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Ovarian preservation for premenopausal women with early-stage endometrial cancer: a Chinese retrospective study

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Abstract

Objective: This study aimed to retrospectively investigate the safety of ovarian preservation of premenopausal women with stage 1a endometrial carcinoma.

Methods: We performed a population-based study to identify surgically treated stage Ia endometrial cancer of premenopausal women who were diagnosed between August 1989 and December 2015 in our center. Survival outcomes and recurrence rate were examined for premenopausal women who underwent ovarian preservation. Recurrence-free survival rates were calculated following generation of Kaplan–Meier curves and were compared with the log-rank test. Cox regression analysis was performed to identify the independent factors affecting the recurrence rate.

Results: Patients with ovarian preservation tended to be significantly younger at diagnosis, have less myometrial invasion, and were less likely to undergo lymphadenectomy compared with women treated with bilateral salpingo-oophorectomy. There was no significant difference in

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recurrence-free survival between the two groups. In the Cox regression model, ovarian preservation remained an independent prognostic factor for improved overall survival.
Conclusion: Ovarian preservation does not have a negative effect on oncological outcomes. Ovarian preservation can be applied to premenopausal women with stage Ia endometrial carcinoma.

Keywords
Ovarian preservation, endometrial cancer, recurrence-free survival, bilateral salpingo-oophorectomy, lymphadenectomy, premenopausal women

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Introduction

Endometrial cancer is one of the most prevalent malignant tumors of the female genital tract, accounting for 6% of all cases of cancer in women.[1] Over the last decade, there has been a significant increase in the number of Chinese women who have been diagnosed with endometrial cancer.[2] The median age of patients with endometrial cancer is 61 years. Approximately 20% of patients are diagnosed before menopause and 5% are diagnosed before 40 years old.[3,4]

According to the International Federation of Gynecology and Obstetrics and National Comprehensive Cancer Network, standard surgical management of endometrial carcinoma includes total hysterectomy and bilateral salpingo-oophorectomy (BSO), with or without pelvic and/or para-aortic lymphadenectomy. This treatment regimen has not been changed since 1988. The incidence of ovarian malignancy in women with early-stage endometrial cancer has been reported to be as high as 5% in the United States. Therefore, irrespective of the patient's age, BSO is routinely recommended. However, because of abrupt loss of estrogen, this procedure not only causes climacteric symptoms, including hot flushes, vaginal atrophy, sleeping disorders, cardiovascular disease, osteoporosis, and emotional problems, but also places patients at high risk for the long-term effects of estrogen deficiency. Premenopausal women with endometrial cancer often have low-grade, early-stage tumors and have a more favorable prognosis. Therefore, gynecological oncologists face the dilemma of ovarian preservation when managing a young woman with endometrial cancer. This study aimed to determine the safety of ovarian preservation in premenopausal patients with early-stage endometrial carcinoma.

Methods

The study was approved and supported by the Ethics or Institutional Review Board of Obstetrics and Gynecology Hospital of Fudan University. Patients participating in the study provided verbal informed consent.

In the present retrospective study, a cohort of premenopausal women who were diagnosed between August 1989 and December 2015 with endometrial cancer and had primary surgery in our center was included. Medical charts, including admission and discharge notes, as well as surgical pathology reports, were reviewed. Histological data (stage, grade, lymph–vascular space invasion [LVSI], depth of myometrial invasion, and lymph node involvement) and survival data (recurrence-free survival) were extracted. Recurrence-free survival was determined as the number of months from the primary

surgery to the date of recurrence or censored at the date of the last follow-up. The mean follow-up month was 54.9 ± 34.96 months. The International Federation of Gynecology and Obstetrics (FIGO, 2009) was used for tumor staging. Patients with stage Ia (tumor confined to the endometrium or $< 50\%$ of the myometrium) were included. All pathological material had been previously reviewed by gynecological pathologists.

Surgical codes including oophorectomy were considered as the BSO group. Surgical codes without oophorectomy were considered as the ovarian preservation group.

Differences between the baseline characteristics of the ovarian preservation and BSO groups were compared with the chi-square test. Cox regression models were developed to describe predictors of risk factors for recurrence-free survival. The Kaplan–Meier method was used for recurrence-free survival curve analysis. A P value < 0.05 was considered statistically significant. The chi-square test and Kaplan–Meier analysis were carried out using SPSS version 2.0 software (Chicago, IL, USA) and Cox regression was performed using Stata 11.0 software (StataCorp LP, College Station, TX, USA).

Results

A total of 638 patients were included in this study. Ovarian preservation surgery was performed in 33 (5.2%) of the 638 patients. Clinical and pathological characteristics were compared between premenopausal patients with stage Ia endometrial carcinoma in the ovarian preservation and BSO groups (Table 1). Most endometrial cancers were grade 1 (87.1%). Of the 33 patients with ovarian preservation, both ovaries were preserved in 31 patients, and one ovary was preserved in two patients. With informed consent of unknown risks, we preserved at least one ovary and performed hysterectomy and bilateral salpingectomy with or without lymph node dissection. The mean age of patients in the BOS group was 45 ± 6.18 years (range: 25–61 years) and that of patients in the ovarian preservation group was 40 ± 7.01 years (range: 25–51 years). Patients in the ovarian preservation group were younger than those in the BSO group ($P < 0.001$), had less myometrial invasion ($P = 0.025$), and had a lower prevalence of lymphadenectomy ($P = 0.020$). No recurrence occurred in the ovarian preservation group up to the day of the last follow-up, with no significant difference in the recurrence rate between the ovarian preservation and BSO groups.

Of the 638 patients with stage Ia endometrial carcinoma, seven experienced recurrence. Characteristics of these recurrent patients are shown in Table 2. All of the seven patients underwent BSO and their recurrence-free survival varied (8–50 months). Five patients were grade 1 and four patients underwent lymphadenectomy. LVSI was not reported in these patients. Two patients underwent postoperative adjuvant chemotherapy. Three patients died at a mean follow-up of 33.3 months and two of these were in grade 2.

Using univariate Cox analysis, we studied the potential risk factors for recurrence, including age, grade, LVSI, myometrial invasion, and ovarian preservation (Table 3). However, no significant association was found between those potential risk factors and recurrence-free survival. The median recurrence-free survival rate was 54.8 ± 34.9 months (range: 6–301 months). The Kaplan–Meier curves and log-rank test showed no difference in recurrence-free survival between the two groups (Figure 1). Five-year recurrence-free survival was 98.8% for the BSO group and 100% for the ovarian preservation group.

Discussion

Although endometrial cancer is normally considered as a disease of postmenopausal

Table 1. Characteristics of premenopausal women with stage Ia endometrial cancer in the ovarian preservation group and bilateral salpingo-oophorectomy group.

Characteristics	No. of patients (n = 638)	Ovarian preservation group (n = 33)	BSO group (n = 605)	*P* value
Age at diagnosis, years				<0.001
≤35	63	13	50	
36–40	83	8	75	
≥41	492	12	480	
Tumor grade				0.052
1	556	26	530	
2	63	2	61	
3	1	1	0	
Myometrial invasion				0.025
Superficial	228	18	210	
<1/2	410	15	395	
Lymph–vascular space invasion				1.000
No	619	32	587	
Yes	19	1	18	
Lymphadenectomy				0.020
No	316	23	293	
Yes	322	10	312	
Recurrence				1.000
No	631	33	598	
Yes	7	0	7	

Table 2. Characteristics of recurrent patients in the bilateral salpingo-oophorectomy group with stage Ia endometrial cancer (n = 638).

Age (years)	Stage	Grade	Lymph–vascular space invasion	Lymphaden ectomy	Postoperative adjuvant treatment	Recurrence-free survival (months)	Outcome
52	Ia	2	No	Yes	No	50	Died
46	Ia	2	No	Yes	No	21	Died
50	Ia	1	No	Yes	No	12	Alive
46	Ia	1	No	No	Chemotherapy	12	Alive
53	Ia	1	No	No	No	28	Alive
44	Ia	1	No	Yes	Chemotherapy	29	Died
56	Ia	1	No	No	No	8	Alive

women, the incidence of endometrial cancer in younger women is increasing. Evans-Metcalf et al.[3] reported that up to 14% of endometrial cancer occurs in premenopausal women. Standard surgical treatments, including hysterectomy and BSO, often accompanied by lymphadenectomy, cause surgical menopause, increase the risk of cardiovascular disease, and osteoporosis, and decrease the quality of life of young women.

The safety of ovarian preservation is challenged by two theoretical concerns as follows: the risk of potential coexisting

Table 3. Cox proportional hazards model of factors associated with overall survival of young women with early-stage endometrial cancer.

Characteristic	Hazard ratio	95% Confidence interval		*P* value
Surgery (ovarian preservation/bilateral salpingo-oophorectomy)	1.58E-15	0		1
Grade	3.221277	0.65379	15.8715	0.151
Age	1.149842	0.994951	1.328847	0.059
Lymph–vascular space invasion	0.980731	0.12141	7.922207	0.985
Myometrial invasion	3.399121	0.40921	28.23497	0.257

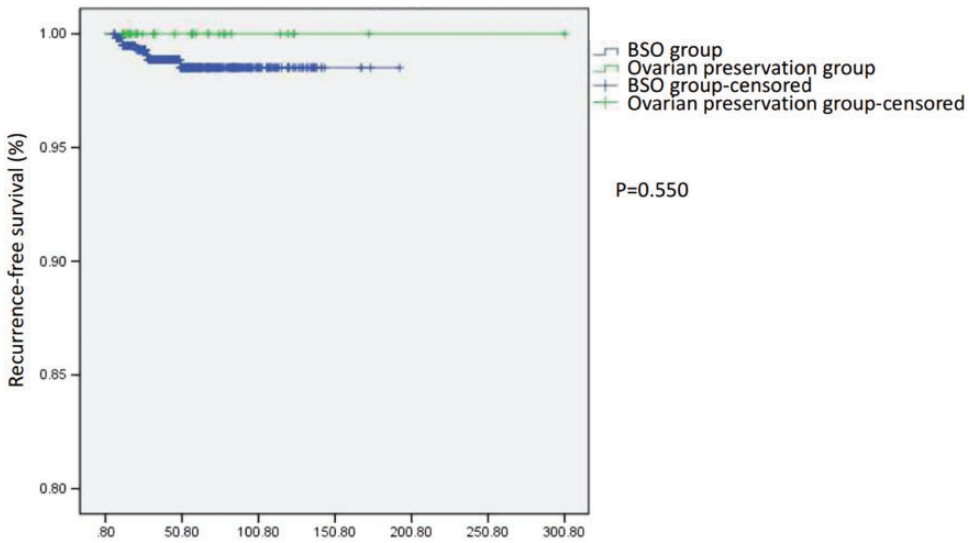

Figure 1. Recurrence-free survival of premenopausal women with stage Ia endometrial cancer stratified by performance of ovariectomy (n = 33 and n = 638 in the ovarian preservation and BSO groups, respectively; *P* = 0.550 from the log-rank test). BSO: bilateral salpingo-oophorectomy.

ovarian malignancy and the effect of stimulation of estrogen production in the ovaries on residual microscopic foci of endometrial cancer. Some studies have shown varied results on the incidence of coexisting ovarian malignancy in early-stage endometrial cancer. Pan et al.[5] reported that only 20 patients were histologically diagnosed with coexisting ovarian cancer among 976 patients with stage I endometrial carcinoma. Lin et al.[6] found that microscopic ovarian involvement occurred in 0.8% of patients with endometrial cancer. However, Walsh et al.[7] reported that 25% of young patients with endometrial carcinoma had coexisting epithelial ovarian tumors. These results emphasized that great caution should be taken when considering ovarian preservation in young women.

Moreover, the risk of estrogen stimulation on patients with endometrial cancer is still doubtful. A prospective trial of estrogen replacement therapy in 1236 patients

conducted by Barakat et al.[8] showed that the absolute recurrence rate was 2.1% and the incidence of new malignancy was low. A matched control study[9] and a retrospective review[10] also showed that estrogen replacement therapy did not appear to increase the rate of recurrence and death among endometrial cancer survivors.

In our study, ovarian preservation did not affect recurrence and survival rates, which is consistent with previous studies.[11–19] Gonthier et al.[20] found that ovarian conservation was not associated with decreased disease-specific or overall survival in young women with grade 2 or 3 endometrial adenocarcinoma confined to the endometrium. A recent meta-analysis showed that ovarian preservation was associated with better overall survival and was not associated with reduced recurrence-free survival in premenopausal patients with early-stage endometrial cancer.[21,22] Our group had previously performed a retrospective analysis of 144 patients with early endometrial cancer in young and premenopausal women.[23] Univariate analysis showed that deep myometrial invasion, lymphatic metastasis, LVIS, and grade (G2–G3) were associated with ovarian lesions. Multivariate analysis showed that deep myometrial invasion was an independent risk factor for ovarian malignancy. Therefore, ovarian preservation could be safely applied to premenopausal women with stage Ia endometrial carcinoma (odds ratio = 12.81, $P = 0.046$).[23]

The present study showed that there was no significant difference in recurrence-free survival in stage Ia patients with ovarian preservation and in those with BSO. This finding indicates that ovarian preservation might be a safe choice in early-stage endometrial carcinoma in premenopausal women after providing a full explanation of the potential risks and a thorough preoperative evaluation. However, some limitations of this study should be considered when interpreting our results. First, the sample size was inadequate, and no significant difference in recurrence rate was found between the ovarian preservation and BSO groups. Therefore, we will expand the sample size in future research. Because of the limited number of cases and follow-up, some previously established prognostic factors, such as grade, age, and LVSI, did not significantly affect recurrence of endometrial cancer in our study. Tumor mass is another high risk factor for endometrial carcinoma that we did not address in our study. Many researchers have proposed that a mass < 2 cm is a prerequisite for ovarian conservation.[12] A randomized, controlled trial to determine the safety of ovarian preservation for young women with early-stage endometrial cancer is clearly warranted.

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Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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