

HE4 in endometrioid and non- endometrioid subtype of endometrial cancer does not mean the same

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Summary

Objective: To study the association between the preoperative value of serum HE4 marker and poor histological prognostic factors depending on the subtype of endometrial cancer (EC): endometrioid and non-endometrioid tumors. **Methods:** Prospective and multicenter cohort study including patients with EC in Miguel Servet University Hospital of Zaragoza (Spain) and Hospital Clínico San Carlos of Madrid (Spain) from January 2017 to March 2020. Preoperative serum levels of HE4 were analyzed by clinical and pathological characteristics. **Results:** Overall, 190 patients were included. Of them, 158 were subtype I of EC and 32 were subtype II tumors. In endometrioid EC, a statistically significant association was found between the preoperative HE4 value and tumor size ($p < 0.001$), deep myometrial invasion ($p = 0.001$), lymphovascular space invasion (LVSI) ($p = 0.002$), cervical ($p = 0.001$), adnexal ($p = 0.023$), isthmus ($p < 0.001$) and parametrial involvement ($p = 0.012$), lymph node metastasis ($p = 0.025$) and FIGO stage ($p < 0.001$). On the contrary, no histological factors showed statistical association except LVSI ($p = 0.025$) in the non-endometrioid subtype. **Conclusions:** The preoperative value of HE4 is related differently with several established prognostic factors for EC according to the histological type of tumor. These results could be relevant in order to standardize a prognostic value of HE4 in EC.

Key words: HE4; Endometrioid endometrial cancer; Serous endometrial cancer; Clear cells endometrial cancer.

Introduction

Endometrial cancer (EC) is the most common gynecological malignancy in developed countries and its incidence is increasing year-by-year [1].

The endometrioid subtype, also known as subtype I, is the most common and is the best prognostic subtype, as it is usually diagnosed at an early stage, low grade and with superficial myometrial invasion. The non-endometrioid subtype, or subtype II, includes especially uterine serous cancer (USC) and clear-cell carcinoma (CCC). These subtypes show a more aggressive development and they are associated with a higher risk of recurrence, and despite its low prevalence, they account for the majority of deaths related to uterine cancer [2, 3].

HE4 is a recent application tumor marker, described by first time in 1991 by Kirchhoff *et al.* whose utility has been demonstrated in the diagnosis and monitoring of ovarian cancer with the Risk of Ovarian Malignancy Algorithm (ROMA) [4]. However, there is increasing evidence of its possible application in EC. Currently, there is no consensus on the possible application of HE4 as a preoperative marker for EC. However, there seems to be a correlation between EC prognostic factors and preoperative HE4 levels [5].

The aim of the present study is to explore if the HE4 marker is related to histological prognostic factors of EC by histologic subtype.

Methods

We conducted a prospective and multicenter study in a cohort of patients diagnosed of EC at two medical centers in Spain: "Hospital Universitario Miguel Servet" in Zaragoza and "Hospital Clínico San Carlos" in Madrid, from January 1st, 2017 to March 1st, 2020. In both Centers EC is managed following the same clinical guidelines and protocols.

In the period under review, 208 patients diagnosed and treated of EC had a preoperative determination in serum of HE4. Blood samples were collected within 2 weeks before planned surgery. Serum was stored at -80°C until analysis in routine clinical laboratory of both hospitals. This study used the serum HE4 electrochemiluminiscent kits Cobas e411 (Roche Diagnostics®). Women with pleural effusion, hepatic failure or renal insufficiency were excluded due to possible interference with HE4 values. Patients diagnosed with other histological subtypes, synchronous or metachronous tumors or who had received neoadjuvant treatments were also excluded.

In all cases, HE4 was assessed in serum preoperatively. All patients underwent hysterectomy and salpingoophorectomy. Pelvic, or pelvic and para-aortic lymphadenectomy (LDN) was performed following guidelines of the Spanish Society of Gynecology and Obstetrics and the European Society of Gynecological Oncology [6, 7]. LDN was performed in all subtype II cases.

We carried out two comparative groups based on the classic cancer classification: subtype I included endometrioid subtype and subtype II included USC and CCC. We studied the possible relationship of the preoperative HE4 value depending on this classification.

All postoperative specimens were studied by at least two pathologists specialized in oncological gynecology and when controversy existed, a third pathologist reviewed the surgical sample. Patients were classified according to histological FIGO grade in low-moderate grade (G1-G2) and high grade (G3), and according to FIGO stage in early stage (I and II) and advanced stage (III and IV). The histotype was reviewed by at least two gynecological pathologists using current World Health Organization criteria [8].

The present study was approved by the Research Ethics Committee in Aragón (CEICA), with the study reference code PI16/0252. All patients gave written informed consent. The study was conducted in accordance with applicable laws and regulations, including the ethical principles contained in the Declaration of Helsinki.

Statistical analysis

Data was collected in accordance to privacy policies. Statistics Process Social Sciences (SPSS) 22.0 for Windows (Copyright© Inc., 2013) was used for further statistical analysis.

For the descriptive analysis the categorical variables were expressed with their frequencies and percentages. The parametric distribution of the HE4 marker was studied with the Kolmogorov-Smirnov test. The variables that did not follow a normal distribution were expressed with the median and interquartile range (IQR) and those that present a normal distribution were expressed in mean and standard deviation (SD).

U Mann-Whitney test was used for the analysis of dichotomous qualitative variables, and Kruskal-Wallis test for non-dichotomous qualitative ones. In all statistical tests, $p < 0.05$ was considered as the reference value of significance.

Results

We included 190 patients with subtype I EC ($n = 158$) and subtype II tumors ($n = 32$). The mean age of women at diagnosis was 64.8 years (SD 10.4) for subtype I and 69.1 (SD 11.6) years for subtype II. The median of the preoperative HE4 marker variable was 72.7 pmol/L (IQR 68.6 pmol/L) and 85.1 pmol/L (IQR 60), respectively, with no statistical differences between the groups ($p = 0.340$). LDN was performed in 59 patients (62.7%) with endometrioid EC and 28 patients (87.5%) with USC or CCC. The reasons for not performing LDN in these cases were advanced age and coexistence of severe medical comorbidities that significantly increased the surgical risk. The demographic and histological characteristics depending on the subtype of EC are shown in Table 1.

We performed an analysis to study the relationship be-

tween HE4 preoperative value and the histological risks factors for EC. In endometrioid EC group, the preoperative value of HE4 marker was associated with all studied histological prognostic factors, finding a statistically significant association with all of them. However, in subtype II g, only lymphovascular space invasion (LVSI) was significantly associated with the preoperative HE4 value ($p = 0.025$). The rest of the studied histological factors did not show a statistically significant association with the preoperative HE4 value in this group. This data is shown in Table 2.

Discussion

In our sample, the preoperative value of HE4 in subtype I of EC was correlated with all studied histological prognostic factors: a higher HE4 marker value was associated with poor histological prognostic factors. However, in subtype II of EC, preoperative HE4 value only showed statistical association with LVSI. Thus, we think that the HE4 serum levels must be interpreted differently for endometrioid and non-endometrioid EC.

The classic dualistic classification proposed by Bokhman in 1983 is still in use today [9]. Following this classification, there are two different histological types of endometrial tumors, with different behavior and prognosis. Histological features are also different between them. Thus, type II tumors can have an aggressive behavior without being associated with other histological classic factors of poor prognosis. Conversely, this is not the case in subtype I, in which histological factors are usually correlated especially in well or moderately differentiated tumors [3, 10].

The significance of the HE4 marker in EC has been less studied than in other types of tumors such as ovarian cancer [4, 11-13]. There are few studies that analyze the relationship of serum HE4 marker with histological risk factors, and their results are heterogeneous. They do not usually take into account the differences in behavior of both tumors reported by the dualistic classification. To date, this is the first study comparing the significance of preoperative HE4 in EC based on the histological subtype.

Bignotti *et al.* studied the relationship between HE4 and the clinic-pathological features in 138 patients with EC and found out that HE4 serum levels were significantly associated with several variables of poor prognosis: myometrial invasion, LVSI, cervical and adnexal involvement, lymph node status and FIGO stage. There was no difference in HE4 value between the endometrioid ($n = 109$) and non-endometrioid subtype ($n = 29$) groups. The authors demonstrated for the first time that high HE4 preoperative levels may identify patients harboring a more aggressive EC phenotype [14]. One year later, Zanotti *et al.* reached a very similar conclusion, but only 15 cases of serous carcinoma and clear cells were included in their study [15]. None of them studied whether the association showed between HE4 and histological factors was different when the analysis was performed taking into account the histological EC subtype.

Table 1. — Demographic and histological features in endometrioid and non-endometrioid EC groups.

		Endometrioid n (%)	Non-endometrioid n (%)
Parity	Nulliparous	35 (22.2)	8 (25)
	< 3 birth	89 (56.3)	14 (43.7)
	≥ 3 births	34 (21.5)	10 (31.3)
Arterial hypertension		87 (55.1)	13 (40.6)
Diabetes Mellitus		33 (20.9)	5 (15.6)
Menopausal status		139 (88)	30 (93.8)
Obesity	BMI* < 25	63 (39.9)	12 (37.5)
	BMI* 25-40	77 (48.7)	20 (62.5)
	BMI* > 40	18 (11.4)	0
Tumor size	< 20 mm	55 (34.8)	10 (31.2)
	≥ 20 mm	103 (65.2)	22 (68.8)
Histological grade	High grade (G3)	23 (14.6)	32 (100)
	Low grade (G1-G2)	135 (85.4)	0
Myometrial invasion	No invasion	27 (17.1)	4 (12.5)
	Invasion < 50 %	82 (51.9)	14 (43.8)
	Invasion > 50%	49 (31.1)	14 (43.8)
Lymph-vascular space invasion	Presence	13 (8.2)	11 (34.4)
	Absence	145 (92)	21 (65.6)
Histological subtype	Endometrioid	158 (100)	0
	Serous	0	27 (84.4)
	Clear cell	0	5 (15.6)
FIGO stage	I-II	144 (91.1)	18 (56.3)
	III-IV	14 (8.9)	14 (43.7)
Lymphatic node involvement	Presence	8 (5.3)	10 (31.2)
	Absence	150 (94.7)	22 (68.8)
Uterine isthmus involvement	Presence	19 (12)	4 (12.5)
	Absence	139 (88)	28 (87.5)
Adnexal involvement	Presence	6 (3.8)	5 (15.6)
	Absence	152 (96.2)	27 (84.4)
Uterine cervical involvement	Presence	11 (7)	5 (15.6)
	Absence	147 (93)	27 (84.4)
Parametrial involvement	Presence	4 (2.5)	4 (12.5)
	Absence	154 (97.5)	28 (87.5)

*BMI (Body Mass Index).

Other subsequent studies have reviewed the correlation between HE4 and several histological prognostic factors [16-20]. One of the most important is the study by Wang *et al.* which included 258 patients. A correlation of the marker with histological factors of poor prognosis was observed again. However, in this notable study, the histological type of tumors was not reported [16]. Other studies included exclusively endometrioid tumors showing the prognostic significance of HE4 value in this group [17, 18].

In our study, there were no significant differences in the HE4 value based on the histological subtype. This result is consistent with other previous studies [14, 15, 19, 21] and implies that its preoperative absolute value is not an accurate tool to differentiate the histological type of the tumor. These do not negate our finding that the HE4 value must be interpreted differently between the two classic types of EC.

The correlation between preoperative HE4 levels and the FIGO stage has been studied in the literature. The majority of studies analyze the differences between early (I-II) and advanced (III-IV) stages, however, some authors make alternative comparisons [14, 16, 22]. Therefore, the results when analyzing the possible association between the HE4 marker and the stage are heterogeneous and difficult to compare.

Li *et al.* studied the risk factors of node metastasis from the clinicopathological characteristics and preoperative laboratory results of 393 patients surgically staged with EC [23]. The majority (84.2%) was subtype I of EC. Higher preoperative levels of serum HE4 (OR 4.25, 95% CI 1.65-10.94, $p = 0.003$), and non-endometrioid histology (OR 16.64, 95% CI 5.96-46.47, $p < 0.001$) were independent risks factors for pelvic lymphatic metastasis in EC. The au-

Table 2. — Statistical analysis of the relationship of HE4 marker with prognostic factors in endometrioid and non-endometrioid EC groups.

		Endometrioid HE4	<i>p</i> value	Non-endometrioid HE4	<i>p</i> value
		Median (IQR)*		Median (IQR)*	
Tumor size	< 20 mm	55.5 (35.6)	< 0.001	57.9 (55.6)	0.096
	≥ 20 mm	86.4 (80.6)		97.1 (96.9)	
Myometrial invasion	No invasion	45.3 (16)	< 0.001	81.6 (47.5)	0.508
	Invasion < 50 %	69 (50.9)		65.6 (56.8)	
	Invasion > 50%	105.3 (98.1)		95.3 (99.5)	
Lymph-vascular space invasion	Presence	152 (183.9)	0.002	115.4 (117.7)	0.025
	Absence	68.5 (57.3)		76.1 (42.6)	
FIGO stage	I-II	69 (57.5)	< 0.001	61.3 (54.1)	0.071
	III-IV	119.4 (253.4)		98 (325.2)	
Lymphatic node involvement	Presence	144.1 (296.3)	0.025	102.5 (76.3)	0.114
	Absence	70 (59.6)		75.1 (50.7)	
Uterine isthmus involvement	Presence	148.3 (240)	< 0.001	77 (50.5)	0.345
	Absence	68.5 (53.2)		130 (265.5)	
Adnexal involvement	Presence	105.9 (388.8)	0.023	88.1 (53.5)	0.749
	Absence	70.6 (60.8)		75.1 (203.4)	
Uterine cervical involvement	Presence	148.3 (287.7)	0.001	79.6 (50.6)	0.579
	Absence	69.5 (56.8)		150 (117.9)	
Parametrial involvement	Presence	210.6 (733.2)	0.012	77 (51)	0.305
	Absence	71.3 (62.6)		101.7 (243.2)	

*IQR: interquartile range.

thors proposed a cut-off point for all cases of EC (≥ 132 pmol/L) with a high sensitivity for the detection of lymphatic metastases. But no distinction was made based on the histological EC subtype, despite being independent factors in the statistical analysis. As we have shown in our study, the preoperative HE4 value does not have the same clinical significance in subtype I and II of EC. Therefore, we think that it might be more appropriate to propose a different cut-off point for each subtype.

LVSIs are considered one of the first steps of metastatic spread in EC, and it is an important prognostic factor of recurrence and survival [24]. In the last European consensus conference on EC, LVSIs were agreed to be an important risk factor that can be utilized to define new risk groups and guide adjuvant therapy use. However, this is only applicable to well or moderately differentiated tumors, not to high grade EC [25]. A small number of studies show a significant association between the presence of LVSIs and HE4 marker increase [14, 26, 27]. Curiously, in our study it was the only histological factor related to HE4 in both types of tumors. Currently, this finding does not seem to have an impact on clinical management in this subgroup, because all cases are high grade tumors. Further studies are needed to investigate whether higher HE4 value might be useful to differentiate a more aggressive subgroup within type II of EC.

Two recent meta-analysis studied the value of HE4 marker in the diagnosis and prognosis of EC [28, 29]. In the first one, 6 studies with a total of 781 patients with EC were

included, but with a limited number of non-endometrioid cases. The results suggested that expression of HE4 was associated with a worse prognosis in patients with EC. In the second, the authors suggested that serum HE4 is generally an accurate tool in EC diagnosis, but with differences depending on the histological type.

Therefore, it has been shown that the value of the preoperative HE4 marker has an important prognostic significance in EC. However, it is not verified if it has the same meaning depending on the type of tumor. Based on our results, we believe that there are important differences in the association of HE4 with well-established histological risk factors for EC according to the histological type.

Our main limitation is the sample size of subtype II, only 28 cases. This implies that at the moment these results should be taken with caution. The authors assume that perhaps a larger sample in this group could draw different conclusions. More studies with a larger sample are needed to verify these findings and to establish if a different cut-off point associated to prognostic value is necessary depending on the type of tumor.

Conclusions

Preoperative value of HE4 is related differently to histological prognostic factors for EC depending on the histological type of tumor. While in endometrioid subtype, higher HE4 preoperative value is related to multiple histological factors of poor prognosis, in non-endometrioid subtype, it

is only related to LVSI. These results can be very relevant/significant in order to standardize the prognostic value of HE4 in EC, which probably is different depending on the histological subtype. Further studies with a larger sample, especially with more non-endometrioid subtype cases, are needed to verify these findings.

Authors' contributions

LBM has elaborated the research project. LBM and AER have designed the study and database. They have participated on the elaboration of the article. PJCM has been responsible for supervising the methodology. LBM, AER and PJCM have contributed to data collection. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

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Conflict of Interest

The authors declare no competing interests.

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