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Outcomes of ovarian preservation in a cohort of premenopausal women with early-stage endometrial cancer: A Korean Gynecologic Oncology Group study

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HIGHLIGHTS

- Ovarian preservation was not associated with increased mortality, even after adjusting other covariates.
- This study suggests that ovarian preservation may be performed safely in young patients with early stage endometrial cancer.

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ABSTRACT

Objective. The aim of this study was to evaluate the impact of ovarian preservation on the recurrence and survival rates of premenopausal women with early-stage endometrial cancer.

Methods. Using medical records of premenopausal women who received primary surgical treatment for stage I–II endometrial cancer, the demographics and survival rates were compared retrospectively for patients who had ovarian preservation and those who underwent bilateral salpingo-oophorectomy. Cox proportional hazards models with inverse probability of treatment weighting (IPTW) based on propensity score were performed to adjust for selection bias between the two groups.

Results. A total of 495 women were identified, including 176 patients who had ovarian preservation. The ovarian preservation group was younger ($P < 0.001$) and had an earlier year of diagnosis ($P = 0.014$), a lower prevalence of lymphadenectomy ($P < 0.001$), and a marginally significant association with lower tumor grade ($P = 0.052$). The Kaplan–Meier curve and the log rank test showed no difference in either recurrence-free survival ($P = 0.742$) or overall survival ($P = 0.462$) between the two groups. In a multivariate Cox model adjusted by IPTW and covariates, ovarian preservation had no effect on either recurrence (hazard ratio [HR], 0.73; 95% CI, 0.29–1.81) or overall survival (HR, 1.33; 95% CI, 0.43–4.09).

Conclusions. Ovarian preservation does not appear to be associated with an adverse impact on the outcomes of premenopausal women with early-stage endometrial cancer. The present study has useful implications for physicians counseling young women who want to preserve their ovaries.

Introduction

Endometrial cancer is the most common gynecologic malignancy in Western countries and its incidence in Asian countries, including Korea, is increasing [1,2]. A 2010 report on annual cancer statistics in Korea showed that approximately 37.0% of patients diagnosed with endometrial carcinoma were premenopausal women and 10.4% were under

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the age of 40 [3]. The prognosis for endometrial cancer among premenopausal women tends to be favorable, with early-stage diagnoses and well-differentiated tumor grades being reported more frequently [4]. As a result, quality of life and fertility preservation are a matter of great interest in young endometrial cancer patients.

The current guidelines recommend surgical staging, including total hysterectomy, and bilateral salpingo-oophorectomy (BSO) for early-stage endometrial cancer regardless of age [5]. Routine BSO at the time of surgery is based on the concept of removing the occult, coexisting ovarian malignancy and estrogen production source. However, this decision should take into consideration the significant long-term morbidity and mortality of premature menopause [6]. Surgical castration may affect the quality of life for young women without coexisting ovarian cancer. In addition to the loss of fertility, early surgical menopause is known to be linked to increased risk of cardiovascular disease and osteoporosis in the future [7,8].

Although previous studies have demonstrated the risk of coexisting malignancy in patients with early-stage endometrial cancer [9–11], only a limited number of studies have described the long-term oncologic outcomes of ovarian preservation. Several investigators, including our group, have shown that ovarian preservation does not impact the survival of early-stage endometrial cancer adversely [12–14]. However, uncertainty still remains about the safety of patients who have undergone ovarian preservation. In particular, a large number of clinicians think that they may not need to remove the ovaries in early-stage endometrial cancer. In a Korean survey, 69% of gynecologic oncologists stated that grossly normal-looking ovaries can be preserved in young patients with early-stage disease [15]. Our objective in this cohort study was to evaluate the impact of ovarian preservation on the recurrence and survival rates of premenopausal women with early-stage endometrial cancer.

Methods

Patient cohort

From January 1997 to December 2008, 1032 patients with endometrial cancer were identified in the tumor registries of 20 tertiary hospitals. These patients were screened for enrollment after obtaining the approval of the institutional review board. Advanced-stage (stage III/IV) patients, those with non-endometrioid histology, and postmenopausal women were excluded from the analysis. Consequently, 495 premenopausal women with early-stage endometrioid endometrial adenocarcinoma were identified. Ninety-eight cases in our previous study published in 2009 were also included [13].

Clinical data and pathologic information were collected, including age at diagnosis, year of diagnosis, stage, tumor grade, performance of lymphadenectomy or adjuvant treatment, and follow-up results for recurrence and survival. Age at diagnosis was categorized as follows: ≤35, 36–40, and ≥41. Year of diagnosis was categorized into 1997–2002 and 2003–2008. All patients were surgically staged using the revised 2009 International Federation of Gynecology and Obstetrics (FIGO) staging system for endometrial cancer [16]. Only patients with stages IA, IB, and II were included. Recurrence-free survival was measured from the date of diagnosis to the date of recurrence or censored at the date of last follow-up. Overall survival was calculated as the number of months from cancer diagnosis to the date of death. Patients who were alive at the last follow-up were censored.

Statistical analysis

Differences between the baseline characteristics of the ovarian preservation and BSO groups were compared using the chi-square test or Fisher's exact test for categorical variables. The recurrence-free and overall survival curves were estimated using the Kaplan–Meier method and differences in survival between the groups were compared using the log rank test. To reduce the impact of treatment selection bias and potential confounding in an observational study, rigorous adjustment was performed for significant differences in the characteristics of patients using the weighted Cox proportional hazards models with the inverse probability of treatment weighting (IPTW) [17]. With this technique, weights for patients who underwent BSO were the inverse of (1-propensity score) and weights for patients who had ovarian preservation were the inverse of the propensity score. Multiple logistic-regression analysis was used to estimate the propensity scores. The following variables were included in the propensity score model: age, year of diagnosis, tumor grade, stage, and the performance of lymphadenectomy or adjuvant treatment. The discrimination of each propensity score model was assessed by means of the C statistic. In addition, for more rigorous adjustment to avoid selection bias and profile effects, a second Cox model was created with IPTW as the weights, the performance of BSO, and all pre-specified covariates. *P*-values less than 0.05 were considered significant and all statistical tests were two-sided. All statistical tests were performed using R, version 2.15.2 (Foundation for Statistical Computing, Vienna, Austria, http://www.r-project.org/).

Results

A total of 495 patients were included in this study. 176 had ovarian preservation and 319 underwent BSO. The baseline characteristics of the two groups are shown in Table 1. The ovarian preservation group was younger ($P < 0.001$) and had an earlier year of diagnosis ($P = 0.014$), a lower prevalence of lymphadenectomy ($P < 0.001$), and a marginally significant association with lower tumor grade ($P = 0.052$). After adjustment by IPTW, there is no significant difference in variables between the two groups. Reasons for ovarian preservation were listed under two categories based on a review of the medical charts. First, clinicians decided to preserve grossly normal-looking ovaries in young women as per the patients' desire. In 110 cases, at least one ovary was preserved for this reason. Second, endometrial cancer was found incidentally after the operation. In 63 cases, only a hysterectomy was performed as the preoperative diagnosis was a benign disease such as endometrial hyperplasia, leiomyoma, or adenomyosis. No additional surgery was performed to remove these ovaries. A clear reason for ovarian preservation could not be identified for three patients. In 71 patients, only one ovary was preserved based on surgeon's discretion considering the risk of occult metastasis despite grossly-normal looking finding.

Table 1
Baseline characteristics.

	Ovarian preservation ($n = 176$)	BSO ($n = 319$)	*P*-value	Adjusted by IPTW *P*-value
Age at diagnosis, years			<0.001	0.871
≤35	80 (45.5%)	36 (11.3%)		
36–40	45 (25.6%)	35 (11.0%)		
≥41	51 (29.0%)	248 (77.7%)		
Year of diagnosis			0.014	0.822
1997–2002	48 (27.3%)	57 (17.9%)		
2003–2008	128 (72.7%)	262 (82.1%)		
Tumor grade			0.052	0.192
1	133 (75.6%)	251 (78.7%)		
2	40 (22.7%)	52 (16.3%)		
3	3 (1.7%)	16 (5.0%)		
Stage			0.622	0.503
IA	159 (90.3%)	283 (88.7%)		
IB	6 (3.4%)	17 (5.3%)		
II	11 (6.3%)	19 (6.0%)		
Lymphadenectomy			<0.001	0.620
No	101 (57.4%)	77 (24.1%)		
Yes	75 (42.6%)	242 (75.9%)		
Adjuvant treatment			0.065	0.504
No	157 (89.2%)	265 (83.1%)		
Yes	19 (10.8%)	54 (16.9%)		

Abbreviations: BSO, bilateral salpingo-oophorectomy; IPTW, inverse probability of treatment weighting.