

# Attitudes and practices of Korean gynecologists towards hormone replacement therapy in endometrial cancer survivors

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## Summary

**Purpose:** To investigate the attitudes of Korean gynecologists towards prescribing hormone replacement therapy (HRT) after treatment for endometrial cancer. **Materials and Methods:** A questionnaire, addressing attitudes towards HRT and treatment strategies for patients previously treated for endometrial cancer, was distributed to 163 Korean gynecologists. **Results:** Of the 163 gynecologists that were sent this questionnaire, 98 (60.1%) responded. Among the respondents, 81 (82.7%) had previously prescribed HRT to patients with endometrial cancer. Of the latter, 75 (92.6%) had prescribed HRT to patients with Stage I, and more than half to patients with Stage II, endometrial cancer. Of the respondents who had prescribed HRT, 33 (40.7%) did so without regard for cancer-cell type and 33 (40.7%) began patients on HRT more than two years after endometrial cancer treatment. Tibolone was the most commonly prescribed drug (61.9%). The most common reason not to prescribe HRT was fear of cancer recurrence (38.1%). **Conclusion:** Most of the Korean gynecologists surveyed had experience prescribing HRT to endometrial cancer patients. Although HRT is not actively recommended, HRT given post-therapy to endometrial cancer patients is considered acceptable.

**Key words:** Endometrial cancer; Menopause; Hormone replacement therapy; Tibolone; Estrogen; Progesterone.

## Introduction

Endometrial adenocarcinoma is the most common gynecological cancer in Western countries, with an incidence of 22 per 100,000 women. The disease occurs more frequently in postmenopausal women, although 25% of endometrial cancers occur in premenopausal women [1]. Recently, the incidence of endometrial cancer has increased in Korean women [2]. The treatment of choice in women with endometrial cancer consists of a total hysterectomy and bilateral salpingo-oophorectomy, which can induce an abrupt onset of menopausal symptoms in premenopausal women. Postmenopausal women can also suffer from discomfort arising from estrogen-deficiency. Therefore, hormone replacement therapy (HRT) is utilized to relieve menopausal symptoms in endometrial cancer patients [3].

In 2003, the North American Menopause Society stated that menopausal symptoms, such as vasomotor symptoms and sleep disruption, may be primary indicators of the need for systemic HRT [4]. HRT has been shown to be beneficial in the prevention of osteoporosis, coronary heart disease, and colon cancer, and in promoting patient quality of life [5, 6]. However, HRT has also been reported to increase the risk of breast cancer [7] and is absolutely contraindicated in endometrial cancer patients. Factors associated with an increased risk of recurrence in women who are administered HRT after treatment for endometrial cancer have not been identified [3]. Practi-

cally, HRT is often administered to women treated for Stages I or II endometrial cancer who complain of menopausal symptoms [3]. Although the safety of exogenous estrogen with regard to the risk of endometrial cancer recurrence has not been established, the absolute recurrence rate was low [8]. Thus, gynecologists have had difficulty deciding on whether to prescribe HRT to endometrial cancer patients.

Although many surveys of gynecologists have assessed their use of HRT in cancer patients, only two studies to date have reported a consensus among gynecologists in recommending HRT for endometrial cancer patients [9, 10]. In Korea, the indications for HRT in endometrial cancer patients have not been clearly determined. The authors therefore evaluated the attitudes of Korean gynecologists towards the use of HRT in survivors of endometrial cancer and their practices in prescribing HRT for these patients.

## Materials and Methods

From September to December 2011, a questionnaire was sent by e-mail to 163 gynecologists registered as members of the Korean Gynecologic Oncology Group, part of the Korean Society of Gynecologic Oncology, and to other oncologists who did not join the group or had retired. The questionnaire addressed the attitudes and practices of gynecologists with respect to prescribing HRT for patients who had been previously treated for endometrial cancer.

Gynecologists who had expressed their wish not to participate in the study were excluded. The questionnaire asked for the following information: (1) personal data on the gynecologist,

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### Survey of current HRT tendency among patients with endometrial cancer

1. Please fill out all requested information

Date of birth: (year) :  
Institution/Organization :

2. What is your expertise area?

- ① General Gynecology
- ② Gynecologic Oncology
- ③ Medical Oncology
- ④ Radiation Oncology
- ⑤ Endocrinology

3. How many endometrial cancer patients do you treat a year?

- ① <10
- ② 11~20
- ③ 21~50
- ④ > 51

4. Have you performed HRT on endometrial cancer patients?

- ① Yes
- ② No

If your answer is "yes," please answer to question #5-14  
If your answer is "no," please answer to question #15

5. What percentage of your patients with endometrial cancer patients have you prescribed HRT after cancer therapy, including those using, starting or restarting HRT?

- ① <10%
- ② 25%~50%
- ③ 50%~75%
- ④ 75%~100%

6. What is the most common reason why you do not perform HRT on all of the endometrial cancer patients?

- ① Patient refusal
  - ② Concerns for cancer prognosis
  - ③ Due to comorbid disease
  - ④ Due to old age
  - ⑤ Not to complain the menopausal symptoms
  - ⑥ Others
- Please briefly explain your reason

7. What is the clinical stage of your patient who gets HRT? (Select all that apply)

- ① I
- ② II
- ③ III
- ④ IV
- ⑤ Recurred patients

8. What is the cell type of your endometrial cancer patient who gets HRT?

- ① Endometrioid type

- ② Non-endometrioid type
- ③ Regardless of cell type

9. Among your patients with endometrial cancer under the treatment of HRT, what is patient's grade of cell differentiation? (Select all that apply)

- ① Grade I
- ② Grade II
- ③ Grade III

10. When do you start performing HRT?

- ① During the cancer therapy if they complain the menopausal symptom
- ② After completion of therapy
- ③ Two years after completion of therapy
- ④ Five years after completion of therapy
- ⑤ When cancer has recurred
- ⑥ Others
- ⑦ -Please briefly explain your reason.

11. How long do you perform HRT?

- ① Less than 5 years
- ② More than 5 years

12. What type of HRT do you use? (E: estrogen, P progesterone)

- ① Tibolone
- ② Selective estrogen receptor modulators (SERM)
- ③ Estrogen 0.625mg only
- ④ combined continuous (E-P is taken daily)
- ⑤ combined cyclic (E-P is given together with 3wk on and 1wk off)
- ⑥ sequential cyclic (E for 3wk, P for 5 to 15 d per month, and 1week off)
- ⑦ others

13. Have your patients experienced any side effect after HRT?

- ① Yes
- ② No

-If yes, please briefly explain the side effect that experienced.

14. Based on your clinical experiences, do you think that HRT is related to the prognosis of endometrial cancer?

- ① Yes
- ② No

15. What is the main reason why you do not perform HRT on endometrial cancer patients?

- ① Concerns for cancer prognosis
- ② Concerns for side effects of HRT
- ③ Patient refusal
- ④ Due to comorbid disease
- ⑤ Others

-Please briefly explain your reason.

Figure 1. — The questionnaire.

including his or her age, sex, place of work, and areas of expertise; (2) the number of patients per year and the number of patients with endometrial cancer per year treated by the gynecologist and the rate of administration of HRT to the latter; (3) the Stage, grade, and cell type of endometrial cancer; (4) the types of HRT prescribed to patients with endometrial cancer; and (5) the side-effects of HRT. All of the questions were

designed as closed questions except for those relating to personal information about the gynecologists and the side-effects of HRT (Figure 1).

Collected responses were analyzed using SAS statistical software (version 8.0). Differences in frequency were evaluated using Student's *t* tests. A *p* value < 0.05 was considered statistically significant.

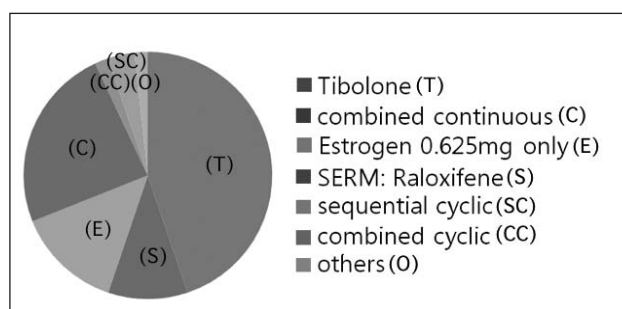


Figure 2. — The percentage and types of HRT prescriptions by Korean gynecologists.

Among the respondents who prescribed HRT, 61.7% preferred to prescribe tibolone, 33.3% preferred combined continuous estrogen/progesterone therapy, 14.3% preferred SERMs, and 18.5% preferred estrogen only ( $p = 0.03$ ). (Some of respondents chose more than two types of HRT prescriptions that they preferred). SERM and combined continuous estrogen/progesterone were taken orally every day. Combined cyclic estrogen/progesterone was taken daily for three weeks with no pills for one week. The sequential cyclic treatment was as follows: estrogen was taken for the first three weeks, and progesterone was taken for five to 15 days per month, followed by a break of one week.

## Results

### Demographic data of the responding gynecologists

Of the 163 gynecologists sent questionnaires, 98 responded (60.1%). Table 1 shows the demographic characteristics of the study sample. Of the 98 respondents, 88 (90.0%) reported expertise in gynecologic oncology; 93 (94.9%) were male, and five (5.1%) were female. The authors found that 87 (88.8%) worked in academic settings and nine (9.2%) in private offices ( $p < 0.05$ ); the other two (2.0%) had recently retired. In Korea, most patients with endometrial cancer, except for those undergoing incidental or emergency operations, are treated by a gynecologic oncologist, and most patients prefer an academic hospital. Over a one-year period, 72 of the 98 respondents (73.5%) had treated more than ten patients newly-diagnosed with endometrial cancer, and 12 (12.5%) had treated more than 50 such patients.

### Prescription of HRT

Of the 98 respondents, 81 (82.7%) had previously prescribed HRT to patients with endometrial cancer, although 54 (54.8%) had prescribed HRT to fewer than 10% of their patients with endometrial cancer. When the authors divided the gynecologists into two groups according to age,  $< 45$  and  $> 45$  years, they found that the younger gynecologists were more willing to prescribe HRT than the older gynecologists (86.8% vs 73.3%), but this difference was not statistically significant. There was no significant difference in HRT prescription rate between male and female gynecologists, most likely due to the small number of the latter included in this study.

Table 1. — Demographic characteristics of the study ( $n = 98$ ).

Clinical factors	Number	(%)
Age		
Younger than 45 years	68	(69.4)
Older than 45 years	30	(30.6)
Gender		
Male	93	(94.9)
Female	5	(5.1)
Expertise		
Gynecologic oncology	91	(92.9)
General gynecology	6	(6.1)
Endocrinology	1	(1.0)
Number of endometrial cancer patient per year		
~10	26	(26.5)
11~20	39	(39.8)
21~50	23	(23.5)
51~	10	(10.2)
Experience to prescribe HRT to endometrial cancer patients		
Yes	81	(82.7)
No	17	(17.3)

### Indications for HRT

**Stage:** When the authors evaluated patient selection criteria for prescribing HRT, they found that 75 of the 81 (92.6%) respondents who prescribed HRT to endometrial cancer patients did so for patients with Stage I, and more than half for patients with Stage II, endometrial cancer.

**Cell type:** Of the 81 gynecologists who had prescribed HRT to endometrial cancer patients, 44 (54.3%) did so only for patients with endometrioid-cell tumors, whereas 33 (40.7%) prescribed HRT to endometrial cancer patients without regard for cancer cell type.

**Grade of tumor:** The authors found that 79 of the 81 (97.5%) respondents who had prescribed HRT to endometrial cancer patients did so for patients with tumor grades I and II, with 19 (23.5%) prescribing HRT only to patients with grade I tumors.

**Onset of treatment:** Thirty-three of the 81 respondents who had prescribed HRT (40.7%) did so two years or more after the patient had completed treatment for endometrial cancer, whereas 19 (23.5%) started patients on HRT after the onset of climacteric symptoms, even during cancer treatment.

### Duration of HRT

The authors found that 62 of the 81 (76.5%) gynecologists who had prescribed HRT preferred that patients be treated for less than five years.

### Choice of medication for HRT

Of the 81 respondents who had prescribed HRT, 50 (61.7%) preferred tibolone, 27 (33.3%) preferred combined continuous estrogen/progesterone therapy, 12 (14.3%) preferred selective estrogen receptor modulators (SERMs), and 15 (18.5%) preferred estrogen only ( $p =$



0.03). Preferences were unrelated to the location of the practice or the age or sex of the gynecologist. Figure 2 shows the preferred types of HRT.

#### *Side-effects of HRT*

Nine (11.1%) of the gynecologists reported minimal adverse effects of HRT, including breast tenderness, headache, and weight gain. The only serious adverse effect was thromboembolism in one patient, but a direct relationship between this thromboembolism and HRT was not identified. Furthermore, the authors could not determine whether any of the adverse effects was correlated with treatment for endometrial cancer.

#### *Reasons not to recommend HRT*

The three most frequent reasons cited by respondents to avoid HRT in women with endometrial cancer were (1) HRT may promote the recurrence of endometrial cancer (38.1%); (2) the patient has no complaints of menopausal symptoms (26.2%); and (3) patient refusal (21.4%).

### **Discussion**

In Korea, the tendency to treat menopausal women with HRT has increased, with 25% of menopausal Korean women having a history of undergoing HRT [7]. HRT contributes to the relief of menopausal symptoms, such as hot flashes, sweating, and vaginal dryness. In the Women's Health Initiative clinical trial, treatment with estrogen plus progestin reduced the risks of colon cancer and bone fractures; however, it increased the risks of breast cancer and deep vein thrombosis [11]. These findings have led to changes in HRT prescription patterns, including decreasing the number of prescriptions and increasing the use of alternative medications, such as psychoactive drugs and phytoestrogen [12, 13].

Menopausal symptoms are a serious problem for endometrial cancer survivors [8]. Since endometrial cancers are estrogen-dependent, prescribing HRT has been generally contraindicated in endometrial cancer survivors, since HRT may stimulate cancer recurrence. Gynecologists have more confidence than other physicians regarding the role of HRT during the climacteric [14]. Of four studies assessing the use of HRT in endometrial cancer survivors, there was no increased risk of recurrence or death in the HRT group [8, 15-17]. Together, these findings suggest that HRT is safe in endometrial cancer patients.

Sixty-seven percent of Belgian physicians preferred to prescribe HRT to endometrial cancer survivors, with 49% of the latter prescribing estrogen-only therapy [9]. In contrast, 69.6% of Greek gynecologists reported not recommending HRT because of fears of endometrial cancer recurrence [10]. A review of other gynecological cancers showed that 48% of Greek gynecologists prescribed HRT to ovary cancer survivors, with 60% of the latter prescribing tibolone [18].

The present authors found that the percentage of Korean gynecologists who had prescribed HRT to endometrial cancer patients was very high (82.7%), although 54.8% prescribed HRT to fewer than 10% of their patients with endometrial cancer. These findings suggest that Korean gynecologists were generally hesitant to prescribe HRT to endometrial cancer patients. Similar to Greek gynecologists, the most common reason cited by Korean gynecologists for not offering HRT was the fear of stimulating endometrial cancer recurrence.

The present authors found that 61.9% of the Korean gynecologists who responded to this survey preferred tibolone as an alternative to HRT after endometrial cancer treatment. In comparison, 24.8% of Greek gynecologists preferred alternatives to HRT, such as selective estrogen receptor modulators (SERMs) and phytoestrogen [10]. Tibolone is useful for treating menopausal symptoms arising from estrogen deficiency, without inducing endometrial proliferation [19]. Raloxifene, a SERM, has also been reported to not have a proliferative effect on the endometrium. Unfortunately, the safety of tibolone and raloxifene as alternatives to HRT after endometrial cancer treatment has not been adequately investigated [4]. Therefore, women must be informed about the potential risks of using these alternatives [3].

The present authors found that 33.3% of Korean gynecologists gave combined continuous estrogen/progesterone treatment (CCEPT) to survivors of endometrial cancer. A German study found that CCEPT did not induce *de novo* hyperplasia in any woman, but restored endometrium with complex hyperplasia to normal histology [20]. CCEPT is still frequently used as a form of HRT in post-endometrial cancer patients [4].

The main factor influencing the attitudes of breast cancer patients toward HRT is the presence or absence of menopausal symptoms, with more postmenopausal than premenopausal women willing to try HRT [21].

Although the available evidence indicates no association between HRT and endometrial cancer, many Korean gynecologists are reluctant to prescribe HRT to survivors of endometrial cancer, mainly because of the fear of triggering disease recurrence or of adverse professional and legal consequences.

In conclusion, the majority of the Korean gynecologists who responded to this survey had prescribed HRT to endometrial cancer patients. Although HRT is not recommended for these patients, it is considered relatively acceptable in Korea.

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