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How specific are CA-125 levels in ruling out extra-uterine extension of uterine papillary serous carcinoma?

CA-125 seviyeleri, uterin papiller seröz karsinomun uterus dışı yayılımının dışlanmasında ne kadar spesifiktir?

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ÖZ

Amaç: Uterin papiller seröz karsinom hastalarında preoperatif serum CA-125 düzeylerini hastalığın yayılımını predikte etmek için araştırmak.

Gereç ve Yöntemler: Uterin papiller seröz karsinom için opere edilen hastalarda preoperatif CA-125 seviyelerinin yanı sıra yaş, bildirilen tümör boyutu, lenf nodu tutulumu, lenfovasküler boşluk invazyonu, myometriyal invazyon derinliği ve evre gibi verileri toplandı.

Bulgular: Yirmi bir uterin papiller seröz karsinom olgusu analizimize dahil edildi. Hastalarının ortalama yaşları 63.9 idi. Uterin papiller seröz karsinom grubunu CA-125 açısından incelediğimizde; CA-125 ile yaş (≤60 vs >60), tümör boyutu (≤40 vs >40mm), myometriyal invazyon derinliği, nod metastazı veya lenfovasküler boşluk invazyonu arasında hiçbir ilişki yoktu. Öte yandan, ortalama CA-125 seviyeleri, FIGO (Uluslararası Jinekoloji ve Obstetrik Federasyonu) Evre III/IV (medyan=54 U/ml) olan hastalarda FIGO evre I/II'ye (medyan=11 U/mL) anlamlı olarak yüksekti (p=0,002). Uterus dışına yayılan tümörler için ortalama CA-125 düzeyi 281,2 U/ml ve uterusta sınırlı tümörler için 14,3 U/ml idi (p=0,002). Ekstrauterin yayılmayı tahmin etmek için optimum eşik değeri 28.5 U/mL idi (duyarlılık%75, özgüllük%89). Preoperatif CA-125 düzeyi, ekstrauterin tutulum ve ileri evre ile ilişkilendirildi.

Sonuç: Preoperatif CA-125 düzeyi, ekstrauterin tutulum ve ileri evreyi predikte etmek için yararlı olabilir. Ca 125 düzeyi 28,5 U/mL üstünde olan hastalar için preoperatif görüntülemede yaygın hastalığın değerlendirilmesi ve buna yönelik hazırlık ile daha radikal bir cerrahi önerilebilir.

Anahtar Kelimeler: CA-125, Endometrium kanseri, Uterin papiller seröz karsinom

ABSTRACT

Aim: To investigate the CA-125 levels in uterine papillary serous carcinoma (UPSC) patients to predict the extent of disease.

Materials and Method: Medical records of patients operated for UPSC, their preoperative CA-125 levels, as well as parameters including age, tumor size, lymph node involvement, lymphovascular space invasion (LVSI), depth of myometrial invasion (MI) and stage were documented.

Results: Twenty-one UPSC cases were included. When we analyzed the serous cancer group in terms of CA-125; there was no association between CA-125 and age (≤60 vs >60), tumor size (≤40 vs >40mm), MI, lymph node metastasis or LVSI. The mean CA-125 levels were significantly higher among patients with stage III/IV (median=54 U/ml), compared to stage I/II (median=11 U/mL). The mean CA-125 value for tumors spread beyond the uterus were 281.2 U/ml, and 14.3 U/ml for the tumors confined within the uterus (p=0.002). The optimum threshold value to predict extrauterine spread was 28.5 U/mL. CA-125 level was related to extrauterine involvement and advanced stage.

Conclusion: CA-125 level may be a useful test for extrauterine involvement and advanced stage. We suggest patients with a pre-operative CA 125 level of >28.5 U/mL be evaluated regarding extra-uterine dissemination with preoperative imaging and be prepared for radical surgery.

Keywords: CA-125; endometrial cancer; uterine papillary serous carcinoma

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INTRODUCTION

Cancer of the uterine corpus is the most common gynecologic cancer among women in developing countries [1]. Endometrial cancer (EC) is divided into two groups according to pathological, epidemiological, clinical behavior, and genetic profiles. While endometrioid cancers are classified as Type I tumors, uterine papillary serous carcinoma (UPSC) is in Type II.

Uterine papillary serous carcinoma accounts for only 10% of EC but causes about half of the deaths [2,3]. UPSC presents in more advanced stages and has lower survival rates than its endometrioid carcinoma counterparts [2].

Due to the histological similarities between UPSC and serous ovarian cancers, CA-125 as a tumor-associated-antigen commonly used in epithelial ovarian cancers could also have a significant role in endomerial cancer. As a result, many studies have been conducted regarding the role of CA-125 in endometrial cancer.

Firstly, Niloff et al. [4] demonstrated that CA-125 levels are elevated in most women with advanced or recurrent disease. Several studies demonstrated a relationship between CA-125 and the presence of extrauterine disease at the time of presentation [4-6]. However, the use of this parameter is still controversial.

We aimed to investigate whether CA-125 is a useful biomarker to predefine advanced stages of uterine papillary serous carcinoma.

MATERİAL AND METHODS

Patients with uterine papillary serous carcinoma who underwent surgical staging in our institution from January 2015 to December 2018 were reviewed retrospectively through electronic medical records. Ethical approval was obtained from the Research Ethics Committee (2019/78).

All patients underwent comprehensive surgical staging by the 2009 FIGO (The International Federation of Gynecology and Obstetrics) staging system. Women other than the diagnosis of uterine papillary serous carcinoma and those with missing data were excluded from the study. Abstracted data included the demographic characteristics, serum CA-125 measurements, intraoperative findings, and histopathological results.

Statistical analysis

All statistical analyses were performed using Statistical Package for the Social Science (IBM SPSS version 20) for Windows software. Median, lowest, and highest values were used in descriptive statistics of the data. Continuous and normally distributed data were indicated as mean (± standard deviation) and categorical variables as number (percentage). Mann-Whitney U Test, Chi-square test, and Student's t-test were performed where necessary for statistical analysis. ROC (Receiver Operating Characteristic) analysis was performed for determining the cut-off value of CA-125 in defining the stages of the disease. A p-value of <0.05 was considered significant.

RESULTS

Out of 325 patients with EC who underwent gynecological surgery during the study period, twenty-one patients with UPSC were remained to be analyzed.

The mean age of patients with UPSC was 63.9 (range: 42-73) years. Lymphovascular space invasion (LVSI)-positive in 16 (16/21; 76.2%) patients with uterine papillary serous carcinomas. The mean CA-125 value for UPSC was 26 U/ml (4–1454 IU/mL). Twelve (57.1%) patients were in the serous group had advanced stage (stage III-IV) disease. In addition, lymph node involvement was found in 19% of patients with uterine papillary serous carcinoma (Table 1).

Table 1: Characteristics of the patients (n=21)

	n (%)
Age at diagnosis (year)	63.9
Tumor size (mm) (Median) (Min-Max)	40 (10-110)
Myometrial Invasion (%)	
≤ 50	12 (57.1)
> 50	9 (42.9)
Presence of LVSI	
No	5 (23.8)
Yes	16 (76.2)
Lymph Node Involvement	
No	17 (81.0)
Yes	4 (19.0)
FIGO Stage	
1 or 2	9 (42.9)
3 or 4	12 (57.1)
CA-125 (U/mL)	26 (4-1454)

LVSI= Lymphovascular Space Invasion, mm= Millimeter, Min= Minimum, Max= Maximum, %= Percent, FIGO= The International Federation of Gynecology and Obstetrics CA= Cancer Antigen, U= International Unit, mL= Milliliter.

There were no associations between CA-125 and demographic, clinical, and pathological factors. But, mean CA-125 levels were significantly higher in advanced stage endometrial serous cancers (median=54, than in early cases (median=11) (p=0.002). The mean CA-125 level for tumors that extended beyond the uterus was 281.2 IU/ml, and for the tumors that were confined to the uterus, 14.3 IU/ml (p=0.002). In our study, preoperative Ca-125 levels were significantly associated with extrauterine involvement of the disease (Table 2).

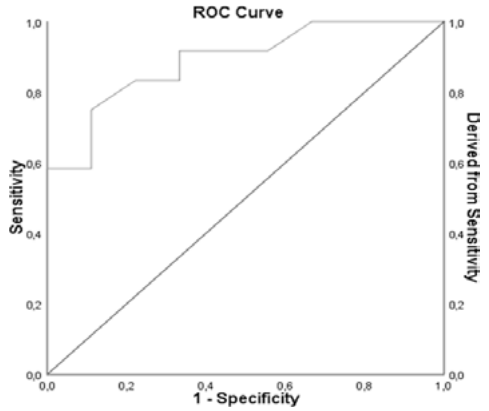
Table 2: Analyzing of CA-125 according to pathological features in uterine serous carcinoma.

Serous Carcinomas	*Mean*	*Min*	*Max*	***P Value***
Myometrial Invasion (%)				*P*= 0.508
≤ 50	165	4	1454	
> 50	169.2	7	708	
Presence of LVSI				*P*= 0.660
No	129.2	11	315	
Yes	178.6	4	1454	
Lymph Node Involvement				*P*= 0.698
No	197.2	4	1454	
Yes	37.5	10	57	
FIGO Stage				***P= 0.002***
1 or 2	14.3	4	36	
3 or 4	281.2	10	1454	
Age (year)				*P*= 0.698
≤ 60	189.5	4	708	
> 60	161.5	5	1454	
Tumor size (mm)				*P*= 0.114
≤ 40	98.8	4	403	
> 40	241.6	10	1454	

Statistical analysis performed using by Mann-Whitney U Test, CA-125= Cancer Antigen-125, U= International Unit, mL= Milliliter, Min= Minimum, Max= Maximum, %= Percent, LVSI= Lymphovascular Space Invasion, FIGO= The International Federation of Gynecology and Obstetrics. mm= Millimeter

CA-125 value for the extrauterine spread in UPSC was determined using the ROC. Preoperative serum CA-125 measurements had an AUC (Area under the curve) of 0.889 (95% CI, 75-100) (Figure 1).

Figure 1: Receiver Operating Characteristic (ROC) Curve analysis of CA-125 (U/mL) regarding of tumor stage 1-2 or 3-4.



An optimum threshold value of 28.5 U/mL was determined with a sensitivity of 75% (95% CI,42 –94) and specificity of 89% (95% CI, 51–99). The positive predictive value and negative predictive values were 90 (95% CI,57–98) and 72 (95% CI,49–87), respectively.

DISCUSSION

Uterine papillary serous carcinoma is a distinct subtype of EC that morphologically resembles serous ovarian cancer and occurs at an advanced stage of the disease with an unfavorable prognosis. While reviewing the FIGO Annual Report data, Creasman et al. stated that 46% of UPSC patients were admitted at stage II-IV [7]. In our research, stage III-IV patients comprised 57 % of the UPSC group.

Lachance et al. [8] found that patients younger than 45 years likelihood to have favorable histology, early-stage, and low-grade tumors, while those over 65 years have papillary serous histology, advanced-stage, and high-grade tumors. Similar to other studies [9,10], the average age of UPSC patients was 63.9 years in our study.

Many researchers reported that there is no proven assessment for extrauterine disease based on uterine features such as myometrial invasion or lymphovascular space invasion. Goff et al. [6] demonstrated that comprehensively staged UPSC patients lacking myometrial invasion or lymphovascular space invasion had similar lymph node involvement and intraperitoneal metastasis. A recent study reported that 38% of patients with tumors developing within the endometrial polyp had extrauterine spread [11]. In our study, 23% of the patients without myometrial invasion had extrauterine involvement.

The preoperative pathological examination should have an imperfect concordance with the final pathology. As a result, the preoperative histopathological assessment provides crucial information for further surgical planning. Havrilesky et al. were able to report the preoperative diagnosis only in 20% of early-stage UPSC patients in their study [12]. And besides that, Wang Y. et al. [1] found the 29.2% of patients had discordance between the preoperative and postoperative pathology. This has led to the need for a more accurate preoperative tool such as serum CA-125 measurement for preoperative diagnosis.

Although many studies have examined the relationship between CA125 measurement and uterine papillary serous carcinoma, only a few investigated whether there is a reliable CA125 breaking point for tailoring patient management out of the ac-

cepted CA125 cutoff value [13-17]. In the presented research, the cutoff value of <28.5 achieved a high specificity to distinguish between stage I/II and III/IV, but particularly for early stages. In all, we suggest that further investigation may be beneficial in women diagnosed with UPSC with a pre-operative CA 125 level of >28.5 U/mL.

Firstly, Alagöz et al. [18] proposed that a lower CA-125 cutoff level in EC would be more appropriate to use in their research in 1994. Then, some researchers suggested that it would be more convenient to use 20 U/L for threshold value in predicting extrauterine spread [17], while others 35 U/mL (5,19-21). Several researchers [22,23] noted that the CA-125 optimum threshold value as 28.5 U/mL that this value below showed better five years OS and DFS. Our findings are in agreement with these studies. In our view, our results constitute a step towards enhancing the knowledge on the significance of the CA 125 cut-off level in the prediction of extrauterine involvement. Given that our findings are based on a limited number of women with UPSC, these results thus need to be interpreted with care and validated with larger sample-sized studies.

A mere pathological diagnosis of UPSC according to available evidence stands for a rather high chance for a disease state extending beyond the uterus, namely advanced stages of disease (stage III-IV). In our study, we aimed at defining the dissipation of UPSC outside of the uterus through serum CA-125 measurements. Our findings, however, do not seem to significantly surpass the sole predictive capability of the pathological reporting of UPSC (sensitivities of 62 to 99% vs 75%, the specificity of 89% and PPV was 90) [24]. On the contrary, a more distinct contrast was plausible when CA-125 levels were below the defined threshold ruling out advanced disease (specificity of 89%). An additional useful take-home message could be that for those UPSC cases with higher than this threshold, a further evaluation with additional diagnostic workups may be beneficial, and an aggressive treatment modality may be considered in planning surgical procedures.

We are aware that our research may have several limitations. The first is a single-center, small sample-sized study; however, this is accounted for due to the relative rarity and poor prognosis of this disease. Although there is a satisfactory agreement with previous studies, large-scale multicenter studies are needed to support our findings. The second is the retrospective nature of the study. The strengths of the study were that it constituted the experience of one of the largest tertiary institutions in the field of obstetrics and gynecology in the country and experienced gyneco-pathologists evaluated the histopathological specimens. However, we believe that our results will provide a comprehensive flow of information into the growing body of literature on the significance of the CA 125 cut-off level in the prediction of extrauterine dissemination.

CONCLUSION

The cutoff value of CA125 may help clinicians to triage and tailor individualized patient management. For patients with preoperative CA 125 levels >28.5 U/ml, further evaluation and additional diagnostic tests may be helpful in assessing extra-uterine spread and preparing for comprehensive surgery.

Ethics Committee Approval: Ethical approval was obtained from the Research Ethical Committee of the Zeynep Kamil Women's and Children's Disease Training and Research Hospital (Approval number: 2019/78). This research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki.

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Authors' Contributions

The literature review was performed by EK, SA, UKO, MA, CK. The data of study was acquired by EK, analysed and interpreted by SA, YEP, SEO. The conception of the study was contributed bu MA, SEO, CK, EK, UKO, SA. All authors contributed to drafting the manuscript and also approved the final version of the manuscript to be published.

REFERENCES

1. Wang Y, Yu M, Yang JX, Cao DY, Shen K, Lang JH. Clinicopathological and survival analysis of uterine papillary serous carcinoma: a single institutional review of 106 cases. Cancer Manag Res 2018;10:4915-28.

2. Hendrickson M, Ross J, Eifel P, Martinez A, Kempson R. Uterine papillary serous carcinoma: a highly malignant form of endometrial adenocarcinoma. Am J Surg Pathol 1982;6(2):93-108.

3. Slomovitz BM, Burke TW, Eifel PJ, Ramondetta LM, Silva EG, Jhingran A, et al. Uterine papillary serous carcinoma (UPSC): a single institution review of 129 cases. Gynecol Oncol 2003;91(3):463-9.

4. Niloff JM, Klug TL, Schaetzl E, Zurawski VR Jr, Knapp RC, Bast RC Jr. Elevation of serum CA125 in carcinomas of the fallopian tube, endometrium, and endocervix. Am J Obstet Gynecol 1984;148(8):1057-8.

5. Olawaiye AB, Rauh-Hain JA, Withiam-Leitch M, Rueda B, Goodman A, del Carmen MG. Utility of pre-operative serum CA-125 in the management of uterine papillary serous carcinoma. Gynecol Oncol 2008;110(3):293-8.

6. Goff BA. Surgical treatment of unusual endometrial cancer. In: American Society of Clinical Oncology Educational Book. 40th annual meeting of the American Society of Clinical Oncology; 2004 June 5-8, New Orleans, LA. 2004. p. 298-302.

7. Creasman WT, Kohler MF, Odicino F, Maisonneuve P, Boyle P. Prognosis of papillary serous, clear cell, and grade 3 stage I carcinoma of the endometrium. Gynecol Oncol 2004; 95(3):593–6.

8. Lachance JA, Everett EN, Greer B, Mandel L, Swisher E, Tamimi H, et al. The effect of age on clinical/pathologic features, surgical morbidity, and outcome in patients with endometrial cancer. Gynecol Oncol 2006;101(3):470-5.

9. İyibozkurt AC, Doğan M, Baştu E, Sözen H, Vatansever D, Topuz S, et al. Efficacy of endocervical curettage and CA-125 measurement in endometrial serous carcinoma: A case series and literature review. Turk J Obstet Gynecol 2015;12(3):164-7.

10. Üreyen I, Karalok A, Akdağ Cırık D, Taşçı T, Türkmen O, Kimyon Cömert G, et al. A comparison of clinico-pathologic characteristics of patients with serous and clear cell carcinoma of the uterus. Turk J Obstet Gynecol 2016;13(3):137-43.

11. Hui P, Kelly M, O'Malley DM, Tavassoli F, Schwartz PE. Minimal uterine serous carcinoma: a clinicopathological study of 40 cases. Mod Pathol 2005;18(1):75-82.

12. Havrilesky LJ, Secord AA, Bae-Jump V, Ayeni T, Calingaert B, Clarke-Pearson DL, et al. Outcomes in surgical stage I uterine papillary serous carcinoma. Gynecol Oncol 2007;105(3):677-82.

13. Duk JM, Aalders JG, Fleuren GJ, de Bruijn HW. CA 125: a useful marker in endometrial carcinoma. Am J Obstet Gynecol 1986;155(5):1097-102.

14. Patsner B, Mann WJ, Cohen H, Loesch M. Predictive value of preoperative serum CA 125 levels in clinically localized and advanced endometrial carcinoma. Am J Obstet Gynecol 1988;158(2):399–402.

15. Koper NP, Massuger LF, Thomas CM, Kiemeney LA, Verbeek AL. Serum CA 125 measurements to identify patients with endometrial cancer who require lymphadenectomy. Anticancer Res 1998;18(3B):1897-902.

16. Cherchi PL, Dessole S, Ruiu GA, Ambrosini G, Farina M, Capobianco G, et al. The value of serum CA 125 and association CA 125/CA 19-9 in endometrial carcinoma. Eur J Gynaecol Oncol 1999;20(4):315-7.

17. Yildiz A, Yetimalar H, Kasap B, Aydin C, Tatar S, Soylu F, et al. Preoperative serum CA 125 level in the prediction of the stage of disease in endometrial carcinoma. Eur J Obstet Gynecol Reprod Biol 2012;164(2):191-5.

18. Alagoz T, Buller RE, Berman M, Anderson B, Manetta A, DiSaia P. What is a normal CA125 level?. Gynecol Oncol 1994;53(1):93-7.

19. Powell JL, Hill KA, Shiro BC, Diehl SJ, Gajewski WH. Preoperative serum CA-125 levels in treating endometrial cancer. J Reprod Med 2005;50(8):585-90.

20. Sebastianelli A, Renaud MC, Grégoire J, Roy M, Plante M. Preoperative CA 125 tumour marker in endometrial cancer: correlation with advanced stage disease. J Obstet Gynaecol Can 2010;32(9):856-60.

21. Goksedef BP, Gorgen H, Baran SY, Api M, Cetin A. Preoperative serum CA 125 level as a predictor for metastasis and survival in endometrioid endometrial cancer. J Obstet Gynaecol Can 2011;33(8):844-50.

22. Sood AK, Buller RE, Burger RA, Dawson JD, Sorosky JI, Berman M. Value of preoperative CA 125 level in the management of uterine cancer and prediction of clinical outcome. Obstet Gynecol 1997;90(3):441-7.

23. Povolotskaya N, Das N, Dhar K, Brinkmann D, Gardner F, Woolas R. Utility of preoperative CA125 assay in the management planning of women diagnosed with uterine cancer. Surg Res Pract 2014;2014:497478.

24. Visser NCM, Reijnen C, Massuger LFAG, Nagtegaal ID, Bulten J, Pijnenborg JMA. Accuracy of endometrial sampling in endometrial carcinoma: A systematic review and meta-analysis. Obstet Gynecol 2017;130(4):803-13.