RESEARCH ARTICLE

The Value of Preoperative CA 125 Levels in Prediction of Myometrial Invasion in Patients with Early-stage Endometrioid-type Endometrial Cancer

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Abstract

Aim: To evaluate the relationship between pre-operative CA-125 levels and myometrial invasion in patients with early-stage endometrioid-type endometrial cancer. **Materials and Methods**: Two-hundred and sixty patients were diagnosed with endometrial cancer between January 2007 and December 2012. Of these, 136 patients with stage 1 endometrioid histologic-type and documented pre-operative serum CA-125 levels were included in the study. Age, preoperative CA-125 level, histologic grade, surgical grade, and presence of deep myometrial invasion were recorded. Additionally, 16, 20, and 35 IU/ml cutoff values were used and compared to evaluate the relationship between pre-operative CA-125 levels and myometrial invasion. **Results**: The average serum CA-125 level was 35.4±36.7 in patients with deep myometrial invasion, and 21.5±35.8 in cases without deep myometrial invasion. The relationship between the presence of deep myometrial invasion and CA-125 cut-off values (16, 20, 35 IU/ml) was statistically significant, although the correlation was weak (p<0.05). When the relationship between 16, 20 and 35 IU/ml CA-125 cut-off values and the presence of deep myometrial invasion was studied, specifity and sensitivity values were identified as: 0.60-0.68 for 16 IU/ml; 0.73-0.48 for 20 IU/ml; and 0.89-0.33 for 35 IU/ml. The sensitivity of 16 IU/ml cut-off value was higher when compared to other values. **Conclusions**: This study demonstrates that preoperative serum CA-125 values maybe used as a predictive test in patients with early stage endometrioid-type endometrium cancer, and as a prognostic factor alone. Further studies should be conducted to identify different CA-125 cut-off values in patients with low risk endometrial cancer.

Keywords: Endometrial cancer - deep myometrial invasion - CA-125 - cut-off value

Introduction

Research on risk factors, early diagnosis, screening methodology, prognostic factors, and effective treatments to improve survival in endometrial cancer has increased. This is in part due to increased incidence of the disease such that endometrial cancer has become the most common malignancy of the female genital tract. The most common histologic type of endometrial cancer is endometrioid-type adenocarcinoma (86.4%). The5-year survival rate is 80-90% in these cases. (Jemal et al., 2006) In general, endometrial carcinogenesis occurs in 1-3% of women during their lifetime. (Lo et al., 1997; Dotters et al., 2000; Chan et al., 2007)

The most important prognostic factors for endometrioid-type adenocarcinoma are histologic grade, depth of myometrial invasion, and lymphovascular involvement. In patients with early-stage endometrial lcancer limited to the uterus without poor prognostic factors such as cervical involvement, tumor diameter >2 cm, and extrauterine spread, the presence of over 50% of myometrial invasion can affect the prognosis separately. (Yıldız et al., 2013)

There is research suggesting that 35 IU/ml cut-off value of CA-125 that is used in ovarian cancer is better than the currently used CA-125 level of 20 IU/ml in endometrial carcinoma. (Price et al., 1998; John et al., 2007; Yıldız et al., 2012). Powell et al. reported that CA-125 levels >35 U/ml strongly predicted extrauterine disease and were shown to be a strong predictor of poor prognosis in patients with endometrial cancer (Powell et al., 2005). Measurement of preoperative CA-125 has been found to be a clinically useful test in patients with endometrial cancer. In fact,

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CA-125 appears to be a significant independent predictor of extrauterine spread of disease, and has been shown to be a better predictor of disease than depth of invasion or grade (Yıldız et al., 2012). Serum CA-125 measurement has also been recommended for post-treatment follow-up. (Jemal et al., 2005).

Conversely, there has been some research reporting an insignificant correlation between CA-125 levels and spread of endometrial carcinoma. (Jemal et al., 2005; Longacre et al., 2005; Geisinger et al., 2006) Clinically, patients with localized disease and normal CA-125 levels have a lower risk of extrauterine disease. (Atasu et al., 2001; John et al., 2007).

The aim of this study was to determine whether pre-operative serum CA-125 levels alone can be used as a prognostic factor in predicting myometrial invasion of endometrioid-type endometrial carcinoma.

Materials and Methods

This was a retrospective study to determine whether pre-operative serum CA-125 levels are a prognostic factor alone in predicting myometrial invasion of endometrioid-type endometrial carcinoma. The study was approved by the hospital's Ethics Committee.

Two hundred and sixty patients diagnosed with endometrial cancer at the Department of Obstetrics and Gynecology in İzmir Katip Celebi University Ataturk Training and Research Hospital between January 1, 2007 and December 31, 2012 were chosen. The study included 136 cases with known pre-operative CA-125 values and surgically staged as stage 1 endometrioid-type endometrial cancer. There was no other malignancy, endometriosis, or pelvic infection present in these patients.

Endometrial cancer was diagnosed initially using dilatation and curettage.CA-125 levels were identified with Roche E170 Moduler system via chemiluminescence.

During the operation, abdominal exploration was performed in all patients, followed by cytological examination of the abdominal fluid sample. Total abdominal hysterectomy, bilateralsalpingo-oopherectomy (TAH+BSO), bilateral pelvic lymph node dissection ± para-aortic lymph node dissection was then performed. Biopsies of suspicious lesions were taken. The degree of myometrial invasion was assessed with by frozen sections. Patients with good prognostic factors (myometrial invasion with depthless than 50%, absence of isthmus-cervix invasion, tumor diameter less than 2 cm, and absence of extra-uterine spread) received only pelvic lymph node sampling, while patients with poor prognostic factors (myometrial invasion greater than 50%, presence of isthmus-cervix invasion, tumor diameter greater than 2 cm, and presence of extra-uterine spread) received total pelvic and para-aortic lymph node dissection. In these patients, omental biopsy was also performed. All materials were examined in the pathology laboratories at our center. The degree of myometrial invasion after histo-pathological examination of intra-operative sections was evaluated.

The 2009 FIGO surgical staging system was then used for endometrial cancer staging. The FIGO for grade stratification and World Health Organization Classification of Tumors system was used for histological stratification. The average age, pre-operative CA-125 level, histological grade, surgical grade, and the presence and degree of myometrial invasion were noted in all patients.

Pre-operative CA-125 levels and clinicopathological parameters were then compared using16.85, 20, and 35 IU/ ml cut off values for CA-125 levels.

Results

Table 1 shows the average age and average CA-125 values of 136 patients with stage 1 endometrioid-type endometrial cancer included in the study, and the relationship of these two parameters with deep myometrial invasion (DMI).

Average age and average CA-125 values of patients with DMI was statistically higher comparing to patients without DMI. (p=0.042)

70.6% of patients were Stage 1A and 29.4% of patients were Stage 1B.While 72.8% of patients were grade 1, 22.1% of patients were grade 2, and 5.1% of patients were grade 3. There were no patients with DMI with CA-125 value below 6.2.(Table 2)

A CA-125 value of 16.85 IU/ml had the highest sensitivity (0.650) and specificity (0.656) when CA-125 values were analyzed according to the depth of myometrial invasion, with a 66.7% (95% CI:0.563-0.772) diagnostic strength on ROC analysis. (Figure-1)
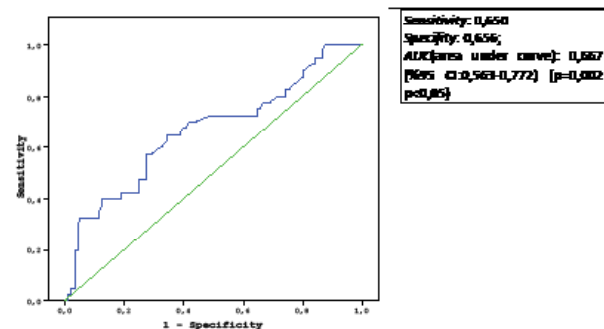

Figure 1. ROC Curve for CA-125 Values According to the Presence of Myometrial Invasion

Table 1. Relationship of Average age and Average CA-125 Values of Patients with Myometrial Invasion

DMI	N	Mean±SD	P
Age			
Positive	40	63,43±7,27	0.028
Negative	96	59,75±9,37	
Total	136	60,83±8,94 (min.47, max.82)	
CA-125			
Positive	40	35,43±36,71(min.6.2, max.199)	0.042
Negative	96	21,48±35,76(min.2, max.322)	
Total	136	25,58±36,47(min.2, max.322)	

Table 2. Mean Distribution of CA-125 Values in Terms of the Presence of Myometrial Invasion

Myometrial invasion	Ca125 (Mean.±SD)	Minimum	Maximum
Positive	35,43±36,71	6.2	199.1
Negative	21,48±35,76	2	322

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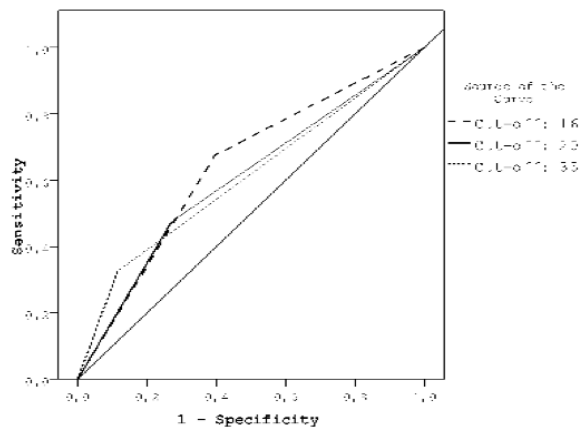

Figure 2. ROC Curve According to 16, 20, and 35 IU/ml Cut-off values of CA-125

Table 3. Results of ROC Analysis According to 16, 20, and 35 Cut off Values of CA-125

	16 IU/ml	20 IU/ml	35 IU/ml
Sensitivity	0.68	0.48	0.33
Specifity	0.6	0.73	0.89
AUC	0.64	0.602	0.605
AUC p	0.01	0.061	0.054
AUC 95% CI	0,538-0,741	0,495-0,709	0,496-0,715

AUC:(area under curve)

Table 4. Correlation analysis for the Relationship Between Myometrial Invasion and CA-125 values.

	Deep Myometrial Invasion	
	r	p
	correlation coefficient	The value of the correlation coefficient significance
CA-125	0.264	0.002

Table 5. Distribution of Stage Proportions According to CA-125 cut off values (16, 20 and 35)

		Stage	
		1A n (%)	1B n (%)
CA-125	16 and more	38 (39,6)	27 (67,5)
CA-125	20 and more	26 (27,1)	19 (47,5)
CA-125	35 and more	11 (11,5)	13 (32,5)

Table 6. Distribution of Average Age According to Grade Stratification

Grade	Age (Mean.±SD)	p*
1	60,18±9,32	0.389
2	65,50±7,93	
3	62,86±7,08	

*Kruskal Wallis H

When cases were assessed on ROC analysis according to the 16, 20 and 35 IU/ml cut-off values, the relationship of DMI,specificity, and sensitivity were: 0.60 - 0.68 for 16 IU/ml; 0.73-0.48 for 20 IU/ml; 0.89-0.33 for 35 IU/ml

(Table-3 and Figure-2) The sensitivity of 16 IU/ml value was found to be the greatest.

The relationship between DMI and CA-125 values was statistically significant. However, when a correlation analysis was performed, it was found to be weak. (p=0.002) (Table 4).

70.6% of patients (96 cases) were Stage 1A, and 29.4% of patients (40 cases) was Stage 1B. The distribution of cases into stages according to CA-125 16, 20 and 35 IU/ml cut off values is shown in table-5. CA-125 values were over 16 U/ml in 39.6% of patients with Stage 1A and 67.5% of cases with Stage 1B disease; CA-125 values were over 20 U/ml in 27.1% of patients who were Stage 1A and 47.5% of patients who were Stage 1B; CA-125 values were over 35 U/ml in 11.5% of patients with Stage 1A and 32.5% of patients with Stage 1B disease. (Table-5)

The Kruskal-Wallis analysis was used to determine the relanship between grade and age, and no statistically significant difference between the ages of the patients in Stage 1, 2, and 3 were found. (p>0.05) (Table 6)

Discussion

The CA-125 tumor antigen is widely accepted as a useful clinical tool for management of patients with ovarian cancer. CA-125 is the most common tumor indicator that is used to identify an increased preoperative risk of lymph node metastasis and to evaluate, diagnose, monitor, and determine prognostic factors in patients with endometrial cancer. A CA-125 level over 35 IU/ml is reported as a strong indicator in extra-uterine spread and has been shown to increase the mortality of endometrial carcinoma. (Powell et al., 2005; Yıldız et al., 2012) The risk of extra-uterine spread is lower in patients with normal CA-125 levels and clinically localized disease. (Atasu et al., 2001).

Chao et al. (2013) found a significant relationship between CA-125 values and cancer prognosis in a study conducted to determine the effect of CA-125 values in patients of different age groups in endometrial cancer. (Chao et al., 2013).

In a study by Chung et al, the effects of pre-operative CA-125 levels on the spread of endometrial cancer and clinical results were assessed. CA-125 levels were distinctly higher in cases with advanced endometrial cancer, lymph node metastasis, positive peritoneal cytology, and myometrial invasion. Lymph node metastasis was found to be the most important factor in elevated preoperative CA-125 levels on multivariate analysis. (Chung et al., 2006).

Chen YI et al, found that a ≥40 cut-off value of CA-125 was statistically significant in predicting poor prognostic factors in a study including 120 cases that were operated for endometrial cancer. (p<0.001) (Hsieh et al., 2008; Chen at al., 2011) Our study also reports a significant relationship between CA-125 levels and myometrial invasion in stage 1 endometrioid-type endometrial cancer; so the relationship between treatment options and prognosis is presented.

In another study we published in 2012, we researched the importance of preoperative CA-125 values in 147

patients with endometrial cancer to determine the treatment choice according to staging. In this study, we mostly compared 20 and 35 IU/ml cut off values in patients with endometrial cancer. We reported that acut-off value of 20 is more sensitive and specific for predicting myometrial invasion and prognosis. (Yıldız et al., 2012) In this recent subgroup analysis study that includes only stage 1 endometrioid-type, we identified a statistically significant relationship between 16, 20 and 35 IU/ml cut-off values for CA-125 and myometrial invasion of over 50%percent. (p<0.05) Sensitivity values were 68%, 48% and 33%, sensitivity values were 60%, 73% and 89%, respectively.

In our study, mean CA-125 levels of 136 patients with stage 1 endometrioid-type endometrial cancer was 25.58 IU/mL, this value was 21.48 for Stage 1A, and 35.43 for Stage 1B.

In a study conducted by Kukura et al to find predictors of serum CA-125 values in extra-uterine spread of the disease, uterine tumors were found in 142 of 174 patients, while there was extra-uterine spread in 32 patients. In tumors limited to uterus, mean CA-125 levelswere64 U/ml, while mean CA-125 levelswere244 U/ml in tumors with extra-uterine spread. The risk of metastases was increased in higher CA-125 values in endometrial cancer. (Kukura et al., 2003) Our study was performed in cases limited to the uterus, and the mean CA-125 level was 25.58 U/ml. Our results are lower than values in the literature. This is caused by the limitation of our sample of early-stage patients.

A 20 IU/ml CA-125 threshold value in endometrial carcinoma is better than the 35 IU/ml CA-125 threshold value that is used in ovarian carcinoma. (Kurihara et al., 1998; Yıldız et al., 2012) In cases with CA-125 levels below 20 IU/ml and grade 1 endometrial carcinoma, the risk of extra-uterine spread is reported to be lower than 3%. (Atasu et al., 2000). Kurihara et al found serum CA-125 levels below 20 IU/ml in 96.2% of 619 normal post-menopausal Japanese women. A novel cutoff level of 20 U/ml of CA-125 could detect myometrial invasion to more than one-half of the myometrium with a sensitivity of 69.0%, specificity of 74.1%, positive predictive value of 58.8%, and negative predictive value of 81.6%. (Kurihara et al., 1998).

When we compared CA-125 levels of 16, 20 and 35 IU/m values in our study, a lower cut off value, 16 IU/ml, was found to be more significant in predicting myometrial invasion over fifty percent (% 67% specificity and 66% sensitivity.) (p<0.05). This is because all of our cases were early stage carcinoma.

Gadduci et al found that high CA-125 values have a poor prognosis in a study that researched the prognostic importance of tissue and serum biomarkers in endometrioid-type endometrial cancer. Myometrial invasion was also a poor prognosis factor. (Gadduci et al., 2011).

Dvalishvilive et al found a statistically significant relationship on comparing clinical parameters and prognostic factors in post-menopausal patients with endometrioid-type endometrial cancer (Dvalishvilive et al., 2006).

The records of 97 women with endometrial carcinoma were analyzed by Goksedef et al. There was a significant relationship between a serum CA-125 level ≥ 35kU/L and depth of myometrial invasion, cervical stromal invasion, stage, frequency of recurrence, and disease-related death. Having deep myometrial invasion, cervical stromal involvement, positive peritoneal cytology, lymph node metastasis, disease recurrence, and disease-related death were each associated with significantly higher mean CA-125 levels. In women with serum CA-125 levels <35 kU/L, five-year progression-free survival rates (88%) and overall survival rates (92%) were significantly better than in women with levels ≥35 kU/L (57% and 70%, respectively; P=0.001 for both) (Goksedef et al., 2011).

Kang, in his recent study conducted in 2012 with 360 patients with endometrial cancer, suggested that serum CA-125 levels and three MRI parameters (deep myometrial invasion, lymph node enlargement, and extension beyond uterine corpus) were found to be independent risk factors for nodal metastasis. According to Kang, using serum CA-125 and MRI as criteria resulted in the accurate identification of a low-risk group for lymph node metastasis among patients with endometrial cancer (Kang et al., 2012).

In 1999, Alcazar conducted a prospective study in 50 consecutive patients diagnosed with endometrial cancer and scheduled for surgical staging. He compared the ability of transvaginal sonography and serum CA-125 levels to predict myometrial invasion in patients with endometrial carcinoma. The sensitivity, specificity, PPV, and NPV of transvaginal ultrasonography were 86.7% (95% CI 59.5-98.3), 94.3% (95% CI 80.8-99.3), 86.7% (95% CI 59.5-98.3), and 94.3% (95% CI 80.8-99.3), respectively. The sensitivity, specificity, PPV, and NPV for CA-125 were 40% (95% CI 16.3-67.7), 91.4% (95% CI 76.9-98.2), 66.7% (95% CI 29.9-92.5), and 78% (95% CI 63.4-89.5), respectively. The sensitivity of transvaginal ultrasonography was significantly higher than that of CA-125 (p = 0.008). The results of the study indicate that transvaginal ultrasonography is more sensitive than CA-125 in predicting myometrial invasion in endometrial cancer (Alcazar et al., 1999).

In conclusion, this study demonstrated that preoperative serum CA-125 values maybe used as a predictive test in patients with early stage endometrioid-type endometrium cancer, and as a prognostic factor alone. Further studies should be conducted to identify different CA-125 cut-off values in patients with low risk endometrial cancer.

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