Elevated CA-125 Level and ER-Negative as Prognostic Factors for Ovarian Metastasis in Patients with Endometrial Cancer: A Retrospective Cohort Study

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Background: The utility of cancer antigen 125 (CA-125), estrogen receptor (ER), and progesterone receptor (PR) in evaluation for ovarian metastasis of endometrial cancer has yet to be determined. The purpose of this study was to investigate the incidence and the possible risk factors of ovarian metastasis.

Material/Methods: A retrospective study was performed in endometrial cancer patients who accepted surgical intervention of hysterectomy and oophorectomy during 2002–2013 in Sun Yat-sen Memorial Hospital, Sun Yat-sen University, China. Clinico-pathologic characteristics and the possible risk factors were investigated.

Results: A total of 565 patients were identified, of which 5.7% had ovarian metastasis. Univariate analysis and multivariate analysis revealed that deeper myometrial invasion, tubal involvement, and parametrial involvement were independent risk factors. In subgroup analysis, univariate analysis showed that elevated CA-125 level and negative ER were associated with ovarian metastasis ($P<0.05$), however multivariate analysis revealed that only high CA-125 level was an independent risk factor ($P<0.05$). The incidence of ovarian metastasis in patients with high CA-125 level and who were ER-negative was 24%. For patients with normal CA-125 level and who were ER-positive, the incidence was 1.19%. The optimal cutoff value that provided the best sensitivity and specificity was 110.5 U/ml.

Conclusions: The incidence of ovarian metastasis in endometrial cancer is low. Ovarian preservation should be considered for women without abnormal CA-125 level and who have deeper myometrial invasion, tubal involvement, parametrial involvement, and who are ER-negative. These findings may facilitate clinical decision-making.

MeSH Keywords: Endometrial Neoplasms • Neoplasm Metastasis • Ovariectomy

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Background

The standard treatment for endometrial cancer includes removing the ovaries to reduce estrogen production [1]. However, the effects of bilateral oophorectomy on the short-term and long-term health of young patients may include cardiovascular disease, osteoporosis, and cognitive decline. Atsma et al. reported a risk ratio of 2.62 [95% confidence interval (CI), 2.05–3.35] for cardiovascular disease in patients with bilateral oophorectomy [2]. Rocca et al. found that the mortality risk was increased by 67% (hazard ratio (HR) to 1.67 [95% CI 1.16–2.40] P=0.006) for patients younger than 45 years who underwent preventive oophorectomy [3]. It is important for patients who want to preserve their ovaries and fertility to evaluate ovarian metastases or the occurrence of coexisting ovarian malignancies.

Preservation of ovaries in young women with endometrial cancer remains controversial [2]. Some reports have demonstrated that preservation of the ovaries is safe in patients with early-stage EC [4]. However, the incidence of metastatic ovarian cancer and coexisting malignancies in endometrial cancer varies from 5% to 29% [5–10]. Therefore, the decision to preserve the ovaries must be carefully considered.

Although prior reports have examined the risk factors associated with ovarian metastasis in patients with EC, reliable preoperative risk factors have not been conclusively demonstrated. Preoperative images may help estimate the predictive factors such as deeper myometrial invasion, lymph node status, and tumor size, but all of these factors need to be confirmed after surgery.

Therefore, an accurate measurement of clinical factors before treatment may be more important. Preoperative elevated CA-125 was associated with poor prognostic features and independently associated with adnexal involvement [11–13], and patients with ovarian and lymph nodes metastasis presented with a higher mean initial serum Ca-125 [14,15]. Several studies support that status for estrogen receptor (ER) and progesterone receptor (PR) from preoperative endometrial biopsy in primary tumors are independent prognostic markers [16,17]. The loss of ER and PR status is associated with type II, higher tumor grade, and deep myometrial invasion, which were considered to be aggressive endometrial cancer. Young endometrial cancer patients need systematic clinical implementation studies of potentially useful clinic-pathologic characteristics.

On this background, we explored the rate of ovarian metastasis and analyzed the risk factors associated with ovarian metastasis in endometrial cancer patients in our center.

Material and Methods

Endometrial cancer patients who underwent total hysterectomy with bilateral salpingo-oophorectomy (BSO) with or without pelvic lymphadenectomy and para-aortic lymphadenectomy at Sun Yat-sen Memorial Hospital were enrolled in this study. If stage II cancer was diagnosed using magnetic resonance imaging (MRI) and hysteroscopy-directed biopsies, modified radical or radical hysterectomy could be performed. The inclusion criteria were: 1) surgery was the initial treatment and no other treatments, such as radiotherapy, chemotherapy, hormonal therapy, or targeted therapy, were performed before surgery; and 2) endometrial cancer was diagnosed by postoperative pathological analysis. The exclusion criteria were: 1) history of noncancerous ovarian tumors or malignant ovarian tumors; 2) coexisting malignancies; and 3) lack of complete medical record. A total of 879 patients were identified. From these, we excluded 206 patients with other treatments preoperative, 37 patients with history of ovarian tumors, 51 patients with coexisting malignancies, and 20 patients without complete medical records. Among the remaining patients, 565 primary endometrial cancer patients with total hysterectomy with BSO as initial treatment met the criteria.

Fresh serum samples were collected before initial surgery, and serum CA-125 levels were calculated at the clinical chemistry laboratory at our hospital with a radioimmunoassay kit (Fujirebio Diagnostics), and normal value of serum CA-125 levels were 0–35 U/mL according to the manufacturer. The determination of ER expression was performed using rabbit monoclonal primary antibody (SP1 RTU) and PR expression was performed with rabbit monoclonal primary antibody (1E2 RTU), using a Roche automatic immunohistochemistry machine (ULTRA). The overall expression levels of ER and PR were detected in formalin-fixed and paraffin-embedded tissue by immunohistochemistry assay in 4-mm thick sections. A cutoff value of 10% for positively stained cells per 10 high-power fields was used in the classification of ER and PR expression.

Information regarding clinical data and pathologic information were abstracted from the medical record. The original pathological reports were reviewed, and at least 2 pathologists confirmed the postoperative pathological diagnosis.

Statistical analysis

Data analysis was performed with SPSS 19.0 statistical software. The categorical data were assessed using the chi-square test or exact probability test. Logistic regression analysis was applied to analyze the relationship of clinicopathological factors and ovarian metastasis. Receiver operating characteristic (ROC) curve and the area under the curve (AUC) were used to

Table 1. Patient, clinical, and pathological characteristics.

Varaible	No. of patients	%
Histological type		
Nonendometrioid	66	11.68%
Endometrioid	499	88.32%
Type		
Type II	110	19.47%
Type I	455	80.53%
Tubal involvement		
Yes	42	7.43%
No	523	92.57%
Myometrial invasion		
≥1/2	114	20.18%
<1/2	451	79.82%
LVSI		
LVSI+	60	10.62%
LVSI−	505	89.38%
Lymph node metastasis		
Yes	57	10.09%
No	508	89.91%
Cervical extension		
Yes	65	11.50%
No	500	88.50%

Varaible	No. of patients	%
Parametrial involvement		
Yes	21	3.72%
No	544	96.28%
Vaginal involvement		
Yes	6	1.06%
No	559	98.94%
Positive peritoneal washings/ascites		
Yes	10	1.77%
No	555	98.23%
Longest tumor diameter		
<2	143	25.31%
2~5	234	41.42%
>5	188	33.27%
Age		
≥50	391	69.20%
<50	174	30.80%
Menopause		
Yes	276	48.85%
No	289	51.15%

evaluate the diagnostic value of CA-125 in ovarian metastasis. $P<0.05$ was considered statistically significant.

This study complied with the tenets of the Helsinki Declaration, and was approved by the Medical Ethics Committee of Sun Yat-sen Memorial Hospital. The research ethics register number was SYSEC-KY-KS-2018-073. The data are anonymous, and the requirement for informed consent was therefore waived.

Results

A total of 565 patients with endometrial cancer were enrolled in the present study from January 2003 to October 2013. The median age of the study population was 53 years (range 17–78 years). There were 366 stage IA cases, 55 stage IB cases, 30 stage II cases, and 114 stage III, and stage IV cases. The clinical and pathological characteristics are presented in Table 1.

The overall incidence of ovarian metastasis was 5.7%. Among them, the incidence in patients with stage IIIC1 and IIIC2 was 7.7% and 16.7%, respectively. The correlations between the risk of ovary metastasis and age, myometrial invasion, tumor

size, histological type, tubal involvement, lymph-vascular space invasion (LVSI), lymph node metastasis, cervical involvement, parametrial involvement, menopause, vaginal involvement, and positive peritoneal washings/ascites are displayed in Table 2. Logistic regression analysis suggested that deeper myometrial invasion, tubal involvement, and parametrial involvement were independent risk factors for ovarian metastasis in endometrial cancer ($P<0.05$).

A total of 458 patients underwent CA-125 serum testing, and the CA125 level of 144 patients was higher than 35 IU/L. When CA-125 was elevated, the incidence of ovarian metastasis was 15.2%, compared to 1.6% when CA-125 was normal (Table 3). In the group of patients with ovarian metastasis, the CA125 concentration was 372.24±704.99 IU/L. In the group of patients without ovarian metastasis, the CA125 concentration was 48.49±123.49 IU/L. We observed significantly higher CA125 concentrations ($P<0.05$) in patients with ovarian metastasis when compared to patients without metastases. Univariate analysis revealed that CA125 level was associated with ovarian involvement ($P<0.05$). Logistic regression analysis indicated that CA125 level was an independent risk factor for ovarian metastasis ($P<0.05$).

Based on the ROC curve analysis carried out in 458 patients, the cutoff point was determined for CA125 as above 110.5 IU/L

Table 2. Univariate analyses of clinical pathological risk factors for ovarian metastasis.

Variables	Ovarian metastasis		P value
	Positive	**Negative**	
Histological type			
Nonendometrioid	7	59	0.065
Endometrioid	25	474	
Type			
Type II	12	98	0.001
Type I	20	435	
Tubal involvement			
Yes	17	26	0
No	15	506	
Myometrial invasion			
≥1/2	19	95	0
<1/2	13	438	
LVSI			
Yes	9	51	0.001
No	23	482	
Lymph node metastasis			
Yes	7	50	0.023
No	25	483	
Cervical extension			
Yes	12	53	0
No	20	480	
Parametrial involvement			
Yes	10	11	0
No	22	522	
Vaginal involvement			
Yes	2	4	0.003
No	30	529	
Positive peritoneal washings/ascites			
Yes	3	7	0.001
No	29	526	
Longest tumor diameter			
<2	6	137	0.017
2~5	8	226	
5	18	170	
Age			
≥50	21	370	0.652
<50	11	163	
Menopause			
Yes	21	255	0.051
No	11	278	

Table 3. CA125 level, ER, and PR of patients with endometrial cancer.

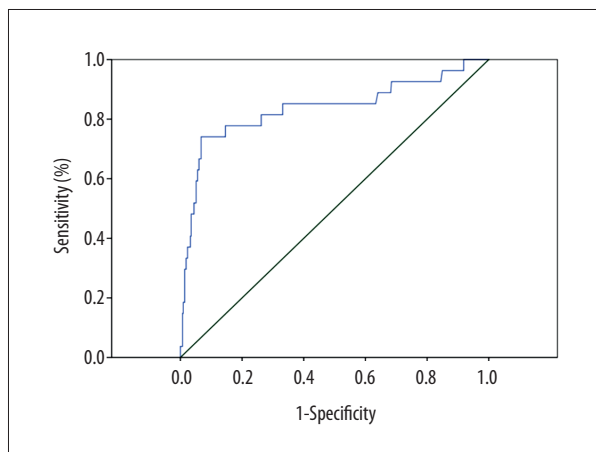| Variables	No. of patients	Ovarian metastasis		P value
		Positive	Negative	
CA125 (n=458)				
≥35	144	22 (81.48%)	122 (28.31%)	0
<35	314	5 (18.52%)	309 (71.69%)	
ER (n=504)				
Negative	69	9 (29.03%)	60 (12.68%)	0.01
Positive	435	22 (70.97%)	413 (87.32%)	
PR (n=504)				
Negative	49	6 (19.35%)	43 (9.09%)	0.062
Positive	455	25 (80.65%)	430 (90.91%)	

Figure 1. Receiver operating characteristic curves of CA125 in endometrial cancer patients.

(sensitivity 74.1%, specificity 93.7%; 95%CI: 0.726–0.900; $P<0.0001$). The obtained area under the ROC curve for CA125 was AUC=0.836 ($P=0$) (Figure 1).

For further analysis, immunohistochemistry was used to examine ER and PR in a total of 504 patients. Ovarian metastasis was seen in 13% of 69 patient samples with loss of estrogen receptor (ER–) staining and in 12.2% of 49 patient samples with progesterone receptor loss (PR–). Univariate analysis revealed that loss of estrogen receptor (ER–) were associated with ovarian metastasis ($P<0.05$). Multivariate analysis showed that ER– was not an independent risk factor for ovarian metastasis ($P=0.596$) (Table 4).

Of 253 patients with normal CA125 and positive ER, only 3 (1.19%) had ovarian metastasis, and the CA125 concentration was 17.62±7.55 IU/L. However, among the 25 patients with

Table 4. Multivariate analyses of clinical pathological risk factors for ovarian metastasis.

Variables	Regression coeffi (B)	Standard error	OR	95% CI	Wald	P value
Parametrial involvement	1.536	0.747	4.647	1.074–20.109	4.225	0.040
Myometrial invasion	1.063	0.541	2.896	1.002–8.369	3.859	0.049
tubal involvement	2.831	0.534	16.968	5.955–48.353	28.083	0.000

Table 5. Status for ER and CA125 level in patients with ovarian metastasis.

CA125	ER	Number	Ovarian metastasis	%	CA125 (IU/L)
CA125 ≤35	ER+	253	3	1.19%	17.62±7.55
CA125 ≤35	ER–	28	2	7.14%	17.98±6.44
CA125 >35	ER+	111	15	13.51%	167.00±394.2
CA125 >35	ER–	25	6	24.00%	236.92±309.87

elevated CA125 and ER–, 6 (24.00%) had ovarian metastasis, a much greater incidence (Table 5).

Among the 32 patients with confirmed ovarian malignancy, 21 were younger than 50 years old. Of note, 24 cases occurred in patients with masses larger than 2 cm and 19 occurred in patients with more than 50% myometrial invasion. Nine patients had LVSI, 7 had lymph node metastasis, and 10 were ultimately found to have parametrial involvement.

Discussion

The menopausal transition usually begins in the middle to late 40s, with menopause occurring at a median age of 49.5 years in China. In the present study, 52.1% of patients with endometrial cancer were premenopausal, 30.5% were younger than 50 years, and 10.3% were younger than 40 years. These findings supported that among women who have been diagnosed with cancer in the uterus, there was a fairly large percentage of younger women. However, the present study did not find an association between younger age and clinicopathologic risk factors for ovarian metastasis.

Previously studies have reported that the incidence of metastatic ovarian cancer and coexisting malignancies in endometrial cancer varies from 5% to 29%, which may be due to sample size, cancer characteristics, ethnic group, and different pathological diagnostic criteria [5–10]. Lee et al. found that it is possible to preserve ovaries in young women with early-stage endometrial carcinoma with a thorough and extensive intraoperative exploration, and only 2 out of 206 (0.97%) patients without a visible extra-uterine lesion detected during surgery had ovarian cancer [6]. However, Walsh et al. retrospectively studied 102 patients younger than 45 years with endometrial cancer and found that 26 of 102 (25%) patients had coexisting epithelial ovarian cancers, 15% of patients (4/26) had preoperative diagnostic imaging of normal ovaries, and 15% of patients (4/26) had normal morphological appearance of the ovarian adnexa. Therefore, these researchers believed that patients with ovarian preservation are at high risk [5]. In the present study, patients with ovarian coexisting malignancies were excluded, and the incidence of ovarian metastasis in endometrial cancer was 5.7%, which is consistent with previous findings.

Multiple clinicopathological factors have been consistently demonstrated to predict ovarian metastasis [18–22]. Deep myometrial invasion in the excised uterus was the strongest predictive factor for ovarian metastasis, associated with a 66-fold increased risk of ovarian metastasis [18]. In the present study, univariate analysis and multivariate analysis revealed that deeper myometrial invasion, tubal involvement,

and parametrial involvement were independent risk factors for ovarian metastasis. Currently, for the preoperative identification of ovarian metastasis, assessment of myometrial invasion and tumor involvement by images are recommended. However, in a preoperative setting, the assessment of deep myometrial invasion by MRI, CT, or transvaginal ultrasound has several challenges.

The wide use of CA-125 in the management of epithelial ovarian cancer, as a tumor marker for screening and monitoring, suggest the likelihood of a specific correlation between CA-125 and ovarian metastasis. Earlier studies showed that preoperative elevated CA-125 was also associated with poor prognostic features and was an independent prognosticator for poor outcome [11,12]. In our study, further analysis of CA125 level revealed that the incidence of ovarian metastasis was 15.2% when CA125 was elevated, compared to only 1.6% when CA-125 was normal. Multivariate analysis revealed that elevated CA125 level was associated with ovarian metastasis. Similar results were also observed in a retrospective study of 61 patients with uterine papillary serous carcinoma [13].

There have been calls for systematic clinical implementation studies of the cutoff values that may be useful for prediction of ovarian metastasis in endometrial cancer patients. Patients with ovarian and lymph nodes metastasis presented with a higher mean initial serum Ca-125; the mean (range) was 308.4 (5–1086) U/mL, the optimal cutoff value was 40.8 U/mL, and >70 U/mL were independent risk factor for poor progression-free and overall survival [14,15]. According to our data, in patients with ovarian metastasis, the CA125 concentration was 372.24±704.99 IU/L, a CA-125 level of 110.5 IU/L was the best cutoff for predicting ovarian metastasis. In addition, the accuracy of serum CA-125 levels for preoperative diagnostic was 74.1%. Thus, we recommend that the optimal cutoff value of serum CA-125 levels higher than the common value (0–35 U/ml) should be considered for young endometrial patients before undergoing initial treatment.

Low ER immunohistochemical staining was reported to be significantly correlated with an aggressive clinicopathologic phenotype and reduced survival in all endometrial cancer patient cohorts studied [23–26]. On the other hand, double-negative hormone receptor status in endometrial cancer preoperative curettage histology independently predicted lymph node metastasis and poor prognosis in a prospective multicenter study [16]. Using hormone receptor status to improve risk-stratification for selecting patients unlikely to benefit from oophorectomy seems justified. In the present study, ovarian metastasis was high in patient samples with ER loss (13%) and PR loss (12.2%), and univariate analysis revealed that ER loss was associated with ovarian metastasis (P<0.05); however, it could not be confirmed in multivariate analysis, perhaps due to the

low number of patients investigated. PR– was not considered statistically significant, which may be due to the small sample size, and endometrial cancer is an estrogen-dependent cancer and may not be affected by high level of progesterone. Thus, we speculated that additional predictive methods such as serum levels of CA-125 and hormone receptor status should be required for preoperative counseling because we demonstrated that preoperative hormone receptor status alone is insufficient to predict adnexal involvement.

However, this study is limited owing to the relatively small sample size. The study was retrospective and performed in a single institution, which may have caused selection bias. Because ovarian metastasis is not common in Chinese patients (only 32 of 565 patients were identified), it was hard to determine the exact histopathological type of ovarian metastasis that affects CA-125 levels. Another limitation is that the data regarding recurrence in ovarian metastasis patients could not be analyzed. Subsequent studies should thoroughly investigate the relationship between recurrence and prognosis in this population.

Conclusions

The present study suggests that elevated serum CA-125 levels contribute to preoperative prediction, and patients with serum Ca-125 >110.5 U/mL could have higher potential risk. Use of estrogen receptor status may improve identification of patients at risk of ovarian metastasis. Preoperative workup should be complete to make an appropriate treatment plan, as ovarian metastasis can occur in women with abnormal CA-125 level, deeper myometrial invasion, tubal involvement, parametrial involvement, and who are ER-negative. Preoperative assessment of serum CA-125 level and hormone receptor status is easily performed, and these could be attractive methods to preoperatively identify high-risk patients.

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