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The predictive role of CA-125 value in early-stage endometrioid endometrial cancer

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ABSTRACT

Background: We aimed to evaluate the prognostic role of preoperative serum cancer antigen 125 (CA-125) in endometrioid endometrial cancer for determining the cut-off values for clinicopathological factors.

Methods: 161 patients were included in the study. The inclusion criteria were histopathological confirmation of endometrioid endometrial cancer and patients with CA-125 levels measured at most ten days before surgery. The association between CA-125 value and clinicopathological variables were analyzed. Receiver operating characteristic curve statistical tests with clinicopathological factors were used to determine the cut-off values and the prognostic role of CA-125.

Results: The median value of CA-125 level was 15.4 (3, 2-577) IU/L. These CA-125 cut-off values ranged from 14.30 to 18.67 IU/L (sensitivity 53%– 100%, specificity 30%–59%). The statistical analysis showed a significant relation between CA-125 value and stage and pelvic-paraaortic lymph nodes metastasis. The average life expectancy of patients with CA-125 ≥15.4 was 102.8±5.9 months, whereas that of patients with CA-125 <15.4 was 120.1±3.4 months.

Conclusion: This study shows that preoperative serum CA-125 values can be used as a predictive test in patients with early stage EEC and as a stand-alone prognostic factor. We consider the preoperative CA-125 level to be a valuable preoperative tool that can be used to customize the treatment offered for EEC. CA-125 can be used as a biomarker to preoperatively stratify patients into low-risk and high-risk groups. Lower cut-off values compared to the traditional 35 IU/ml value used in ovarian cancer can be a prognostic factor in patients with endometrioid endometrial cancer.

Keywords: CA-125 antigen; cut-off value; endometrial carcinoma; prognosis; survival.

Erken evre endometrioid endometrial kanserde CA-125 değerinin öngörücü rolü

Süreç

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ÖZ

Amaç: Bu çalışmada, endometrioid endometrial kanserde preoperatif serum kanser antijeni 125 (CA-125) değerinin prognostik rolünü değerlendirmeyi ve klinikopatolojik faktörler için kesim değerlerini belirlemeyi amaçladık.

Yöntemler: Çalışmaya 161 hasta dahil edildi. Dahil etme kriterleri, endometrioid endometrial kanser histopatolojik onayı olan ve cerrahi öncesi en fazla on gün içinde CA-125 düzeyi ölçülen hastalardı. CA-125 değeri ile klinikopatolojik değişkenler arasındaki ilişki analiz edildi. Kesim değerlerini ve CA-125'in prognostik rolünü belirlemek için klinikopatolojik faktörlerle alıcı işletim karakteristik eğri istatistiksel testler kullanıldı.

Bulgular: CA-125 düzeyinin ortanca değeri 15.4 (3, 2-577) IU/L idi. Bu CA-125 kesim değerleri 14.30 ile 18.67 IU/L arasında değişmekteydi (duyarlılık %53-%100, özgüllük %30-%59). İstatistiksel analiz, CA-125 değeri ile evre ve pelvik-paraaortik lenf nodu metastazı arasında anlamlı bir ilişki olduğunu gösterdi. CA-125 ≥15.4 olan hastaların ortalama yaşam süresi 102.8±5.9 ay iken, CA-125 <15.4 olan hastaların ortalama yaşam süresi 120.1±3.4 aydı.

Sonuç: Bu çalışma, preoperatif serum CA-125 değerlerinin erken evre endometrioid endometrial kanserli hastalarda prediktif bir test olarak kullanılabileceğini ve bağımsız bir prognostik faktör olarak işlev görebileceğini göstermektedir. Preoperatif CA-125 düzeyini, EEC için sunulan tedaviyi özelleştirmek için değerli bir ön operatif araç olarak düşünmekteyiz. CA-125, hastaları düşük riskli ve yüksek riskli gruplara ön operatif olarak sınıflandırmak için bir biyobelirteç olarak kullanılabilir. Endometrioid endometrial kanserli hastalarda, yumurtalık kanserinde kullanılan geleneksel 35 IU/ml değerine kıyasla daha düşük kesim değerleri prognostik faktör olabilir.

Anahtar sözcükler: CA-125 antijeni; kesim değeri; endometrial karsinom; prognoz; sağkalım.

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Introduction

In developed countries endometrial cancer is the most common gynecological malignancy, and its incidence is gradually increasing [1]. Although histological type is the essential factor for the prognosis of endometrial cancer, tumor grade, stage, myometrial invasion, lymphovascular space involvement, and patient age can be counted as other important prognostic factors. Endometrioid type endometrial cancer (EEC) is the most common histological subtype with a good prognosis. Older age, advanced stage, high grade, and lenfovasculer involvement have been associated with poor prognosis and worse survival. The global obesity problem is one of the most important reasons for increased endometrial cancer incidence. 81% of endometrial cancer patients are obese [2].

And also, previous studies have shown that preoperative serum serum cancer antigen 125 (CA-125) level, is a useful marker in predicting extrauterine disease spread and recurrence in patients with endometrial cancer [3]. In gynecology units, the CA-125 test is accessible for patients, and it is widely used. There are studies suggesting a preoperative CA-125 level of 35 IU/L in determining survival and prognostic factors in endometrial cancer [4-7], but lower cut-off values have been used recently [8-10]. In conclusion, CA-125 level in endometrial cancer is still uncertain and open to discussion. This study was planned to evaluate the prognostic role of preoperative CA-125 in EEC and to determine the cut-off values for clinicopathological factors.

EEC mainly occurs in the early stages. International guidelines recommend myometrial invasion evaluation for preoperative identification in high-risk, low-grade patients [11]. Myometrial invasion can be evaluated preoperatively, by magnetic resonance imaging, and by transvaginal ultrasound. However, the sensitivity and specificity (85% and 97%, respectively) in the intraoperative evaluation of myometrial invasion with frozen section during surgery are higher [12]. Time constraints and performance costs should also be considered when performing frozen sections. And frozen section is not widely used, especially in developing countries. Preoperative evaluation of CA-125 level can be an alternative to myometrial invasion to identify patients with high-risk preoperatively, and it is an economical, fast, simple and noninvasive method and more accessible than imaging techniques [3].

MATERIALS AND METHODS

Study data were collected from patients' documents who underwent surgery for endometrial cancer between 2009 and 2021 in a tertiary cancer center. Non-Invasive Clinical Research Ethics Committee approved the study (Decision no: 2021-08/23). Patients with coexisting malignancies or synchronous cancers and incomplete medical records and follow-ups were excluded from the analysis. The inclusion criteria were histopathological confirmation of EEC and patients with serum CA-125 levels measured at most ten days before surgery. The association between clinicopathological variables and CA-125 were analyzed. Thus, the study included 161 patients who met the inclusion criteria. Endometrial cancer histologic types and grades were evaluated according to the pathology results using the International Federation of Gynecologists and Obstetricians for disease staging.

The chi-square test was used for performing relationships between categorical variables. Using the SPSS for Windows 22.0 software, analyses were performed. Receiver operating characteristic curve analysis was performed to determine the sensitivity and specificity of the various threshold values. The optimum cut-off value was correlated with tumor grade, lymph node involvement, and disease stage. To assess survival, Kaplan-Meier analyzes were used. The time from the date of surgery to the date of death was defined as overall survival (OS). Significance was determined using 95% confidence interval and $p<0.05$ levels.

Results

The median age was 57, 00 (26-83) years of the patients. Total abdominal hysterectomy and bilateral salpingo-oophorectomy were performed on all patients, and 160 patients underwent pelvic (± para-aortic) lymph node dissection, 148 (91, 9%) patients underwent omentectomy. All patients had EEC, and 115 were grade 1 tumor histology (Table 1). The median value of CA-125 level was 15.4 (3, 2-577). CA-125 cut-off values ranged from 14.30 to 18.67 IU/L (sensitivity 53%– 100%, specificity 30%–59%) (Table 2). Statistical analyzes revealed a significant correlation between the CA-125 value and the advanced stage (2, 3, and 4) and pelvic-paraaortic lymph nodes metastasis, compatible with this median CA-125 value (Table 3). The mean life expectancy of patients with CA-125 ≥15.4 was 102.8±5.9 months (95% CI, 91.09.-114.58), whereas that of patients with CA-125 <15.4 was 120.1±3.4 months (95% CI, 113.5-126.7). The mean life expectancy of all patients was 113.3±3.6 months (95% CI, 106.25-120.37). When both groups were compared, this difference was significant (p: 0.003). (Figure 1).

Table 1: Analysis of categorical measures to detect early postoperative recurrence

	n	%
Grade		
G1	115	71,4
G2	29	18
G3	16	9,9
Stage		
I	132	82
II	11	6,8
III	15	9,3
IV	3	1,9
Omental involvement		
Yes	1	0,6
No	147	91,3
Pelvic lymph node involvement		
Yes	23	14,3
No	137	85,7
Paraaortic lymph node involvement		
Yes	5	3,1
No	155	96.3
Status		
Alive	139	86,3
Not alive	22	13,7

Table 3: Preoperative CA-125 cut-off values, sensitivity, specificity, AUC* (95% CI) in EEC

	Cutt-off value	Sensitivity-specifity	AUC (95 CI %)	p value
Stage (2, 3, 4)	15,98	82%-59%	0,70 (0,59-0,81)	0,001
Grade (2, 3)	14,30	53%-30%	0,41 (0,31-0,50)	0,063
Pelvic lymph node involvement	16,75	93%-57%	0,78 (0,67-0,90)	0,00
Paraaortic lymph node involvement	18,67	100%-58%	0,74 (0,62-0,86)	0,065
Stage 1a-1b	15,49	63%-59%	0,61 (0,52-0,70)	0,015

** Area under the curve*

Table 2: Comparison of clinicopathological factors of patients with EEC, when CA-125 cut-off is 15.4 IU/L

	CA-125 ≥15,4 IU/L, n (%)	CA-125 <15,4 IU/L, n (%)	p value
Stage (2, 3, 4)	24 (82,8)	5 (17,2)	0.00
Grade (2,3)	28 (62,2)	17 (37,8)	0.06
Pelvic lymph node involvement	14 (93,3)	1 (6,7)	0.001
Paraaortic lymph node involvement	5 (100)	0 (0)	0.025
Stage 1a-1b	16 (47,1)	18 (52,9)	0.59

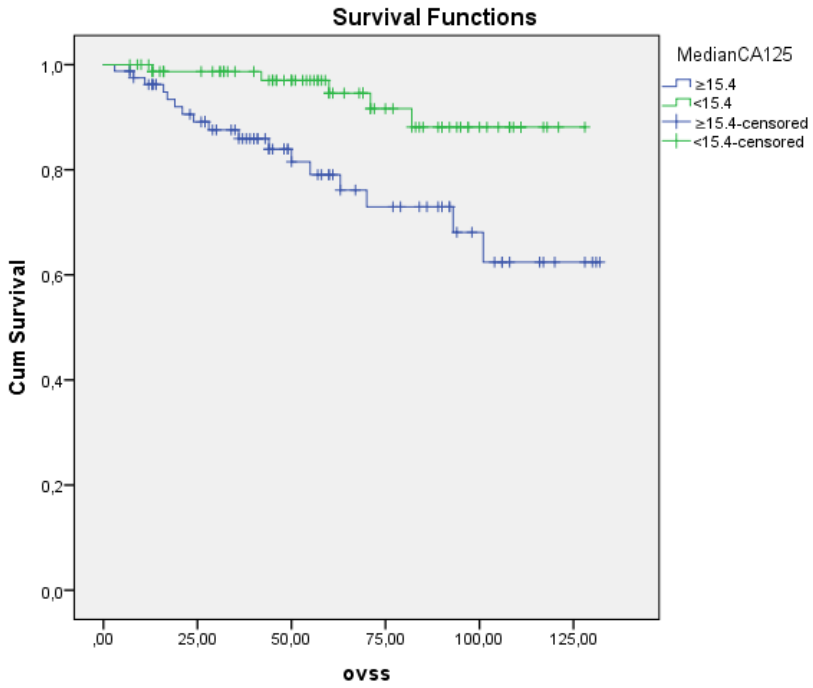

Figure 1: Graphical presentation of the median CA-125 level on overall survival by Kaplan-Meier analysis.

Discussion

Many women with endometrial cancer are elderly and often have significant comorbidities [13]. While the prognosis is good for patients with the limited disease to the uterus, the recurrence risk and death are higher in those with advanced disease. The International Federation of Gynecology and Obstetrics recommends complete surgical staging as the initial treatment for endometrial cancer [14]. However, complete surgical staging does not appear to be the first choice for patients with significant comorbidities that increase their risk for adverse intraoperative and postoperative outcomes. Systematic lymph node dissections result in 13-22% lymphedema of the lower extremities and also cause prolonged anesthesia and operation time [15, 16]. Customizing the scope of the surgical staging procedure for endometrial cancer requires careful consideration of preoperative prognostic information and a flexible approach by gynecological oncologist.

Complete cytoreduction in advanced endometrial cancer, has been shown to improve median survival. However, the difficulty of detecting micrometastases that cannot be seen during surgery limits the effectiveness of the surgery. In this 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.

Bağcı et al. 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 [17]. Atguden et al. showed that CA-125 values could be used as a predictive test and alone as a prognostic factor in patients with early-stage EEC [18]. Hsieh et al. showed that 78% of endometrial cancer with lymph node metastases had high CA-125 levels 19. 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 [19, 20]. According to Göksedef et al., the preoperative CA-125 value can help plan the use of adjuvant therapy to ensure the optimal outcome and the extent of the surgery in patients with endometrial cancer 4. Previous studies have also shown that cut-off values of CA-125 are in the range of 15 to 35 IU/L for poor prognostic factors in endometrial cancer [4, 21, 22].

In a study by Unsal et al., which included 423 patients with EEC, it was found that high CA-125 levels were associated with tumor spread and lymph node metastasis; however, after adjusting for age, in patients >50 years, the CA-125 cutoff value for predicting lymph node metastasis was found to be 16 IU/L 23 Zhong et al. found that the red cell distribution width coefficient of variation and CA-125 levels were significantly increased in the advanced stage compared to within the early stage of endometrial cancer, showing that these patients had worse overall survival [24]. Yilmaz Baran et al. showed that choosing a CA-125 level of 16 IU/L may be more beneficial for early stage endometrial cancer with negative prognostic factors. Therefore they reported that the CA-125 test should be added to the routine preoperative evaluation of endometrial cancer [25].

In our study, we found the mean life expectancy of patients with CA-125 ≥15.4 to 102.8±5.9 months and the life expectancy of patients with CA-125 <15.4 to 120.1±3.4 months. When the groups were compared, this difference was found to be significant. To define the prognostic role of CA-125 in our study, we determined the cut-off values using clinicopathological factors and ROC curve statistical tests. In the differentiation of early and advanced stages, 15.98 (sensitivity-specificity: 82%-59%) for pelvic lymph node involvement, 16.75 (sensitivity-specificity: 93%-57%), and 15.49 (sensitivity-specificity: 63%-59%) for myometrial invasion in stage 1 values were found to be statistically significant. Our findings are consistent with the literature. Consistent with the median CA-125 value of 15.4, it also showed a significant correlation between stage and the CA-125 value and pelvic-paraaortic lymph node metastasis. However, we could not find a significant relationship between tumor grade and CA-125 level.

As a result, CA-125 levels in EEC are related to the stage of the disease. Lower cut-off values compared to the traditional 35 IU/ml value used in ovarian cancer can be used as a prognostic factor in patients with early-stage EEC and can help in making preoperative decisions about the extent of surgery. For individualized treatment, this result is clinically helpful and informs the prognosis of the disease. CA-125 can be used as an evaluation indicator to aid in early detection and early treatment of the population with high risk. The CA-125 test is an inexpensive, repeatable test that provides valuable information about the risk of metastatic disease and the overall probability of long-term survival. A high CA-125 level may require more imaging and multidisciplinary management, but patients with significant comorbidities may benefit from avoiding the full staging procedure.

The limitations of our study are the lack of a control group in healthy women and the limited number of patients.

This study shows that preoperative serum CA-125 values can be used as a predictive test in patients with early-stage EEC and as a stand-alone prognostic factor. We consider the preoperative CA-125 level to be a valuable preoperative tool that can be used to customize the treatment offered for EEC. CA-125 can

be used as a biomarker to stratify patients into low-risk and high-risk groups preoperatively. This information may be useful for gynecologists to refer high-risk patients to gynecological oncologists for complete surgical staging. Preoperative serum CA-125 is an important predictor for patients with endometrial cancer and should be considered when determining surgical treatment, especially if lymphadenectomy is to be performed in clinical stage I patients.

References

1. Miller KD Nogueira L Mariotto AB Rowland JH Yabroff KR Cancer treatment and survival statistics 2019. CA:A Cancer Journal for Clinicians . 2019; 69:363–385.

2. Pearson-Stuttard J, Zhou B, Kontis V, Bentham J, Gunter MJ, Ezzati M. Worldwide cancer burden attributable to diabetes and high body mass index: a comparative risk assessment. Lancet Diabetes Endocrinol. 2018; 6:e6–e15.

3 Reijnen, C., Visser, N. C., Kasius, J. C., Boll, D., Geomini, P. M., Ngo, H., Van Hamont, D., Pijlman, B. M., Vos, M. C., Bulten, J., Snijders, M. P., Massuger, L. F., & Pijnenborg, J. M. (2019). Improved preoperative risk stratification with CA-125 in low-grade endometrial cancer: a multicenter prospective cohort study. Journal of gynecologic oncology, 30(5), e70. https://doi.org/10.3802/jgo.2019.30.e70

4. Pinar Cilesiz Goksedef, B., Gorgen, H., Baran, S. Y., Api, M., & Cetin, A. (2011). Preoperative serum CA 125 level as a predictor for metastasis and survival in endometrioid endometrial cancer. Journal of obstetrics and gynaecology Canada: JOGC = Journal d'obstetrique et gynecologie du Canada : JOGC, 33(8), 844–850. https://doi.org/10.1016/S1701-2163(16)34988-X

5. Preoperative evaluation of Soper JT Berchuck A Olt GJ Soisson AP Clarke-Pearson DL Bast RC Serum CA 125. American Journal of Obstetrics & Gynecology. 1990; 163 :1204–1209. [PubMed] [Google Scholar]

6. Chao A Tang YH Lai. CH Chang Chang SC The potential for age-stratified CA125 cutoff to improve the prognostic classification of patients with endometrial cancer. Gynecological Oncology. 2013; 129 :500–504. [PubMed] [Google Scholar]

7. Patsner B Yim GW Estimated value of preoperative serum CA-125 levels in patients with uterine cancer: Asian experience 2000 to 2012. Science of Obstetrics and Gynecology. 2013; 56 :281–281. [PMC free article] [PubMed] [Google Scholar]

8. Chen YL Huang CY Chien TY Huang SH Wu Ho C Value of preoperative serum CA125 level for prognosis prediction in patients with endometrial cancer. Australian and New Zealand Journal of Obstetrics and Gynecology. 2011; 51 :397-402. [PubMed] [Google Scholar]

9. Ebina Y Sakuragi N Hareyama H Todo Y Nomura E Serum CA 125 levels in endometrial carcinoma and para-aortic lymph node metastasis in relation to nuclear grade. Acta Obstetricia et Gynecologica Scandinavica. 2002; 81 :458–465. [PubMed] [Google Scholar]

10. Modarres-Gilani M Vaezi M Shariat M Zamani N Nourizadeh R. The prognostic role of preoperative serum CA125 levels in patients with advanced endometrial carcinoma. Cancer Biomarkers. 2017; 20 :135–141. [PubMed] [Google Scholar]

11. Colombo N, Creutzberg C, Amant F, Bosse T, González-Martín A, Ledermann J. ESMO-ESGO-ESTRO consensus conference on endometrial cancer: diagnosis, treatment and follow-up. Radioter Oncol. 2015; 117 :559-581.

12. Alcazar JL, Dominguez-Piriz J, Juez L, Caparros M, Jurado M. Intraoperative gross examination and intraoperative frozen section in patients with endometrial cancer for detection of deep myometrial invasion: a systematic review and meta-analysis. Int J Gynecol Cancer. 2016; 26 :407–415.

13. Creasman, W. (2009), Revised FIGO staging for carcinoma of the endometrium. International Journal of Gynecology & Obstetrics, 105: 109-109. https://doi.org/10.1016/j.ijgo.2009.02.010

14. International Agency for Reseach on Cancer, GLOBOCAN 2008 v, IARC, European age-standardised rates calculated by the Statistical Information Team at Cancer Research UK, 2011.

15.Beesley VL, Rowlands IJ, Hayes SC, Janda M, O'Rourke P, Marquart L. Incidence, risk factors and estimates of a woman's risk of developing secondary lower limb lymphedema and lymphedema-specific supportive care needs in women treated for endometrial cancer. Gynecol Oncol. 2015;136:87–93.

16.Salani R, Preston MM, Hade EM, Johns J, Fowler JM, Paskett EP. Swelling among women who need education about leg lymphedema: a descriptive study of lymphedema in women undergoing surgery for endometrial cancer. Int J Gynecol Cancer. 2014;24:1507–12.

17. Bağcı, M., Gülhan, İ., M., Saygılı, U., & Demir, N. (2005). The Diagnostic Accuracy Of Magnetic Resonance Imaging In The Prediction Of Myometrial Invasion And Correlation Between Serum Ca - 125 Level

And Myometrial Invasion In Endometrial Cancer. J Clin Obstet Gynecol, 15(6), 296-303.

18. Atguden Z, Yildiz A, Aksut H, Yalcin SE, Yalcin Y, Uysal D, Yetimalar H. The Value of Preoperative CA 125 Levels in Prediction of Myometrial Invasion in Patients with Early-stage Endometrioid- type Endometrial Cancer. Asian Pac J Cancer Prev. 2016;17(2):497-501. doi: 10.7314/apjcp.2016.17.2.497. PMID: 26925634.

19. Hsieh CH, Chang Chien CC, Lin H. Can a preoperative CA-125 level he a criterion for full pelviclymphadenectomy in surgical staging of endometrial cancer'? Gynecol Oncol 2002: 86: 28-33.

20. Dotters D. Preoperative Ca-125 in endometrial cancer: is it useful. Am J Obstet Gynecol 2000; 182: 1328-35.

21. Jiang T Huang L Zhang S. Preoperative serum CA125: a useful marker for surgical treatment of endometrial cancer. BMC Cancer. 2015; 15 :396–396. [PMC free article] [PubMed] [Google Scholar]

22. Kim HS Park CY Lee JM Lee JK Evaluation of serum CA-125 levels for preoperative counseling in endometrioid endometrial cancer: A multicenter study. Gynecological Oncology. 2010; 118 :283-288. [PubMed] [Google Scholar]

23. Unsal M., Kimyon Comert G., Karalok A., Baaran D., Turkmen O. Preoperative serum CA125 can predict lymph node metastasis in endometrioid type endometrial cancer. Ginecologia Polska. 2018; 89 :599–606.

24. Zhong, W., Zhou, C., Chen, L., Wang, Z., Lin, H., Wu, K., & Zhang, S. (2021). The Coefficient of Variation of Red Blood Cell Distribution Width Combined with Cancer Antigen 125 Predicts Postoperative Overall Survival in Endometrial Cancer. International journal of general medicine, 14, 5903–5910. https://doi.org/10.2147/IJGM.S323136.

25. Yilmaz Baran Ş, Alemdaroğlu S, Doğan Durdağ G, Yüksel Şimşek S, Bolat F, Köse F, Çelik H. What is the predictive value of preoperative CA 125 level on the survival rate of type 1 endometrial cancer? Turk J Med Sci. 2021 Feb 26;51(1):335-341. doi: 10.3906/sag-2005-331. PMID: 32979897; PMCID: PMC7991883.