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The role of preoperative serum CA-125 levels in predicting lymph node metastasis in patients undergoing treatment for endometrial cancer

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ABSTRACT

Aims: Endometrial cancer stands as the most prevalent gynecological malignancy in developed nations, often detected at an early stage, and generally carries a positive prognosis. The stage of the disease is important for survival, but many factors such as tumor grade, histopathology, myometrial invasion, age, and spread are also effective. Our objective was to assess the significance of preoperative Cancer antigen 125 (CA-125) concentrations in the prediction of lymph node metastasis in patients with endometrial cancer and to identify a suitable threshold value.

Methods: This retrospective analysis was carried out on 286 female patients diagnosed with endometrial cancer at a specialized gynecologic oncology facility from 2012 to 2022. We examined clinical-pathological and demographic attributes, including preoperative serum CA-125 concentrations, surgical interventions conducted for each patient, post-treatment physical assessments, imaging findings, and cytological outcomes. CA-125 was measured using electrochemiluminescence immunoassay.

Results: Statistically significant differences were observed in CA-125 levels among patients in terms of grade, invasion depth, lymph node involvement, cervical involvement, and stage (respectively, $p<0.001$, $p=0.042$, $p<0.001$, $p<0.001$, $p<0.001$). The FIGO advanced stage ratio was 30.6 times higher for serum CA-125 concentrations above the cutoff of 21 IU/ml (95% CI: 10.7-87.6) ($p<0.001$). Lymph node involvement was 29.7 times more likely for serum CA-125 values above the cutoff of 35 IU/ml (95% CI: 25.3-74.8) ($p<0.001$).

Conclusion: Early identification of high-risk endometrial cancer patients is vital for prognosis and guiding adjuvant therapy. CA-125, a tumor marker, has been found useful in assessing myometrial invasion depth, lymph node involvement, stage differentiation, and tumor grade.

Keywords: CA-125, endometrial cancer, metastasis, lymph node, predictive marker

INTRODUCTION

Endometrial cancer (EC) stands as the most common gynecological malignancy in developed nations.[1] The majority of cases are identified in the initial stages and typically carry a positive outlook. The 5-year survival rate for women with Stage I EC is around 80-90%, while for Stage III, it drops to only 50-60%, and for Stage IV, it decreases to 15-17%.[2] While standard treatments for EC typically involve surgical procedures such as bilateral salpingo-oophorectomy along with total hysterectomy, either with sentinel lymph node sampling or systematic lymphadenectomy; adjuvant therapy, including chemotherapy and radiotherapy, depending on the recurrence risk factor, is also considered.[3] Although the stage of the disease is the most critical variable affecting survival, various factors such as tumor grade, histopathology, depth of myometrial invasion (MI), the woman's age, extrauterine disease spread, surgical/pathological findings, and recurrence risk have been identified as significant contributors to survival.[4] Hence, it is imperative to identify patients with an elevated risk of recurrence for treatment and planning follow-up procedures.[5]

Cancer antigen 125 (CA-125) is a glycoprotein produced by the MUC16 gene situated on the short arm of chromosome 19 at 19p13.3.[6] CA-125 is a protein found in the bloodstream and is extensively employed for the

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early identification of ovarian cancer.[7] Evaluating CA-125 exhibits limited specificity for ovarian cancer diagnosis, yet it holds the capability to assess, track, and appraise responses to ovarian cancer treatment.[8] However, the use of CA-125 as a predictor for lymphovascular stromal invasion (LVSI) and lymph node metastasis in endometrial cancer has not been extensively studied.[9] This tumor marker has proven to be beneficial in women with endometrial cancer characterized by unfavorable prognostic factors, including high recurrence rates, grade 3 tumors, lymph node metastasis, and deep myometrial invasion.[10] The preoperative evaluation of CA-125 can serve as an additional resource in preoperative risk stratification for recognizing patients with adverse outcomes. Although some studies have proposed a cutoff of 35 IU/L for preoperative CA-125 levels to assess prognostic factors and survival in EC, different studies have employed different cutoff values.[11]

In this study, our primary aim is to measure the predictive capacity of preoperative CA-125 concentrations in anticipating lymph node metastasis in patients with endometrial cancer. Our secondary goal is to ascertain a suitable threshold value for our study population and assess the connection between preoperative serum CA-125 and postoperative histopathological results.

METHODS

The study was initiated with the approval of the İstanbul Prof. Dr. Cemil Taşçıoğlu City Hospital Clinical Researches Ethics Committee (Date:23.10.2023, Decision No:232). Additionally, written authorization was secured from the establishments where the research was carried out, and informed agreement was acquired from the patients. The study was conducted by the Principles of the Declaration of Helsinki.

This retrospective study involved the examination of medical records of 316 women diagnosed with endometrial cancer at a tertiary gynecologic oncology center between the years 2012 and 2022. A total of 286 women completed the study after excluding individuals with secondary malignancies (n=10), those with a history of blood transfusion or complications related to hematologic diseases within 3 months (n=10), patients who received radiotherapy or chemotherapy before surgery (n=3), those with a history of hormonal therapy within 12 months (n=2), complications related to any infectious diseases (n=0), and individuals who had surgery at an external center (n=5).

In all instances of primary endometrial cancer that required surgery, procedures included total abdominal hysterectomy, salpingo-oophorectomy, and staging surgery.[12] The selective lymphadenectomy based on the surgical algorithm is determined according to the histology of the tumor, grade, tumor size, degree of myometrial invasion, and the presence of extrauterine disease. Lymphadenectomy is not performed in patients with endometrioid tumors smaller than <2 cm and myometrial invasion less than 50%. The decision to administer postoperative radiotherapy, chemotherapy, or both is based on defined criteria and the final results of the pathological examination of surgical specimens and cytology. Following the completion of definitive treatment, all patients were subjected to a follow-up schedule, with assessments conducted every 3 months for 2 years, every 6 months for 2-5 years, and subsequently on an annual basis for routine check-ups.

For every patient, an extensive examination of clinical-pathological and demographic attributes was conducted, encompassing preoperative serum CA-125 concentrations, the surgical interventions carried out, post-treatment physical evaluations, imaging findings, and cytological outcomes. In addition, based on histopathological assessments, various factors such as tumor size, histological type, grade, depth of myometrial invasion (MI), peritoneal cytology, lymphovascular stromal invasion (LVSI), cervical involvement, adnexa involvement, parametrial involvement, and lymph node (LN) participation were documented. CA-125 was measured using electrochemiluminescence immunoassay (ECLIA).

Statistical Analysis

Statistical analysis was performed using the SPSS 15.0 for Windows program. Descriptive statistics were furnished, encompassing counts and percentages for categorical variables, as well as the mean, standard deviation, minimum, and maximum values for numerical variables. Comparisons of proportions between groups were conducted using the Chi-Square Test. Since the assumption of normal distribution was not met for the independent two-group comparisons of numerical variables, the Mann-Whitney U test was employed. Cut-off values were examined using ROC Curve Analysis. The alpha significance level was set at $p<0.05$.

RESULTS

The average age of women with endometrial cancer was 63.7±9.4 years, and 86% of them were postmenopausal. Based on surgical pathology results, 78.3% were diagnosed with stage I, 39.2% with grade I, and 60.8% with grade II-III tumors. Histopathology reports indicated that 87.4% of the patients had endometrioid endometrial cancer. Among surgical specimens, 98.3% had an invasion depth of >50%. Adnexal involvement was present in 1% of patients, and cervical involvement was observed

in 7%. Lymph node involvement was present in 17.48% of women with endometrial cancer. The median (IQR) number of lymph nodes collected during surgery was 16 (12-20) for pelvic and 4 (3-5) for paraaortic nodes. The mean CA-125 level for patients was 28.8±33.0.

Statistically significant differences in CA-125 levels were observed among patients in terms of grade, depth of invasion, lymph node involvement, cervical involvement, and stage (respectively, p<0.001, p=0.042, p<0.001, p<0.001, p<0.001). In particular, patients with Grade II and III exhibited elevated CA-125 levels in comparison to those with Grade I. Patients with invasion depth exceeding 50% displayed higher CA-125 levels than those with 50% or less invasion. Furthermore, patients with lymph node metastasis had higher CA-125 levels than those without, patients with cervical involvement showed higher CA-125 levels than those without, and patients in Stages II-III-IV had higher CA-125 levels in contrast to those in Stage I. The findings are summarized in Table 1.

The FIGO advanced stage ratio was 26.6 times higher for a serum CA-125 value above the cutoff of 20 IU/ml and 9 times higher for a cutoff of 35 IU/ml. This is summarized in Table 2.

According to the ROC Curve analysis in our study, a cutoff value of >21 was determined for the advanced stage with a sensitivity of 93.55% and specificity of 67.9%. The FIGO advanced stage ratio was 30.6 times higher for a serum CA-125 value above the cutoff of 21 IU/ml. The AUC is shown in Figure 1. The findings are summarized in Table 3.

Table 1. Histopathological results and CA-125 values

Variable	N(%)	Median (IQR) CA-125 Level (IU/ml)	Mean±SD (Min-Max) CA-125 Level (IU/ml)	p value
Histological tumor type				
Endometrioid	250 (87.4)	19 (11-33.25)	28.9±34.3 (4-299)	0.102
Serous	28 (9.8)	30 (13-43.5)	32.6±22.5 (7-96)	
Clear cell*	2 (0.7)	4 (3-5)	4.0±1.4 (3-5)	
Mucinous*	2 (0.7)	18,5 (9-28)	18.5±13.4 (9-28)	
Carsinosarcoma*	4 (1.7)	9,5 (8-23.75)	13.8±9.6 (8-28)	
Stage (FIGO)				
I	224 (78.3)	17 (10-28)	20.5±15.3 (3-116)	<0.001
II	37 (12.9)	33 (24.5-50)b	48.9±48.4 (9-265)	
III	18 (6.3)	39 (35.75-89)b	72.6±72.7 (25-299)	
IV	7 (2.4)	66 (57-111)b	74.3±28.8 (35-112)	
Grade				
I	112 (39.2)	13 (10-28)	22.4±23.1 (3-141)	<0.001
II	138 (48.2)	24 (14.75-37)a	32.1±33.3 (4-265)	
III	36 (12.6)	22,5 (14.75-37.5)a	36.1±51.0 (5-299)	
Depth of invasion				
<%50	5 (1.7)	10 (5-20)	12.0±9.5 (5-28)	0.042
>%50	281 (98.3)	19 (11-35)	29.1±33.2 (3-299)	
Lymph node involvement				
Absent	236 (82.52)	17 (11-26)	18.6±10.1 (3-46)	<0.001
Present	50 (17.48)	58 (44.75-85.5)	76.8±54.8 (33-299)	
Adnexal Involvement				
Absent*	283 (99)	19 (11-33)	28.3±32.7 (3-299)	-
Present	3 (1.0)	66 (35-112)	71.0±38.7 (35-112)	
Cervical involvement				
Absent	266 (93.0)	19 (11-32)	26.7±28.4 (3-265)	<0.001
Present	20 (7.0)	38 (33-49.25)	57.0±64.9 (5-299)	
CA-125 Mean±SD (Min-Max)		28.8±33.0 (3-299)		

Mann-Whitney U, * Inadequate sample, a : Different from Grade 1, b : Different from Stage 1, SD: Standard deviation

Table 2. Serum CA-125 values for FIGO stages based on cutoffs of 20 IU/ml and 35 IU/ml

Stage (FIGO)	CA-125<20 IU/ml n(%)	CA-125>20 IU/ml n(%)	Total n(%)	p-value
Early stage (I)	145 (64.7)	79 (35.3)	224 (78.3)	<0.001 OR:26,6
Late stage (II-IV)	4 (6.5)	58 (93.5)	62 (21.7)	(%95 CI:9.3-76)
Stage (FIGO)	**CA-125<35 IU/ml n(%)**	**CA-125>35 IU/ml n(%)**	**Total n(%)**	**p-value**
Early stage (I)	194 (86.6)	26 (13.4)	220 (76.9)	<0.001 OR:9
Late stage (II-IV)	30 (41.9)	36 (58.1)	66 (23.1)	(%95 CI:4.8-16.9)

Chi-Square Test

Table 3. Serum CA-125 value for FIGO stages based on a cutoff of 21 IU/ml

Stage (FIGO)	CA-125<21 IU/ml n(%)	CA-125>21 IU/ml n(%)	Total n(%)	p-value
Early stage (I)	152 (67.9)	72 (32.1)	224 (78.3)	<0.001 OR:30.6 (%95 CI:10.7-87.6)
Late stage (II-IV)	4 (6.5)	58 (93.5)	62 (21.7)	

Chi-Square Test

Table 4. Serum CA-125 values for lymph node involvement based on cutoffs of 20 IU/ml and 35 IU/ml

Lymph node involvement	CA-125<20 IU/ml n(%)	CA-125>20 IU/ml n(%)	Total n(%)	p-value
Absent Present	149 (63.1) 0 (0.0)	87 (36.9) 50 (100)	236 (82.5) 50 (17.5)	<0.001 -
Lymph node involvement	**CA-125<35 IU/ml n(%)**	**CA-125>35 IU/ml n(%)**	**Total n(%)**	**p-value**
Absent Present	218 (92.4) 2 (4.0)	18 (7.6) 48 (96.0)	236 (82.5) 50 (17.5)	<0.001 OR:29.7 (%95 CI:25.3-74.8)

Chi-Square Test, OR: Odds ratio

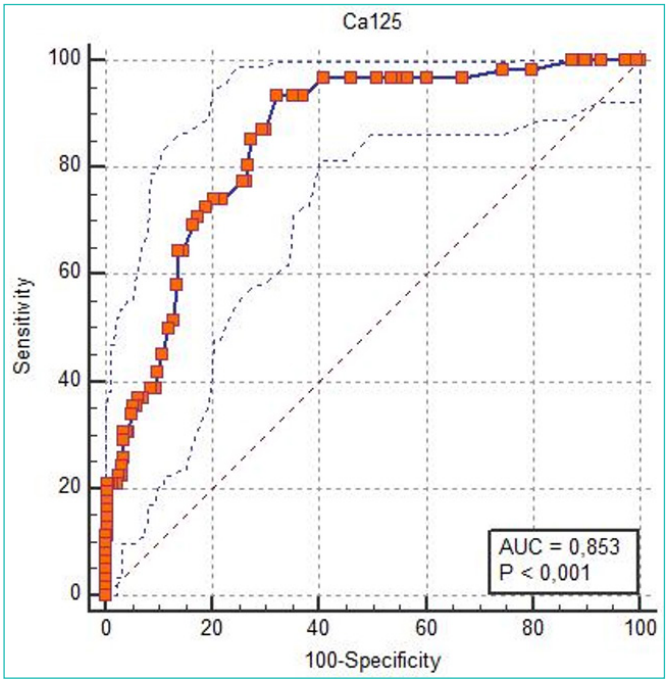

Figure 1. Receiver operating characteristic (ROC) examination of CA-125>21IU/ML

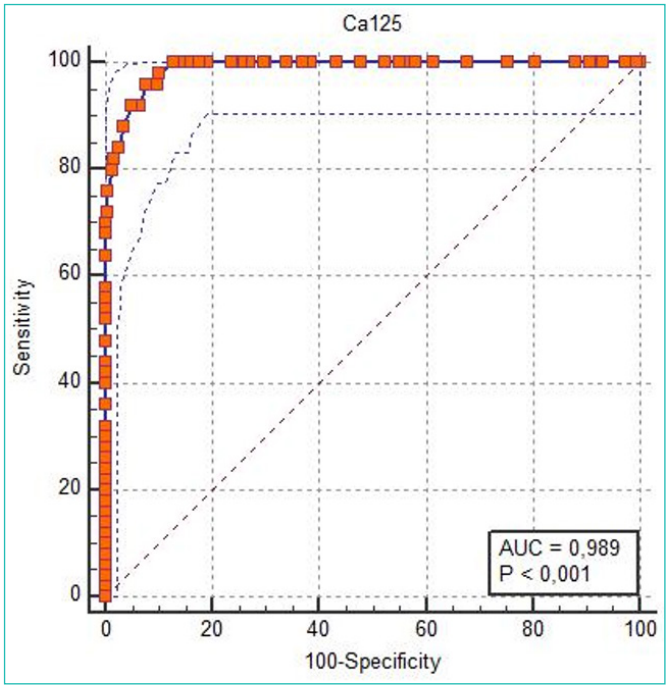

Figure 2. Receiver operating characteristic (ROC) examination of CA-125>35IU/ml

A cutoff value of >35 was determined for the advanced stage with 96% sensitivity and 92.4% specificity according to the ROC Curve analysis in our study. Serum CA-125 value was 29.7 times higher for lymph node involvement with a cutoff of 35 IU/ml. The findings are summarized in Table 4. The ROC curve for cutoff 35 is presented in Figure 2.

DISCUSSION

In the literature, the studies on the use of CA-125 as a tumor marker in endometrial cancer are limited, and it has been primarily employed in the diagnosis and postoperative follow-up of ovarian cancers.[13] Its elevation in benign pathologies, in addition to malignant events, makes it challenging to determine the optimal cutoff for this tumor marker. On the other hand, in benign ovarian cases such as endometriomas, its high elevation has led to a significant number of false-positive results.[14]

In our study, we found that the FIGO advanced stage ratio was 30.6 times higher in patients with a serum CA-125 value above the cutoff of 21 IU/ml. Additionally, concerning positive lymph nodes, we demonstrated that in endometrial cancer patients with a serum CA-125 value above 35 IU/ml, lymph node involvement was 29.7 times higher compared to those below the cutoff of 35. In the literature, many studies have associated poor prognostic factors and extrauterine spread with endometrial cancer.[15] On the other hand, in a study encompassing risk factors affecting overall survival and disease-free survival in early-stage endometrial cancer, it was found that CA-125 had no significant effect on overall survival and disease-free survival.[16]

The accurate staging of endometrial cancer relies on well-established and evidence-based surgical staging protocols. Clinical staging alone lacks precision and cannot evaluate critical factors such as LVSI, grade, or

lymph node metastasis. Thorough surgical staging, which includes lymph node assessment, is especially essential for delivering precise prognostic details in women with high-risk endometrial cancer. In a previous study, a preoperative CA-125 level above the cutoff of 21.2 was associated with lymphovascular stromal invasion in endometrial cancer patients.[17] In a recent study, similar to our results, CA-125 was considered a useful marker in predicting high-risk patients, including those with positive lymph nodes.[18]

For low-grade disease, the evaluation of myometrial invasion and tumor size is recommended to define high-risk cases. However, differences in sensitivity, specificity, and interobserver correlation coefficients between ultrasound (USG) and magnetic resonance imaging (MRI) in assessing preoperative myometrial invasion have suggested that CA-125 may be a suitable alternative for assessing myometrial invasion and tumor size.[19] In a similar study, it was found that in patients over 65 years old, with high tumor grade and high CA-125 levels, there was a correlation with decreased disease-free survival, and high tumor grade, non-endometrioid endometrial cancer, and high CA-125 levels were associated with increased disease-specific survival.[11,20]

A related study showed that in type 1 EC patients with negative prognostic factors, it may be more beneficial to choose a lower threshold value for CA 125 level (16 IU/L) instead of 35 IU/L.[21] In the literature, a respective number of studies have mostly included whole histological types of endometrial cancer and reported that elevated serum CA 125 levels might be useful in determining poor prognostic factors, such as extrauterine spread and LN metastasis in EC.[22]

In other study, preoperative serum CA-125 value of 16.75 U/ml in patients with EEC was 93% sensitivity and 57% specificity in predicting pelvic lymph node metastasis. Therefore, a preoperative serum CA-125 value of 16.75 U/ml may be useful in determining which patients would benefit from complete cytoreduction.[23] Bağcı et al.[24] treated 61 patients for endometrial cancer and were surgically diagnosed with stage I. They found a correlation between myometrial invasion and CA-125 values in postmenopausal patients. Atguden et al.[25] showed that CA-125 values could be used as a predictive test and alone as a prognostic factor in patients with early-stage EEC. Hsieh et al.[26] showed that 78% of endometrial cancer with lymph node metastases had high CA-125 levels. Thus, CA-125 levels can help to determine the extent of surgical staging, and if it is found to be high, it can be helpful as a marker in evaluating the response to subsequent chemotherapy.[27]

New findings in endometrial cancer have led to genomic analysis and immunohistochemistry, resulting in the current molecular classification of EC, which is divided into four groups: polymerase epsilon mutated (POLEmut), p53 abnormal (p53abn), mismatch repair deficient (MMRd), and no specific molecular profile (NSMP). Incorporating this molecular classification into the European Society of Gynaecological Oncology (ESGO) guidelines not only holds prognostic significance but also shows promise in guiding decisions regarding adjuvant therapy. Customizing treatments for endometrial cancer (EC) according to molecular and clinicopathological criteria is pivotal in striving for more refined and personalized outcomes.[28]

Limitations

The following limitations of the current study must be acknowledged. First, this was a retrospective study, and the intraoperative and postoperative management of patients with elevated serum CA-125 levels were not different from those with normal values. Second, we could not discriminate or identify false positive CA-125 elevations preoperatively. The patients might have had other medical comorbidities that contributed to elevated serum CA-125 levels independent of extrauterine disease. Third, elevations of tumor markers other than CA-125 were not evaluated in the study. In the coming years, advancements in technology will further aid our understanding of molecular oncology, contribute to the development of sensitive biomarkers, and provide valuable information, particularly in early-stage endometrial cancer prognosis, postoperative follow-up, and recurrence prediction.

CONCLUSION

CA-125 has been found to be useful in assessing deep myometrial invasion, lymph node involvement, differentiation between early and advanced stages, and grading for predicting high-risk patients. Preoperative assessment of CA-125 can be used as an additional tool in preoperative risk stratification to identify patients with poor outcomes.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of İstanbul Prof. Dr. Cemil Taşçıoğlu City Hospital Clinical Researches Ethics Committee (Date:23.10.2023, Decision No:232).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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