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The role of HE4 and CA125 in differentiation between malignant and non-malignant endometrial pathologies

Nabil Abdalla, Monika Pazura, Anna Słomka, Robert Piórkowski, Włodzimierz Sawicki, Krzysztof Cendrowski

Chair and Clinic of Obstetrics, Gynecology and Oncology, Second Faculty of Medicine, Medical University of Warsaw, Poland

ABSTRACT

Objectives: The aim of the study was to assess the role of HE4 and CA125 in differentiation between malignant and non-malignant endometrial pathologies.

Material and methods: A retrospective study of 87 patients with endometrial pathologies was conducted. Tumor markers were assessed two weeks before surgical intervention in each subject. The final diagnosis was established on the basis of the histopathological examination of the endometrium.

Results: Serum HE4 levels were significantly higher in patients with endometrial cancer (EC) as compared to non-malignant endometrial pathologies ($p < 0.001$), patients with stage I EC as compared to non-malignant endometrial pathologies ($p < 0.001$), and patients with stage Ia EC as compared to non-malignant endometrial pathologies ($p = 0.003$). Serum CA125 levels were not significantly different as far as these groups of patients were concerned. Both tumor markers were significantly higher in patients with stage II-III as compared to stage I EC and non-malignant endometrial pathologies ($p < 0.001$ for both markers). Sensitivity and specificity of HE4 at the cut-off level of 70 pmol/L for detecting endometrial malignancies were 73.08% and 85.71%, respectively. Sensitivity and specificity of CA125 at the cut-off level of 35 U/mL were 29.41% and 94.29%, respectively. The area under the curve (AUC) for HE4 was 0.875, suggesting that this marker reliably differentiates malignant from non-malignant endometrial pathologies ($p < 0.001$). AUC for CA125 was 0.552, suggesting that this marker does not reliably differentiate between malignant and non-malignant endometrial pathologies ($p = 0.414$).

Conclusion: HE4, in contrast to CA125, might be a useful tool for detecting malignant endometrial pathologies.

Key words: HE4, CA125, endometrial cancer, endometrial hyperplasia, endometrial polyp

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INTRODUCTION

Endometrial cancer (EC) is the sixth most common malignancy among women worldwide and the fourteenth most common cancer overall. Poland has the 16th highest rate of EC globally, with an age-standardized rate of 16.9 per 100 000 women. In 2012, a total of 320 000 new cases were diagnosed in the world [1]. The incidence rate is higher in the developed countries [1, 2]. The majority of EC cases are diagnosed in the early stages due to early symptommaticity. As a result, the 5-year survival rate for all EC stages has been estimated at 80% [3]. Endometrial hyperplasia is characterized by non-invasive proliferation of the endometrial epithelium and can be further classified as simple or complex, with or without atypia, depending on architecture complexity and nuclear cytology. The existence of endometrial hyperplasia is associated with the development of EC [4]. An endometrial polyp is a localized hyperplastic growth of the endometrial stroma and glands [5]. The etiology of all these histological changes is related to an excess of estrogen exposure, together with insufficient progesterone levels [5,6]. Cancer antigen 125 (CA125) was described for the first time by Bast et al. [7], and has been widely used in ovarian cancer (OC) ever since. However, its levels can be elevated in healthy individuals, as well as in many malignant and non-malignant gynecological and non-gynecological diseases [8]. Human epididymis protein 4 (HE4) is the product of the HE4 gene, located on chromosome 20q 12-13.1 [8]. The initial evidence that

Corresponding author:
Nabil Abdalla
Kondratowicza St. 8, 03–242 Warsaw, Poland
tel./fax: +48 22 326 53 80
e-mail: drnabilabdalla@yahoo.com

HE4 can act as an oncogenic or tumor-promoting agent was shown in an experimental study of Li et al. [9]. HE4 and CA125 have been widely used in routine management of OC [10]. Recent studies have considered the role of HE4 in the diagnosis, staging and prognosis of EC [11–13]. In this study, we present our experience in the assessment of the role of HE4 and CA125 in differentiating between malignant and non-malignant endometrial pathologies.

The aim of the study was to assess the diagnostic performance of tumor markers HE4 and CA125 in differentiating between malignant and non-malignant endometrial pathologies and to search for statistically significant differences between serum HE4 and CA125 levels in patients with malignant and non-malignant endometrial pathologies.

MATERIAL AND METHODS

A retrospective study of 87 patients admitted to our clinic between October 2012 and June 2015 was conducted. All patients with endometrial pathologies were reviewed and their eligibility for the study was verified. The inclusion criteria were as follows: age > 18 years and serum levels of HE4 and CA125 within two weeks before the surgical intervention, in which histological material was obtained and analyzed later on by a pathologist. Only tumor marker measurements from the proliferative phase of a regular menstrual cycle taken into consideration. The reason for surgical operation in case of non-malignant endometrial pathologies was abnormal uterine bleeding. The exclusion criteria were as follows: hepatic and renal diseases, simultaneous adnexal disease, uterine fibroids > 5 cm, secondary malignancy, and history of chemotherapy or radiotherapy. EC staging was performed according to the International Federation of Gynecology and Obstetrics (FIGO) criteria. The final histological diagnosis was made according to the 1994 World Health Organization (WHO) classification [6]. Both, HE4 and CA125 were measured simultaneously with kits (Fujirebio Diagnostics, Inc.), in the same apparatus Cobas 8000 e602, using Electro-chemiluminescence immunoassay (ECLIA).

The Shapiro-Wilk (S-W) test was used to check variable distribution of the tumor markers. Sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of the tumor markers were calculated. Then, the diagnostic performance of HE4 and CA125 for detecting malignancy was analyzed using the chi-squared test. The p-value of < 0.05 was considered as statistically significant. Statistical Package for the Social Sciences (SPSS) Software was used for statistical analysis.

RESULTS

A total of 87 patients (aged 27–86 years) were included in the study. Mean age was 61.8 years (standard deviation (SD) = 13.2 years, median: 64 years). The majority of the patients (64, 73.56%) were post-menopausal and only 23 (26.44%) were pre-menopausal. There were 52 (59.77%) patients with EC. A total of 46 (88.46%) subjects were diagnosed with endometrioid EC, while 4 (7.69%) and 2 (3.85%) women were diagnosed with serous and clear cell carcinoma subtypes, respectively. The number of patients with histological grading G1, G2, and G3 was 34 (73.9%), 9 (19.5%), and 3 (6.5%), respectively. Serum HE4 levels in these groups of patients were 91.70 ,120, and 213 pmol/L, respectively, while CA125 levels were 16.11, 22.3. and 96.3 U/mL, respectively.

The number of patients with stage I, II and III was 37 (71.15%), 3 (5.77%), and 12 (23.08%), respectively. Within stage I, 19 (51.35%) and 18 (48.65%) women were diagnosed with stage Ia and Ib disease, respectively. A total of 35 (40.23%) subjects were diagnosed with pathologies of the endometrium other than malignancy. Only 2 (5.71%) patients were diagnosed with hyperplasia with atypia. A total of 33 (94.29%) patients were diagnosed with other pathologies, including 17 (48.57%) women with endometrial polyps, 2 (5.71%) with hyperplasia without atypia, and 14 (40.00%) with both, endometrial polyp and hyperplasia without atypia. The statistical significance of the S-W test was < 0.001 for both tumor markers. The distribution of the variables was not normal. Therefore, non-parametric tests (Mann-Whitney U test and Kruskal-Wallis test) were used to assess whether serum HE4 and/or CA125 levels were significantly different between certain groups of patients with endometrial pathologies. The results of these statistical analyses are shown in Table 1.

Serum HE4 levels were significantly higher in patients with EC as compared to non-malignant endometrial pathologies ($p < 0.001$), with stage I EC as compared to non-malignant endometrial pathologies ($p < 0.001$), and with stage Ia EC as compared to non-malignant endometrial pathologies ($p = 0.003$). Serum CA125 levels were not significantly different among these groups of patients. Both, HE4 and CA125 were significantly higher in patients with stage II–III as compared to stage I EC and non-malignant endometrial pathologies ($p < 0.001$ for both markers). Neither HE4 nor CA125 were significantly higher in patients with endometrial hyperplasia with atypia as compared to other non-malignant endometrial pathologies. The diagnostic performance of the tumor markers in differentiating between malignant and non-malignant endometrial pathologies at certain cut-off levels is shown in Table 2. The results of the chi-squared test with p-values are presented in Table 3.

A receiver operating characteristic (ROC) curve was constructed to compare both tumor markers (HE4 and CA125) as far as differentiation between malignant and non-malignant endometrial pathologies was concerned. The area under

Table 1. Comparison of different groups of patients with regard to HE4 and CA125

Compared groups	Group	Number of patients (out of the total of the compared groups)	HE4		CA125	
			Median level [pmol/L]	p-value	Median level [U/mL]	p-value
EC *vs.* non-malignant endometrial pathologies	EC	52 (59.8%)	97.25	< 0.001	18.56	0.414
	Non-malignant endometrial pathologies	35 (40.2%)	41.80		17.99	
Stage Ia EC *vs.* non-malignant endometrial pathologies	Stage Ia EC	19 (35.2%)	73.20	0.003	12.82	0.065
	Non-malignant endometrial pathologies	35 (64.8%)	41.80		17.99	
Stage I EC *vs.* non-malignant endometrial pathologies	Stage I EC	37 (51.4%)	89.20	< 0.001	15.72	0.398
	Non-malignant endometrial pathologies	35 (48.6%)	41.80		17.99	
Stage II–III EC *vs.* non-malignant endometrial pathologies	Stage II–III EC	15 (30%)	176.60	< 0.001	66.03	< 0.001
	Non-malignant endometrial pathologies	35 (70%)	41.80		17.99	
Stage II–III EC *vs.* non-malignant endometrial pathologies and stage I EC	Stage II–III EC	15 (17.2%)	176.60	< 0.001	66.03	< 0.001
	Non-malignant endometrial pathologies and stage I EC	72 (82.8%)	57.45		16.17	
Hyperplasia with atypia *vs.* other non-malignant endometrial pathologies	Hyperplasia with atypia	2 (5.71%)	41.10	0.659	12.89	0.484
	Other non-malignant endometrial pathologies	33 (94.3%)	41.80		20.26	

Table 2. The diagnostic performance of HE4 and CA125 for detecting EC

The diagnostic test with the cut-off level	Sensitivity (95% CI)	Specificity (95% CI)	Positive predictive value (95% CI)	Negative predictive value (95% CI)	Accuracy (95% CI)
CA125 Cut-off level 35 U/mL	29.41% (17–42)	94.29% (87–100)	88.24% (73–100)	47.83% (36–60)	55.81% (45–66)
HE4 Cut-off level 70 pmol/L	73.08% (61–85)	85.71% (74–97)	88.37% (79–98)	68.18% (54–82)	78.16% (69–87)
HE4 Cut-off level 150 pmol/L	28.85% (17–41)	100.00% (100–100)	100.00% (100–100)	48.61% (37–60)	57.47% (47–68)
HE4 Cut-off level 70 for pre- and 150 pmol/L for post-menopausal patients	28.85% (17–41)	97.14% (92–100)	93.75% (82–100)	47.89% (36–60)	56.32% (46–67)

the curve (AUC) is shown in Figure 1. AUC for both tumor markers with statistical significance is shown in Table 4.

ROC-AUC for HE4 was 0.875, suggesting that HE4 reliably differentiates between malignant and non-malignant endometrial pathologies ($p < 0.001$), whereas AUC for CA125 was 0.552, suggesting that CA125 does not reliably differentiate between malignant and non-malignant endometrial pathologies ($p = 0.414$). The Hanley and McNeil method was used to compare the AUC of tumor markers, and revealed that HE4 was significantly more important than CA125 as far as reliable differentiation between malignant and non-malignant endometrial pathologies was concerned ($Z = 4.42$; $p < 0.001$).

DISCUSSION

At present, there is no single tumor marker that can be used for the diagnosis, monitoring and follow-up of EC. In 1991 Kirchhoff et al., described for the first time HE4 in the distal part of the epididymis [14]. HE4, along with CA125 and the menopausal status, is used to determine the risk of malignancy through an algorithm in patients with adnexal tumors [15]. Recent studies have shown that HE4 levels are elevated in patients with EC [11, 16, 17]. The role of tumor markers in detecting early stages of EC may be limited since postmenopausal bleeding is an early symptom of the disease [18]. However, elevated levels of HE4 may be of great

Table 3. Results of the chi-squared test and p-values for CA125 and HE4 in differentiating between malignant and non-malignant endometrial pathologies

The diagnostic test with the cut-off level	Type of endometrial pathology according to the diagnostic test	Final histological diagnosis				Result of chi^2 test and p-value
		Non-malignant endometrial pathologies		Malignant endometrial pathologies		
		Number of patients	Percent of the total	Number of the patients	Percent of the total	
CA125 Cut-off level 35 U/mL	Non-malignant	33	94.29	36	70.59	$chi^2(1) = 7.35$ p = 0.007,
	Malignant	2	5.71	15	29.41	
HE4 Cut-off level 70 pmol/L	Non-malignant	30	85.71	14	26.92	$chi^2(1) = 28.93$ p < 0.001
	Malignant	5	14.29	38	73.08	
HE4 Cut-off level 150 pmol/L	Non-malignant	35	100.00	37	71.15	$chi^2(1) = 12.00$ p < 0.001
	Malignant	0	0	15	28.85	
HE4 Cut-off level 70 for premenopausal patients and 150 pmol/L for postmenopausal patients	Non-malignant	34	97.14	37	71.15	$chi^2(1) = 9.41$ p = 0.002
	Malignant	1	2.86	15	28.85	

Table 4. ROC-AUC for HE4 [pmol/L] and CA125 [U/mL] in diagnosing malignant endometrial pathologies in 87 patients included in the study

Tumor marker	AUC	95% CI	p-value
HE4	0.875	0.802–0.948	< 0.001
CA125	0.552	0.430–0.674	0.414

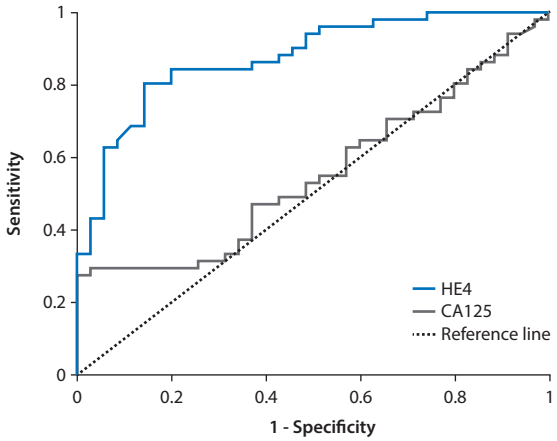

Figure 1. ROC-AUC for HE4 and CA125 in differentiating between malignant and non-malignant endometrial pathologies

importance for patients at high risk of EC, such as patients with hereditary non-polyposis colorectal cancer (HNPCC) syndrome [19]. One of the most important issues is the diagnosis of EC in young women, for whom a fertility-preserving treatment is the preferable choice [12].

In this study, we used the WHO classification which adopted four categories of hyperplasia (simple or complex hyperplasia, with or without atypia). This classification was modified in 2014 into two categories: hyperplasia without atypia and atypical hyperplasia/endometrioid intraepithelial neoplasia. The new classification is simpler to implement in clinical practice, particularly regarding the choice of treatment. We considered atypical hyperplasia as one group since it is associated with a high relative risk of progression into invasive carcinoma [6]. Tumor markers were measured in the proliferative phase of the menstrual cycle. In the study of Anastasi et al. significant fluctuation of the HE4 level was observed in different phases of the menstrual cycle. The peak level of HE4 was observed during the ovulatory phase. The HE4 level was significantly higher during the ovulatory phase as compared to the follicular phase in women < 35 years. This statistically significant difference was not observed in patients > 35 years. Serum CA125 level was not significantly different considering different phases of the menstrual cycle in both age groups [20].

To the best of our knowledge, there has been no consensus about the optimal HE4 level to diagnose EC [11, 17]. In our study, the cut-off level for HE4 was set at different levels, taking into account the menopausal status of the patients. In the study of Escudero et al. their results showed higher HE4 serum concentrations in postmenopausal as compared to premenopausal patients [8]. We believe that including the menopausal status into the cut-off level of HE4 in our study reflects greater accuracy of the results, since we expect fewer false positive results among postmenopausal patients.

Patients with renal disease were excluded from the study in order to reduce the false positive rate of HE4 among patients with renal disease. In a study of Lv et al. a higher level of HE4 was observed in patients with chronic renal disease as compared to OC and EC, although the difference was not statistically significant. In their study, no statistically significant differences in CA125 serum levels between patients with chronic renal disease and controls were observed [21].

Although the role of CA125 in the diagnosis, staging and prognosis of EC has been widely investigated, at present CA125 is not routinely used in the clinical practice [8, 22, 23]. In modern practice, the role of the novel marker HE4 is still under investigation, although the recent reports on HE4 in the literature are promising.

In the study of Li et al. immunohistochemistry was used to detect HE4 expression in 102 cases of EC, 30 cases of endometrial hyperplasia, and 20 cases of normal endometrium. The expression of HE4 in the tissues was confirmed in 84.62%, 66.67% and 15% cases of EC, atypical hyperplasia, and normal endometrium, respectively. HE4 expression was significantly higher in EC as compared to atypical hyperplasia and normal endometrium. Moreover, a significantly higher expression of HE4 was observed in poorly differentiated malignancies as compared to highly differentiated malignancies [18]. Similar results were found in the study of Deng et al. In their study, HE4 expression in endometrial tissues was significantly higher in EC tissues as compared to the normal endometrium. HE4 was also significantly correlated with the degree of cancer differentiation [24].

In our study, significantly higher levels of HE4 were found in patients with malignant endometrial pathologies as compared to non-malignant endometrial pathologies. At the same time, there were no statistically significant differences in CA125 levels between these groups of patients. Our results are supported by the results of Antonsen et al., who reported a significantly higher level of HE4, in contrast to CA125, in patients with malignant endometrial pathologies as compared to atypical endometrial hyperplasia. The sensitivity and specificity of HE4 at the cut-off level of 70 pmol/L in their study found that the ability to differentiate malignancy from atypical endometrial hyperplasia was 43.9% and 76.5%, respectively, while the sensitivity and specificity of CA125 at the cut-off level of 35 U/mL were 19.7% and 78.2%, respectively [25]. Our finding are also supported by results of Minar et al., in which a significant higher level of HE4 was found in patients with EC as compared to benign endometrial pathologies [26]

In the study of Chen et al. a significantly higher level of HE4 was found in patients with uterine cancer as compared to benign uterine disease, among all patients studied and among the premenopausal patients in particular. No such statistically significant difference was found among postmenopausal patients. On the contrary, serum CA125 levels were not significantly different in the whole study population, or either in premenopausal or postmenopausal group [27].

Gasiorowska et al. investigated for the first time the value of HE4 as a complementary diagnostic method in the management and diagnosis of EC in the Polish population. Their results revealed statistically significant differences of HE4 levels in differentiating between malignant and non-malignant endometrial pathologies . These authors demonstrated significant higher levels of HE4 in the aggressive histological grades of EC. Patients who needed lymphadenectomy had significant higher levels of HE4, suggesting that HE4 can be a useful preoperative counselling tool to identify those who may require pelvic and para-aortic lymphadenectomy [28].

Our study is not without certain limitations, chief among them lack of the control group. In the study of Presl et al. a significantly higher level of HE4 was found in patients with EC as compared to the control group. On the contrary, CA125 levels were not significantly different between the two groups [29]. However, the aim of our study was to assess whether there existed a statistical difference of tumor marker levels between groups of patients with endometrial pathologies. The number of patients in our retrospective, single-center study was relatively small. Serum levels of both tumor markers did not differ significantly between patients with atypical hyperplasia and other endometrial pathologies. These results should be considered with caution due to the low number of patients with atypical hyperplasia in our study.

Serum HE4 levels were significantly elevated not only among patients with endometrial malignancies as compared to non-malignant endometrial pathologies, but also among patients with stage Ia and stage I EC as compared to non-malignant endometrial pathologies. This may indicate the usefulness of HE4 in detecting malignancy even in earlier stages of the disease. On the contrary, CA125 was not significantly different between groups of patients with EC, stage I and stage Ia, and with the group of patients with non-malignant endometrial pathologies. We believe that oncologists should consider our results with caution in daily clinical practice.

Our findings concerning both tumor markers (HE4 and CA125) in the Polish population are in agreement with the results of the meta-analysis by Chen et al., assessing the role of these markers in the diagnosis of EC. A total of 1832 cases from 8 studies were enrolled in that meta-analysis. Control groups were represented by healthy subjects in 5 studies, benign endometrial cases in 2 studies, and a mixture of healthy and benign endometrial cases in 1 study. HE4 was superior to CA125 in diagnosing EC, with the area under

summary receiver operation characteristic curve for HE4 and CA125 being 0.77 and 0.37, respectively [30]. The usefulness of these tumor markers may provide an impetus to develop a model for predicting endometrial malignancy which uses tumor markers in combination with other clinical and radiological parameters for the purposes of risk stratification. This algorithm can help in the early diagnosis of EC, precise pre-surgical staging of the disease, eliminating the necessity for lymphadenectomy, and appropriate methods for follow-up to detect recurrence as early as possible [28].

CONCLUSIONS

In patients with endometrial pathologies, serum HE4 level may be a useful marker for detecting endometrial malignancies, even during the early stages of disease.

Serum CA125 level is not useful in differentiating between malignant and non-malignant endometrial pathologies.

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