The oncologic outcome after fertility-sparing hormonal management more than 9 months treatment for early stage endometrioid endometrial cancer

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INTRODUCTION

● Most common gynecologic cancer in USA, and its incidence rising in Korea

● < 40 years incidence = 5%

● Stage IA, EC patients who want to be pregnant or want to preserve fertility → Fertility-sparing management

● Systemic progestin and/or levonorgestrel intrauterine device (LNG-IUD)

● The complete response (CR) rate of hormonal treatment (HT) is demonstrated in some studies and is about 55-89%.

● CR rate in Meta-analysis: 76.3% (oral progestin), 72.9% (LNG-IUD)

Kim et al. Int J Gynecol Cancer. 2011
Tangjitgamol et al. Gynecol Obstet Invest. 2009
Gunderson et al. Gynecol Oncol. 2012
Fan et al. Int J Gynecol Cancer 2018
NCCN Guidelines Version 1.2018
Endometrial Carcinoma

CRITERIA FOR CONSIDERING FERTILITY-SPARING OPTIONS FOR MANAGEMENT OF ENDOMETRIAL CARCINOMA (All criteria must be met)

- Well-differentiated (grade 1) endometrioid adenocarcinoma on dilation and curettage (D&C) confirmed by expert pathology review
- Disease limited to the endometrium on MRI (preferred) or transvaginal ultrasound
- Absence of suspicious or metastatic disease on imaging
- No contraindications to medical therapy or pregnancy
- Patients should undergo counseling that fertility-sparing option is NOT standard of care for the treatment of endometrial carcinoma

PRIMARY TREATMENT

- Consultation with a fertility expert prior to therapy
- Genetic counseling/testing in selected patients (See UN-1)

SURVEILLANCE

- Complete response by 6 mo

Endometrial sampling every 3-6 mo (either D&C or endometrial biopsy)

Encourage conception (with continued surveillance every 3-6 mo)

Endometrial cancer present at 6-12 months

TH/BSO with staging after childbearing complete or progression of disease or endometrial sampling (see ENDO-1)

TH/BSO with staging after childbearing complete or progression of disease or endometrial sampling (see ENDO-1)
Fertility-Sparing Therapy

- TH/BSO with staging is recommended
  1. after childbearing is complete
  2. if patients have documented progression on the biopsies
  3. if endometrial cancer is still present after 6 to 12 months of progestin-based therapy
INTRODUCTION

- SEER data base (1993-2012)

# Table 2: Cumulative Probability (95% CIs) of Endometrial Cancer-Specific and All-Cause Mortality by Treatment Group

<table>
<thead>
<tr>
<th>Cause of Death</th>
<th>Time Since Diagnosis, Years</th>
<th>HT Group N=161</th>
<th>Full Surgery Group N=6178</th>
<th>Propensity Score-Matched Surgery Group N=161</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endometrial cancer (as defined by SEER)</td>
<td>2</td>
<td>0.66% (0.09%-4.59%)</td>
<td>0.25% (0.15%-0.42%)</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>1.67% (0.41%-6.70%)</td>
<td>0.70% (0.51%-0.98%)</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>5.28% (1.88%-14.38%)</td>
<td>1.53% (1.18%-1.98%)</td>
<td>1.09% (0.15%-7.50%)</td>
</tr>
<tr>
<td></td>
<td>15</td>
<td><strong>9.22% (3.35%-24.04%)</strong></td>
<td><strong>2.05% (1.52%-2.76%)</strong></td>
<td><strong>1.09% (0.15%-7.50%)</strong></td>
</tr>
<tr>
<td>All causes plausibly related to endometrial cancer</td>
<td>2</td>
<td>0.66% (0.09%-4.59%)</td>
<td>0.78% (0.58%-1.05%)</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>1.67% (0.41%-6.70%)</td>
<td>1.96% (1.59%-2.41%)</td>
<td>2.74% (0.89%-8.30%)</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>8.16% (3.59%-17.97%)</td>
<td>4.10% (3.46%-4.86%)</td>
<td>5.97% (2.34%-14.77%)</td>
</tr>
<tr>
<td></td>
<td>15</td>
<td>11.99% (5.25%-26.10%)</td>
<td>6.79% (5.69%-8.10%)</td>
<td>8.69% (3.61%-20.13%)</td>
</tr>
<tr>
<td>All causes</td>
<td>2</td>
<td>0.66% (0.09%-4.59%)</td>
<td>0.55% (0.39%-0.78%)</td>
<td>0.66% (0.09%-4.58%)</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>1.67% (0.41%-6.70%)</td>
<td>1.72% (1.39%-2.12%)</td>
<td>3.38% (1.27%-8.87%)</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>10.35% (4.85%-21.34%)</td>
<td>4.34% (3.70%-5.08%)</td>
<td>6.59% (2.78%-15.18%)</td>
</tr>
<tr>
<td></td>
<td>15</td>
<td>14.08% (6.66%-28.41%)</td>
<td>8.04% (6.88%-9.38%)</td>
<td>9.29% (4.07%-20.48%)</td>
</tr>
</tbody>
</table>

Abbreviations: 95% CI, 95% confidence interval; HT, hormone therapy; NA, not applicable; SEER, Surveillance, Epidemiology, and End Results.

*Values in bold denote a significantly higher risk of death for the HT group.*

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Figure 2. Cumulative survival curves up to 15 years after diagnosis according to primary course of treatment (hormone therapy [HT] vs surgery).

(A) Endometrial cancer-specific deaths in the full cohort. There were 66 deaths in the surgery group and 5 deaths in the HT group (log-rank test, $P=.0056$).

(B) Endometrial cancer-specific deaths in the propensity score-matched cohort. There was 1 death in the surgery group and 5 deaths in the HT group (stratified log-rank, $P=.5637$).
INTRODUCTION

KGOG 2002

- Total enroll patient n=148
- Inclusion criteria: Age ≤40, Stage IA, grade 1, endometrioid adenocarcinoma, fertility-sparing management (MPA or MA daily)
- Maintenance treatment n=24
- Complete response 77.7% (115/148), Recurrence 30.4% (35/115)
- Median time interval to CR 18 (8-55) weeks
- Median progestin treatment 8 (2-31) months
- Median follow-up time 66 (14-194) months
- Median time interval to recurrence 15 (4-61) months
OBJECTIVE

- There is no consensus of optimal time duration for treatment.
- To determine **the time duration** of fertility sparing hormone therapy in patients with early stage endometrioid endometrial cancer.
MATERIAL AND METHODS

- Retrospective
- Single center (Konkuk University Medical Center)
- Endometrioid endometrial carcinoma, Stage IA, Grade 1
- High dose hormonal treatment (Oral progestin with/without LNG-IUD)
- Who wanted to preserve fertility
- < 9 months treatment duration group vs. 9 ≤ months duration group

Exclusion criteria
1) Over presumed Stage IB, Grade 2/3
2) Patients who are middle in treatment and the duration were less than 9 months
3) Synchronous primary cancer patient
4) Patient who has no medical record of treatment duration
MATERIAL AND METHODS

Definition

- Complete remission (CR): absence of hyperplasia or carcinoma in pathologic confirm by endometrial biopsy
- Partial response (PR): present of hyperplasia in pathologic confirm
- Stable disease (SD): present of carcinoma in pathologic confirm
- Progressive disease (PD): upgrading in pathologic confirm or disease progression detected by image
MATERIAL AND METHODS

- Statistical analysis (SPSS Inc. version 17.0)
  - Student’s t-test, Mann-Whitney U-test
  - Chi-squared test, Fisher’s exact test
  - Kaplan-Meier method
- P <0.05 in two side tests
RESULTS

- Total enrolled patients number = 120
- Total CR rate : 84.2%
- Total recurrence rate : 31.7 %

Compared in 2 Groups

- < 9 months treatment duration n=45
- 9 ≤ months treatment duration n=75
Table 1. The basic characteristics of fertility sparing treatment patients with comparing treatment group of less than 9 months and more than 9 months.

<table>
<thead>
<tr>
<th></th>
<th>Total (n=120)</th>
<th>Less than 9 months (n=45)</th>
<th>More than 9 months (n=75)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>33.5 (22-43)</td>
<td>33 (26-40)</td>
<td>34 (22-43)</td>
<td>0.20</td>
</tr>
<tr>
<td>BMI (kg/m2)</td>
<td>24.1 (17.7-46.4)</td>
<td>23.0 (18.0-46.4)</td>
<td>25.6 (18.0-43.6)</td>
<td>0.13</td>
</tr>
<tr>
<td>Parity</td>
<td></td>
<td></td>
<td></td>
<td>0.87</td>
</tr>
<tr>
<td>0</td>
<td>110 (91.7)</td>
<td>41 (91.1)</td>
<td>69 (92.0)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>10 (8.3)</td>
<td>4 (8.9)</td>
<td>6 (8)</td>
<td></td>
</tr>
<tr>
<td>Unmarried status at diagnosis</td>
<td>35 (29.2)</td>
<td>13 (28.9)</td>
<td>22 (29.3)</td>
<td>0.93</td>
</tr>
<tr>
<td>History of Infertility</td>
<td>82 (68.3)</td>
<td>16 (35.6)</td>
<td>20 (26.7)</td>
<td></td>
</tr>
<tr>
<td>Polycystic ovary</td>
<td>65 (54.2)</td>
<td>18 (40.0)</td>
<td>47 (58.7)</td>
<td>0.03</td>
</tr>
<tr>
<td>Irregular menstruation</td>
<td>43 (35.8)</td>
<td>15 (33.3)</td>
<td>28 (37.3)</td>
<td>0.85</td>
</tr>
<tr>
<td>Progestin type</td>
<td></td>
<td></td>
<td></td>
<td>0.73</td>
</tr>
<tr>
<td>MPA</td>
<td>111 (92.5)</td>
<td>41 (91.1)</td>
<td>70 (93.3)</td>
<td></td>
</tr>
<tr>
<td>500mg once daily</td>
<td>76 (63.3)</td>
<td>40 (88.9)</td>
<td>36 (48.0)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>1000mg once daily</td>
<td>41 (34.2)</td>
<td>4 (8.9)</td>
<td>37 (49.3)</td>
<td></td>
</tr>
<tr>
<td>MA</td>
<td>3 (2.5)</td>
<td>2 (4.4)</td>
<td>1 (1.3)</td>
<td></td>
</tr>
<tr>
<td>LNG-IUDs insertion</td>
<td>92 (76.7)</td>
<td>29 (64.4)</td>
<td>63 (84.0)</td>
<td>0.01</td>
</tr>
<tr>
<td>Aromatase inhibitor</td>
<td>10 (8.4)</td>
<td>0 (0)</td>
<td>10 (13.4)</td>
<td>0.16</td>
</tr>
<tr>
<td>CA125 at initial diagnosis (U/ml)</td>
<td>16.8 (4-172)</td>
<td>17.7 (4-56)</td>
<td>16.1 (5-172)</td>
<td>0.81</td>
</tr>
</tbody>
</table>

\( N (\%), \text{median (range)} \)
### RESULTS

Table 2. The oncologic outcome of treatment group of less than 9 months and more than 9 months.

<table>
<thead>
<tr>
<th></th>
<th>Total (n=120)</th>
<th>Less than 9 months (n=45)</th>
<th>More than 9 months (n=75)</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Time of treatment duration</strong> (months)</td>
<td>10.8 (3-102)</td>
<td>6.6 (3-8)</td>
<td>14.8 (9-102)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td><strong>Follow-up time</strong> (months)</td>
<td>32.9 (5-130)</td>
<td>28.8 (5-129)</td>
<td>35.5 (10-130)</td>
<td>0.09</td>
</tr>
<tr>
<td><strong>Time to CR</strong> (months)</td>
<td>9.3 (2-84)</td>
<td>4.5 (2-9)</td>
<td>13.3 (3-84)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td><strong>Time to recur</strong> (months)</td>
<td>11 (1-92)</td>
<td>16 (1-92)</td>
<td>9 (3-67)</td>
<td>0.12</td>
</tr>
<tr>
<td><strong>CR rate, N (%)</strong></td>
<td>101 (84.2)</td>
<td>39 (86.7)</td>
<td>62 (82.7)</td>
<td>0.62</td>
</tr>
<tr>
<td><strong>SD rate, N (%)</strong></td>
<td>9 (7.5)</td>
<td>4 (8.9)</td>
<td>5 (6.7)</td>
<td>0.73</td>
</tr>
<tr>
<td><strong>PD rate, N (%)</strong></td>
<td>5 (4.2)</td>
<td>1 (2.2)</td>
<td>4 (5.3)</td>
<td>0.65</td>
</tr>
<tr>
<td><strong>Recurrence rate, N (%)</strong></td>
<td>38 (31.7)</td>
<td>16 (35.6)</td>
<td>22 (29.3)</td>
<td>0.55</td>
</tr>
</tbody>
</table>

*median (range)*  
CR, complete remission; SD, stable disease; PD, progressive disease
RESULTS

Figure 1. The cumulative complete remission rate of fertility-sparing hormone therapy in early stage endometrioid endometrial cancer patients.
RESULTS

$P = 0.85$
RESULTS

• No CR: n=19
• Surgical staging: n=7
• Upstaging, Upgrading
  • < 9 months treatment group: n=0
  • 9 ≤ months treatment: n=1

<table>
<thead>
<tr>
<th>Age</th>
<th>Para</th>
<th>CA 125</th>
<th>Time of treatment</th>
<th>Progestin</th>
<th>Surgical stage</th>
<th>Surgical grade</th>
<th>Adjuvant chemotherapy</th>
<th>recur</th>
<th>Follow-up time</th>
<th>Last status</th>
</tr>
</thead>
<tbody>
<tr>
<td>38</td>
<td>1</td>
<td>8.5</td>
<td>16 months</td>
<td>MPA 500/day → MPA 1000/day</td>
<td>1B</td>
<td>2</td>
<td>No</td>
<td>No</td>
<td>110 months</td>
<td>NED</td>
</tr>
</tbody>
</table>

12 months DCB : SD → imaging work-up

✓ MRI : R/O Ovary metastasis
✓ PET-CT : R/O Lymph node metastasis.
CONCLUSION

• The treatment of fertility-sparing therapy in stage IA, grade 1 endometrioid EM cancer can be extended to 15 months.

• There is always a risk that the disease might progress.

• Therefore, staging work-up should be necessary in 12 months of treatment duration.

• If longer duration than 12 months of treatment is desired, the patient should be advised the risk before ongoing the treatment.
Thank you for your attention