it can be inferred that adequate randomization and allocation concealment occurred in those latter two trials. Each of the trials reported a comparison of patient baseline characteristics and important prognostic variables that could potentially influence outcome, such as the depth of myometrial invasion and histologic grade. In seven trials (7,8,10-14), baseline characteristics between patients in the treatment groups and those of the control groups were comparable, demonstrating an adequate randomization process. In the trial by Urbanski et al. (9), the progestagen group had noticeably more patients with favourable characteristics in terms of stage and depth of myometrial invasion, a clinically relevant difference between groups. Conversely, in the trial by Lewis et al. (15), the placebo group had more patients with favourable characteristics with regard to depth of myometrial invasion.

All the trials maintained their comparison groups, except for the trial by Quinn (8). In that trial, if recurrence was observed in the control group, the patients were offered adjuvant hormonal therapy and crossed over to the treatment group.

Overall survival (7,12,14-15) or recurrence-free survival (13) were described or inferred as the primary outcomes of interest upon which power calculations were based. Only two trials specifically reported their power calculation (8,12); however, this may be a reflection of how reporting standards for the methodology of clinical trials have changed over time. Five trials randomized greater than 200 patients per arm (8,10,11,12,15), two trials (7,9) randomized less than 135 patients per arm, and two trials (13,14) randomized less than 30 patients per arm. It is

questionable whether the latter four trials were adequately powered to detect meaningful differences between treatment arms.

An intention-to-treat analysis was reported in five of the nine trials (8-10,12,14) and not in the remaining four trials (7,11,13,15). The intention-to-treat is a more conservative approach to data analysis whereby all patients are analyzed according to their original randomization assignment, regardless of factors such as drop out, non-compliance to treatment, or crossover. Seven studies had a follow up rate of greater than 80% (7,9,11-15), one study had a follow up of 75% (10), and one study did not report follow-up data (8). Where reported, overall survival was measured at or beyond the point of median follow-up.

**Trial Characteristics**

To be eligible to participate in the trials, patients were to have a histologic diagnosis of endometrial adenocarcinoma, and, with the exception of one trial (15), patients first had surgery that included at least a total abdominal hysterectomy and bilateral salpingo-oophorectomy, followed by adjuvant radiation therapy if indicated according to pathologic criteria. In the trial by Lewis et al. (15), patients were randomized into two groups, one offering preoperative radiation therapy and surgery and one offering surgery alone. Preoperative radiation therapy is no longer done in current practice. The progestagen agents in the adjuvant hormonal therapy groups included medroxyprogesterone acetate (MPA) (7,8,10,12,15), hydroxyprogesterone caproate (9,11,14), and gestonorone caproate (13). The doses of hormonal therapy were relatively equivalent in all the trials, even when compared across formulations.

In four trials (10,13-15), only patients with stage I disease (confined to the uterine corpus) were eligible to participate in the randomized trials, whereas in the remaining five trials (7-9,11,12) patients with more advanced stages of endometrial cancer were eligible as well. In those latter trials, at least 60% of patients were diagnosed with stage I disease (7-9,11-12). The trial reported by Quinn had specific inclusion criteria for patients with histologically high-risk endometrial cancer in addition to stage I disease (8). Furthermore, that trial performed a subgroup analysis of the patients, after removing 117 women considered ineligible after pathology review. Three other trials included subgroup analyses of high-risk endometrial cancer (7,11,13). In these three trials, the subgroup analyses were not decided upon a priori, and therefore, likely did not have the adequate power for significant results. In this review, data on subgroup analyses are not reported.

Protocols for changes in treatment were specified in three of the nine randomized trials, where patients who had a recurrence in the control group could cross over to the hormone group (8), or in the event of side effects, patients had the option to stop treatment (10,12). In the latter two trials, if patients stopped treatment because of side effects, they were still analyzed according to the intention-to-treat approach (10,12).

The trials were conducted in Germany (7), Australia (8), Poland (9), Italy (10,13), Norway (11), United Kingdom (12), and United States (14-15).

**Outcomes**

Does hormonal therapy used as adjuvant treatment for early stage endometrial cancer improve recurrence and survival outcomes for patients, and is overall quality of life affected? Is hormonal therapy more likely to be useful for well-differentiated tumours than for poorly differentiated tumours? The sections below outline the key findings regarding recurrence rates, survival, and adverse events that include non-cancer related deaths. There were no trials identified that answered the questions regarding quality of life or tumour differentiation nor was compliance to treatment reported. It should also be noted that reporting conventions have changed over time, and since the identified trials span a thirty-year period, some data considered standard by today’s convention are missing in the reporting of the trials (e.g. reporting of hazards ratios, common point in time estimates, adverse events, compliance to...
Data from the trials were extracted as available. Table 1 summarizes the recurrence and survival results of the nine trials.

**Table 1: RCTs of adjuvant hormonal therapy in early stage endometrial cancer.**

<table>
<thead>
<tr>
<th>Study</th>
<th># of Pts.</th>
<th>Treatment Groups</th>
<th>Duration</th>
<th>% with Stage I disease</th>
<th>Median F/U months (range)</th>
<th>Outcomes *</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Von Minckwitz</td>
<td>121</td>
<td>None MPA 500 mg/d PO Tamoxifen 30 mg/d</td>
<td>2 years</td>
<td>82%</td>
<td>(3-199)</td>
<td>4.5 year</td>
</tr>
<tr>
<td>2002 (7)</td>
<td>132</td>
<td></td>
<td>2 years</td>
<td>83%</td>
<td></td>
<td>11%</td>
</tr>
<tr>
<td>Quinn</td>
<td>505</td>
<td>None MPA 200 mg/bid PO</td>
<td>≥ 3 years</td>
<td>80%</td>
<td>(36-120)</td>
<td>5 year</td>
</tr>
<tr>
<td>1998 (8)</td>
<td>507</td>
<td></td>
<td></td>
<td>80%</td>
<td></td>
<td>21%</td>
</tr>
<tr>
<td>Urbanski</td>
<td>100</td>
<td>None HPC 500 mg/2wks IM c</td>
<td>1 year</td>
<td>65%</td>
<td>NR</td>
<td>5 year</td>
</tr>
<tr>
<td>1993 (9)</td>
<td>105</td>
<td></td>
<td></td>
<td>78%</td>
<td></td>
<td>23%</td>
</tr>
<tr>
<td>De Palo</td>
<td>348</td>
<td>None MPA 100 mg/bid PO</td>
<td>1 year</td>
<td>100%</td>
<td>84 (NR)</td>
<td>7 year</td>
</tr>
<tr>
<td>1993 (10)</td>
<td>370</td>
<td></td>
<td></td>
<td>100%</td>
<td></td>
<td>6%</td>
</tr>
<tr>
<td>Vergote</td>
<td>553</td>
<td>None HPC 1000 mg/bid IM d</td>
<td>1 year</td>
<td>89%</td>
<td>72 (42-132)</td>
<td>5 year</td>
</tr>
<tr>
<td>1989 (11)</td>
<td>531</td>
<td></td>
<td></td>
<td>90%</td>
<td></td>
<td>14%</td>
</tr>
<tr>
<td>Macdonald</td>
<td>214</td>
<td>None MPA 100 mg/d PO e</td>
<td>≥ 5 years</td>
<td>72%</td>
<td>&gt;60 (12-120)</td>
<td>NR</td>
</tr>
<tr>
<td>1988 (12)</td>
<td>215</td>
<td></td>
<td></td>
<td>68%</td>
<td></td>
<td>NR</td>
</tr>
<tr>
<td>De Palo</td>
<td>32</td>
<td>None Gestonorone 200 mg/wk IM</td>
<td>≥ 1 year</td>
<td>100%</td>
<td>NR</td>
<td>5 year</td>
</tr>
<tr>
<td>1983 (13)</td>
<td>30</td>
<td></td>
<td></td>
<td>100%</td>
<td></td>
<td>15%</td>
</tr>
<tr>
<td>Malkasian</td>
<td>18</td>
<td>Placebo IM HPC 500 mg/wk IM</td>
<td>14 weeks</td>
<td>100%</td>
<td>60 (NR)</td>
<td>5 year</td>
</tr>
<tr>
<td>1978 (14)</td>
<td>17</td>
<td></td>
<td>14 weeks</td>
<td>100%</td>
<td></td>
<td>5%</td>
</tr>
<tr>
<td>Lewis</td>
<td>285</td>
<td>Placebo IM MPA 500 mg/wk IM</td>
<td>14 weeks</td>
<td>100%</td>
<td>48 (NR)</td>
<td>4 year</td>
</tr>
<tr>
<td>1974 (15)</td>
<td>287</td>
<td></td>
<td>14 weeks</td>
<td>100%</td>
<td></td>
<td>92%</td>
</tr>
</tbody>
</table>

# of Pts. = number of patients; NR = not reported; MPA = medroxyprogesterone acetate; HPC = hydroxyprogesterone caproate; bid = twice a day; IM = intramuscular; PO = oral; q = every.

a results based on all subjects in the trial, not only Stage I patients, unless specified
b reviewer's calculation
c Some patients received oral doses (Number of patients = NR)
d Initially, patients in the treatment arm received a loading dose of 5000mg in the course of 5 days
e Initial dose for the first year was 100 mg/d PO three times daily

**Survival**

One of the nine randomized trials detected a statistically significant difference in overall survival between the treatment group who received hydroxyprogesterone caproate and the control group who received no further treatment (9). In the trial by Urbanski et al. (9), the overall survival rate at five years was 97% in the treatment group compared to 69% in the control group. Although 70% of the patients had stage I disease, these results were based on all 205 patients with stage I-III endometrial cancer. A criticism of the trial is that the prognostic variables in the two groups were not equally distributed at baseline: 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. The remaining eight trials did not find any statistically significant differences between the treatment and control groups (7,8,10-15). The overall survival results from the trial reported by Quinn (8) may have been tempered by the crossover of 64 of the 107 control patients to hormonal therapy upon recurrence; however, outside of subgroup analysis, the impact of crossover upon survival is unknown.
There were sufficient data to pool the total number of deaths in both the treatment and control groups across all trials (7-15); however, because the reporting of data was variable, it was not possible to conduct meta-analyses using hazard ratios nor were identical points in time captured. The total numbers of deaths were pooled across different time points as an alternate method of pooling data. In one trial where data were not directly reported, data were estimated from information reported in the trial using the intent-to-treat population as the denominator (13).

As seen in Figure 1, the meta-analysis demonstrated no statistically significant difference in overall survival between patients who received adjuvant hormonal therapies and those in the control groups (OR = 0.96; 95% CI, 0.67-1.37). The data were statistically heterogeneous (P=0.0004; I²=72.1%) and it was determined through sensitivity analysis that the source of the statistical heterogeneity was the trial by Urbanski et al. (9). Given that the trial was the source of statistical heterogeneity, and that it was clinically relevant that the prognostic variables were not equally distributed at baseline; the decision was made to remove the trial from the pooled analysis. As seen in Figure 2, when the trial by Urbanski et al. (9) was removed from the analysis, the heterogeneity was no longer statistically significant (P=0.27; I²=20.6%), and the difference in overall survival remained non-significant between groups (OR = 1.10; 95% CI, 0.91-1.34).

Figure 1. Meta-analysis of deaths with adjuvant hormonal therapy versus control (9 trials).

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>Treatment (n)</th>
<th>Control (n)</th>
<th>OR (random) 95% CI</th>
<th>Weight %</th>
<th>OR (random) 95% CI</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Van Minckwitz et al.</td>
<td>23/133</td>
<td>23/134</td>
<td>12.20</td>
<td>1.93</td>
<td>1.90</td>
<td>2002</td>
</tr>
<tr>
<td>QUICK (8)</td>
<td>143/505</td>
<td>165/627</td>
<td>27.82</td>
<td>0.07</td>
<td>0.66</td>
<td>1.10</td>
</tr>
<tr>
<td>Urbanski (9)</td>
<td>3/109</td>
<td>2/106</td>
<td>1.97</td>
<td>0.07</td>
<td>0.60</td>
<td>1.20</td>
</tr>
<tr>
<td>Ehrlich (10)</td>
<td>35/248</td>
<td>36/302</td>
<td>14.42</td>
<td>1.17</td>
<td>0.73</td>
<td>1.85</td>
</tr>
<tr>
<td>Vergote (11)</td>
<td>112/273</td>
<td>92/231</td>
<td>10.15</td>
<td>1.25</td>
<td>0.69</td>
<td>1.20</td>
</tr>
<tr>
<td>Macdonald (12)</td>
<td>62/214</td>
<td>56/215</td>
<td>1.28</td>
<td>1.11</td>
<td>0.72</td>
<td>1.69</td>
</tr>
<tr>
<td>De Felice (13)</td>
<td>6/32</td>
<td>2/32</td>
<td>1.29</td>
<td>0.12</td>
<td>0.02</td>
<td>1.94</td>
</tr>
<tr>
<td>Muscat (14)</td>
<td>6/38</td>
<td>2/17</td>
<td>1.58</td>
<td>0.24</td>
<td>0.04</td>
<td>1.20</td>
</tr>
<tr>
<td>Lommel (15)</td>
<td>30/286</td>
<td>20/280</td>
<td>4.03</td>
<td>2.26</td>
<td>1.04</td>
<td>1976</td>
</tr>
<tr>
<td>Total (95%)</td>
<td>2185</td>
<td>2165</td>
<td>10.00</td>
<td>0.96</td>
<td>0.67</td>
<td>1.95</td>
</tr>
</tbody>
</table>

Note: OR indicates Odds Ratio; 95% CI, 95% confidence interval; Chi², chi-square test; df, degrees of freedom

Figure 2. Meta-analysis of deaths with adjuvant hormonal therapy versus control (8 trials).

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>Treatment (n)</th>
<th>Control (n)</th>
<th>OR (random) 95% CI</th>
<th>Weight %</th>
<th>OR (random) 95% CI</th>
<th>Year</th>
</tr>
</thead>
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<td>1.20</td>
</tr>
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<td>1.11</td>
<td>0.72</td>
<td>1.69</td>
</tr>
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<td>6/32</td>
<td>2/32</td>
<td>1.29</td>
<td>0.12</td>
<td>0.02</td>
<td>1.94</td>
</tr>
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<td>2/17</td>
<td>1.58</td>
<td>0.24</td>
<td>0.04</td>
<td>1.20</td>
</tr>
<tr>
<td>Lommel (15)</td>
<td>30/286</td>
<td>20/280</td>
<td>4.03</td>
<td>2.26</td>
<td>1.04</td>
<td>1976</td>
</tr>
<tr>
<td>Total (95%)</td>
<td>2095</td>
<td>2091</td>
<td>10.00</td>
<td>1.18</td>
<td>0.91</td>
<td>1.35</td>
</tr>
</tbody>
</table>

Note: OR indicates Odds Ratio; 95% CI, 95% confidence interval; Chi², chi-square test; df, degrees of freedom
Recurrence

Recurrence rates were reported in six of the nine randomized trials (7-11,13). Of the six trials, two reported a statistically significant difference in recurrence rates between treatment groups (8,9). In the trial by Quinn (8), where all patients were at a high risk of recurrence, 21% of the control group had a relapse versus 16% of the hormone group (p<0.05). In the trial by Urbanski et al. (9), 23% of patients in the control group recurred versus 7% of the patients in the hormone therapy group (p<0.001). The remaining four trials did not show any statistically significant difference in recurrence rates between treatment and control groups (7,10,11,13).

Six of the nine trials provided sufficient information to pool the total number of recurrences in both the treatment and control groups using point-in-time estimates (7-11,13). The reporting of data was again variable across the randomized trials; thus, the total numbers of recurrences were pooled across different time points. Data were estimated from information reported in one trial, using the intention-to-treat population as the denominator (13).

As seen in Figure 3, while there were fewer recurrences associated with adjuvant progestagens, no statistically significant differences in recurrence rate was detected between patient groups (OR = 0.74; 95% CI, 0.51-1.08), and statistically significant heterogeneity was detected (P=0.04; I²=57.2%). The source of the statistical heterogeneity was once again deemed to be from the trial by Urbanski et al. (9). As seen in Figure 4, when that trial was removed from the pooled analysis, the remaining five trials (7,8,10,11,13) were statistically homogeneous (P=0.26; I²=24.5%), and the difference in recurrence remained non-significant between groups (OR = 0.85; 95% CI, 0.65-1.10).

Figure 3. Meta-analysis of recurrences with adjuvant hormonal therapy versus control (6 trials).

![Figure 3](image)

Note: OR indicates Odds Ratio; 95% CI, 95% confidence interval; Chi², chi-square test; df, degrees of freedom

Figure 4. Meta-analysis of recurrences with adjuvant hormonal therapy versus control (5 trials).

![Figure 4](image)

Note: OR indicates Odds Ratio; 95% CI, 95% confidence interval; Chi², chi-square test; df, degrees of freedom
**Adverse Events**

Table 2 summarizes the adverse effects reported across the nine randomized trials (7-15). Five trials reported data on major harmful side effects or deaths unrelated to the malignancy, while three trials reported on minor symptomatic side effects or withdrawals due to toxicity (7,10,12). The most common minor side effects included weight gain, peripheral edema, and nausea (7,10). One trial reported an incidence of overall minor side effects of 53% in the progestin group and 16% in the control group; however, there was no indication of whether this difference was statistically significant (7). Another trial reported a minor side effect rate of 12% but did not calculate side effects for patients in the control group (10). Macdonald et al. reported that 4% of patients in the hormonal therapy group developed hypertension, which disappeared after stopping the drug (12). The dropout rate due to toxicity ranged from 5% to 19% in the three trials that reported data on that outcome (7,10,12).

Serious side effects included thromboembolic events such as deep vein thrombosis, pulmonary embolus, and stroke, or cardiovascular disease such as myocardial infarction and deterioration of congestive heart failure. In the trials that reported these events, there were no statistically significant differences reported between treatment and control groups (7,8,10-12). One trial (7) indicated a serious side effect rate of 6% in the progestagen group versus 2% in the control group (p-value not reported), while another trial (11) reported higher rates of death due to cardiovascular disease in the first two years in the progestagen group versus those in the control group (5% versus 3%, p=0.07). Additionally, deaths that were not due to malignancy were mainly cardiovascular or thromboembolic-related. Only one trial (11) showed a statistically significant difference of deaths that were unrelated to malignancy of 9% of patients in the hormonal group and 6% of patients in the control group (p=0.04). In the trial by Urbanski et al. (9), the only trial to report an overall survival difference, there were 11 patient deaths unrelated to malignancy in the control arm and none in the treatment arm (p=NR). The remaining trials that reported deaths unrelated to malignancy did not detect any statistically significant differences between the treatment and control groups (7,8,10,12).

<table>
<thead>
<tr>
<th>Study</th>
<th># of Pts.</th>
<th>Treatment Groups</th>
<th>Minor Adverse Events</th>
<th>Serious Adverse Events</th>
<th>Withdrawal due to toxicity</th>
<th>Second Primary Malignancy</th>
<th>Non-cancer related deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Von Minckwitz 2002 (7)</td>
<td>134</td>
<td>None Progestagen</td>
<td>16%</td>
<td>2%</td>
<td>NA</td>
<td>6%</td>
<td>9%</td>
</tr>
<tr>
<td></td>
<td>133</td>
<td>Tamoxifen</td>
<td>53%</td>
<td>6%</td>
<td>19%</td>
<td>7%</td>
<td>10%</td>
</tr>
<tr>
<td></td>
<td>121</td>
<td></td>
<td>34%</td>
<td>3%</td>
<td></td>
<td>2%</td>
<td>6%</td>
</tr>
<tr>
<td>Quinn 1998 (8)</td>
<td>507</td>
<td>None Progestagen</td>
<td>NR</td>
<td>4%</td>
<td>NA</td>
<td>&lt;1%</td>
<td>13%</td>
</tr>
<tr>
<td></td>
<td>505</td>
<td>Tamoxifen</td>
<td>NR</td>
<td>5%</td>
<td>NR</td>
<td>2%</td>
<td>15%</td>
</tr>
<tr>
<td>Urbanski 1993 (9)</td>
<td>105</td>
<td>None Progestagen</td>
<td>NR</td>
<td>NR</td>
<td>NA</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>100</td>
<td></td>
<td>NR</td>
<td>NR</td>
<td></td>
<td>NR</td>
<td>10%</td>
</tr>
<tr>
<td>De Palo 1993 (10)</td>
<td>370</td>
<td>None Progestagen</td>
<td>NR</td>
<td>3%</td>
<td>NA</td>
<td>3%</td>
<td>5%</td>
</tr>
<tr>
<td></td>
<td>348</td>
<td></td>
<td>12%</td>
<td>2%</td>
<td>5%</td>
<td>1%</td>
<td>4%</td>
</tr>
<tr>
<td>Vergote 1989 (11)</td>
<td>531</td>
<td>None Progestagen</td>
<td>NR</td>
<td>3%</td>
<td>NA</td>
<td>&lt;1%</td>
<td>6% (p=0.04)</td>
</tr>
<tr>
<td></td>
<td>553</td>
<td></td>
<td>NR</td>
<td>5%</td>
<td>NR</td>
<td>1%</td>
<td>9%</td>
</tr>
<tr>
<td>Macdonald 1988 (12)</td>
<td>215</td>
<td>None Progestagen</td>
<td>NR</td>
<td>4%</td>
<td>NA</td>
<td>NR</td>
<td>11%</td>
</tr>
<tr>
<td></td>
<td>214</td>
<td></td>
<td>4%</td>
<td>3%</td>
<td></td>
<td>NR</td>
<td>10%</td>
</tr>
<tr>
<td>De Palo 1983 (13)</td>
<td>30</td>
<td>None Progestagen</td>
<td>NR</td>
<td>NR</td>
<td>NA</td>
<td>3%</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>32</td>
<td></td>
<td>NR</td>
<td>NR</td>
<td></td>
<td>3%</td>
<td>NR</td>
</tr>
<tr>
<td>Malkasian</td>
<td>17</td>
<td>Placebo</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>6%</td>
<td>6%</td>
</tr>
</tbody>
</table>
Quality of life

None of the studies had data on quality of life.

Meta-Analysis identified in the Search of the Literature

Martin-Hirsch et al. (16) conducted a published data meta-analysis comparing adjuvant progestin therapy to no adjuvant therapy in endometrial cancer. The authors identified seven (8-12,14,15) of the nine trials included in the present systematic review of the evidence (7-15). The authors of the meta-analysis also excluded the trial by Urbanski et al. (9) on the basis of clinical and statistical heterogeneity, and reported no significant difference in overall survival between patients who received progestin therapy and those who received no adjuvant treatment (OR = 1.05; 95% CI, 0.88-1.24, p=0.6). The authors also identified three trials that reported recurrence rates (8,10,11). Again, with the removal of the trial by Urbanski et al. (9), there was a marginal reduction in recurrence rate among women receiving progestin therapy compared to women receiving no adjuvant therapy (OR 0.81; 95% CI 0.65-1.01, p=0.06); however, the rate was not statistically significant. Meanwhile, the authors report that the rate of non-cancer-related deaths was significantly higher in the progestin group, presumably because of the adverse cardiovascular effects of progestin treatment (OR 1.33; 95% CI, 1.02-1.73).

The current meta-analysis included two additional trials, the trials by Von Minckwitz (7) and De Palo (13). Overall, aside from the additional trials, the results from the two meta-analyses were highly comparable.

CONCLUSION

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 I 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...

---

### Table:

<table>
<thead>
<tr>
<th>Year</th>
<th># of Pts.</th>
<th>Drug</th>
<th>NR</th>
<th>NR</th>
<th>NR</th>
<th>NR</th>
<th>NR</th>
<th>11%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1978 (14)</td>
<td>18</td>
<td>Progestagen</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Lewis 1974 (15)</td>
<td>287</td>
<td>Placebo</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>285</td>
<td>Progestagen</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td></td>
</tr>
</tbody>
</table>

*NOTE: No p-values were reported unless indicated*

# of Pts. = number of subjects, NR = not reported

*Author: the only minor adverse event reported was hypertension*
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 (8) 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. (9) 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. (16) 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.

FUTURE RESEARCH
The randomized trials completed to date have studied the use of specific types of
progestagens in early endometrial cancers, and one trial included tamoxifen as a comparison
group (7). Future trials can potentially include other anti-estrogenics, selective estrogen receptor
modulators (SERMs), aromatase inhibitors, and estrogen receptor down-regulators.

CONFLICT OF INTEREST
Members of the Gynecology DSG were asked to disclose potential conflict of interest
information. No conflicts were reported.

JOURNAL REFERENCE
A practice guideline has been published in the peer-reviewed journal Current Oncology
(http://www.current-oncology.com/index.php/oncology) :

- Gien L, Kwon JS, Oliver TK, Fung-Kee-Fung M. Adjuvant hormonal therapy for Stage I

ACKNOWLEDGEMENTS
The Gynecology DSG would like to thank Lilian Gien, Janice Kwon, Tom Oliver, and Michael
Fung-Kee-Fung for taking the lead in the development of this evidence series. The DSG would
also like to thank Alexandra Chambers for her assistance in the early development of this
evidence series.

For a complete list of the Gynecology DSG members, please visit the CCO website at
http://www.cancercare.on.ca/
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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

For information about the PEBC and the most current version of all reports, please visit the CCO Web site at http://www.cancercare.on.ca/ or contact the PEBC office at: Phone: 905-525-9140, ext. 22055    Fax: 905-522-7681

Funding
The PEBC is a provincial initiative of Cancer Care Ontario supported by the Ontario Ministry of Health and Long-Term Care through Cancer Care Ontario. All work produced by the PEBC is editorially independent from its funding source.

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REFERENCES

Adjuvant Hormonal Therapy for Stage I Endometrial Cancer: Guideline Development and External Review—Methods and Results

L. Gien, J. Kwon, T. Oliver, M. Fung-Kee-Fung, and the Gynecology Cancer Disease Site Group

A Quality Initiative of the
Program in Evidence-based Care (PEBC), Cancer Care Ontario (CCO)
Developed by the Gynecology Cancer Disease Site Group

Report Date: October 25, 2007

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 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 adjuvant hormonal therapy for stage I endometrial cancer, developed through systematic review, evidence synthesis, and input from practitioners in Ontario.

Report Approval Panel

The report was reviewed by the Assistant Director of the PEBC and the Report Approval Panel (RAP), which consists of two members, including an oncologist, with expertise in clinical and methodology issues. Key issues raised through internal review were primarily methodological in nature and included:

- Clarification in the Key Evidence that a published data meta-analysis was performed
- Discussion in the Outcomes section around the reporting and inclusion of non-cancer deaths as an outcome of interest given that attribution of death is a complex topic. If the outcome were to be included, more background would be required with a more systematic presentation of the data. It was noted that the DSG describes a pooled analysis on the outcome; thus, the requirements regarding the description of methods should be applied to the analysis, and the data should be reported in a systematic manner.
- The Methods section should indicate which outcomes are to be evaluated, and the manner for extracting data should be detailed. It was questioned how differences in follow-up between studies were accounted for when evaluating time-dependent data, and it was pointed out that adverse events should not be used as a surrogate for quality of life.
- In the Synthesizing the Data section, the rationale for the type of meta-analyses chosen (point in time versus hazards ratio) should be provided
- As part of the Study Quality section, the provision of a more explicit and balanced assessment of study quality for all of the trials was required. It was commented that statistical comparisons of baseline features do not always identify clinically relevant differences between patient groups, and the DSG should use other terminology to indicate that imbalances are evident.
- In the Results section, the presentation of recurrence and survival data requires clarification in Table 1. Typically, data are presented as time-dependent/actuarial outcomes; thus, it is unclear whether this had been done, and if so, at what time point each item of data has been measured.
- As part of the Meta-analyses, greater rationale was requested concerning the inclusion and exclusion of trials from the meta-analysis based on differences in study quality. In addition, it was suggested that all of the relevant trials in the meta-analyses be included and sensitivity analyses be conducted if statistical heterogeneity were present. More explicit information on the inclusion or exclusion of trials and their impact on the point
estimate of effect was recommended, and a comparison of the characteristics and results of the meta-analyses with those of the published meta-analyses was advised.

- As part of other minor comments, it was advised that the DSG reference their other guidelines about endometrial cancer, with respect to other treatment options/selected populations, and clarify if other forms of hormonal therapy extended beyond one trial with a tamoxifen treatment arm and the generic name for Provera be used in Table 1.

**Modifications/Actions**

In response to the comments raised through internal review, the Gynecology Cancer DSG made the following revisions to the draft document:

- It was clarified in the *Key Evidence* section and throughout the text that the meta-analysis identified in the search of the literature and the current meta-analyses were both based on published data.
- In the *Outcomes* section, non-cancer related deaths were identified as an outcome of interest associated with adverse events due to the possibility of increases in cardiovascular or thromboembolic events with adjuvant hormonal therapies. Because it is a complex outcome to assess and any post hoc analyses amount to subgroup analyses, the pooled analysis for that outcome was removed from the document. The individual trial data was still reported in the text, as were the meta-analysis results by Martin-Hirsch et al (16).
- The *Methods* section was expanded to include all the outcomes of interest, and data were extracted according to the availability of information in the trials. It was noted in the *Outcomes* section that there was variability of reporting across the trials; however, there was sufficient data to add time points to Table 1. There were insufficient data in the trials to link outcome data to a specific clinically relevant time point (such as the five-year point). This is a weakness of the review, based on limited reporting in the trials, and is most evident in the meta-analyses with point-in-time estimates. The comment suggesting a link between adverse events and quality of life was removed.
- Rationale for conducting point-in-time meta-analyses were provided in the *Synthesizing the Evidence* section as well as in the *Outcomes* section, under the survival and recurrence subheadings.
- Under the *Study Quality* section, given that the level of reporting across trials was modest, specific mention of study assessment was removed from the text, and a more explicit and balanced description of study quality was added to the text. In addition, the discussion around baseline patient characteristics was revised to focus on clinically relevant differences between patient groups and not statistically significant differences.
- Under the *Results* section, a column was added to Table 1 to show the point in time where overall survival was measured. As now mentioned under study quality, where reported, survival was measured at or beyond the point of median follow-up.
- The *Meta-analyses* were revised to include all the relevant trials, and sensitivity analyses were conducted to determine the cause of statistical heterogeneity. Two additional forest plots were added to the analyses to show the results of all the trials and those with the source of heterogeneity removed from the analysis. In addition, it was reported that the two meta-analyses were consistent in their assessment of statistical heterogeneity, the direction of effect, and the lack of statistically significant differences detected between patient groups.
- As part of other comments, related PEBC guidelines were added to Section 1 of the document, the reference to other forms of hormonal therapy was removed, the fact that tamoxifen was used in one patient group only was clearly stated, and the generic name for Provera was added to Table 1.
Conclusion

This report reflects the integration of feedback obtained through the internal review process, with final approval given by the Gynecology Cancer 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.

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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Funding
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REFERENCES
