Preoperative Serum CA125 and Extrauterine Disease in Patients with Endometrial Cancer

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Objective:
To study whether the preoperative serum CA125 level was associated with clinicopathological variables in patients with endometrial cancer and whether the level could be used for predicting extrauterine disease.

Methods:
Records of 132 patients with endometrioid endometrial cancer treated surgically were reviewed and analysed to check for any correlation between preoperative CA125 levels and clinicopathological variables. Receiver operating characteristics (ROC) curves were constructed to determine the best cutoff values of CA125 indicative of extrauterine disease including lymph node metastases. Patient outcomes were reviewed and survival analyses were performed.

Results:
15 patients (11%) had extrauterine disease, and 14 had lymph node metastases. Deep myometrial invasion and lymph node metastasis were found to be significantly associated with elevated preoperative CA125 levels. The ROC curves showed the best cutoff level to be 26.2 U/ml. Serum CA125 level above this value had a sensitivity of 93% and positive predictive value of 44% for extrauterine disease. Among those with preoperative CA125 levels below this value, only 1% had extrauterine disease. Despite the more common use of radiotherapy (78% vs 28%), patients with raised CA125 level had more recurrences (16% vs 2%) and poorer survival outcomes.

Conclusion:
Raised preoperative CA125 levels were associated with extrauterine disease in patients with endometrioid endometrial cancers. Using a cutoff of 26.2 U/ml, raised serum CA125 levels could identify the high-risk patients. Serum CA125 should be checked during preoperative assessment.

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Introduction

Since 2004, endometrial cancer had become the most common gynaecological malignancy in Hong Kong, where new patients with this condition increased from 304 in 1997 to 570 in 2006[1]. Surgery is usually the primary treatment for endometrial cancer, and it includes staging procedures to check for any spread outside the uterus, as the extent of disease guides further treatment. The presence of extrauterine disease also affects the prognosis significantly[2], which most commonly manifests as extrauterine lymph node metastasis. Lymph node dissections are performed in patients with risk factors, such as high-grade tumour, high-risk histological subtypes, and deep myometrial invasion[3]. Preoperative endometrial biopsy or uterine curettage identifies patients with high-grade tumour and high-risk histological subtypes. Ultrasound and magnetic resonance imaging (MRI) may be used for measuring the myometrial invasion; ultrasound requires expertise and MRI is expensive and may not

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be available as a routine preoperative investigation. Moreover, preoperative and intraoperative findings may differ from the final histopathological result. Also, preoperative imaging does not accurately detect the microscopic extrauterine disease and lymph node metastases. Serum CA125 is a simple blood test, more commonly used in patients with ovarian cancer. Accordingly, an analysis was undertaken to check for a correlation between preoperative serum CA125 and extrauterine disease, and to evaluate its clinical usefulness in predicting extrauterine disease in patients with endometrial cancer in particular.

Methods

Between January 2005 and December 2008, 132 patients with endometrioid endometrial cancer, treated primarily by surgery and with serum CA125 levels checked preoperatively were included in this study. Patients with uterine sarcoma, high-risk histological subtypes (clear cell, adenosquamous and serous adenocarcinoma), endometrioid adenocarcinoma with components of high-risk histological subtypes and patients with adnexal mass larger than 5 cm were excluded.

Preoperative assessment included physical examination and chest radiography. Serum CA125 was taken at the time the operation was booked, and measured by immunoassay (Access OV Monitor Assay; Beckman Coulter, Fullerton [CA], USA). Operative procedures included peritoneal washing, exploration of the peritoneal cavity, total hysterectomy, bilateral salpingo-oophorectomy, and pelvic and / or para-aortic lymph node dissection. Lymph node dissection was not performed in patients with well-differentiated tumours and no gross myometrial invasion.

The entire study was approved by the Ethics Committee of Princess Margaret Hospital. Operative, histopathological, hospital, and specialty clinic records, as well as electronic patient records were retrieved and reviewed. The clinicopathological factors studied included menopausal status, histological grade, myometrial invasion, cervical invasion, peritoneal cytology, lymph node metastases, extrauterine diseases and FIGO (International Federation of Gynecology and Obstetrics) surgical stages.

Statistical Package for the Social Sciences (Windows version 15.0; SPSS Inc, Chicago [IL], USA) was used for statistical analysis. Univariate analyses were performed using the Mann-Whitney *U* test and Kruskal-Wallis test to evaluate the association of preoperative CA125 levels with various clinicopathological factors. The χ^2 / Fisher's exact tests (univariate analysis) and a logistic regression model (multivariate analysis) were employed to examine the association between clinicopathological factors and serum CA125 levels. Receiver operating characteristics (ROC) curves were constructed to show the relationship between the sensitivity and 1-specificity at different cutoff serum CA125 levels, to detect extrauterine diseases and lymph node metastases. Survival analysis was undertaken by the Kaplan-Meier method, using the log-rank test to compare survival curves. A p value of less than 0.05 was considered statistically significant.

Results

The study included 132 patients, with an age range of 34 to 83 (median, 54) years. Of these patients, 57% were postmenopausal. Sampling for CA125 levels was carried out within 2 months (median, 13 days; range, 0-60 days) before the operation; 83% of the blood specimens were taken in the last 4 weeks before the operation. Serum CA125 levels ranged from 1 to 2355 (median, 15) U/ml; 22 patients (17%) had levels exceeding 35 U/ml, which was the reference upper limit value usually quoted.

Surgical treatment included hysterectomy and bilateral salpingo-oophorectomy. Regarding the types of hysterectomy, 123 hysterectomies were abdominal, 2 were radical, and 9 were laparoscopically assisted. Lymph node dissections were performed in 105 (80%) of the patients. The surgical procedures depended on clinical findings, uterine curettage grading, and intraoperative findings, which were all performed under the supervision of gynaecological oncologists.

In all, 15 (11%) of the patients had extrauterine diseases, as listed in Table 1. In the patients having lymph node dissection, metastatic lymph nodes were found in 14 (11%) of the patients, and constituted the most common form of extrauterine disease. Pelvic lymph node metastases were present in 11 patients, 3

of whom had both pelvic and para-aortic lymph node involvement, and 2 had abnormal peritoneal cytology. One patient had cellular atypia and another had suspicious cells, both of whom had other extrauterine disease. Surgical stages of the patients are summarised in Table 2. The relationship between preoperative serum CA125 level and surgical stage is shown in Table 3. Patients with extrauterine or stage III disease had significantly higher CA125 level.

Univariate analysis of serum CA125 and clinicopathological factors are shown in Table 4. Only patients having lymph node dissection were included in the correlation of CA125 level and lymph node metastasis, associations being found between prevailing levels and all the variables. On multivariate analysis, only deep invasion and lymph node metastasis were significantly associated with the serum CA125 level.

The ROC curves for extrauterine disease and for lymph node metastases are shown in Figures 1 and 2, respectively. The area under the curve was 0.93 and 0.92, respectively, indicating that CA125 level was a very good discriminator for extrauterine disease or lymph node metastases. The best cutoff for CA125 level was found to be 26.2 U/ml for both curves. Thirty-two patients (24%) had CA125 level above 26.2 U/ml. For various levels of serum CA125, sensitivity, specificity, positive predictive value and negative predictive value are shown in Tables 5 and 6. Among the patients with serum CA125 levels of 26.2 U/ml or more, 44% and 42% had extrauterine diseases and lymph node metastases, respectively. These figures were compared to corresponding values of 1.0% and 1.4% in patients with levels of 26.2 U/ml or less. Thus, a raised CA125 level was associated with relative risks of 44 and 30 for extrauterine diseases and lymph node metastases, respectively.

Data regarding postoperative radiotherapy are presented in Table 7. Radiotherapy was opted for jointly by a clinical oncologist and gynaecological oncologists, according to histopathological risk factors and surgical stages. Significantly more patients with high than low CA125 levels had radiotherapy; the proportions being 78% compared to 28% ($p < 0.001$).

Patient outcome after treatment was reviewed in September 2010. The results are shown in Table 8. At the time of analysis, nine patients had died, four from endometrial cancer and five from other diseases. There were four patients who defaulted follow-up (0.2, 0.3, 0.3 and 1.1 years after treatment). The median follow-up of the remaining patients was 3.1 (range, 1.6-5.6) years. There were seven patients with recurrences, all of which were outside the pelvic cavity, three of whom were still

Table 1. Patients with extrauterine disease

Extrauterine location	No. of patients
Lymph node metastasis only	8
Lymph node metastasis and parametrial involvement	2
Lymph node and ovarian metastasis	2
Lymph node metastasis, ovarian metastasis, and cytology	1
Lymph node metastasis and cytology	1
Pelvic peritoneum	1

Table 2. FIGO (International Federation of Gynecology and Obstetrics) stages of patients

Stage	No. (%) of patients
IA	36 (27)
IB	50 (38)
IC	6 (5)
IIA	10 (8)
IIB	15 (11)
IIIA	1 (1)
IIIC	14 (11)
IV	0 (0)

Table 3. Serum CA125 level and disease stage

Stage	No. (%)	Median (range) serum CA125 level (U/ml)	p Value
I	92 (70)	14 (1-290)	-
II	25 (19)	15 (2-152)	-
III	15 (11)	61 (18-2355)	<0.001

Table 4. Univariate analysis of preoperative serum CA125 levels and clinicopathological variables

Variable	No. (%)	Median (range) serum CA125 level (U/ml)	p Value
Menopausal status			0.033
Premenopausal	57 (43)	13.6 (1.0-2354.6)	
Postmenopausal	75 (57)	16.7 (1.0-634.2)	
Grade			0.012
1	85 (64)	14.1 (1-596.6)	
2	30 (23)	16.5 (1-127.3)	
3	17 (13)	25.6 (5-2354.6)	
Myometrial invasion			<0.001
Nil	38 (29)	12.2 (1.0-62.2)	
Superficial	72 (55)	15.4 (1.0-290.3)	
Deep	22 (17)	54.7 (7.5-2354.6)	
Cervical involvement			0.018
Nil	98 (74)	14.7 (1.0-2354.6)	
Gland only	11 (8)	18.8 (5.3-151.5)	
Stroma	23 (17)	24.3 (1.7-634.2)	
Peritoneal cytology			0.035
Negative	130 (98)	15.1 (1-2354.6)	
Positive	2 (2)	323.7 (50.7-596.6)	
Lymph node metastasis*			<0.001
No	91 (69)	14.9 (1-290.3)	
Yes	14 (11)	92.0 (17.8-2354.6)	
Extrauterine diseases			<0.001
No	117 (89)	14.4 (1-290.3)	
Yes	15 (11)	60.5 (17.8-2354.8)	

* Only patients with lymph node dissection were included in analysis for correlation of CA125 level and lymph node metastasis

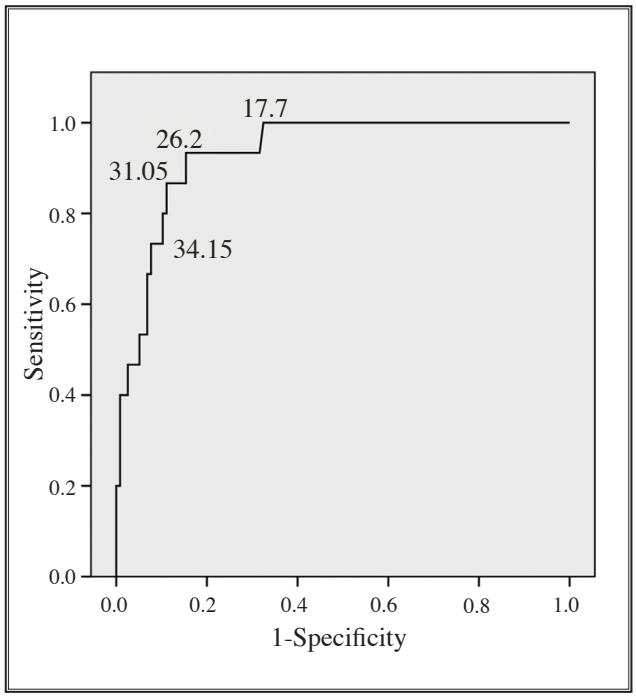

Figure 1. Receiver operating characteristics curve drawn at different cutoff values of the CA125 level for extrauterine diseases. The area under the curve was 0.93

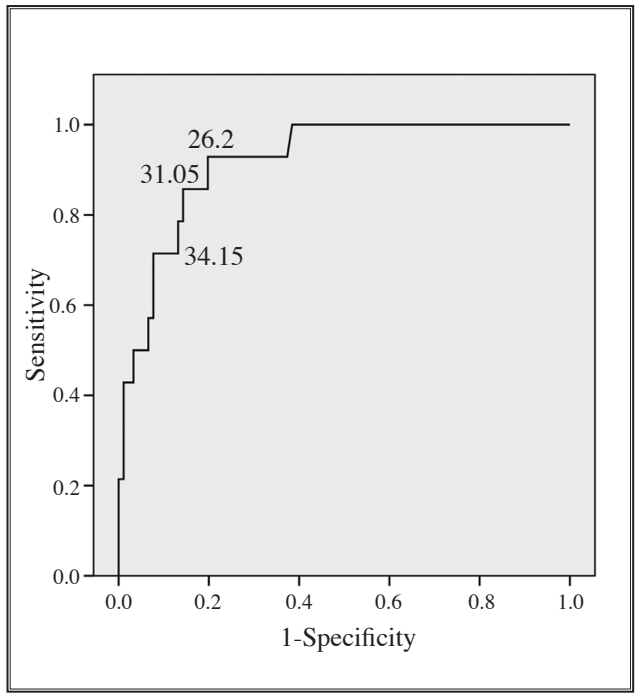

Figure 2. Receiver operating characteristics curve drawn at different cutoff values of the CA125 level for lymph node metastases. The area under the curve was 0.92

Table 5. Serum CA125 levels and extrauterine disease

Cutoff (U/ml)	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
5	100.0	7.7	12.2	100.0
20	93.9	94.8	32.6	98.9
25	93.9	82.1	40.0	99.0
26.2	93.9	84.6	43.8	99.0
30	86.7	87.2	46.4	98.1
35	73.3	90.6	50.0	96.4
50	60.0	93.2	52.9	94.8
65	46.7	96.6	63.6	93.4
80	46.7	96.6	63.6	93.4
95	46.7	96.6	63.6	93.4
155	40.0	99.1	85.7	92.8

Table 6. Serum CA125 levels and lymph node metastases

Cutoff (U/ml)	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
5	100.0	6.6	14.1	100.0
20	92.9	71.4	33.3	98.5
25	92.9	78.0	39.4	98.6
26.2	92.9	80.2	41.9	98.6
30	85.7	83.5	44.4	97.4
35	71.4	87.9	47.6	95.2
50	64.3	92.3	56.3	94.4
65	50.0	95.6	63.6	92.6
80	50.0	95.6	63.6	92.6
95	50.0	95.6	63.6	92.6
155	42.9	98.9	85.7	91.8

Table 7. Use of postoperative radiotherapy

Stage (FIGO 1988)	No. (%)
I (n = 92)	17 (18)
IA (n = 36)	1 (3)
IB (n = 50)	11 (22)
IC (n = 6)	5 (83)
II (n = 25)	23 (92)
III (n = 15)	13 (87)

alive. Overall survival, cause-specific survival, and disease-free survival are shown in Figures 3, 4 and 5 respectively. Patients with high CA125 levels had poorer survival outcomes.

Discussion

Serum CA125 is a tumour marker commonly used for ovarian cancers. Its use for endometrial cancer is much less common. Niloff et al[4] first reported raised levels of serum CA125 in patients with advanced and recurrent endometrial cancers. Immunohistochemical study showed positive CA125 tissue staining in most endometrioid endometrial carcinomas, but elevated serum levels were only found in a small proportion of patients. There seems to be a mechanism that prevents CA125 access into the circulation[5]. In our series using multivariate analysis, deep myometrial invasion and lymph node metastasis correlated with raised serum CA125 levels. Deep myometrial invasion and lymph node metastases may somehow result in the release of CA125 antigens into the circulation. Powell et al[6] found an association between CA125, lymphovascular invasion and extrauterine disease. Lymphovascular

Table 8. Patient outcomes

	Serum CA125 level, No. (%)	
	≤26.2 U/ml (n = 100)	>26.2 U/ml (n = 32)
Alive with no evidence of disease	94 (94)	26 (81)
Recurrences	2 (2)	5 (16)
Alive with disease	2 (2)	1 (3)
Died of endometrial cancer	0 (0)	4 (13)
Died of other causes	4 (4)	1 (3)

invasion may well be the mechanism for extrauterine spread of tumour cells and the raised CA125 levels.

Increased preoperative serum CA125 levels have been reported in patients with extrauterine diseases[7-11], and suggested as a means of predicting such diseases. On the contrary, in one study no correlation was found[12]. The present study found a strong association between extrauterine diseases and preoperative serum CA125 level. Different from the other studies, the present study only included patients with endometrioid adenocarcinoma and without gross adnexal mass.

Histologically high-risk tumours, such as clear cell and serous carcinomas, are known to spread outside the uterus, for which staging procedures including lymph node dissection and omentectomy are carried out. Also, Price et al[13] found that for patients with serous endometrial carcinoma, serum CA125 levels had limited utility in monitoring the effects of adjuvant therapy and did not predict recurrence. The present study only included patients with endometrioid adenocarcinoma, which accounts for about 84% of all endometrial cancers[2].

One possible cause for increased serum CA125 levels is ovarian pathology. Ovarian masses larger than 5 cm can be picked up preoperatively by physical examination or pelvic ultrasonography. Apart from metastasis from the endometrial tumours, an adnexal mass could be concomitant ovarian primary or other benign pathology, both of them can cause an increase in CA125 level and confuse the picture. These cases were also excluded from this study.

In this retrospective study, serum CA125 level was known before the operation and might have affected the extent surgical staging procedures carried out. For patients with levels exceeding 26.2 U/ml, 97% had lymph node dissection performed, while for patients with lower levels, 74% had lymph node dissection. This was because the decision to perform lymph node dissection depended mainly on the tumour grade and myometrial invasion, both of which were associated with high serum CA125 levels. After excluding patients having no lymph node dissection from the analysis, there was still a significant association between lymph node metastases and CA125 levels.

Using a cutoff value of 35 U/ml, Bast et al[14] found that 1% of 888 apparently healthy blood donors of both genders had increased serum CA125 levels compared with 82% of 101 patients with ovarian carcinoma. Since then, a reference cutoff level of 35 U/ml has been adopted as a guide to screen for this cancer. For endometrial cancer however, and particularly for predicting extrauterine spread, this cutoff level may not be appropriate. As determined by their ROC curve for lymph node metastasis, Chung et al[11] suggested 28.5 U/ml and Hsieh et al[10] 40 U/ml; both of them included patients with all histological subtypes. The current study only included patients with endometrioid adenocarcinoma, for which ROC curves that were constructed identified 26.2 U/ml as the best cutoff value. Using the latter, patients could be stratified into two groups with significantly different risks of extrauterine disease, 44% versus 1.0%. Patients with raised serum CA125 levels also received more postoperative radiotherapy and endured poorer survival outcomes.

Serum CA125 level was found to be higher in premenopausal patients, which may be an effect of ovarian hormones[15,16]. For serum CA125 levels and endometrial cancer, studies have indicated different cutoff values for premenopausal and postmenopausal women. Respective values suggested by Todo et al[17] were 70 U/ml and 28 U/ml. Ebina et al[18] also

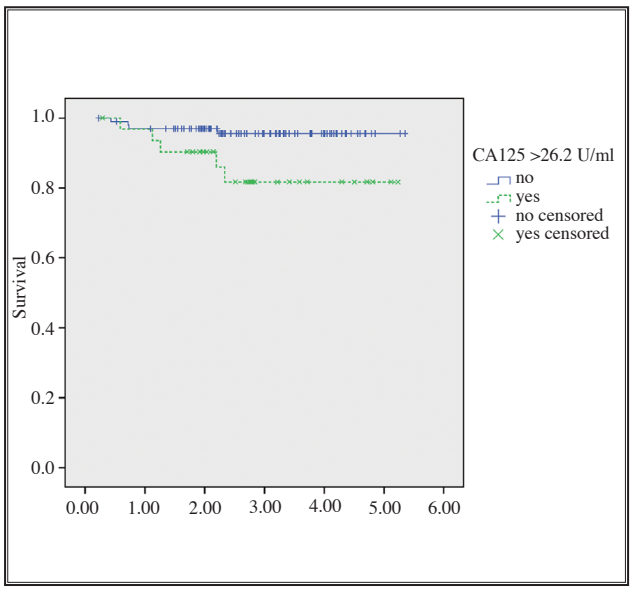

Figure 3. Overall survival (p = 0.0218)

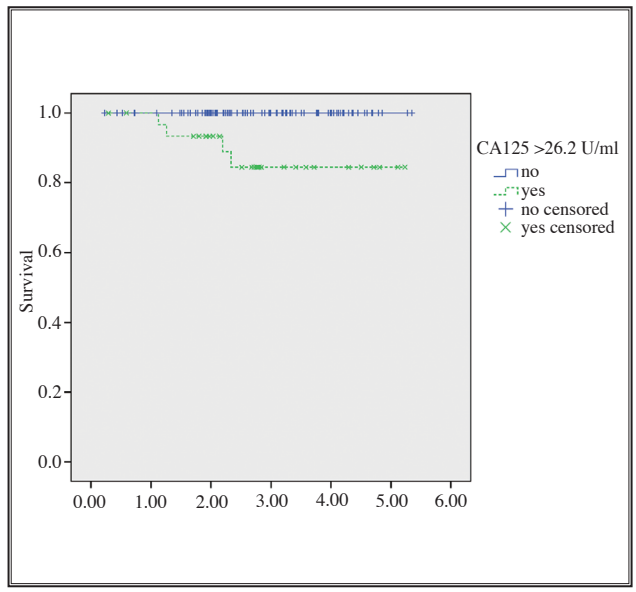

Figure 4. Cause-specific survivl (p = 0.0003)

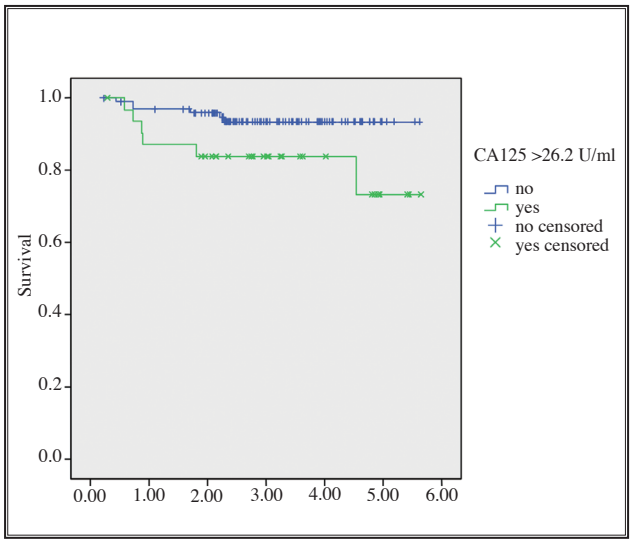

Figure 5. Disease-free survival (p = 0.0328)

found a higher cutoff for premenopausal than postmenopausal patients with para-aortic lymph node metastasis. However, Han et al[19] found a cutoff of 20 U/ml for premenopausal patients and 28 U/ml for postmenopausal patients. The present study was not large enough to analyse the two groups of patients separately. Further studies are required to resolve this issue.

Conclusion

Increased preoperative serum CA125 levels were associated with extrauterine disease in patients with endometrioid endometrial cancers. Using a cutoff of 26.2 U/ml, elevated levels could identify high-risk patients and serum CA125 should be checked preoperatively.

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