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The Importance of HE4 and CA 125 in Overall Survival and Recurrence-free Survival of Endometrial Cancer

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Abstract

Objectives: The present study aimed to assess the significance of human epididymis protein 4 (HE4) and cancer antigen 125 (CA 125) in the overall survival (OS) and the recurrence survival of endometrial cancer.

Materials and Methods: The study was conducted on 99 patients with a mean age of 53±64. The patients were all cases with a definitive diagnosis of endometrial cancer. With regard to the histology and the surface measurement, the HE4 and CA 125 were both confirmed within 1 to 2 week(s) prior to hysterectomy by implementing the standard-procedure treatment of extra facial total hysterectomy and bilateral salpingo-oophorectomy with selective pelvic and para-aortic node dissection. Then, risk-assessment for possible recurrence (Mayo criteria) was carried out as well. Patients with the variables of HE4 and CA 125 in the upper third (66th) percentiles were grouped as high-risk. Finally, the data were analyzed using SPPS 23, and P <0.05 was considered statistically significant.

Results: The mean (SE) of OS among patients with the serum CA 125 of ≤22 kU/L and higher 22 kU/L was 47.97 (±2.58) and 41.78 (3.75) months ($P=0.466$). In addition, the mean (SE) of OS in patients with the serum HE4 level of ≤ 98 ρmol/L and >98 ρmol/L was 50.14 (2.06) and 38.54 (3.74), respectively. The log-rank test revealed a substantial difference between low- and high-risk groups by HE4 ($\chi^2=4.98$, $P=0.025$). Accordingly, there is no significant difference between recurrence-free survival (RFS) with CA 125 ($P=0.264$) and HE4 ($P=0.114$), respectively.

Conclusions: In general, the serum HE4 level is a significant independent prognostic factor for OS in endometrial cancer and is useful in survival studies.

Keywords: Endometrial carcinoma, CA 125 antigen, HE4 protein, Overall survival, Recurrence-free survival

Introduction

Endometrial cancer is the most common type of malignant complication in women so that it ranks fourth on the list of cancer malignancies in the world. In developing countries, the occurrence of such cancer is reported as 2% to 3% among women (1,2). The ever-increasing rate of obesity in women has led to an increase in the occurrence of such cancer. Nevertheless, previous reports suggest that fortunately most women with endometrial cancer can receive prognosis at the early stages of development and have a 5-year survival (83%) rate (1,3).

The primary process central to the development of endometrial cancer is the overgrowth of the endometrium in response to excess unopposed estrogen due to older age, nulliparity, late menopause, early menarche, history of infertility, obesity, and some drugs (4).

The most significant factors in an endometrial cancer prognosis are the International Federation of Gynecology Obstetrics (FIGO) stage, type of the tissue, tumor grade, and tumor infiltration depth in the myometrium, lymphatic metastasis, lymphovascular space invasion, and the patient's age upon diagnosis (5,6). There have been contradicting results regarding the value of the cancer antigen prognosis of (CA 125) 125 as a means of diagnosing endometrial cancer. However, previous evidence shows that the levels of CA 125 prior to surgical operation cannot be relied upon as an independent prognosis for survival (7). Thus, CA 125 cannot be recognized as a dependable marker of endometrial cancer (6, 8). There is a potential value in human epididymis protein 4 (HE4) as an indicator of endometrial cancer (8, 9). The results of the study by Stiekema et al revealed that HE4 serum concentration prior to surgery can be associated with some of the factors of prognosis in endometrial cancer and survival. Similarly, the mentioned concentration in the serum of HE4 can pertain to the groups of high-risk endometrial cancer. Furthermore, it was suggested that the HE4 serum can be of significance in the magnetic resonance imaging

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Key Messages

- There is a potential value in human epididymis protein4 (HE4) as an indicator of endometrial cancer.
- The mentioned concentration in the serum of HE4 can pertain to the groups of high-risk endometrial cancer.

scan and clinicopathological procedures for patients who are at the risk of disease recurrence and must undergo aggressive treatment (6).

In this respect, the present study sought to evaluate the correlation of serum biomarkers HE4 and CA 125 with prognostic variables, overall survival (OS), and recurrence-free survival (RFS) in endometrial cancer. Thus, these kinds of biomarkers can be used in addition to clinical parameters for better stratification in high- or low-risk endometrial cancer that may be helpful in the planning of individual treatment.

Materials and Methods

The present cross-sectional study was performed between 2015 and 2019. A total of 99 25-70-year-old patients, who were histologically confirmed to have endometrial cancer, were referred to the Imam Khomeini Medical Education Center, Tehran, Iran for treatment.

The inclusion criteria were a definitive diagnosis of the endometrial cancer pathology (types I and II) employing biopsy pipelle, dilation, and curettage. The standard-procedure medical operations included a facial total hysterectomy and bilateral salpingo-oophorectomy with selective pelvic and para-aortic node dissection according to risk for recurrence.

On the other hand, the exclusion criteria included renal failure, cardiovascular disease, liver disease, synchronous malignant disease, and smoking habits. The histological categorization was based on the guidelines provided by the World Health Organization, and the staging classification was based on the updated FIGO staging systems (3,10).

Serum CA 125 and HE4 levels were evaluated in all participants one to two week(s) prior to surgery in the same laboratory using the electrochemiluminescence immunoassay (Electrogenerated Chemiluminescence) by the Cobas analyzer (ARCHITECHT CA 125 II and HE4 assay, Abbott GmbH, Wiesbaden, Germany) according to (11).

The patients' final follow-up was carried out on November 30, 2019. For the purpose of survival rate assessment, two endpoints of recurrence and death were devised to calculate RFS and OS. The RFS is described as the time period between the surgical operation and the recurrence of the disease, and the OS is the time period between the surgical operation and the date of death.

The 66th percentile was selected for HE4 and CA 125 as the cut-off value because it was the best way to isolate patients with a good and poor prognosis (12). The serum concentrations of HE4 and CA 125 were divided into upper and lower groups of the third percentile (66th). Patients with biomarkers above the third percentile were considered as the high-risk group.

Statistical Analysis

According to the Kaplan-Meier method, this cut-off (66th percentile) value was 98 ρmol/L and 22 kU/L for HE4 and CA 125, respectively. Man-Whitney and Kruskal-Wallis tests were employed for the analysis of serum biomarker levels and their relation to clinicopathological parameters. Then, univariate survival analysis was executed using the Kaplan-Meier method and Log-rank statistics to compare survival plots. Data analysis was performed using the SPSS software, version 23, and a score value of $P > 0.05$ yielded a significant result.

Results

A total of 99 cases with endometrial cancer (types I and II) were entered into the study during 2015-2019. Among them, 7 cases were patients with disease recurrence and 15 cases died (Table 1). The mean age of the patients was 53.64 (SD: 10.04).

In general, 89 patients (89.9%) were diagnosed with the endometroid type (type I) and non-endometroid (type II) including papillary serous, clear cell, and carcinosarcoma was detected in 10 patients (10.1%).

Table 2 presents the mean serum levels of CA 125 and HE4 and the correlation between these tumor markers with clinicopathological variables.

With a cut-off value of 22 kU/L for CA 125 (12), for patients with CA 125 levels below the 66th percentile, the OS mean was 47.97 months (Standard error [SE] = 2.25 months). In addition, for patients with CA 125 levels above the 66th percentile, the OS mean was 41.78 months (SE of 3.75 months) (Figure 1).

Table 1. Patients' Characteristics and Clinicopathological Parameters

Variable	Variable	No. (%)
Stage	IA	47 (47.5)
	IB	26 (26.35)
	II	13 (13.1)
	III	12 (12.1)
	IV	1 (1)
Grade	G1	39 (39.4)
	G2	33 (33.3)
	G3	26 (26.3)
Histology	EEC	89 (89.9)
	Non-EEC	10 (10.1)
Myometrial invasion	Below 50%	51(51.5)
	Above 50%	48 (48.5)
LVSI	Positive	23 (23.2)
	Negative	76 (76.8)
LNP	Positive	10 (10.1)
	Negative	89 (89.9)

Note. EEC: Endocervical curettage; LVSI: Lymphovascular Space Invasion; LNP: Lymph node positive.

Table 2. Serum CA 125 and HE4 Values According to Clinicopathological Parameters

		Mean ± SD	Median (IQR)	*P*-value
CA 125				
Histology	EEC	27.98± 56.98	15 (15)	0.001
	Non-EEC	153.70 ±239.13	49 (233.50)	
Stage	IA	23.31±24.73	14 (15)	0.653
	IB	51.61±147.32	16 (19.75)	
	II	20.53±13.02	15 (23.50)	
	III	109.41±162.22	40 (173.75)	
Grade	G1	22.51±24.15	14 (16)	0.201
	G2	25.51±24.98	17 (20)	
	G3	80.26±179.62	16 (31.75)	
Myometrial invasion	Below 50%	23.62±24.61	14 (15)	0.287
	Above 50%	58.81±136.95	17 (27.25)	
LVSI	Positive	73.69±122.93	27 (56)	0.046
	Negative	30.69±87.74	14 (13)	
LNP	Positive	50.50±98.44	12.50 (34.25)	0.727
	Negative	50.50±98.52	15 (20.50)	
HE4				
Histology	EEC	104.05 ±122.30	64 (54.5)	0.001
	Non-EEC	277.90 ±193.97	253.5 (333)	
Stage	IA	78.21±61.34	59 (32)	0.01
	IB	109.26 ± 85.88	83 (59)	
	II	205.23 ±270.01	106 (175.50)	
	III	233.83±179.50	198 (263.50)	
Grade	G1	112.02 ±172.87	55 (35)	0.007
	G2	96.72 ±59.08	81 (62)	
	G3	158.65±150.39	99 (148.50)	
Myometrial invasion	Below 50%	84.54 ±76.34	54 (32)	0.0001
	Above 50%	161.00±178.08	96.50 (119.25)	
LVSI	Positive	165.22 ±148.55	106 (135)	0.002
	Negative	108.42±135.84	61 (54.75)	
LNP	Positive	183.90±195.10	76 (221.75)	0.212
	Negative	114.61± 132.32	68 (58.50)	

Note. CA 125: Cancer Antigen 125; HE4: Human epididymis protein 4; SD: Standard deviation; IQR: Interquartile range; EEC: Endocervical curettage; LVSI: Lymphovascular Space Invasion; LNP: Lymph node positive.

The log-rank ($\chi^2=0.53$) estimate of the OS mean for both groups (low- and high-risk) showed no significant differences ($P=0.466$). The mean-RFS was 42.00 (SE, 3.658 months) and 49.567 (SE, 2.668 months) months for patients with CA 125 levels above the 66th percentile (high-risk group) and those with CA 125 levels below the 66th percentile (low-risk group), respectively. Therefore, the log-rank test ($\chi^2=1.249$) demonstrated no significant difference in RFS in both high- and low-risk groups ($P=0.264$) (Figure 2).

With a cut-off value of 98 ρmol/L for HE4 (12), the mean OS was 50.138 (SE, 2.06 months) and 38.535 (SE, 3.74 months) months for low-risk (below the 66th percentile) and high-risk (above the 66th percentile) patients, respectively.

The log-rank test ($\chi^2=4.98$) represented a significant difference in OS in both high- and low-risk groups ($P=0.025$) and there was a difference of 11.603 months in the mean OS in the two groups.

The mean-RFS for patients with HE4 levels below the 66th percentile (low-risk group) and high-risk patients (above the 66th percentile) was 50.59 (SE, 1.89 months) and 41.03 (SE, 3.55 months) months, respectively. Finally, the log-rank test ($\chi^2=2.50$) showed no significant difference in RFS in both high- and low-risk groups ($P=0.114$).

Discussion

Endometrial cancer is considered as a form of malignancy with a favorable prognosis and can be diagnosed in the first stage in the 5-year OS of 83%. Notwithstanding, there is no accurate serum biomarker for predicting and early detecting tumor recurrence.

Information on the high levels of HE4 and CA 125 in endothelial cancer is heterogeneous. The biomarker CA 125, which is used to diagnose these cases, has less sensitivity and characteristics (13).

Several different studies suggested that the HE4 biomarker is potentially more reliable in diagnosis and prognosis processes (9-14). Abbink et al revealed that high levels of HE4 are an independent factor in lower disease-free survival and OS (15). Furthermore, Moore et al concluded that HE4 can detect possible recurrences with significant precision (16). In another study, Sebastianell et al reported that the

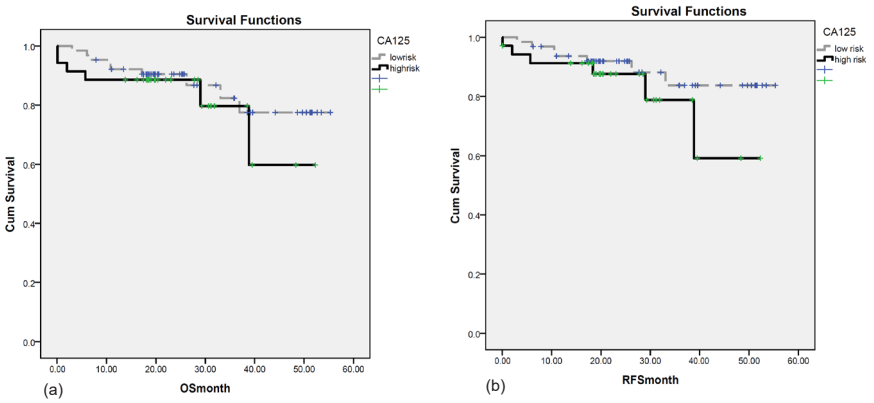

Figure 1. Kaplan-Meier Curves of OS (a) and RFS (b) According to Serum CA 125 Values (based on 66th percentile). *Note*. OS: Overall survival; RFS: Recurrence-free survival.

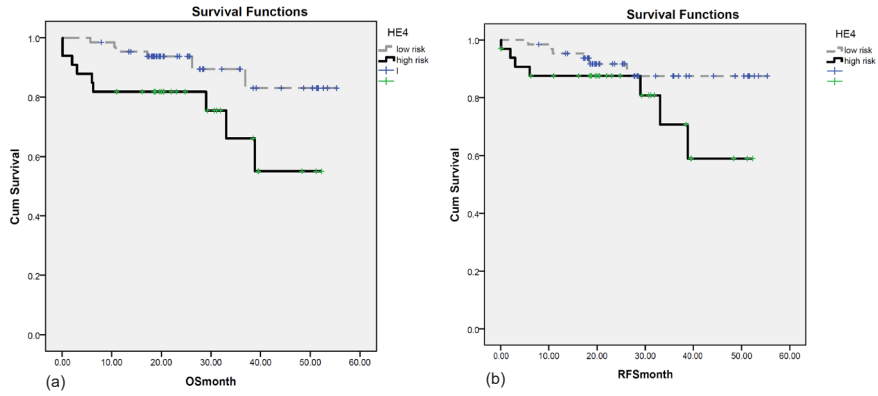

Figure 2. Kaplan-Meier Curves of OS (a) and RFS (b) According to Serum HE4 Values (based on 66th percentile). *Note*. OS: Overall survival; RFS: Recurrence-free survival.

levels of CA 125 in pre-operation stages can be measured in progressive endometrial cancer (17). Additionally, Stiekema et al found that the HE4 serum level can act as a strong independent factor for RES and OS (6). Likewise, Mutz-Dehbalaie et al reported that HE4 in combination with CA 125 can perform as an independent marker for the prognosis of endometrial cancer (8).

In this study, with a cut-off value of 98 ρmol/L for HE4 (12), a significant difference was found in OS in both high- and low-risk patients. However, there was no correlation between HE4 levels and RFS. Furthermore, no significant correlation was observed between CA 125 (with a cut-off value of 22 kU/L) and both OS and RFS. The results of our study are in agreement with the result of Abbink et al and other studies regarding the correlation of OS with HE4 levels (6,8,14,15).

Contrary to other studies, there is no considerable correlation between CA 125 levels and both OS and RFS, which may be due to small amounts of the non-endometroid group in our study.

Based on the findings of our study, 74% of patients were in stage-I and the serum CA 125 level increased advanced endometrial cancer (17), thus this contrast with other studies (8,17) about CA 125 is persuadable.

Furthermore, despite other studies (6,14,15,18), no exact correlation was found between RFS and both CA 125 and HE4 in our study due to the small sample size. In this study, survival analysis was performed based on cut-off values that were obtained from the 66th percentile for CA 125 and HE4 (12), and these cut-off values were different from those of other studies.

Likewise, the results of several other studies (3,19) confirmed the predictive relationship between molecular subtypes. However, the 'histomolecular' approach has not so far been used in clinical trials.

There are on-going investigations regarding the combination of molecular characteristics. Further, the pathological categorization may lead to a change or adjustment of treatment methods and produce an acceptable approximation of possible recurrence and survival while decreasing over and under treatment. Nonetheless, there are potential challenges regarding patient management in medical centers that lack the infrastructure for the implementation of such methods (3,19).

Today, the overexpression of HE4 in endometrial cancer has exponentially grown, and it has been in close relation to the degree of aggressiveness and progressiveness of

such cancer. Thus, using biomarkers for treatment and supervision can be desirable in low-income countries that stand in a need of new histomolecular findings (20, 21) In this study, we had data size limitations due to the use of one referral center.

Conclusions

Serum HE4 levels is a significant independent prognostic factor for OS. Accordingly, the preoperative evaluation of this biomarker is helpful for the prognostic factor and is useful in survival studies, but conducting large investigations is required in this area.

Availability of Data and Materials

The obtained data in the course of the present study are off-limits to the public as per the guidelines of the Ethics Committee in the Medical Sciences University of Tehran. Nevertheless, they are available from the corresponding author on reasonable request.

Authors' Contribution

MMG, SGDM, AM and SA contributed to the conception and design of the study and literature review. SA, NZ, SS and LS collected all data and contributed to data interpretation and manuscript drafting. All authors approved the final manuscript.

Conflict of Interests

Authors declare that they have no conflict of interests.

Ethical Issues

The Ethics Committee of Tehran University Medical Sciences approved the study (ethics code: IR.TUMS.IKHC.REC.1398.074) and patients signed informed consent for the analysis and publication of their data.

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