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Original Research Article

Utility of HE4 to identify patients with endometrioid endometrial cancer who may require lymphadenectomy

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ABSTRACT

Purpose: The aim of the study was to establish whether preoperative serum levels of HE4 and CA125 could be a good predictor for lymphadenectomy in the early stage of endometrioid adenocarcinoma of the uterus.

Material and methods: Preoperative serum HE4 and CA125 were measured in 78 postmenopausal patients treated surgically. The ROC curves were generated to determine the optimal cutoff values of HE4 and CA125 levels with optimum sensitivity and specificity for the prediction of lymphadenectomy.

Results: Based on ROC curve, we found that the HE4 value of 78 pmol/l is the best cutoff to identify candidates who may require lymphadenectomy with the sensitivity of 86.6% and the specificity of 67.2% (NPV = 88.4% and PPV = 51.2%). The area under the curve (AUC) equals 0.814 (95% CI = 0.721–0.886). The cutoff level of CA125 that shows the prognostic indices is 26 U/ml, with the sensitivity of 66.6% and the specificity of 61.2% (NPV = 69.4% and PPV = 44.3%). For CA125 the AUC amounts to 0.671 (95% CI = 0.568–0.764). We also found a statistically significant difference, comparing HE4 and CA125 AUC (0.814 vs. 0.671, respectively, $p < 0.001$). The combination of HE4 and CA125 established in our study as the cutoff point has the sensitivity of 81.2% and the specificity of 65.9% with NPV = 83.4% and PPV = 47.9%.

Conclusions: Our findings indicate that in the early stage of endometrioid endometrial cancer, HE4 can serve as a preoperative tool that can help to identify postmenopausal women who may require lymphadenectomy.

1. Introduction

Endometrial cancer is the sixth most common malignancy among females worldwide with an estimated incidence of about 320,000 new cases in the year 2012. In developed countries, endometrial cancer is the fourth most common cancer in women. Every year about 88,000 new cases are registered in the European Union [1]. The highest incidence of endometrial cancer was in North America (the age-standardized rate is 19.1). In Europe the age-standardized rate is 13.9 [2].

Approximately 75% of endometrial cancer cases are diagnosed at an early stage with a favorable prognosis, although about 15–20% of patients with early stage endometrial cancer experience a recurrence [3]. Because endometrial cancer is a surgically staged disease, one purpose of the surgery is to assess the extent of the disease. The standard surgical treatment for endometrial cancer includes hysterectomy and bilateral salpingo-oophorectomy; however, the benefit of full surgical staging with lymph node dissection in patients with an apparent early stage disease remains a topic of debate [4]. Although most women diagnosed with endometrial cancer present with an early stage disease confined to the uterus, metastatic disease is identified in a significant percentage of cases when comprehensive staging is performed [5]. The poor sensitivity of imaging modalities in detecting deep myometrial invasion and extrauterine disease suggests the role of endometrial cancer specific serum biomarkers in assisting with the preoperative stratification of patients into risk groups, surgical planning and prognostication [6–8]. However, there are no nomograms for predicting the risk of endometrial cancer; therefore, our primary goal is to develop a new

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scoring system, called the risk of endometrial malignancy (REM) score, capable to classify patients with endometrial abnormalities into high- or low-risk groups for endometrial cancer using clinical, ultrasound, and serum markers features. This could help identify the appropriate timing of imaging and surgery in a more personalized manner, thus contributing to the improvement of overall patient care, and eventually triaging patients to centers of excellence [9].

Human epididymis protein 4 (HE4) may become an established marker in ovarian cancer for distinguishing benign from malignant ovarian masses. HE4 has been shown to be of superior performance in early stages, as compared to the present gold standard CA125 [10,11]. Recent studies suggest that HE4 also possesses a potential value as a biomarker in endometrial cancer. Serum HE4, measured during clinical follow-up, may identify a recurrent disease particularly in patients with endometrioid endometrial cancer [12] but we have not enough data to estimate its value in clinical practice [13].

Moore et al. [14] showed the superiority of HE4 over CA125 in the detection of endometrial cancer, especially in early stages. Although CA125 is routinely used in some practices, it has poor sensitivity and specificity [15–18]. Only 10–20% of patients with early stage endometrial cancer and approximately 25% of patients with asymptomatic recurrent disease have an elevated CA125 level [19,20].

Good prognostic marker that is sensitive and specific for endometrial cancer and correlates with the risk factors associated with nodal metastases in early stage disease could be useful in identifying the cases that would benefit from lymphadenectomy and exclude those that would not [21]. The development of assays for accurate identification of patients with low-grade early stage endometrial cancers, who might not need lymphadenectomy is a priority. Thus, the aim of our study was to evaluate if preoperative serum levels of HE4 and CA125 are good predictors for lymphadenectomy in early stage endometrioid adenocarcinomas and to determine the cutoff value with the maximum prognostic power.

2. Material and methods

We conducted a pilot study with 78 postmenopausal patients treated surgically for early stage endometrioid adenocarcinomas at the Department of Gynecologic Oncology Bialystok Oncology Center and Department of Gynecology Provincial Hospital in Bialystok between 2009 and 2013. The study group consisted of women with a biopsy proven endometrioid adenocarcinoma of the uterus. The median age of the patients was 64.5 years (ranging from 56 to 78 years). Using the new 2009 FIGO staging system, 42 (53.8%) patients had surgical stage IA disease, 29 (37.2%) had stage IB disease and 7 (9.0%) patients had stage II. The patients were treated according to the ESMO guidelines [22]. All patients were scheduled for total hysterectomy, bilateral salpingooophorectomy, and peritoneal fluid sampling. Pelvic and paraaortic lymphadenectomy was performed when indicated. None of the patients had received chemotherapy, hormonal therapy or radiation therapy prior surgery. All patients had primary cancers and were receiving first treatment; no patients with disease relapse or follow-up were included. The patients were originally staged according to the FIGO 2009 guidelines [1]. All surgical specimens were reviewed by dedicated gynecologic pathologists. The patients were informed about and gave their consent for the study. The protocol was previously approved by the Bioethics Committee of the Medical University of Bialystok (R-I-002/68/2012). Preoperative serum samples were collected at the preoperative outpatients' office visit or on the day preceding the operation, frozen and stored at −80 °C until analyzed. The levels of HE4 and CA125 were determined using assays and kits developed by Fujirebio Diagnostic, Inc. (Malvern, PA, USA) and were performed according to the manufacturer's specifications on Roche Cobas system (Roche Diagnostics GmbH, Mannheim, Germany).

Due to the non-normal distribution of the HE4 and CA125 results, the marker levels for each prognostic factor and/or patient subgroup were summarized using median values. HE4 and CA125 serum levels were individually juxtaposed with two independent groups using the two-sided Wilcoxon rank-sum test (Mann–Whitney test). The receiver operating characteristic (ROC) curves were generated to determine the optimal cutoff values of preoperative HE4 and CA125 levels with optimum sensitivity and specificity for the prediction of lymphadenectomy. We calculated the accuracy, sensitivity, specificity, the positive and negative predictive value (PPV and NPV) for each prognostic marker alone and combined using these cutoff points. The level of $p < 0.05$ was considered statistically significant for all statistical comparisons. Statistical analyses were performed using the Statistica software version 10.0PL (StatSoft, Inc., StatSoft Polska Sp. z o.o., Poland).

3. Results

Serum samples were obtained from 78 postmenopausal patients with endometrioid adenocarcinomas. Table 1 displays the median serum HE4 and CA125 concentrations for cancer stages and grades. Patients with stage IA disease had significantly lower median serum HE4 and CA125 value than patients with stage IB disease (72.6 vs. 119.2 pmol/l; $p = 0.012$ and 24.4 vs. 33.7 U/ml; $p = 0.046$, respectively). In addition, patients with stage IA disease had significantly lower median serum HE4 and CA125 levels than patients with other more advanced stages (IB-II) (72.6 vs. 129.8 pmol/l; $p = 0.001$ and 24.4 vs. 34.2 U/ml; $p = 0.016$, respectively). The examination of tumor grade revealed a significant difference in median serum HE4 levels between G1 and G2 tumors (75.4 vs. 98.2 pmol/l; $p = 0.032$) and between G1 versus G2 and G3

Table 1
Serum HE4 and CA 125 concentrations depending on the stage and grade.

Characteristic	No. of cases (%)	HE4 pmol/l Median (range)	p	CA125 U/ml Median (range)	p
Stage					
IA	42 (53.8)	72.6 (18.4–526.7)		24.4 (5.5–169.6)	
IB	29 (37.2)	119.2 (31.5–1439.5)	0.012[a]	33.7 (6.1–389.3)	0.046[a]
II	7 (9.0)	148.8 (24.2–461.4)	0.001[b]	35.9 (4.7–292.5)	0.016[b]
Grade					
1	36 (46.2)	75.4 (18.4–431.5)		21.7 (5.5–118.3)	
2	27 (34.6)	98.2 (32.2–569.2)	0.032[c]	33.3 (4.7–292.5)	0.342[c]
3	15 (19.2)	106.6 (38.1–1439.5)	0.011[d]	34.2 (6.6–389.3)	0.246[d]

[a] IA vs. IB.
[b] IA vs. IB and II.
[c] G1 vs. G2.
[d] G1 and G2 vs. G3.