Endometrial and Ovarian Cancer with MR Imaging Importance of Serum HE4 and CA 125 Levels in the Extent of Disease at Evaluation

Endometrium ve Over Kanserinde MR Görüntüleme ile Serum HE-4 ve CA 125 Düzeylerinin Hastalığın Yaygınlığını Değerlendirmedeki Önemi

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ABSTRACT

Objective: Currently, no clinically useful tumor marker is available for primary diagnosis in endometrial cancer. Human epididymis protein-4 (HE-4) has high sensitivity and specificity as a tumor marker. Further, HE-4 has been shown to be elevated in early stage endometrial cancer and is more sensitive than CA 125. In our study, CA 125 and HE-4 reputation as a tumor marker for diagnosis of ovarian and endometrial cancer with the use of both the availability and affect the way we investigated the rate of diagnosis.

Materials and Methods: Here 20 patients with ovarian cancer, 26 patients with endometrial cancer, which had been histologically diagnosed, and 40 healthy volunteers were included. Peripheral blood samples were taken and serum CA 125 and HE-4 were tested.

Results: Serum CA 125 and HE-4 levels in patients with ovarian cancer were found to be significantly higher than those in healthy volunteers ($p<0.05$). Receiver-operating characteristic (ROC) analysis was performed. For patients with ovarian cancer and healthy controls, the CA 125 (0.83) and HE-4 (0.84) levels showed increased sensitivity (95%). There was no significant difference in the CA 125 levels in patients with endometrial cancer and healthy controls ($p>0.05$), whereas HE-4 levels were found to be higher in patients with endometrial cancer than in healthy controls ($p<0.05$). ROC analysis was performed. For endometrial cancer patients and healthy controls, the CA 125 (0.59) and HE-4 (0.63) levels showed increased sensitivity (88.5%).

Conclusion: In ovarian and endometrial cancer, wherein early diagnosis is the most important factor for prognosis and survival, HE-4 is a new serum tumor marker that can be used with the aim of noninvasive diagnoses. For early diagnosis, the concomitant use of CA 125 and HE-4 is more effective and reliable than using either of them alone.

Keywords: Ovary, endometrium, cancer, diagnosis, tumor marker

ÖZ

Amaç: CA 125 erken evre over kanserlerinin sadece %50'sinde yükselir. Endometrium kanserinde klinik pratikte rutin olarak kullanılan tümör marker yoktur. Human epididimis protein-4 (HE-4) over kanserlerinde yüksek sensitivite ve spesifiteye sahiptir. Endometrial kanserde CA 125 den daha sensitif olduğu ve erken evrede yükseldiği gösterilmiştir. Çalışmamızda CA 125 ve HE-4'ün over ve endometrium kanserinde tümör markerı olarak kullanılabilirliğini ve ikisinin birlikte kullanımın teşhis oranını ne şekilde etkileyeceğini araştırdık.

Gereç ve Yöntem: Çalışmamıza histopatolojik olarak tanısı konulan 20 over kanseri, 26 endometrium kanseri hasta ile jinekolojik problemi olmayan 40 sağlıklı gönüllü dahil edilmiştir. MR görüntülemesiyle FIGO sistemine göre evreleri belirlendi. Hastalardan preoperatif olarak ve sağlıklı gönüllülerden periferik kan alınarak serum CA 125 ve HE-4 düzeyleri çalışıldı.

Bulgular: Over kanseri hastalarının serum CA 125 ve HE-4 düzeyleri sağlıklı kontrollerinkinden anlamlı yüksek bulundu ($p<0,05$). ROC (Receiver Operatör Characteristic) analizi uygulandığında over kanseri hastalarında CA 125 (0,83) ve HE-4 (0,84)'ün birlikte kullanımının sensitiviteyi arttırdığı (%95) görüldü. Endometrium kanseri hastaları ile sağlıklı kontrollerin CA 125 düzeyleri arasında anlamlı fark yok iken ($p>0,05$), HE-4 düzeyleri yüksek bulunmuştur ($p<0,05$). Endometrium kanseri hastaları ile sağlıklı kontroller arasında CA 125 (0,59) ve HE-4'ün (0,63) birlikte kullanımın sensitiviteyi (%88,5) arttırdığı gözlendi.

Sonuç: Erken teşhisin prognoz üzerindeki en önemli etken olduğu over ve endometrium kanserinde HE-4 non-invazif teşhis amacıyla kullanılabilecek tümör markerıdır. Erken teşhis amacıyla CA 125 ve HE-4'ün birlikte kullanımı herhangi birisinin tek başına kullanılmasına göre daha etkin ve güvenilirdir.

Anahtar Kelimeler: Over, endometrium, kanser, teşhis, marker

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Introduction

It is known that a prognosis will be poor and survey rates will be lower if endometrial cancer, similar to ovarian cancer, is diagnosed at a later stage [1]. As ovarian cancer symptoms are nonspecific, a distinctive diagnosis is based, in general, on the viewing techniques and preoperative serum tumor markers [2]. The ideal tumor marker needs to have high sensitivity and specificity for the distinction of patients with cancers and benign diseases as well as healthy controls [3]. Serum CA 125 is suitable for the diagnosis of advanced phase ovarian cancers, but there are no reliable serum biomarkers that can be clinically used for the diagnosis of endometrial cancer [4].

Our study researched the usability of HE-4, a non-marker, for endometrial and ovarian cancers. It has been recognized as a noninvasive method in terms of its significance during early diagnosis of cancers, both singly or in combination with CA 125.

Materials and Methods

Our study included 20 patients in the Obstetrics and Gynecology Polyclinic at our hospital; these patients had masses in their ovaries that were determined through viewing techniques while they were being investigated due to nonspecific complaints such as abdominal pain, swelling, and asthenia. Further, 26 patients were diagnosed with endometrial cancer on the basis of histopathological results of the probe curettage performed while investigating the etiology of menstrual irregularity. For the control group, blood was extracted from 40 healthy volunteers with no gynecological conditions. An application was filled with the ethics board of our hospital for the study protocol and approval was obtained.

The pelvic mass of all the patients was documented with magnetic resonance imaging using a 1.5T system equipped with a phase-contrast abdominal coil. Three-dimensional images of the T2-weighted views were obtained (uterus axial, axial oblique, and sagittal cross sections). Axial oblique images were shot vertical to the endometrial cavity. Additionally, they were obtained in the sagittal cross section in the native T1-weighted images. The patients were injected with 0.1 mmol/kg of contrast substance. The axial oblique and sagittal images were repeated after intravenous administration of the contrast. The classification developed by the International Federation of Gynecology and Obstetrics (FIGO) was used for the staging of ovarian cancer, and the FIGO staging revised in 2009 was used for endometrial cancers [5, 6]. The MRI findings of patients with ovarian and endometrial cancers were staged according to the FIGO criteria [7].

The invasion of the lymphovascular area of the endometrial cancer patients was noted and the depth of the myometrial invasion was determined.

Blood was extracted from the patients during the pre-operative surgery visit or in the morning of the surgery to measure serum CA 125 and HE-4 levels. Post-operative specimens were evaluated in the pathology major and histopathologically diagnosed. The operational findings of all patients were noted.

Collection of Samples and Lab Analysis: Approximately 4–5 mL of blood samples extracted from all the patients were collected in non-heparinized tubes. Serum was collected and stored at –80°C until the examination. The measurement of HE-4 and CA 125 levels were simultaneously performed from the serum samples.

Analysis was performed with HE-4 using an enzyme immunometric assay kit according to the manufacturer's instructions (Fujirebio Diagnostics, Inc. Malvern, Sweden). Serum CA 125 level was measured using a Beckman-Coulter kit, model DXI. All samples were run on the same day after the same calibration. The threshold value for CA 125 was accepted as 35 U/mL for ovarian cancer patients.

Statistical analysis

Statistical Package for Social Sciences for Windows 20.0 (IBM Corp., Armonk, New York, United States) and medCalc.12 programs were used for statistical calculation and comparison of numerical data. The numerical values, percentages, averages, and standard deviation of data as well as their normality distribution were analyzed using the Kolmogorov–Smirnov analysis test. The ROC characteristics curve was used to calculate the sensitivity and specificity values of the tumor markers. Among parametric tests, the t-test was used for independent samples, and the Mann–Whitney U-test was used as a non-parametric test. Data were recorded as the arithmetic average ± standard deviation, and $p<0.05$ was found to be statistically significant.

Results

The average age of the ovarian cancer patients was found as 53.8±14.9 (32–87) years. The average age of the control group was 47.4±8.9 (21–60) years. No statistical difference was found in terms of age between the control and cancer groups ($p=0.82$).

According to their first complaints, six of the patients presented with abdominal pain (30%); 4 patients, swelling (20%); 4 patients, vaginal bleeding (20%); and 6 patients, loss of weight and asthenia (30%). Patients diagnosed with ovarian cancer presented with an adnexal mass during routine gynecological examinations. According to the first complaints of endometrial cancer patients, 5 patients had menstrual irregularity (19.2%) and 21 patients had vaginal bleeding (premenopausal or post-menopausal bleeding) (80.8%). The endometrial pathology was found during the gynecological examination of the patients.

According to the histopathological evaluation of these patients, 13 cases of serous adenocarcinoma (65%, most frequent), 5 cases of granulose cell tumor (25%), 1 case of neuroendocrine tumor (5%), and 1 case of Sertoli–Leydig cell tumor (5%) were recorded. According to the histopathological evaluation of the endometrial cancer patients, 25 cases (96.2%) of adenocarcinoma and only 1 case (3.8%) of carcinosarcoma were recorded.

There was a statistically significant difference between CA 125 values of the control group (median=27.6; min=5, max=70) and those of all the patients with ovarian cancer (median=128.5; min=10, max=4969), with no regard to the stage ($p=0.0001$). CA 125 values were higher in the ovarian cancer group than in the control group.

There was a statistically significant difference between HE-4 values of the control group (median=53; min=30, max=77) and those of all the patients with ovarian cancer (median=162.2; min=34, max=879), with no regard to the stage ($p=0.0001$). HE-4 values were higher in the ovarian cancer group than in the control group.

According to postoperative MR results and the FIGO staging of the ovarian cancer patients, 12 patients were stage I (60%); 7 patients, stage III (35%); and 1 patient, stage IV (5%). There were no stage II patients. Stage I and II patients were accepted as early stage (n=12, 60%) and stage III and IV patients (n=8, 40%) as advanced stage. Accordingly, a positive significant statistical relation was found between both groups in terms of preoperative serum CA 125 values ($p=0.001$). However, there were no statistically significant relations in term of HE-4 when both groups were compared ($p=0.1$).

The area under the curve (AUC) for serum CA 125 in the ROC analysis performed for the distinctive diagnosis of the ovarian cancer patients and healthy controls was 0.83 (95% GA: 0.71–0.92; $p<0.0001$).

According to the ROC analysis performed for the distinctive diagnosis of the ovarian cancer patients and healthy controls, the sensitivity of CA 125 value in the 95% confidence interval was 80% (95% GA: 56.3–94.3) and the specificity was 62.5% (95% GA: 45.8–77.3). A statistically significant relation was found between them ($p<0.0001$) (Figure 1).

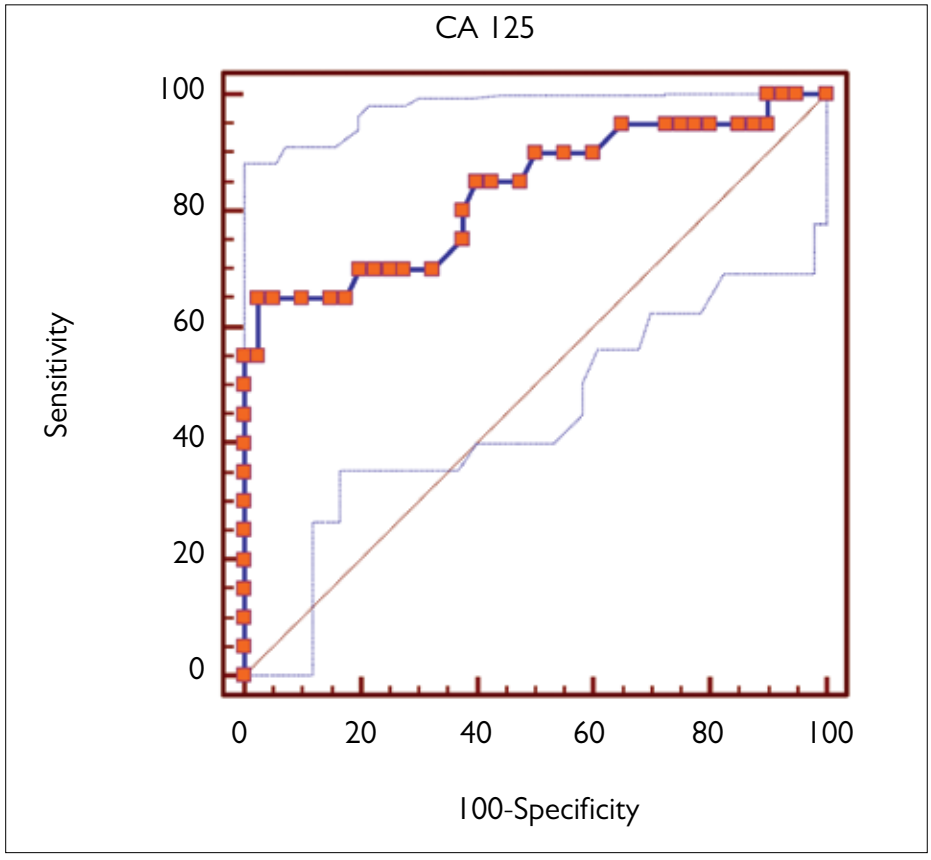

Figure 1. ROC analysis of CA 125 levels between over-cancer patients and controls.

Area under the ROC curve (AUC)				
AUC			0.83	
95% confidence interval (CI)			0.71–0.92	
p			<0.0001	
Criterion	Sensitivity	95% CI	Specificity	95% CI
>35	80.00	56.3–94.3	62.50	45.8–77.3
ROC: receiver-operating characteristic				

Table 1. Median values of CA 125 and HE-4 used in over cancer diagnosis

			Group		
			Over Ca	Control	
CA 125 + HE4	Negative	n	1	21	22
		%	5.0	52.5	36.7
	Positive	n	19	19	38
		%	95.0	47.5	63.3
		n	20	40	60
		%	100.0	100.0	100.0

The AUC for HE-4 in the ROC analysis performed for the distinctive diagnosis of the ovarian cancer patients and healthy controls was 0.84 (95% GA: 0.72–0.92; p<0.0001).

According to the ROC analysis performed for the distinctive diagnosis of the ovarian cancer patients and healthy controls, the sensitivity of the HE-4 value in the 95% confidence interval was 80% (95% GA: 56.3–94.3) and the specificity was 92.5% (95% GA: 79.6–98.4). A statistically significant relation was found between them (p<0.0001) (Figure 2).

These results were obtained when the cut-off values were taken as HE-4 > 89 pmol/L and CA 125>35.0 U/mL, according to the study population.

When the combined and single use of these two markers are compared, the sensitivity increases (95%) but the specificity decreases (52.5%) (Table 1).

According to postoperative MR results and FIGO staging of endometrial cancer patients, 22 patients were classified as stage I (84.6%); 1 patient, stage II (3.8%); and 3 patients, stage III (11.6%). There were no statistically significant relations in terms of CA 125 values when both groups were compared without regarding the stage of the endometrial cancer (p=0.07).

There was a statistically significant difference between HE-4 values of healthy controls and all endometrial cancer patients without regarding the stage (p=0.03). HE-4 values of endometrial cancer patients were higher than those of healthy controls (Table 2).

There were no statistically significant relations in terms of postoperative serum CA 125 values of both groups when the stage I patients were considered as early stage (n=22, 84.6%) and stage II–IV patients as advanced stage (n=4, 15.4%) (p=0.48). There was also no statistically significant relation in terms of HE-4 when both groups were compared (p=0.16).

The lymphovascular area invasion was found only in 5 patients (19.2%), according to their preoperative MR images. While there was a statistically significant relation in terms of serum CA 125 values between patients with lymphovascular area invasion and noninvasion (p=0.04), there was no statistically significant relation in terms of their serum HE-4 values (p=0.06).

According to the preoperative MR images of our patients, 21 of them were considered stage I. Four of these patients had myometrial invasion (19%) (stage Ib) and 17 of the patients (81%) did not. There was no statistically significant relation in terms of CA 125 values between patients who had and did not have myometrial invasion (p=0.6). Further, there was no statistically significant relation in terms of serum HE-4 values between patients who had and did not have myometrial invasion (p=0.36) (Table 3).

ROC analysis was performed for endometrial cancer patients to detect the tumor, if the combined use of CA 125 and HE-4 increases the sensitivity or not compared with the single use of either of them.

The AUC for serum CA 125 in ROC analysis performed for the distinctive diagnosis of endo-

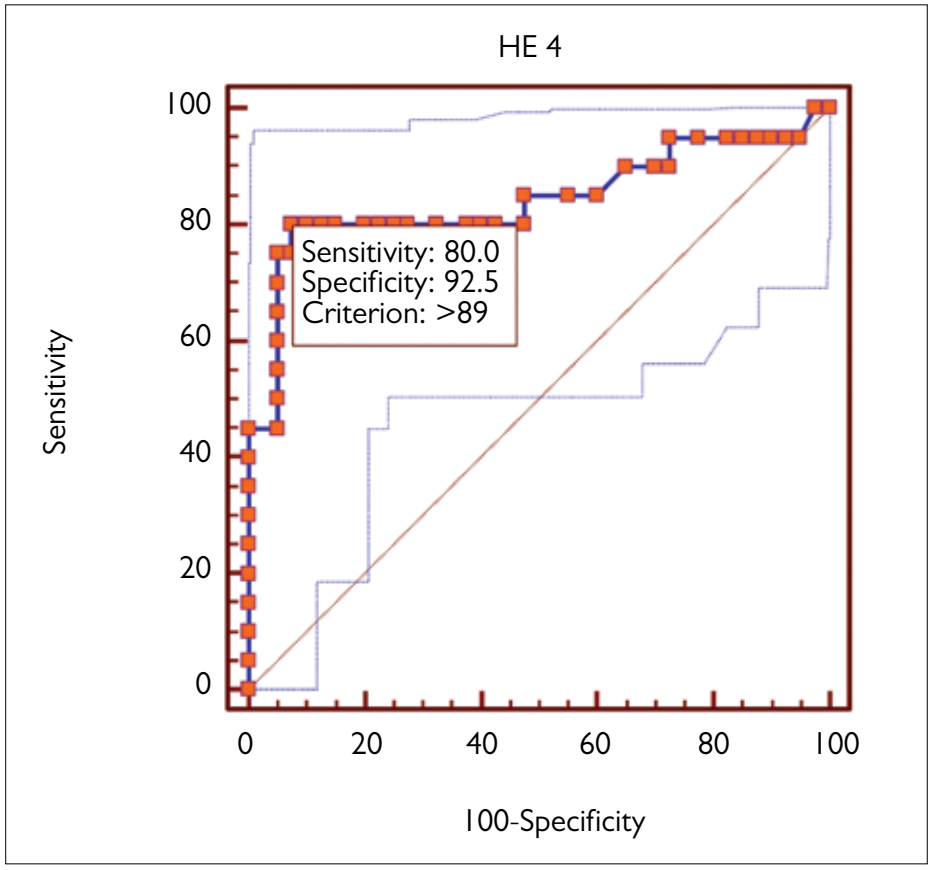

Figure 2. ROC analysis of HE-4 levels between over-cancer patients and controls.

Area under the ROC curve (AUC)				
AUC	0.84			
95% confidence intervalb (CI)	0.72–0.92			
P	<0.0001			
Criterion	Sensitivity	95% CI	Specificity	95%CI
>89	80.00	56.3–94.3	92.50	79.6–98.4
ROC: receiver-operating characteristic				

Table 2. Evaluation of sensitivities of 95% confidence interval of tumor markers in patients with over and endometrium cancer and healthy control group

	CA 125 (U/mL)		HE4 (pmol/L)		CA 125 + HE4
	AUC-ROC (%95 CI)	Sensitivity (%)	AUC-ROC (%95 CI)	Sensitivity (%)	Sensitivity (%)
Over Ca	0.83 (0.71–0.92)	80.0	0.84 (0.72–0.92)	80.0	95.0
Endometrium Ca	0.60 (0.47–0.72)	76.9	0.63 (0.51–0.75)	57.7	88.5

Table 3. Median values of CA 125 and HE-4 for endometrial cancer patients

Group		n	Mean	Std. Deviation	p
CA 125	Endometrium Ca	26	56.2	68.8	0.07
	Control	40	30.0	15.5	
HE4	Endometrium Ca	26	84.8	45.6	0.03
	Control	40	61.2	31.4	

metrial cancer patients and healthy controls was 0.59 (95% GA: 0.47–0.71; p=0.18). According to the ROC analysis performed for the distinctive diagnosis of the endometrial cancer patients and healthy controls, the sensitivity of CA 125 was found as 76.9% (95% GA: 56.4–91)and the specificity as 45% (95% GA: 29.3–61.5). A statistically significant relation was not found between them (p=0.18) (Figure 3).

The AUC for HE-4 in ROC analysis performed for the distinctive diagnosis of endometrial cancer patients and healthy controls was 0.63 (95% GA: 0.50–0.75; p=0.08).

According to the ROC analysis performed for the distinctive diagnosis of the endometrial cancer patients and healthy controls, the sensitivity of HE-4 in the 95% confidence interval was 57.7% (95% GA: 36.9–76.6) and the specificity was 77.5% (95% GA: 61.5–89.2). A statistically significant relation was found between them (p=0.08) (Figure 4).

These results were obtained when the cut-off values were taken as HE-4 > 63 pmol/L and CA 125 > 25.0 U/mL according to the study population for endometrial cancer patients. When the combined and single use of these two markers are compared, the sensitivity increases (88.5%) but the specificity decreases (30%) (Table 4).

Discussion

The most effective method for curing cancer is early diagnosis [8]. The major issue in ovarian cancer is that the disease is generally diagnosed in the advanced stages. Overall, only 19% of ovarian cancer is diagnosed in the early stages due to the lack of overt symptoms [1]. The 5 years living percentage in case of endometrial cancers is 95%, if the cancer is diagnosed in the local stage; in case of remote metastasis, it is 23% [9]. Thus, it is necessary to have biomarkers with sufficient sensitivity and specificity, which are both economic and non-invasive and may be used for the diagnosis of either ovarian or endometrial cancer [10]. Compared with normal cells, tumor markers are biochemicals that are excessively secreted by cancerous cells by activating their genes [11]. The only acceptable serum marker currently used for ovarian cancer is CA 125 [12]. Gynecologic oncologists have stated that this marker has decreased sensitivity as it delays the diagnosis rather than speeding it up because it attains normal values during the early stage or in the nonserous ovarian cancer subtypes [13]. In their study, Zacharakis et al. [2] recorded blood values and ultrasonographic findings of 66 borderline and 99 stage I epithelial ovarian cancer patients to measure the efficiency of CA 125. They indicated that the possibility of epithelial ovarian cancer increases 3 times in women with CA 125>100 IU/mL

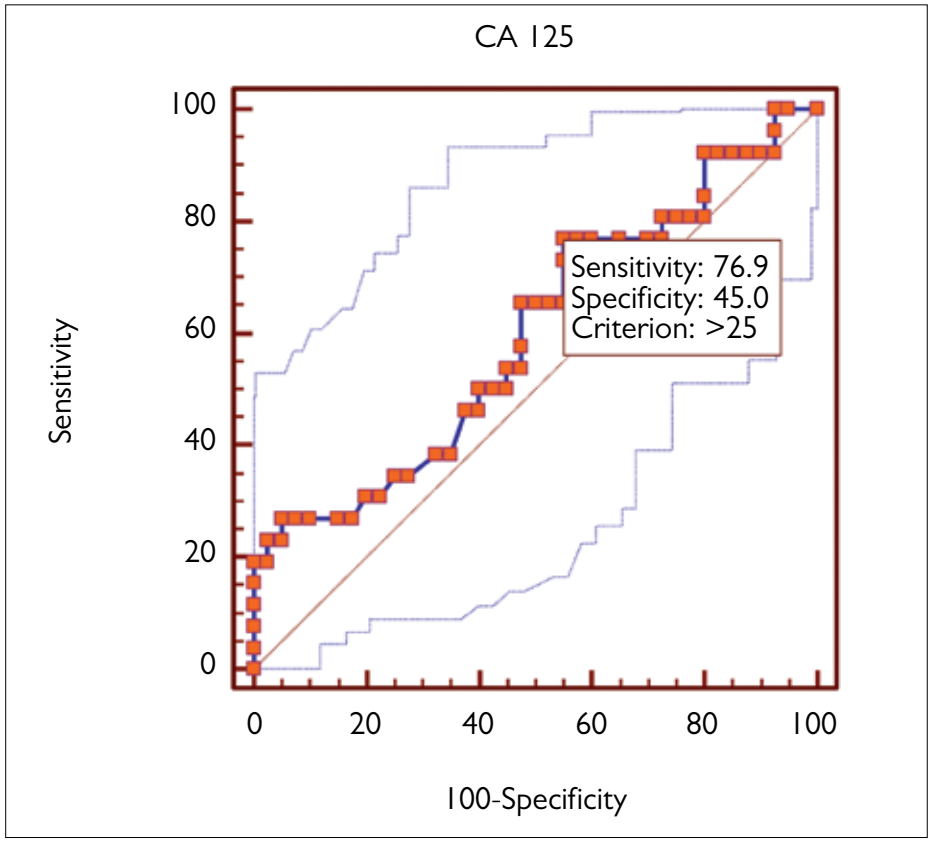

Figure 3. ROC analysis of CA 125 levels between endometrium cancer patients and Controls
Area under the ROC curve (AUC).

Area under the ROC curve (AUC)				
AUC			0.599038	
95% confidence intervalb			0.471053–0.717837	
p (Area=0.5)			0.1780	
Criterion	Sensitivity	95% CI	Specificity	95% CI
>25	76.92	56.4–91.0	45.00	29.3–61.5

ROC: receiver-operating characteristic

Table 4. Median values when CA 125 and HE4 are used together for the diagnosis of endometrial cancer

			Group		
			Endometrium Ca	Control	
CA 125 + HE4	Negative	n	3	12	15
		%	11.5	30.0	22.7
	Positive	n	23	28	51
		%	88.5	70.0	77.3
		n	26	40	66
		%	100.0	100.0	100.0

and 4.25 times in cases with large solid masses detected during imaging (≥20% of the tumor had a solid component) [2].

Mury et al. [14] included 231 ovarian cancer patients in their study and determined that preoperative CA 125 levels were higher at 67% in stage I–II patients and at 96% in stage III–IV patients. They also determined a significant decrease in postoperative CA 125 levels in both stage I–II (p=0.001) and stage III–IV patient (p<0.0001) cohort (14). Both studies emphasize the significance of high serum CA 125 levels for early diagnosis, which is one of the major lacks in terms of the prognosis of ovarian cancer. In our study, we found statistically significant differences between early and advanced stage CA 125, which was in accordance with the literature.

As false positive from benign patients cannot be easily eliminated with imaging methods, scanning based on the height of CA 125 requires several unnecessary surgical interventions. Thus, new markers that can be used in combination with or as a substitute of CA 125 with high sensitivity and specificity are needed [12]. There are plenty of unpublished papers that indicate that HE-4 is not secreted from normal ovarian tissue but is excessively secreted in ovarian cancer tissue [15]. In the efficiency study of HE-4 AND CA 125, Havrrilesky et al. [16] found HE-4 to be the marker with the highest sensitivity among all other markers used for both early and advanced stage ovarian cancer diagnosis without taking into consideration its cutoff value. Wu et al. [15] in the meta analysis of 9 studies with 1087 patients in which they looked at the diagnostic value of serum HE-4 of the gynecologic patients, indicated that for the diagnosis of ovarian cancer, HE-4 has a sensitivity of 83% and a specificity of 90%. They also reported that HE-4 is a serum marker which may be used for an efficient preoperative test and cancer scanning to diagnose the pelvic mass as benign or malign [15]. Steffensen et al. [17] studied the pre-chemotherapy prognostic significance of serum CA 125 and HE-4 in 139 newly diagnosed ovarian cancer patients. They found both HE-4 and CA 125 levels to be higher in FIGO stage III–IV patients and in patients with residual tumors. Based on this study, they reported that serum HE-4 may be used in the diagnosis of epithelial ovarian cancers and also as an independent prognostic factor [17]. Hellström et al. [12] studied the usability of HE-4 as a serum marker for ovarian cancer, and in their study, wherein they compared 37 patients with ovarian cancer, 19 benign ovarian neoplasm patients and 65 healthy controls, they suggested that the biomarker HE-4 is potentially more efficient than CA 125 in the distinction of both localized and advanced stage ovarian cancer patients from healthy controls.

In our study, we found that HE-4 levels of ovarian cancer patients are significantly higher, and the sensitivity and specificity are also higher in accordance with the literature. Although a clear physiologic function of HE-4 is unknown, in terms of early diagnosis, it seems to be more effective than CA 125, which may also increase in benign tumors.

Moore et al. [18] studied different biomarkers, mainly HE-4, to increase the efficiency of CA 125 in the diagnosis of ovarian cancer, in 233 patients with adenexial mass (67 patients with invasive epithelial cancer and 166 patients with benign ovarian neoplasm). They reported that

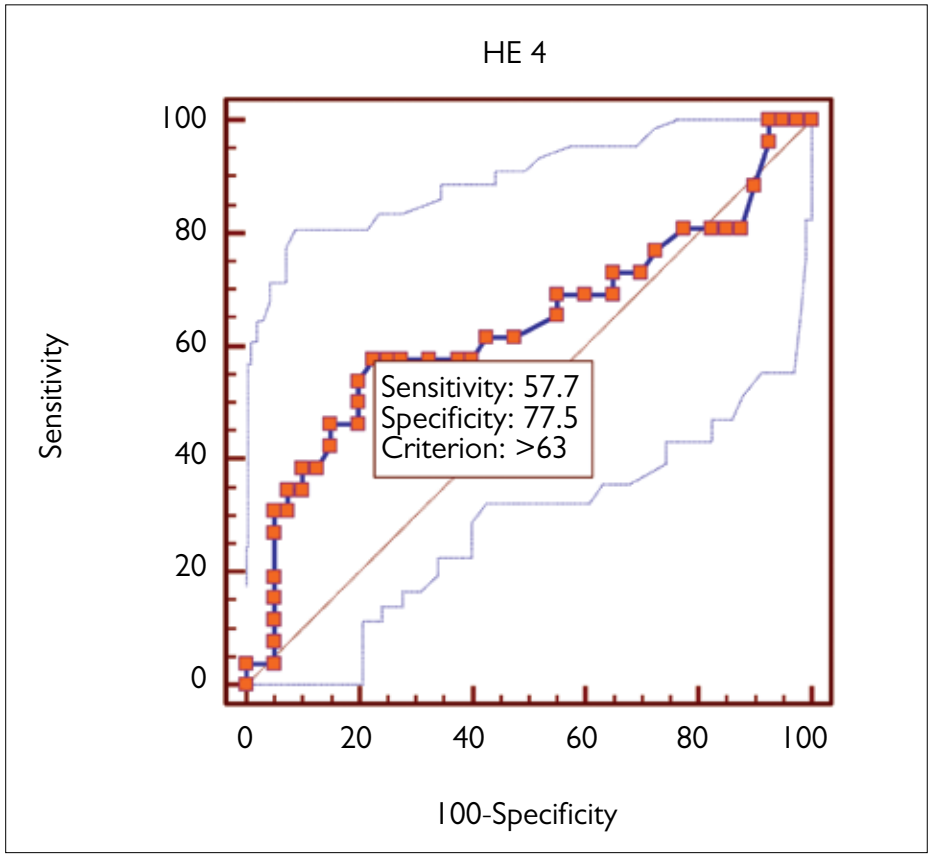

Figure 4. ROC analysis of HE-4 levels between endometrium cancer patients and controls

Area under the ROC curve (AUC)				
AUC			0.633173	
95% confidence interval[b]			0.505491–0.748488	
p (Area=0.5)			0.0814	
Criterion	Sensitivity	95%CI	Specificity	95% CI
>63	57.69	36.9–76.6	77.50	61.5–89.2

ROC: receiver-operating characteristic

HE-4 is the most sensitive marker as a simple marker with a specificity of 95% and that the combination of CA 125 with HE-4 had the highest sensitivity compared with all other single or combined markers.

Huhtinen et al. [19], in their study in which they compared 14 ovarian cancer patients and 69 ovarian endometrial cancer patients with 66 healthy controls, found that in terms of distinction of ovarian cancer patients from healthy controls, the combination of CA 125 with HE-4 increased the sensitivity and specificity. Escuerdo et al. [20], in their study in which they included 10 healthy controls, 292 benign gynecologic patients, and 127 ovarian cancer patients, indicated that the HE-4's diagnostic specificity is higher than that of CA 125 and the combination of CA 125 with HE-4 resulted in an increase in diagnostic rate of all stages and histological types of ovarian cancer. Zheng et al. [21], in their study in which they included 131 ovarian cancer patients and 125 patients with benign pelvic diseases, found the average CA 125 and HE-4 levels to be higher in patients with epithelial ovarian cancer than in those with benign diseases. They indicated that the combination of HE-4 and CA 125 had more significant results than CA 125 or HE-4 alone [21].

CA 125, which is a common tumor marker for the ovarian cancer as indicated in the above mentioned studies of Moore, Huhtinen, Escudero and Zheng, may show increased levels in cases of benign diseases, and not only in malignant cases. Although the physiological function of HE-4 is not clearly understood, it seems to be more efficient because it is only secreted from cancerous tissues and thus does not cause false positives in benign cases. In our study, we found that HE-4 is more sensitive in the distinction of malignant patients from healthy controls and that their combined used is more efficient than the single use of any of them, in accordance with the literature.

Endometrial cancer is the most frequent gynecologic malignancy that occurs in developed countries [22]. Currently, recurring endometrial cancers are in the advanced stage, and they are diagnosed with imaging techniques due to the presence of clinical symptoms. It has been reported that CA 125 may be increased in only 10%–20% of early stage endometrial cancer patients and 25% of recurrent asymptomatic patients [1].

There are no current serologic or biochemical markers in clinical use that may contribute to early diagnosis of endometrial cancer. The most common tumor marker used for the diagnosis of pelvic malignancy is CA 125. However, the literature includes some controversial findings regarding the studies on the prognostic significance of CA 125 as a tumor marker to evaluate the prevalence and therapeutic response of the disease. While some of the reports indicate that the increased preoperative CA 125 levels are an independent prognostic factor for malign surveys, some others indicated the lack of correlation between CA 125 levels and prevalence of the disease [23]. In the multi-centered study of Kim et al. [24] which included 413 patients and in which they looked into the significance of preoperative CA 125 for endometrial cancer, they indicated it will not contribute to the selection of high preoperative risk patients or will not ensure additional contributions to the selection of intermediate to high risk patients who may need adjuvant radiotherapy.

In our study, we found no differences between serum CA 125 levels of endometrial cancer patients and healthy controls, in accordance with the literature, but we found HE-4 levels of cancer patients to be significantly higher than those of healthy controls. However, the increase was not consistent with that of the prevalence of the disease.

In their study, Alcazer JL et al. [25] evaluated the relationship between serum CA 125 levels and myometrial invasion depth in 50 endometrial cancer patients and found the CA 125 levels to be higher in patients with deep invasion. Choi et al. [26] reported the preoperative CA 125 level to be significantly associated with deep myometrial invasion in 42 endometrial cancer patients. Hong Chung et al. [27] also indicated, in their study in which they included 92 endometrial cancer patients, that the preoperative serum CA 125 levels are correlated with the increase from the depth of the myometrial invasion. In our study, we found no statistical relation between preoperative CA 125 and HE-4 levels of patients

and the grade of the depth of the myometrial invasion detected during the MR imaging.

New markers which may substitute CA 125 or may increase predictivity when used in combination with this marker to support the early diagnosis of endometrial cancer were researched.

Bignotti et al. [28], in their study in which they included 138 endometrial cancer patients and 76 healthy controls, indicated that HE-4 is a suitable and sensitive serum marker for early diagnosis and when compared with CA 125, it has a better diagnostic performance. Moore et al. [29], in their study in which they included 171 endometrial cancer patients and 156 healthy postmenopausal women, indicated that CA 125 and HE-4 levels had a significant increase in endometrial cancer patients. They reported HE-4 to be the most reliable marker for both early and advanced stage endometrial cancer. It was also found that the addition of CA 125 to HE-4 increases the sensitivity compared with HE-4 alone [29].

In our study, similar to Bignotti's study, we found a significant increase in HE-4 level in endometrial cancer patients. However, contrary to Moore's study, we found no relation between HE-4 level and the stage and extrauterine invasion, and we determined that in terms of diagnosis, the combined use of CA 125 and HE-4 increases the sensitivity and specificity more than the singly use of either of the markers.

The presence of lymphovascular area invasion (LVAI) is the independent prognostic factor for all endometrial cancer types in terms of occurrence and mortality. While the 5-year survival rate of non LVAI patients is 83%, this rate is only 64.5% in LVAI patients [30]. Chen et al. [31] reported preoperative CA 125 level of 120 endometrial cancer patients to be correlated with the presence of lymphovascular retention.

In our study, a relation was found between CA 125 levels and lymphovascular area invasion. Certainly, the lack of relation between the disease itself and the level of CA 125 and the only significance in terms of LVAI seems controversial. However, our priority was the presence of the disease and relation with the CA 125 and we did not find this relation significant. We had a low number of patients, but maybe if we perform the same study with the higher scale study group, we will be able to eliminate this controversy.

In conclusion, we found HE-4 to be a serum tumor marker that may be used for scanning purposes for ovarian and endometrial cancers, which require urgently new technologies for early stage diagnosis. The test can be used for the diagnosis of both types of cancer and has a high specificity, which can clinically prevent unnecessary surgeries on multiple patients and may ensure early diagnosis. Thus, the clinical use of the combination of CA 125 and HE-4 will be more efficient than using only one of them.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics board of our hospital.

Informed Consent: Informed consent was obtained from all patient.

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