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Original Article

Impact of ovarian preservation in women with endometrial cancer

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Abstract

Background: Bilateral salpingo-oophorectomy (BSO) is standardly performed in the treatment of endometrial cancer. The purpose of this study was to evaluate the impact of ovarian preservation on the outcome of patients with endometrial cancer.
Methods: A retrospective cohort study was performed using the 2000–2010 database of endometrial cancer patients who were treated at Taipei Veterans General Hospital. Information regarding patient age, pathologic reports, and follow-up results was abstracted from medical records.
Results: Five hundred and twenty-nine patients were reviewed in this study. Mean age and follow-up duration were 55.7 ± 11.4 years and 37.5 ± 30.1 months, respectively. The median disease-free survival was 31.2 months (range 0.2–126.9 months). There were no significant differences in disease-free survival between stage I patients with ovarian preservation versus those with oophorectomy ($p = 0.473$). In a multivariate Cox model, ovarian preservation had no effect on disease-free survival [hazard ratio (HR) = 2.72; 95% confidence interval (CI), 0.48–15.59]; however, it was not significantly related to stage and para-aortic lymph node involvement.
Conclusion: Ovarian preservation may be considered in premenopausal women with early-stage low-risk endometrial cancer.

Keywords: disease-free survival; endometrial cancer; outcome; ovarian preservation

1. Introduction

Endometrial cancer is the most common gynecologic malignancy in the United States, with 43,470 new cases and 7950 deaths estimated in 2010, ranking eighth for cancer-related deaths.[1] Endometrial cancer is traditionally considered a disease of postmenopausal women. However, previous research has suggested that up to 14% of women with endometrial cancer are premenopausal.[2] According to the annual report of the Department of Health in Taiwan, there were 1424 newly diagnosed cases in 2008, and the incidence rate then increased to 9.75 per 100,000.[3] More than 30% of cases occurred in a premenopausal state, and the incidence of disease in women under the age of 45 years was 11%.[3]

Total abdominal hysterectomy, bilateral salpingo-oophorectomy (BSO), and surgical staging are usually performed in the treatment of endometrial cancer.[2] Further treatment is tailored according to the presence or absence of various risk factors. This treatment policy has not been changed since 1988, although numerous trials have been conducted. As such, BSO has been recommended routinely, irrespective of the patient's age. BSO is aimed at excluding occult ovarian metastases and decreasing estrogen production; however, the procedure results in surgical menopause and places patients at risk for the long-term sequelae of estrogen deprivation.[2]

The International Federation of Gynecology and Obstetrics (FIGO) staging system for the endometrium was revised in 2009. The purpose of the staging system is to provide the

Conflicts of interest: The authors declare that there are no conflicts of interest related to the subject matter or materials discussed in this article.

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patient with an appropriate prognosis, which would result in treatment improvement. Therefore, reappraisal of existing treatment guidelines, even those that have been accepted for decades, sometimes becomes necessary to determine whether they are based on reliable evidence or hold true in the face of new research.

Many studies have found that young women with endometrial cancer have a more favorable prognosis than older patients. Premenopausal women with endometrial cancer often have low-grade, early-stage tumors that may in part explain the differential survival.[4–10] Therefore, the issue of ovarian preservation in young women should be one that requires further consideration; however, a largely unanswered question is what the adverse effect of ovarian preservation in endometrial cancer might be. The goal of this study was to determine the impact of ovarian preservation on the outcome of patients with endometrial carcinoma.

2. Methods

With institutional review board approval (VGHIRB No: 2012-04-028AC), a retrospective cohort study in Taipei Veterans General Hospital, Taipei, Taiwan reviewed the data of patients with a final diagnosis of endometrial cancer between 2000 and 2010.

Medical charts, including admission and discharge notes, as well as surgical pathology reports and radiation records, were reviewed, and histological data [stage, grade, lymph vascular space invasion (LVSI), depth of myometrial invasion, and lymph node involvement], as well as survival data (disease-free survival and overall survival) were extracted. All histological material had been confirmed by gynecologic pathologists. Disease-free survival was calculated as the number of months from cancer diagnosis to date of recurrence or last follow-up. Tumor staging was in accordance with the 1988 FIGO staging system and was based on available pathologic findings. Unevaluated areas such as adnexa and lymph node status were considered negative for metastatic disease.

The outcome among categorical variables was compared using the χ^2 test. Cox regression models were developed to describe predictors of risk factors for disease-free survival. The Kaplan–Meier test was used for survival analysis. A p value < 0.05 was considered statistically significant. All analyses were carried out using SPSS version 17 software (SPSS Inc., Chicago, IL, USA).

3. Results

A total of 529 patients were evaluated. Ovarian preservation surgery was performed in 17 of the 529 patients. The patients' mean age and follow-up duration were 55.7 ± 11.4 years (range 24.6–90.5 years) and 37.5 ± 30.1 months, respectively. The median disease-free survival was 31.2 months (range 0.2–126.9 months). The clinical and histological characteristics are listed in Table 1. The patients who had ovarian preservation were younger than those who had oophorectomy ($p < 0.001$). Small tumor size ($p = 0.010$), low-grade ($p < 0.001$), no pelvic lymph node ($p < 0.001$), and no para-aortic lymph node ($p < 0.001$) involvement were common in patients who had ovarian preservation. Stage I tumors were found in 100% of those who had ovarian preservation versus 77.1% of women who underwent oophorectomy ($p = 0.173$).

Of the 17 patients with ovarian preservation surgery, 11 expressed the desire for ovarian preservation and six had other preoperative diagnoses, e.g., endometrial hyperplasia, leiomyoma, adenomyosis, or uterine prolapse. After pathologic and postoperative image evaluation, stage I and endometrioid-type tumors were found in all patients who had ovarian preservation. No further surgery was undertaken in the patients whose ovaries were saved incidentally, and two received adjuvant radiotherapy. There was no significant difference in disease-free survival in patients within the desire for ovarian preservation group (median 39.8 months) and the incidental ovarian preservation group (median 47.0 months; $p = 0.749$).

Using univariate analysis, we found that disease-free survival was associated with potential risk factors including age ($p = 0.011$), tumor size ($p = 0.012$), stage (I vs. II, $p < 0.001$; I vs. III, $p < 0.001$; I vs. IV, $p = 0.006$), tumor grade (1 vs. 2, $p < 0.001$; 1 vs. 3, $p < 0.001$), myometrial invasion (superficial vs. <1/2, $p = 0.002$; superficial vs. ≥1/2, $p < 0.001$), lymph vascular space invasion ($p < 0.001$), pelvic and para-aortic lymph node-involvement ($p < 0.001$); however, it was not significantly related to ovarian preservation ($p = 0.472$; Table 2). There were no significant differences in disease-free survival between patients with ovarian preservation and those with oophorectomy ($p = 0.277$). Compared to the patients in stage I of ovarian preservation and oophorectomy, there was no significant difference in disease-free survival (median 21.1 months vs. 33.4 months; $p = 0.473$, log-rank statistic; Fig. 1). No metachronous ovarian malignancies were observed during follow-up.

Multivariate Cox regression analysis was carried out for the following variables: age, tumor size, stage, histological type, tumor grade, depth of myometrial invasion, lymph vascular space invasion, pelvic lymph node involvement, and para-aortic lymph node involvement. Ovarian preservation showed no statistically significant association with disease-free survival [hazard ratio (HR) = 2.72; 95% confidence interval (CI), 0.48–15.59; $p = 0.671$]. However, it was not significantly related to stage I versus stage IV (HR = 0.25; 95% CI, 0.12–0.54, $p < 0.001$) and para-aortic lymph node involvement (HR = 2.00; 95% CI, 1.06–3.75; $p = 0.032$).

4. Discussion

Our review found that advanced stage and para-aortic lymph node involvement were significant factors related to disease-free survival. Ovarian preservation had no effect on survival.

In our study, ovarian preservation was more commonly performed in patients with small tumor size, endometrioid-type, low-grade, and early-stage tumors. The median disease-free survival was 21.1 months. Comparing patients

Table 1
Clinical and histological characteristics.

Characteristics	No. of patients (n = 529)	Ovarian preservation (n = 17)	Oophorectomy (n = 512)	p
Mean age (y)	55.7 ± 11.4 (24.6–90.5)	41.8 ± 11.2 (24.6–61.5)	56.2 ± 11.2 (26.2–90.5)	<0.001
Mean tumor size (cm)	2.5 ± 2.4 (0–18.0)	0.97 ± 1.3 (0–3.5)	2.52 ± 2.5 (0–18.0)	0.010
Stage				0.173
I	412 (77.9)	17 (100)	395 (77.1)	
II	48 (9.1)	0	48 (9.4)	
III	53 (10.0)	0	53 (10.4)	
IV	16 (3.0)	0	16 (3.1)	
Histology				0.361
Endometrioid	474 (89.6)	17 (100)	457 (89.2)	
Nonendometrioid	24 (4.5)	0	24 (4.7)	
Others	31 (5.9)	0	31 (6.1)	
Tumor grade				<0.001
1	150 (28.4)	8 (47.1)	142 (27.7)	
2	296 (55.9)	8 (47.1)	288 (56.3)	
3	82 (15.5)	1 (5.8)	81 (15.8)	
N/A	1 (0.2)	0	1 (0.2)	
Myometrial invasion				0.162
Superficial	79 (14.9)	5 (29.4)	74 (14.5)	
<1/2	320 (60.5)	10 (58.8)	310 (60.5)	
>1/2	130 (24.6)	2 (11.8)	128 (25.0)	
Lymph–vascular space invasion				1.000
No	449 (84.9)	15 (88.2)	434 (84.8)	
Yes	80 (15.1)	2 (11.8)	78 (15.2)	
Pelvic lymph node involvement				<0.001
No	482 (91.1)	17 (100)	465 (90.8)	
Yes	47 (8.9)	0	47 (9.2)	
Para-aortic lymph node involvement				<0.001
No	498 (94.1)	17 (100)	481 (93.9)	
Yes	31 (5.9)	0	31 (6.1)	
Recurrence				0.618
No	494 (93.4)	17 (100)	477 (93.2)	
Yes	35 (6.6)	0	35 (6.8)	

Data are presented as n (range) or n (%).

with desire for ovarian preservation and incidental ovarian preservation, there were no statistically significant differences. Therefore, ovarian preservation may be feasible and safe with early-stage and low-grade endometrial cancer.

Since the change in FIGO guidelines for endometrial cancer staging in 1988,[11] there has been controversy regarding the necessity of aggressive surgical staging, including BSO and lymphadenectomy, particularly in young women with early-stage disease. In addition to the immediate consequences of hot flashes and vaginal atrophy with BSO, surgical menopause in young women results in a number of long-term sequelae, including an increased risk of cardiovascular disease, osteoporosis, hip fracture, and cognitive dysfunction.[12] Rosenberg et al[13] reported that the risk of myocardial infarction is increased more than seven-fold in those who undergo bilateral oophorectomy prior to the age of 35 years. Several studies reported that early oophorectomy seems to have a direct effect on all-cause mortality.[14] Parker et al[15] demonstrated that women who have oophorectomy prior to the age of 55 years have 8.6% excess mortality by the age of 80 years, and those with oophorectomy prior to age 59 years have 3.92% excess mortality. A prospective, population-based cohort study found that women who underwent prophylactic bilateral oophorectomy prior to the age of 45 years had a 67% increase in mortality.[16] Thus, to avoid the short- and long-term consequences of surgical menopause, there is a strong rationale for ovarian preservation in young women.

The rationale for performing oophorectomy in women with endometrial cancer is based on two theoretical risks. First, estrogen production from the ovaries may stimulate microscopic foci of residual endometrial cancer; second, there may be a coexisting synchronous primary tumor within the ovaries. Theoretically, estrogen stimulates the growth of endometrial cancer cells and upregulates the expression of estrogen receptors. However, several studies have been unable to demonstrate an increase in the risk of recurrence or death in women receiving estrogen replacement.[17–19] The largest study [Gynecologic Oncology Group (GOG) No. 317] was a prospective trial of estrogen replacement therapy in more than 1200 women with endometrial cancer. Although the trial ended early, the absolute recurrence rate was 2.1% (HR = 1.27; 95% CI, 0.92–1.77) and the incidence of new malignancy was low.[17]

Synchronous primary tumors of the endometrium and ovary occur in approximately 5% of all women with endometrial cancer.[20] Walsh et al[21] reported a series of 102 women younger than 45 years with endometrial cancer. Twenty-six patients (25%) had coexisting epithelial ovarian tumors—23

Table 2
Cox regression model of factors associated with disease-free survival.

	Univariate			Multivariate		
	HR	95% CI	*p*	HR	95% CI	*p*
Ovarian preservation						
No	Reference			Reference		
Yes	0.35	0.08−1.45	0.472	2.72	0.48−15.59	0.671
Age (y)						
≤60	Reference			Reference		
>60	2.37	1.22−4.59	0.011	1.10	0.89−1.35	0.361
Tumor size						
<2 cm	Reference			Reference		
≥2 cm	2.75	1.25−0.65	0.012	1.15	0.95−1.40	0.154
Stage						
I	Reference			Reference		
II	0.02	0.08−0.70	<0.001	0.51	0.21−1.22	0.128
III	0.03	0.01−0.16	<0.001	0.42	0.17−1.04	0.062
IV	0.23	0.08−0.66	0.006	0.25	0.12−0.54	<0.001
Histology						
Endometrioid	Reference			Reference		
Nonendometrioid	0.35	0.12−1.02	0.054	1.07	0.71−1.61	0.738
Others	1.95	0.55−6.94	0.301	1.01	0.53−1.90	0.984
Tumor grade						
1	Reference			Reference		
2	0.06	0.02−0.21	<0.001	0.30	0.07−1.32	0.112
3	0.28	0.14−0.54	<0.001	0.71	0.31−1.63	0.420
Myometrial invasion						
Superficial	Reference			Reference		
<1/2	0.04	0.01−0.30	0.002	1.08	0.76−1.53	0.678
≥1/2	0.20	0.10−0.40	<0.001	1.20	0.93−1.54	0.160
Lymph−vascular space invasion						
No	Reference			Reference		
Yes	8.45	4.33−16.52	<0.001	1.30	0.93−1.81	0.121
Pelvic lymph node involvement						
No	Reference			Reference		
Yes	6.39	3.12−13.1	<0.001	1.35	0.71−2.56	0.366
Para-aortic lymph node involvement						
No	Reference			Reference		
Yes	8.18	3.66−18.30	<0.001	2.00	1.06−3.75	0.032

CI = confidence interval; HR = hazard ratio.

were classified as synchronous primaries and three were metastatic. Preoperative ovarian imaging of the women with ovarian involvement was normal in 15% of patients. Of those with ovarian tumors, 15% had normal-appearing adnexa intraoperatively. Pan et al[22] reported that the incidence of coexisting ovarian cancer in clinical stage I endometrial carcinoma was low, but 50% (10 of 20) of the ovarian tumors had microscopic ovarian involvement. The authors of these studies recommended a cautious approach when considering ovarian preservation in young women. Despite the potential for occult ovarian tumors in women who undergo ovarian preservation, we found that outcome and survival were not compromised.

Several studies have been conducted to evaluate the safety of ovarian preservation. Wright et al[2] found that ovarian preservation had no effect on either cancer-specific (HR = 0.58, 95% CI, 0.14−2.44) or overall (HR = 0.68, 95% CI, 0.34−1.35) survival. Koskas et al[23] reported that in 184 patients with grade 1 intramucous endometrial adenocarcinoma, ovarian preservation was not associated with an increase in cancer-related mortality. However, longer follow-up is needed to confirm the safety of a conservative approach toward the ovaries. In our study, there was no significant difference in disease-free survival in stage I patients with ovarian preservation and those with oophorectomy ($p = 0.473$). Disease-free survival was not associated with ovarian preservation. Advanced stage and para-aortic lymph node involvement were significant factors related to patient outcome. Multivariate Cox regression analysis revealed that the most important factors associated with disease-free survival were stage I versus stage IV (HR = 0.25, 95% CI, 0.12−0.54) and para-aortic lymph node involvement (HR = 2.00, 95% CI, 1.06−3.75). Para-aortic lymph node involvement had a more than two-fold effect on disease-free survival (14.2 months vs. 33.4 months, $p < 0.001$). The median survivals for stage I, stage II, stage III, and stage IV disease were 40.2 months, 36.8 months, 23.2 months, and 17.6 months, respectively.

Our results are similar to those of a previous study.[24] We found that early-stage disease had a favorable prognosis.

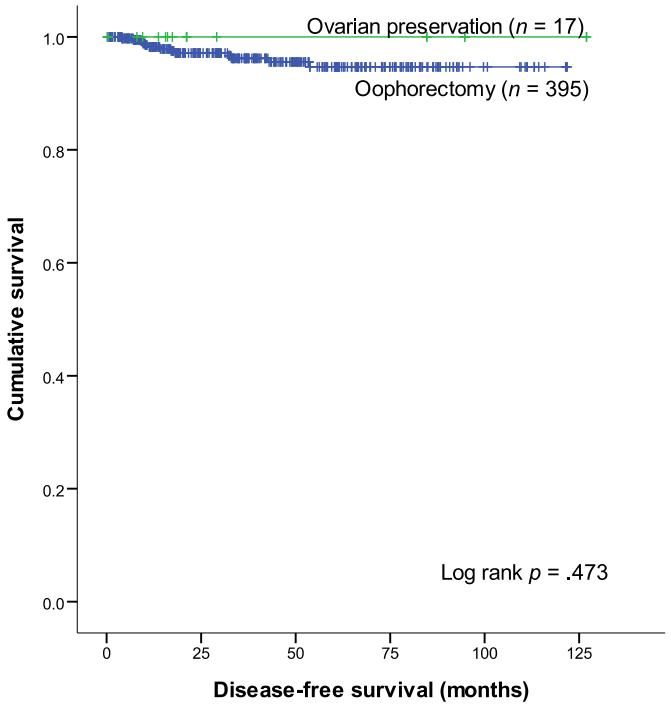

Fig. 1. Disease-free survival in stage I patients with ovarian preservation and oophorectomy. The disease-free survival of patients with ovarian preservation (median 21.1 months) was similar to that of the patients with oophorectomy (median 33.4 months; $p = 0.473$).

Different parameters, including lymph node status, histological type of carcinoma (serous carcinoma and clear-cell carcinomas were poor prognostic types), histological grade, stage of disease, depth of myometrial invasion, LVSI, and cervical involvement, had prognostic importance. However, our findings are notable in that ovarian preservation did not adversely impact the recurrence of endometrial cancer. Advanced stage and para-aortic lymph node involvement had a more significant impact on survival. Therefore, ovarian preservation in premenopausal women with early-stage endometrial cancer may be considered.

Some limitations of this study should be kept in mind when interpreting our results. This was a retrospective study with a low number of cases and ethical considerations. A randomized controlled trial will be conducted to determine the equivalency of ovarian preservation and BSO. Although our survival estimates suggest that ovarian preservation does not negatively impact outcome, the less than 5-year disease-free follow-up interval may not be sufficient to guarantee patient survival. It should be recognized that, based on the 95% CIs that we calculated, ovarian preservation may be associated with a two-fold increase in morbidity. It is therefore imperative that these findings be conveyed in the proper context when counseling patients.

In conclusion, our findings report that ovarian preservation does not adversely impact incidence of recurrence and disease-free survival. Ovarian preservation may be considered in premenopausal women with early-stage and low-risk endometrial cancer. However, preservation of the ovaries should be approached cautiously and consideration given to the patient's desire after providing a full explanation of the potential risks. The long-term risks and benefits of ovarian preservation should be carefully discussed with the patient.

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