Taiwanese Journal of Obstetrics & Gynecology 54 (2015) 532–536

Contents lists available at ScienceDirect

Taiwanese Journal of Obstetrics & Gynecology

journal homepage: www.tjog-online.com

Original Article

Outcome of ovarian preservation during surgical treatment for endometrial cancer: A Taiwanese Gynecologic Oncology Group study

Hei-Yu Lau [a, b], Min-Yu Chen [c], Yu-Min Ke [d], Jen-Ruei Chen [e, n], I-Hui Chen [f], Wen-Shiung Liou [g], Hung-Chun Fu [h], Cheng-Chang Chang [i], Keng-Fu Hsu [j], Kung-Liahng Wang [k, l, m, *]

[a] Department of Obstetrics and Gynecology, Taipei Veterans General Hospital, Taipei, Taiwan
[b] Department of Obstetrics and Gynecology, National Yang-Ming University, Taipei, Taiwan
[c] Department of Obstetrics and Gynecology, Chang Gung Memorial Hospital and Chang Gung University, Taoyuan, Taiwan
[d] Department of Obstetrics and Gynecology, Taichung Veterans General Hospital, Taichung, Taiwan
[e] Division of Gynecology Oncology, Mackay Memorial Hospital, Taipei, Taiwan
[f] Department of Obstetrics and Gynecology, National Taiwan University Hospital, Tsin-Chu Branch, Tsinchu, Taiwan
[g] Department of Obstetrics and Gynecology, Kaohsiung Veterans General Hospital, Kaohsiung, Taiwan
[h] Department of Obstetrics and Gynecology, Kaohsiung Chang Gung Memorial Hospital and Chang Gung University College of Medicine, Kaohsiung, Taiwan
[i] Department of Obstetrics and Gynecology, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan
[j] Department of Obstetrics and Gynecology, National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, Tainan, Taiwan
[k] Department of Obstetrics and Gynecology, Mackay Memorial Hospital, and Mackay Medical College, Taipei, Taiwan
[l] Department of Nursing, Mackay Junior College of Medicine, Nursing, and Management, Taipei, Taiwan
[m] Department of Obstetrics and Gynecology, Taipei Medical University, Taipei, Taiwan
[n] Mackay Medicine, Nursing and Management College, Taipei, Taiwan

ARTICLE INFO

Article history:
Accepted 22 October 2014

Keywords:
early-stage cancer
endometrial cancer
ovarian preservation

ABSTRACT

Objective: The goal of this study was to investigate the impact of ovarian preservation on the survival of women with early-stage endometrial cancer, particularly young women.
Materials and methods: A study cohort of 64 patients with histologically confirmed early-stage endometrial cancer was retrospectively collected from 10 member hospitals of the Taiwanese Gynecologic Oncology Group between 1998 and 2009. Survivorship and overall survival were compared between these two groups using a log-rank test.
Results: All patients who underwent surgery were adult women with a mean age of 40.4 ± 9.2 years (range 24–63 years). Ovary-preserving surgery was performed in 38 (59.4%) patients who desired to preserve their ovaries, incidentally in 19 (29.7%) patients with a preoperative diagnosis other than endometrial carcinoma, and in seven patients (10.9%) with unknown reasons. The 5-year recurrence-free survival rate was 98.3% with a median follow up of 44.6 months (range 1.0–126.9 months). Eight patients required adjuvant treatment (12.5%); one patient had documented local recurrence (1.6%); and no metachronous ovarian malignancy occurred during follow up.
Conclusion: Preservation of bilateral ovaries does not increase cancer-related mortality. A more conservative approach to surgical staging may be considered in premenopausal women with early-stage endometrial cancer without risk factors.

Introduction

Uterine cancer remains one of the leading causes of cancer mortality in women worldwide. Approximately 287,100 women developed uterine cancer with a mortality rate of 1.7 to 2.4 per 100,000 women in 2008 worldwide [1]. In Taiwan, the incidence

* Corresponding author. 1, Lane 303, Changsha Street, Mackay Memorial Hospital, Taitung, Taiwan.
E-mail address: KL421229@ms6.hinet.net (K.-L. Wang).

http://dx.doi.org/10.1016/j.tjog.2014.10.010

rate increased from 6.17 to 10.86 per 100,000 from 2001 to 2011 [2]. The primary treatment for early-stage endometrial cancer involves hysterectomy and bilateral salpingo-oophorectomy (BSO) [3]. The BSO procedure aims to exclude occult ovarian metastases and decrease estrogen production; given that endometrial cancer is an estrogen-responsive disease. However, ever since the 1988 International Federation of Gynecology and Obstetrics (FIGO) guidelines for endometrial cancer staging [4], there has been controversy regarding the necessity of aggressive surgical staging, including BSO and lymphadenectomy, particularly in young women with early-stage disease. Traditionally, endometrial cancer has been considered a disease of postmenopausal women with a median age of 52–54 years [2]. However, a recent study has shown that up to 14% of women with endometrial cancer are premenopausal [5]. In Taiwan, > 30% of cases occur in premenopausal patients and 10% in women under the age of 40 years [2]. The immediate consequence of the BSO procedure leads to surgical menopause in young women, leading to undesired climacteric symptoms, particularly hot flushes, sleep disorders, and long-term effects, as well as long-term risks to cardiovascular and bone health [3]. Nevertheless, the BSO procedure may not be necessary in women with early-stage endometrial carcinoma due to the relatively low incidence of ovarian metastases. Only ~5% of these women have ovarian metastases [6,7]. The prognosis for endometrial carcinoma in premenopausal women tends to be favorable, with a 5-year survival rate > 90% in early-stage disease [8]. Ali-Fehmi et al [9] suggested that early-stage, well-differentiated endometrial cancer is most commonly encountered in young patients. Moreover, Lee et al [10] reported that the risk of a coexisting malignancy is negligible in patients with minimal preoperative risk factors and no intraoperative evidence of advanced disease. Since no prospective clinical trial is currently available on the survival outcomes of BSO versus ovarian conservation at hysterectomy, the present study aimed to investigate the impact of ovarian preservation on the survival of women with early-stage endometrial cancer, particularly in young women.

Materials and methods

Individual patient data of histologically confirmed, early-stage endometrial cancer (Types I and II) were retrospectively collected from the data registry of the 10 member hospitals of the Taiwanese Gynecologic Oncology Group (TGOG) between 1998 and 2009. A total of 6098 patients were initially identified from the registries during the study period, among whom, 72 patients had either unilateral or bilateral ovarian preservation. After excluding patients with unilateral ovarian preservation, 64 patients were included in the final analysis. Detailed information on the patients was carefully reviewed and extracted from individual medical charts. Parameters abstracted from the medical documents included age at diagnosis, gravity and parity, preoperative diagnosis, date of diagnosis, reasons for preserving ovaries, date of recurrence, date of last follow up, follow-up results for recurrence or secondary malignancies, histological type, stage, grade, tumor size, lymphovascular space involvement, lymph node metastases, depth of myometrial invasion, and disease-free and overall survival. Evidence of recurrence was confirmed by pathological or radiological examination. The follow-up time was defined as the time from initial diagnosis to the time of death or last follow up. Disease-free survival was calculated as the number of months from cancer diagnosis to date of recurrence or last follow up. Tumor staging was assigned in accordance with the FIGO 1988 staging system. Stage of tumor was assigned based on available pathological findings, and unevaluated areas such as both adnexa and lymph node status were considered negative for metastatic disease based on intraoperative examination. The research was approved by the respective Institutional Review Boards and Ethics Committees of the 10 member hospitals of the TGOG.

Frequency was presented for categorical variables. Survival analysis was evaluated using Kaplan–Meier test, and statistical differences in survival were compared using a log-rank test. All reported p values corresponded to two-sided tests, and a p value < 0.05 was considered significant. All analyses were carried out using SPSS version 17 software (SPSS, Chicago, IL, USA).

Results

The clinicopathological profiles and treatment modalities of the study cohort are listed in Table 1. More than three-fifths of the patients (67.2%) were young women < 45 years of age (mean 40.4 ± 9.2 years, range 24–63 years) at initial diagnosis. FIGO stages IA and IB were the most common postoperative surgical stages, which represented approximately four-fifths of all patients (53/64, 83%). The most frequent preoperative diagnosis associated with hysterectomy was endometrial carcinoma (46.9%), followed by

Table 1
Patient characteristics.

Characteristics	Patients with retained ovaries (n = 64)	
	n	%
Age, y		
≤30	10	15.6
31–35	11	17.2
36–40	13	20.3
41–45	9	14.1
>45	21	32.8
Type of hysterectomy		
TAH	35	54.7
LAVH	24	37.5
TVH	3	4.7
RH/MRH	2	3.1
Preoperative diagnosis		
Endometrial carcinoma	30	46.9
Endometrial hyperplasia	22	34.4
Leiomyoma/adenomyosis	9	14.1
Uterine prolapse	3	4.6
Reasons for ovarian preservation		
Young age (≤45 y) and/or patient's desire	38	59.4
Other preoperative diagnosis[a]	19	29.7
Unknown	7	10.9
Myometrial invasion		
<1/2	58	90.6
≥1/2	6	9.4
Final histology		
Endometrioid	55	85.9
Nonendometrioid	9	14.1
Histological grade		
1	51	79.7
2	12	18.8
3	1	1.5
Postoperative FIGO stage (incomplete[b])		
Ia	38	59.4
Ib	15	23.4
Ic	4	6.3
IIa	6	9.4
IIb	1	1.5

[a] Diagnosis that does not require oophorectomy and incidental ovarian preservation.

[b] Unevaluated areas, such as both adnexae, or lymph node status were considered negative. FIGO = International Federation of Gynecology and Obstetrics; LAVH = laparoscopy assisted vaginal hysterectomy; MRH = modified radical hysterectomy; RH = radical hysterectomy; TAH = total abdominal hysterectomy; TVH = total vaginal hysterectomy.

endometrial hyperplasia (34.4%), benign leiomyoma or adenomyosis (14.1%), and uterine prolapse (4.6%). Only five patients underwent either total vaginal hysterectomy or (modified) radical hysterectomy, whereas the remaining 59 patients underwent total abdominal hysterectomy or laparoscopy-assisted vaginal hysterectomy. Histological diagnosis of pelvic lymph nodes was available in 14 of the 64 patients, and all were negative for metastasis. Eight patients with high-risk factors had adjuvant treatments without additional bilateral adnexectomy: two with chemotherapy (2/8, 25%) and six with pelvic radiotherapy (6/8, 75%). Ovarian preservation was performed predominately among young patients (≤45 years old), with or without patients' request among those with preoperative diagnosis of endometrial cancer, followed by women who were preoperatively diagnosed with benign disease and without gross findings of adnexa (e.g., endometrial hyperplasia, leiomyoma, or adenomyosis). The reasons for ovarian preservation were not obvious based on the medical record review of seven patients.

The 5-year recurrence-free survival rate was 98.3% with a median follow up of 44.6 months (range 1.0–126.9 months; Figure 1). There was no significant difference in disease-free survival between patients who desired ovarian preservation versus others with incidental ovarian preservation (log-rank test, $p = 0.270$). Overall, one patient had documented local vaginal stump recurrence (1.6%), and another Stage I patient with endometrioid histology had recurrence. No metachronous ovarian malignancy was observed during follow up.

Discussion

We found a relatively low recurrence rate (1.6%) in the preservation of bilateral ovaries at hysterectomy among patients with early-stage endometrial cancer. Although we do not know if the recurrence was associated with hormonal influences due to a residual ovary or occult metastasis, the sites of recurrence offered no evidence to support the suspicion that residual ovaries had influenced disease recurrence. A search of the literature revealed that women who underwent bilateral oophorectomy before the age of 45 years may be associated with an increased risk of 67% in all-cause mortality [11]. To avoid the short- and long-term consequences of surgical menopause, there is a strong rationale for ovarian preservation in young women. We must consider two questions before we can answer whether saving perfectly normal and functional ovaries without predictable risk factors is acceptable in patients with early-stage endometrial cancer. First, we must consider the risk of leaving occult ovarian metastasis or a coexisting synchronous primary tumor within the ovary. Second, we must consider the activation of microscopic foci of residual endometrial cancer by endogenous estrogen.

Most would agree that the risk of leaving occult ovarian metastasis or a coexisting synchronous primary tumor within the ovary is of primary concern. Although the incidence of coexisting ovarian tumors has been shown to range from 5% to 29% [12–16], these reports failed to mention whether these patients had extrauterine diseases. Lee et al [10] reviewed 260 patients with a mean age of 51.8 years. These authors identified a nonendometrioid histological subtype, intraoperative extrauterine disease, lymph node metastases, and age as independent risk factors for adnexal metastases in women with early stage and grade of endometrial carcinoma [10]. They found a 7.3% coexisting malignancy rate, but this was only 0.97% in patients without any evidence of intraoperative gross extrauterine disease. Another study reviewed 178 cases of surgically treated patients with or without BSO, and they suggested that ovarian preservation does not affect disease

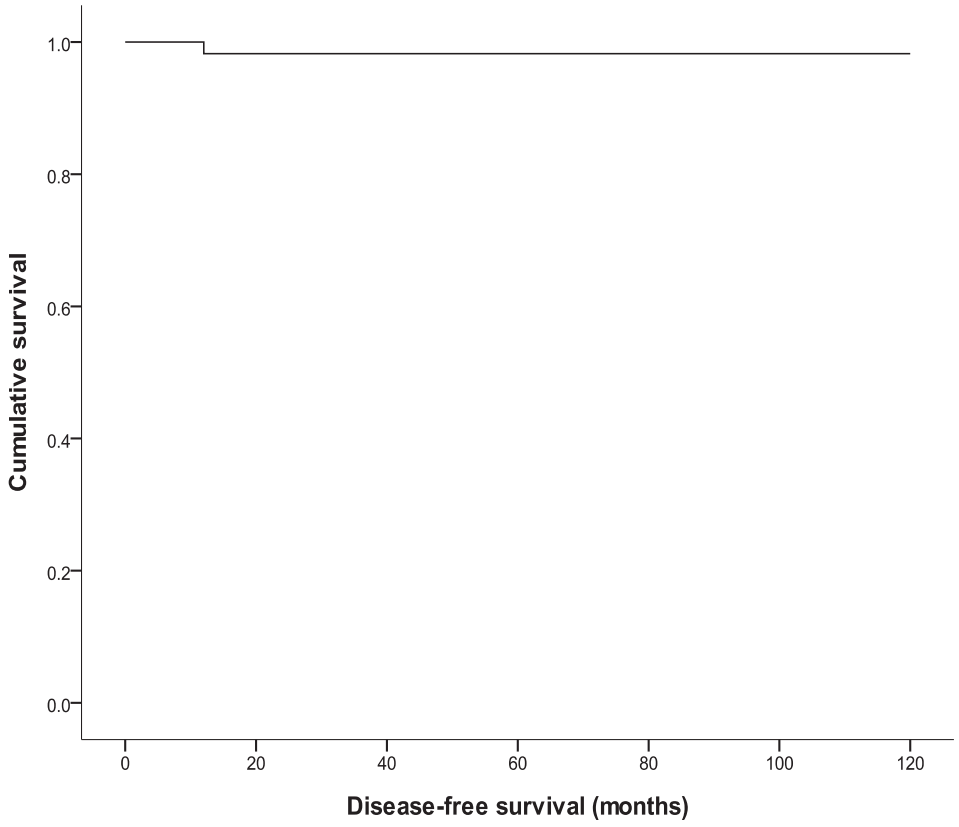

Figure 1. Disease-free survival in patients with ovarian preservation.

Table 2
Characteristics of review literature.

	Authors				
	Wright et al [5]	Richter et al [24]	Sun et al [25]	Lee et al [26]	Present study
Patient, *n* (ovarian preservation)	402	20	34	176	64
Age (y)	≤ 45	≤ 45	≤ 45	≤ 45	40.4 ± 9.2
Stage	Ia–Ic	Ia–Ic	Ia–Ic	I–II	I–II
Ia (%)	64		71	90.3	59.4
Ib (%)	33		22		23.4
Ic (%)	3		7	3.4	6.3
II (%)				6.3	10.9
Grade					
I (%)	79		70	75.6	79.7
II (%)	14		20	22.7	18.8
III (%)	3		10	107	1.5
Histologic type					
Endometrioid (%)	100	87	97	100	85.9
Non-endometrioid (%)		13	3		14.1
5-year survival (%)	98	100	93.2	94.3	98.3
Recurrence (%)		5.0		2.3	1.6

recurrence or overall survival in clinical Stage I and II endometrial cancer [17]. In our study, metachronous ovarian malignancy was not observed during follow up.

Many would suggest that the activation of microscopic foci of residual endometrial cancer by endogenous estrogen is of clinical significance. However, this theoretical relation lacks not only large-scale epidemiological association, but also clinical evidence. Barakat et al [18] reported a prospective trial of estrogen replacement therapy in >1200 women with endometrial cancer conducted by the Gynecologic Oncology Group. Although the study ended early, the absolute recurrence rate was only 2.1% [hazard ratio (HR) 1.27, 95% confidence interval (CI) 0.92–1.77]. Another large cohort study analyzed 3269 women; ovarian preservation had no effect on either cancer-specific survival (HR 0.58, 95% CI 0.14–2.44) or overall survival (HR 0.68, 95% CI 0.34–1.35). The findings suggested that ovarian preservation in premenopausal women with early-stage, low-grade endometrial cancer might be safe and not associated with an increased risk of cancer-related mortality [5]. In our study, favorable survival (98.3%) was also found in patients with ovarian preservation. Comparing the subgroup of ovarian preservation with prediagnosis known and unknown endometrial cancer, a favorable prognosis was likely noted in patients with unknown cancer, even if it was not statistically significant. Therefore, for patients approaching early-stage malignancy incidentally diagnosed on hysterectomy, these women may not need additional procedures if BSO is not performed at the time of initial hysterectomy. Similar to prior studies, there was no significant difference in survival in our study (Table 2), which reveals the feasibility and safety of ovarian preservation in patients with early-stage, low-grade endometrial cancer.

The current study was limited by the inherent nature of a hospital-based, retrospective study, and this must be borne in mind while interpreting the data reported here. There was missing information as well as several patients with an insufficient interval of follow up. Less than a 5-year disease-free interval may not be sufficient to guarantee patient safety, especially with respect to the development of metachronous ovarian tumor. However, there is a need to devise a more reliable predictor. Available evidence supporting the benefit of intraoperative frozen biopsy to helpfully rule out an adnexal pathology is limited, although its clinical value is worthy of study [19]. Furthermore, positron emission/computed tomography advancements might also provide a means of predicting occult metastasis [20,21]. However, several issues remain to be resolved, including the low sensitivity of small occult lesions and its false positivity due to physiological uptake [22,23].

The current study finds that the ovarian preservation is a possible alternative in patients with early-stage endometrial cancer, and does not increase cancer-related mortality. A more conservative approach to surgical staging may be considered in premenopausal women with early-stage endometrioid endometrial cancer. However, the performance of ovarian preservation is highly individualized; patients who desire ovarian preservation should receive a full explanation of the potential risks from their physicians; and genetic tests may be necessary in patients with a family history of related malignancies. We suggest that the preservation of bilateral ovaries is not suitable for endometrial cancer patients with extrauterine spread at preoperative and intraoperative assessment. These patients should also have longer than typical follow up than those who have a BSO procedure at hysterectomy, and careful intraoperative assessment of the adnexa is also mandatory. Nevertheless, the current study is the only study to report the experiences with the follow-up results of patients that have undergone ovary-preserving surgery.

Conflicts of interest

The authors declare no conflicts of interest.

Acknowledgments

This study was supported by a grant from the Taiwanese Gynecological Oncology Group (MOST 103-2325-B-195-002-). The authors would like to thank member hospitals of the Taiwanese Gynecologic Oncology Group (TGOG) and their staffs for helpful comments, discussions, and support during data collection.

References

[1] Jemal A, Bray F, Center MM, Ferley J, Ward E, Forman D. Global cancer statistics. CA Cancer J Clin 2011;61:69–90.
[2] The National Department of Health. The Taiwan Cancer Registry. Cancer Registry Annual Report 2010:82–3.
[3] Lee TS, Kim JW, Kim TJ, Cho CH, Ryu SY, Ryu HS, et al. Ovarian preservation during the surgical treatment of early stage endometrial cancer: a nationwide study conducted by the Korean Gynecologic Oncology Group. Gynecol Oncol 2009;115:26–31.
[4] Creasman WT. New gynecologic cancer staging. Obstet Gynecol 1990;75:287–8.
[5] Wright JD, Buck AM, Shah M, Burke WM, Schiff PB, Herzog TJ. Safety of ovarian preservation in premenopausal women with endometrial cancer. J Clin Oncol 2009;27:1214–9.

[6] Boronow RC, Morrow CP, Creasman WT, Disaia PJ, Silverberg SG, Miller A, et al. Surgical staging in endometrial cancer: clinical–pathologic findings of a prospective study. Obstet Gynecol 1984;63:825–32.
[7] Creasman WT, Morrow CP, Bundy BN, Homesley HD, Graham JE, Heller PB. Surgical pathologic spread patterns of endometrial cancer. A gynecologic oncology group study. Cancer 1987;60:2035–41.
[8] Gotlieb WH, Beiner ME, Shalmon B, Korach Y, Segal Y, Zmira N, et al. Outcome of fertility-sparing treatment with progestins in young patients with endometrial cancer. Obstet Gynecol 2003;102:718–25.
[9] Ali-Fehmi R, Cote ML, Arabi MH, Munkarah AR, Schimp VL, Bryant C, et al. Endometrial carcinoma (EC) in women 35 years of age or younger. ASCO Meeting Abstract. J Clin Oncol 2007;25:16000.
[10] Lee TS, Jung JY, Kim JW, Park NH, Song YS, Kang SB, et al. Feasibility of ovarian preservation in patients with early stage endometrial carcinoma. Gynecol Oncol 2007;104:52–7.
[11] Rocca WA, Grossardt BR, de Andrade M, Malkasian GD, Melton III LJ. Survival patterns after oophorectomy in premenopausal women: a population cohort study. Lancet Oncol 2006;7:821–8.
[12] Duska LR, Garrett A, Rueda BR, Haas J, Chang Y, Fuller AF. Endometrial cancer in women 40 years old or younger. Gynecol Oncol 2001;83:388–93.
[13] Gitsch G, Hanzal E, Jensen D, Hacker NF. Endometrial cancer in premenopausal women 45 years and younger. Obstet Gynecol 1995;85:504–8.
[14] Evans-Metcalf ER, Brooks SE, Reale FR, Baker SP. Profile of women 45 years of age and younger with endometrial cancer. Obstet Gynecol 1998;91:349–54.
[15] Zaino R, Whitney C, Brady MF, DeGeest K, Burger RA, Buller RE. Simultaneously detected endometrial and ovarian carcinomas—a prospective clinicopathologic study of 74 cases: a gynecologic oncology group study. Gynecol Oncol 2001;83:355–62.
[16] Walsh C, Holschneider C, Hoang Y, Tieu K, Karlan B, Cass I. Coexisting ovarian malignancy in young women with endometrial cancer. Obstet Gynecol 2005;106:693–9.
[17] Han CH, Lim SY, Kook IY, Lee KH, Namkoong SE, Park JS, et al. Prognostic outcome of patients with clinical stage I-II endometrial cancer according to bilateral salpingo-oophorectomy. Korean J Obstet Gynecol 2007;50:288–94.
[18] Barakat RR, Bundy BN, Spirtos NM, Bell J, Mannel RS. Randomized double-blind trial of estrogen replacement therapy versus placebo in stage I or II endometrial cancer: a Gynecologic Oncology Group Study. J Clin Oncol 2006;24:587–92.
[19] Benjamin I, Morgan MA, Rubin SC. Occult bilateral involvement in stage I epithelial ovarian cancer. Gynecol Oncol 1999;72:288–91.
[20] Israel O, Mor M, Guralnik L, Hermoni N, Gaitini D, Bar-Shalom R, et al. Is 18F-FDG PET/CT useful for imaging and management of patients with suspected occult recurrence of cancer? J Nucl Med 2004;45:2045–51.
[21] Bristow RE, del Carmen MG, Pannu HK, Cohade C, Zahurak ML, Fishman EK, et al. Clinically occult recurrent ovarian cancer: patient selection for secondary cytoreductive surgery using combined PET/CT. Gynecol Oncol 2003;90:519–28.
[22] Ames J, Blodgett T, Meltzer C. 18F-FDG uptake in an ovary containing a hemorrhagic corpus luteal cyst: false-positive PET/CT in a patient with cervical carcinoma. AJR Am J Roentgenol 2005;185:1057–9.
[23] Short S, Hoskin P, Wong W. Ovulation and increased FDG uptake on PET: potential for a false-positive result. Clin Nucl Med 2005;30:707.
[24] Richter CE, Qian B, Martel M, Yu H, Azodi M, Rutherford TJ, et al. Ovarian preservation and staging in reproductive-age endometrial cancer patients. Gynecol Oncol 2009;114:99–104.
[25] Sun C, Chen G, Yang Z, Jiang J, Yang X, Li N, et al. Safety of ovarian preservation in young patients with early-stage endometrial cancer: a retrospective study and meta-analysis. Fertil Steril 2013;100:782–7.
[26] Lee TS, Lee JY, Kim JW, Oh S, Seong SJ, Lee JM, et al. Outcomes of ovarian preservation in a cohort of premenopausal women with early-stage endometrial cancer: A Korean Gynecologic Oncology Group study. Gynecol Oncol 2013;131:289–93.