

# Investigation of the Role of Preoperative Serum CA 125 Levels in Determining the Necessity of Lymphadenectomy in Cases Diagnosed with Endometrium Cancer: A Retrospective Study

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## ABSTRACT

**Objective:** The aim of this study is to investigate the relationship between preoperative serum CA 125 levels and clinicopathological parameters in patients operated for endometrial carcinoma (EC) and to reveal the effectiveness of preoperative serum CA 125 levels in determining the necessity of lymphadenectomy.

**Materials and Methods:** The study included retrospective data of 88 patients who underwent surgery due to EC. The relationship between the patients' preoperative serum tumor marker CA-125 levels and tumor grade, stage, histological type, lymph node positivity was evaluated statistically. The statistical significance of CA-125 levels in determining the need for lymph node dissection was analyzed.

**Results:** When the preoperative diagnostic methods of the cases were evaluated according to their surgical stage; the mean CA 125 value was  $31.21 \pm 35.54$  (4.4-150.3) IU/ml in early stage (Stage I-II) patients and  $349.13 \pm 497.34$  (19.5-1566) IU/ml in advanced stage (Stage III-IV) patients ( $p=0.001$ ). Considering the depth of myometrial invasion and preoperative CA 125 values, the mean preoperative CA 125 values were  $21.43 \pm 20.06$  (4.4-44.1) IU/ml in cases with myometrial invasion less than 1/2, while this value was  $141.03 \pm 329.47$  (6.8-1566) IU/ml in cases with more than 1/2 and the difference between the groups was found to be statistically significant ( $p=0.025$ ). CA 125 levels of cases with positive lymph nodes were statistically significantly higher than CA 125 levels of cases with negative lymph nodes ( $p<0.05$ ). While the CA 125 level was 35 IU/ml and above in all cases with positive lymph nodes, the CA 125 level was 35 IU/ml and above in 30.2% of the cases with negative lymph nodes ( $p<0.05$ ).

**Conclusions:** The results we obtained in this study support the association of increased preoperative CA 125 levels with lymph node positivity, advanced stage and myometrial involvement above 1/2 in cases with EC.

## KEYWORDS

Endometrial cancer; CA125; lymph node metastases; poor prognostic factors.

doi 10.62093/e2308

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## How to cite this article

Yoğurtçuoğlu EE & Köse G. Investigation of the Role of Preoperative Serum CA 125 Levels in Determining the Necessity of Lymphadenectomy in Cases Diagnosed with Endometrium Cancer: A Retrospective Study. *Adv Res Obstet Gynaecol.* 2023;1(2):e2308. doi: 10.62093/e2308

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## Introduction

Endometrial cancer (EC) is the most common gynecological malignancy in high-income countries and the second most common gynecological malignancy after cervical cancer in low- and middle-income countries<sup>1</sup>.

Endometrial cancers have traditionally been classified as type I or type II. Type I ECs are estrogen-dependent, have mostly endometrioid histology, are lower grade, and are associated with better prognosis. In contrast, type II ECs respond poorly to progestins and are associated with poor prognosis<sup>2</sup>. The World Health Organization (WHO) histologically divides EC into the following subgroups: endometrioid, serous, clear cell, mixed and undifferentiated/dedifferentiated carcinoma, carcinosarcoma, and rare EC subtypes<sup>3</sup>. The International Federation of Gynecology and Obstetrics (FIGO) 2023 staging system divides histological types into aggressive and less aggressive tumors<sup>4</sup>.

Cancer antigen (CA) 125 is a glycoprotein encoded by the mucin 16 (MUC16) gene. Studies have shown that preoperative serum CA 125 level is a useful marker in predicting extrauterine spread and recurrence of the disease in patients with EC<sup>5</sup>. It has been emphasized that in EC, CA 125 levels above 35 IU/ml are a strong indicator of extrauterine spread and death from cancer<sup>6,7</sup>. Serum CA 125 measurement is also recommended for post-treatment follow-up<sup>8</sup>. In addition, it has been stated in some studies that the correlation between CA 125 levels and the spread of the disease in EC is insignificant<sup>9</sup>. Clinically, patients who appear to be localized and have normal CA 125 levels have a lower risk of extrauterine disease<sup>10</sup>.

The aim of this study is to investigate the relationship between preoperative serum CA 125 levels and clinicopathological parameters in patients operated for EC in our clinic and to reveal the effectiveness of preoperative serum CA 125

level in determining the necessity of lymphadenectomy.

## Material and Methods

This retrospective study was performed in accordance with the principles of the Declaration of Helsinki. The records of 88 EC cases operated on in the Gynecology and Obstetrics Clinic of Haydarpaşa Numune Training and Research Hospital were accessed in the hospital information system and files. Patients' ages, diagnostic methods, comorbidities (diabetes mellitus, hypertension), obstetric history (gravida, parity numbers), infertility status, endometrial thickness measurements evaluated by transvaginal US, CA 125 levels measured in the preoperative period (Beckman Coulter DXI 800 Electrochemiluminescence System), endometrial biopsy results, type of surgical operation performed, histological type and degree of differentiation, presence of adnexal metastasis, presence of atypical cells in abdominal wash fluids, pelvic-paraaortic lymph node sampling, presence of metastasis in cases where omentectomy and appendectomy were performed, pathological results of samples, computed tomography (CT) or magnetic resonance imaging (MRI) examination results, postoperative follow-up and treatments were examined.

The relationship between the patients' preoperative serum CA 125 level and stage, histological type, grade and lymph node positivity was evaluated statistically. Additionally, 20 IU/ml and 35 IU/ml values were compared to determine CA 125 cut-off values for all these parameters. While evaluating the findings obtained in the study, SPSS (Statistical Package for Social Sciences) for Windows 15.0 program was used for statistical analysis. While evaluating the study data, in addition to descriptive statistical methods (Mean, Standard deviation), Student t test and Mann Whitney U test were used to compare

quantitative data. Chi-square test and Fisher's Exact Test were used to compare qualitative data. The results were evaluated at the 95% confidence interval and the significance level was  $p < 0.05$ .

## Results

The mean age of 88 EC patients was  $60.6 \pm 12.5$  (25-85) years. When the distribution of histopathological diagnoses of the cases was examined, the most common subgroup was endometrioid adenocarcinoma with 69 (78.4%) cases. Other cases were mixed type 14% ( $n=12$ ), serous papillary type 7% ( $n=6$ ) and small cell type 1% ( $n=1$ ).

The average age of patients diagnosed with endometrioid-type adenocarcinoma was lower

than the average age of other patients ( $p = 0.015$ ). Thirty patients (34%) had hypertension and 19 had diabetes (21.6%) as comorbidities. Hypertension did not affect whether the tumor was at an early (I-II) or late (III-IV) stage ( $p=0.772$ ), nor whether its grade was low (I-II) or high (III) ( $p=0.505$ ). It was also found that the fact that the patients had diabetes did not affect the stage ( $p = 0.897$ ) and grade ( $p = 0.869$ ) of the tumor. The mean gravida in all endometrial cancer cases was  $4.6 \pm 3.2$  (0-18) and parity was  $3.4 \pm 2.3$  (0-13). Infertility was present in 4 (4.5%) patients. All demographic characteristics of the cases are shown in Table 1.

**Table 1.** Demographic characteristics of cases

	Total ( $n=88$ )	Endometrioid Tumor ( $n=69$ )	Mixed Adeno Ca ( $n=12$ )	Serous Papillary Tumor ( $n=6$ )	Small Cell Serous Ca ( $n=1$ )
<b>Age</b>	$60.5 \pm 12.5$	$59.3 \pm 12.3$	$63.2 \pm 8.6$	$72.8 \pm 4.8$	71
<b>Gravida</b>	$4.6 \pm 3.2$	$4.5 \pm 3$	$4.3 \pm 1.9$	$5.2 \pm 5$	14
<b>Parity</b>	$3.4 \pm 2.3$	$3.4 \pm 2.4$	$4 \pm 1.2$	$2 \pm 2.4$	6
<b>Hypertension</b>	30 (%34)	23 (%33.3)	7 (%58.3)	0	0
<b>Diabetes</b>	19 (%21.6)	15 (%21.7)	2 (%16.6)	2 (%33.3)	0
<b>Infertility</b>	4 (%4.5)	3 (%4.3)	0	1 (%16.6)	0

Five of the patients included in the study were diagnosed with EC in an external center and sent to our clinic for surgery. Preoperative endometrial biopsy was performed in 83 cases in our clinic. Malignant results were detected in 72 (86.8%) cases, complex hyperplasia with atypia in 8 cases (9.6%), complex hyperplasia without atypia in 1 case (1.2%), endometrial polyps in 1 case (1.2%), and sparse glandular epithelial cells in 1 case (1.2%). The postoperative diagnosis of these 11 patients with false negative results were reported as endometrioid adenocarcinoma. Endometrial

thickness was measured with TVUS in all cases and the average was found to be  $13.5 \pm 7.8$  (2-36) mm. Endometrial thickness was  $12.4 \pm 5.7$  (2-30) mm in endometrioid adenocarcinomas and  $17.8 \pm 12.1$  (2-36) mm in other subgroups, and the difference between the two groups was not statistically significant ( $p=0.413$ ).

Total abdominal hysterectomy + bilateral salpingo-oophorectomy with abdominal wash fluid sampling + diaphragm swab + omentectomy + appendectomy + staging surgery including pelvic lymph node dissection was

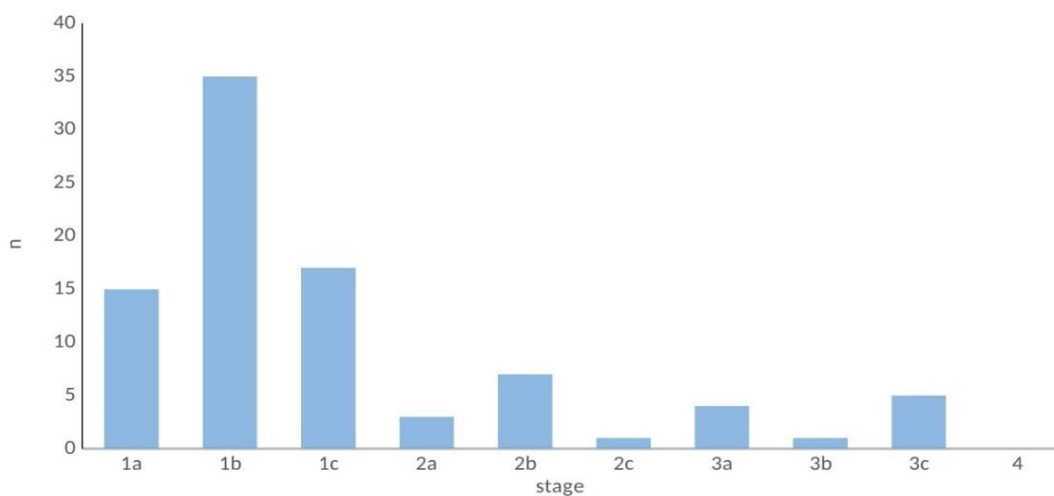
performed in 70 (79.5%) of the operated cases, total abdominal hysterectomy + bilateral salpingo-oophorectomy in 17 cases (19.3%) and vaginal hysterectomy in one case (1.13%). Selective lymphadenectomy (sampling) was preferred in 70 patients who underwent lymphadenectomy. The mean number of lymph nodes removed was  $9.6 \pm 6.4$  (0-32).

In surgical staging, Stage 1b was the most common with 35 cases (39.7%), while Stage 1c was the second most common with 16 cases (18.2%). We had no cases with bladder, rectum, or distant metastases (Stage IV). The distribution of cases according to surgical stages is shown in Figure 1.

When the grades of the cases were scanned, it was found that grade 2 was the most common in 53 (60.2%) cases, followed by grade 1 in 20 cases and grade 3 in 15 cases. In the postoperative pathological examination, the tumor was found limited only to the endometrium in 13 cases (14.7%), while tumor invasion was found to be less than  $\frac{1}{2}$  of the myometrium in 37 cases (42%) and the depth of invasion was more than  $\frac{1}{2}$  of the

myometrium in 34 cases (38.6%). Pelvic lymph node positivity was detected in 4 cases (5.7%), and peritoneal cytology positivity was detected in 8 cases (11.4%). While the endometrial thickness measured by TVUS in the preoperative period was  $12.8 \pm 6.4$  (2-35) in low-grade cases, the endometrial thickness of high-grade cases was  $19.8 \pm 13.6$  (2-36), and when these two groups were compared, the difference between endometrial thicknesses was not statistically significant ( $p=0.341$ ). As another parameter, the preoperatively measured endometrial thickness of cases with less than  $\frac{1}{2}$  myometrial invasion was  $13.8 \pm 7.2$  (2-35), while this value was  $15.1 \pm 9.4$  (2-36) in cases with more than  $\frac{1}{2}$  myometrial invasion, and the difference between the groups was  $13.8 \pm 7.2$  (2-35). The difference was not statistically significant ( $p=0.793$ ). The relationship between age, CA 125 and endometrial thickness values and the prognostic factors (grade and depth of myometrial invasion) is shown in Table 2.

**Figure 1.** Distribution of cases according to surgical stages



**Table 2.** Relationship between age, CA 125 level, endometrial thickness measured on TVUS, grade, and depth of myometrial invasion.

	Grade 1,2	Grade 3	p	M.I. < 1/2	M.I. > 1/2	p
<b>Age (Years)</b>	60.2±11.3	62.6±16.5	0.494	59.1±11.1	64.4±11.5	0.1
<b>CA 125 (IU/ml)</b>	66.3±228.7	149.2±186.4	0.141	18.7±10.7	167.6±329.9	0.025*
<b>Endometrial thickness (mm)</b>	12.8±6.4	19.8±13.6	0.341	13.8±7.2	15.1±9.4	0.793

\*p<0.05; M.I.= Myometrial invasion; Values are given as mean ± SD.

When the relationship between depth of myometrial invasion, histological grade and pelvic lymph node positivity is examined, it is seen that 5.7% of all patients with lymph node positivity have more than 1/2 myometrial invasion. The mean CA 125 level was 75.9±210.2 (4.4-1566) IU/ml in 64 cases. The CA 125 values of endometrioid type adenocarcinomas were 63.6±215.7 (4.4-1566) IU/ml, while this value was 83.7±110.5 (10.7-358.1) IU/ml in mixed adenocarcinomas and 290.1±263.9 (19.5-648) IU/ml in other tumors. The difference between the CA 125 values of endometrioid adenocarcinomas compared to mixed adenocarcinomas and other tumors was not statistically significant (p=0.130).

When the preoperative diagnostic methods of the cases were evaluated according to their surgical stage; the mean CA 125 value was 31.21±35.54 (4.4-150.3) IU/ml in early stage (Stage I-II) patients and 349.13±497.34 (19.5-1566) IU/ml in advanced stage (Stage III-IV) patients. The difference in CA 125 values was found to be statistically significant (p=0.001). Considering the grades, the CA 125 value was 61.75±215.66 (4.4-1566) IU/ml in low-grade (Grade I-II) cases, while this value was 137.22±190.93 (6.8-648) IU/ml in high-grade (Grade III) cases. The difference between the two groups was not statistically significant (p=0.141). Considering the depth of myometrial invasion

and preoperative CA 125 values, the mean preoperative CA 125 values were 21.43±20.06 (4.4-44.1) IU/ml in cases with myometrial invasion less than 1/2, while this value was 141.03±329.47 (6.8-1566) IU/ml in cases with more than 1/2 and the difference between the groups was found to be statistically significant (p=0.025). Of the 63 patients with preoperative CA 125 values, 46 were Stage I (73.01%), 10 were Stage II (15.9%), and 7 were Stage III (11.1%). The number of patients without metastasis in lymph nodes was 43 (91.5%). In 24 of the 43 cases, CA 125 value was below 20 IU/ml. The mean CA 125 values of the patients with negative lymph nodes were 44.8±63.8 IU/ml (median 18 IU/ml), while the mean CA 125 values of the 4 patients (8.5%) with positive lymph nodes were 109.9±69.1 IU/ml (median 99.5 IU/ml). These four cases were non-endometrioid type advanced tumors. One of the cases was histological grade 2 and the others were grade 3. The relationship between CA 125 level and tumor histological type and grade was not statistically significant (Table 3).

CA 125 levels of advanced-stage cases were statistically significantly higher than CA 125 levels of early-stage cases (p<0.01). CA 125 levels of cases with myometrial invasion >1/2 were statistically significantly higher than CA 125 levels of cases with myometrial invasion <1/2 (p<0.05). CA 125 levels of cases with positive lymph nodes



were statistically significantly higher than CA 125 levels of cases with negative lymph nodes ( $p<0.05$ ). While the CA 125 level was 35 IU/ml and above in all cases with positive lymph nodes, the CA 125 level was 35 IU/ml and above in 30.2% of the cases with negative lymph nodes ( $p<0.05$ ). The average CA 125 values of 56

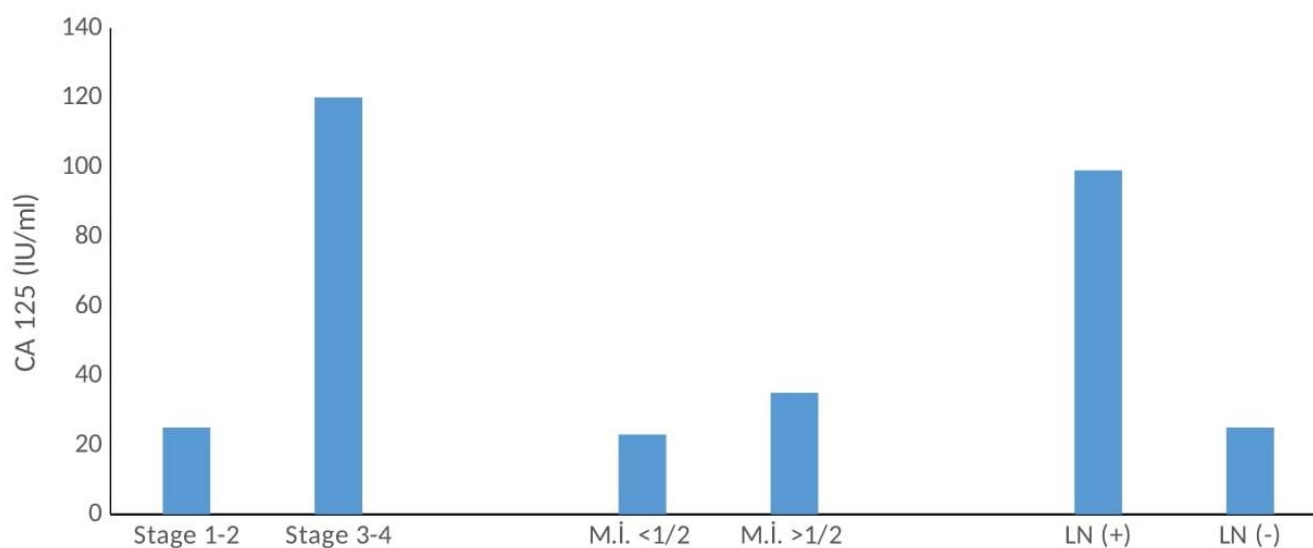
patients in stages I and II were found to be  $31.2\pm35.5$  IU/ml (median 18 IU/ml). The mean CA 125 values of advanced-stage cases were  $349.1\pm497.3$  (median 111 IU/ml) (Table 3, Figure 2).

**Table 3.** Relationship between serum CA 125 levels and some prognostic factors

	CA 125 (IU/ml) mean $\pm$ SD	CA 125 (IU/ml) Median	P
Endometrioid type	63,6 $\pm$ 215,7	18,7	0,130
Non-endometrioid types	129,4 $\pm$ 194,1	30,4	
Early stage	31,2 $\pm$ 35,5	18,0	0,001**
Advanced stage	349,1 $\pm$ 497,3	111,0	
Grade 1-2	61,8 $\pm$ 215,7	18,7	0,141
Grade 3	137,2 $\pm$ 190,9	79,1	
M.I.<1/2	21,4 $\pm$ 20,1	18,1	0,025*
M.I.>1/2	141,1 $\pm$ 329,5	30,2	
Positive lymph nodes	109,9 $\pm$ 69,1	99,5	0,030*
Negative lymph nodes	44,8 $\pm$ 63,8	18,0	

\* $p<0.05$

**Figure 2.** CA 125 levels according to stage, myometrial invasion, and lymph node positivity (M.I.: Myometrial invasion, LN: Lymph node)



## Discussion

In this study, the relationship between preoperative serum CA 125 levels and the stage of the disease, degree of lymphatic spread, and depth of myometrial invasion in individuals diagnosed with EC was investigated. Higher CA 125 levels were detected in patients with more than 1/2 myometrial invasion and lymph node positivity compared to those without.

Many studies state that complete lymphadenectomy should be performed in all cases and preferred to sampling for accurate staging and accurate prognosis, since lymph node positivity is an important prognostic factor<sup>11,12</sup>. We performed total abdominal hysterectomy + bilateral salpingo-oophorectomy + staging surgery in 69 cases. The two most common reasons for not performing staging surgery in the other 19 cases were hyperplasia without atypia or non-neoplastic preoperative endometrial sampling results (47.3%) and advanced age with poor general condition (52.7%). While we advocate performing lymphadenectomy in all possible cases, we can consider performing lymphadenectomy in 53 of 66 Stage I cases as overtreatment, especially considering that the grade of 47 of these cases was grade 1 or 2 (71.2%). As a result, it is seen that performing lymphadenectomy, omentectomy, and appendectomy in all EC cases, regardless of grade and degree of myometrial invasion, increases the overtreatment rate.

High CA 125 level, which is used as a tumor marker, is correlated with high metastatic potential and increased risk of pelvic lymph node positivity in studies and has been reported as an independent risk factor for survival<sup>13</sup>. In our patients, the mean CA 125 value of cases with lymph node metastasis was statistically significantly higher than that of cases with negative lymph nodes. In our study, CA 125 levels

of patients in advanced stages were found to be statistically significantly higher than CA 125 levels of patients in early stages ( $p=0.001$ ). In addition, the fact that CA 125 levels are significantly higher in cases with greater depth of myometrial invasion shows that contrary to some studies, CA 125 levels can be used preoperatively to predict not only lymph node metastasis but also myometrial invasion<sup>14</sup>. Niloff and colleagues<sup>15</sup> investigated serum CA 125 levels in 60 patients with gynecological malignancy. They detected CA 125 values above 35 IU/ml in all 4 patients with fallopian tubal cancer, 14 of 29 EC patients, and 5 of 6 cervical cancer patients. The values of 4 patients with recurrent tubal carcinoma were between 76-8740 IU/ml. In patients with EC, high values were present in 14 of 18 patients with Stage IV or recurrent cancer and did not increase in any of 11 patients with Stage I and Stage II tumors. Patsner et al.<sup>7</sup> examined 89 patients with primary EC. Normal values were considered to be below 35 IU/ml. CA 125 levels were normal in 58 of 81 patients with clinical Stage I and II. The surgical stage was confirmed in 57 of these 58 patients (98%). Extrauterine disease was detected during surgery in 20 of 23 patients (87%) with clinical Stage I-II and elevated CA 125 levels. CA 125 levels were normal in 3 of 75 patients (4%) with clinical Stage I, but surgical extrauterine disease was detected in these patients. Increased preoperative CA 125 levels were present in 28 of 31 patients (90.3%) with extrauterine disease. These results support our results and suggest that serum CA125 levels can be used as a marker of disease spread in patients diagnosed with EC.

In the current study, among all Stage I cases, Stage Ia was 5%, Stage Ib was 55%, and Stage Ic was 40%. Only 10% of the patients were in the reproductive period. Dotters et al.<sup>16</sup> evaluated whether the preoperative CA 125 value was useful in determining the need for lymphadenectomy in 43 women with EC. Of the

19 patients who underwent lymph node sampling, 6 (32%) had positive nodes. Preoperative CA 125 levels averaged 28.5 IU/ml (17-151 IU/ml). It was above 35 IU/ml in only 8 patients. The correlation between stage and CA 125 levels was weak. Higher values were detected in patients with accompanying malignancy. Elevated CA 125 levels correlated with positive peritoneal cytology ( $p=0.01$ ) and angiolymphatic invasion ( $p=0.025$ ), but not with lymph node involvement. The mean CA 125 level of 6 patients with positive nodes was 29.6 IU/ml (7-60 IU/ml), and that of patients with negative lymph nodes was 48.5 IU/ml. Thirty-three patients were preoperatively divided into Stage I, grade 1 or 2 tumors. Twelve of the 33 (36%) were found to be at a more advanced stage at surgery. In 9 of these 12 patients, the CA 125 level was above 20 IU/ml, and in 6, it was above 35 IU/ml. The data here supported the use of a CA 125 cutoff value of 20 IU/ml. There were 16 patients with preoperative CA 125 values below 20 IU/ml and grade 1 tumors. Stage III disease was detected in 2 of 16 patients (13%). In our study, the average CA 125 values of the cases with negative nodes was  $44.8 \pm 63.8$  IU/ml, and the average value of the 4 cases with positive nodes was  $109.9 \pm 69.1$  IU/ml. Additionally, no lymph node positivity was found below 20 IU/ml. Increased preoperative CA 125 levels were found to be statistically significant for the cut-off value of 20 IU/ml ( $p=0.05$ ) and highly statistically significant for the cut-off value of 35 IU/ml ( $p=0.013$ ) when Stage I-II and more advanced stages were compared.

In conclusion, the results we obtained in this study support the association of increased preoperative CA 125 levels with lymph node positivity, advanced stage and myometrial involvement above  $\frac{1}{2}$  in cases with EC. Multicenter studies with large patient groups are needed to better understand the role of CA 125

in EC and its relationship with advanced-stage disease.

### Conflict of interest

The authors declare that they have no conflicts of interest.

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