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RESEARCH ARTICLE

Does HE4 have a role as biomarker in the recurrence of ovarian cancer?

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Abstract Human epididymis protein 4 (HE4) was recently approved by the Food and Drug Administration to monitor recurrence or progressive disease in epithelial ovarian cancer in conjunction with CA125. This is the first prospective controlled study in literature evaluating the sensitivity and specificity of HE4 and CA125 in detecting recurrent ovarian cancer. Serum samples were obtained 24 h before surgery from 34 patients with suspicious recurrent ovarian cancer and from 34 patients with benign adnexal pathology, operated from November 2010 to November 2011 at University Campus Bio-Medico of Rome. The CA125 normal value is considered less than 35 U/mL. Two HE4 cut-off are considered: less than 70 pmol/L and less than 150 pmol/L. The specificity analysis was performed using the parametric *t* test to compare the CA125 series and the Mann–Whitney test for the HE4 series. The level of statistical significance is set at $p<0.05$. The CA125 sensitivity and specificity in detecting recurrent ovarian cancer is 35.29 and 58.82 %, respectively. The HE4 sensitivity is 73.53 and 26.47 %, for 70 pmol/L and 150 pmol/L cut-off, respectively. The HE4 specificity is 100 %. Combining CA125 and HE4 at cut-off of 70 pmol/L, the sensitivity to detect recurrent ovarian cancer is 76.47 % with a specificity of 100 %. The combination of CA125 and HE4 at cut-off of 70 pmol/L improves the overall sensitivity and specificity of CA125 alone, suggesting a useful application of HE4 in strategies for surveillance of ovarian cancer recurrence.

Keywords Ca125 sensitivity · Human Epididymis protein 4 · HE4 sensitivity · Recurrent ovarian cancer

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Background

Despite the treatment for advanced ovarian cancer, including surgery and several months of chemotherapy, the relapse-free survival from FIGO staging at 2 years is between 33.6 and 95.8 %, considering all stages [1]. Strategies for surveillance of recurrence, however, are not standardized. Since it was first described more than 25 years ago, the CA125 serum antigen has been used routinely in the surveillance for recurrence of epithelial ovarian cancer. In the USA, most clinicians use a combination of serial physical examinations and CA125 evaluation typically every 3 months during the first years after primary treatment as well as potentially cross-sectional imaging such as computerized tomography (CT) or magnetic resonance imaging (MRI), on the assumption that early detection of recurrence would translate into more effective second-line treatment [2].

However, CA125 is associated with a high false-positive rate. In fact, its concentration is also grossly increased in non-malignant conditions such as various abdominal conditions not related to ovarian cancer [3].

Thus, to improve the specificity and sensitivity in detecting ovarian cancer, the use of novel biomarkers such as human epididymis protein 4 (HE4) alone or in combination with CA125 has been intensively studied [4–6]. HE4 was first identified in the epithelium of the distal epididymis and

originally predicted to be a protease inhibitor involved in sperm maturation [7].

HE4 has been recently described as a new marker for early ovarian cancer, with higher sensitivity (76,9 %) compared to CA125 [8]. HE4 was also recently approved by the Food and Drug Administration (FDA) to monitor recurrence or progressive disease in epithelial ovarian cancer in conjunction with CA125 [9]. However, there are only two studies on HE4 in recurrent ovarian cancer [4, 10]. Both studies did not focus on HE4 sensitivity and specificity on detecting recurrence of ovarian cancer. Therefore, this is the first study in literature evaluating the sensitivity and specificity of CA125 and HE4 expression in patients affected by recurrence of ovarian cancer (study group), comparing these results with those obtained in patients affected by benign adnexal pathologies (control group).

Methods

Starting November 2010 to November 2011, all patients with suspicious recurrence of ovarian cancer (study group) and benign adnexal pathologies (control group), referred to the Division of Gynecologic Oncology at the University Campus Bio-Medico of Rome, were prospectively included in the study. The institutional internal review board approved the study.

Inclusion criteria for enrollment were as follows: (1) aged between 18 and 80 years; (2) Eastern Cooperative Oncology Group performance status 0–2 according to World Health Organization criteria; (3) informed consent obtained from the patients.

Exclusion criteria included: (1) abnormal cardiac, hematological, renal, respiratory, and/or hepatic functions; and (2) presence of a secondary malignancy.

All patients with suspicious recurrence of ovarian cancer had pelvic ultrasound and at least one of the following radiologic imaging: CT, MRI, and/or Positron Emission Tomography (PET/CT) prior to surgery to document the suspect of recurrence of the disease. The day before surgery, blood samples were obtained for tumor marker analysis.

All sera were collected following a standard protocol. Briefly, samples were collected in a red-top vacutainer, clotted 60–90 min, and centrifuged for 10 min at 1.300×*g*. The serum fractions were aliquoted and stored at −80 °C until analysis.

HE4 levels were determined using the HE4 EIA assay (Fujirebio Diagnostics). The HE4 EIA is a solid phase, non competitive immunoassay based upon the direct "sandwich" technique using two monoclonal antibodies, 2 H5 and 3D8, directed against two epitopes in the C-WFDC domain of HE4. Patient serum samples were incubated with biotinylated anti-HE4 monoclonal antibody 2 H5 aliquots in streptavidin-coated microstrips. HE4 in standard or serum samples was adsorbed in the streptavidin-coated microstrips by the biotinylated anti-HE4 monoclonal antibody during the incubation period.

The strips were then washed and incubated with HRP labeled anti-HE4 monoclonal antibody 3D8. After washing, buffered substrate/chromogen reagent was added to each strip, and the enzyme reaction was able to proceed.

During the enzyme reaction, a blue color developed if the antigen was present. The intensity of the color was directly proportional to the amount of HE4 present in the samples.

CA125 levels were evaluated by a one-step "sandwich" radioimmunoassay (Radim, Netherlands). Polystyrene beads coated with M11 capture antibody reacting with molecules containing OC 125 reactive determinants were incubated with control or patients' serum samples, standards, and tracer (125I-labeled mouse monoclonal OC 125 antibody) aliquots. The bound radioactivity observed was proportional to the concentration of the OC 125 reactive determinant (antigen). Normal levels of CA125 were considered to be less than 35 U/mL.

For this study, we consider two HE4 cut-off: normal values less than 150 pmol/L, according to the manufacturer's indications, and also less than 70 pmol/L, as suggested by Moore et al. [6].

Enrolled patients with recurrence of ovarian cancer underwent secondary surgery, and histological evaluations were performed by expert gynecologic oncology pathologists. Using the statistical software MedCalc Software Version No. 11.6.1.0, we analyzed the chance to describe the collected values as normal distributions. The series of CA125 values satisfied the Kolmogorov–Smirnov test for normal distributions. So we have performed the CA125 values analysis using the parametric *t* test, assuming unequal variances for a more severe evaluation. The series of HE4 values in detecting recurrence of ovarian cancer did not satisfy the Kolmogorov–Smirnov test for normal distribution, so we have performed the HE4 values analysis using the Mann–Whitney test, assuming unequal variances for a more severe evaluation.

The level of statistical significance was set at $p<0.05$. In terms of assays' diagnostic accuracy, the performance was assessed by the evaluation of the receiver operating characteristic (ROC) curve for recurrent ovarian cancer cases (study group) versus benign adnexal pathology (control group) cases. The area under the ROC curve was calculated by MedCalc Software Version No. 11.6.1.0.

Results

Thirty-four patients with radiological suspect of recurrence of ovarian cancer were enrolled in our study. The median

age at secondary surgery was 53 years (range, 38–67 years). Twenty-nine patients (85 %) previously underwent primary cytoreduction followed by adjuvant platinum-based chemotherapy, five patients (11.8 %) received neoadjuvant chemotherapy before first debulking surgery followed by adjuvant platinum-based chemotherapy, and two patients (15 %) underwent primary cytoreduction without adjuvant chemotherapy. Histology subtypes at primary surgery were endometrioid in two cases (5.9 %), clear cell in two cases (5.9 %), and serous in 30 cases (88.2 %). The 30 patients with serous ovarian carcinoma were divided in 20 high-grade (67 %) and 10 low-grade (33 %) cases. The median length of time from the finish of the first treatment series to recurrence was 14.7 months. There was radiological evidence of recurrence in 28 patients (82.3 %) at CT, in four patients (11.8 %) at MRI, and in two patients (5.9 %) at PET/CT. In our patients' cohort, sites of recurrences are: pelvis, only in 15 patients (44 %); Lymph nodes, in 10 patients (29 %): Liver and/or spleen, in 9 patients (27 %). Surgical procedures included: bowel resection and colostomy in 15 patients (44 %), splenectomy in 4 patients (13 %), partial liver resection in 5 patients (14 %), and retroperitoneal lymphadenectomy in 10 patients (29 %).

The median age for control group (benign adnexal pathologies) was 37 years (range, 31–74 years).

A total of 4 patients within the 34 of the control group (11.8 %) underwent laparoscopic mono or bilateral salpingo-oophorectomy, 5 (14.7 %) underwent laparotomic mono or bilateral salpingo-oophorectomy, 22 (64.7 %) underwent laparotomic ovarian cyst removal, and 3 (8.8 %) underwent laparoscopic ovarian cyst removal. Concerning histology in control group, the cyst was endometrioma in 14/34 patients (41.2 %), serous cystadenoma in 12/34 patients (35.3 %), and a simple cyst in 8/34 patients (23.5 %). All patients enrolled with suspected ovarian cancer recurrence have been histologically confirmed at surgery, and final pathology collimated with original histotypes. The clinical characteristics of the study and control group patients are summarized in Table 1.

Mean CA125 plasma concentration for patients with confirmed recurrence of ovarian cancer is 29.68±18.12 U/mL (range 1.1–64.3). Mean HE4 plasma concentration for patients with recurrence of ovarian cancer is 144.56±123.50 pmol/L (range 21.61–633.6). In this patient group, CA125 levels above the cut-off are detected in 12/34 (35.29 %) patients, HE4 levels above the cut-off of 70 pmol/L are detected in 25/34 (73.53 %) patients, while HE4 levels above the cut-off of 150 pmol/L are detected in 9/34 (26.47 %) patients.

Mean CA125 plasma concentration in control group is 36.70±32.60 U/mL (range 1.8–156). Mean HE4 plasma concentration for control group is 41.29±13.69 pmol/L (range 13.5–67.1). In control group patients, CA125 levels above the cut-off are detected in 14/34 (41.17 %) patients, HE4 levels above the cut-off of 70 and 150 pmol/L are never detected.

The sensitivity of CA125 in detecting cancer patients is 35.29 % whereas the sensitivity of HE4 is 73.53 and 26.47 % for 70 and 150 pmol/L cut-off, respectively. In both cases, the specificity of HE4 is absolute (100 %), whereas the CA125 has a lower specificity of 58.8 % with a very low positive predictive value of 41.67 % that indicates a very low capability to identify real cancer patients once an over threshold value of this marker has been found. These results are summarized in Table 2.

For the HE4, the positive predictive value (PPV) is 100 % and negative predictive value (NPV) is 79.06 and 57.62 %, for 70 and 150 pmol/L cut-off, respectively.

The analysis of mean and median CA125 and HE4 values among the considered groups shows a statistically significant difference only for the HE4 series ($p<0.0001$). These results are summarized in Table 3. The distributions of the CA125 and HE4 values for each patient among the considered groups are shown in Fig. 1.

CA125 statistical specificity and sensitivity analysis studied in the two selected groups of patients showed that the area under the ROC curve was 0.519 (95 %; CI 0.395–0.642) (Fig. 2).

HE4 statistical specificity and sensitivity analysis studied in the two selected groups of patients showed that the area under the ROC curve was 0.874 (95 %; CI 0.771–0.942) (Fig. 2). Combining CA125 and HE4 at cut-off of 70 pmol/L, the sensitivity to detect recurrent ovarian cancer is 76.47 % with a specificity of 100 % (Table 4).

Discussion

Strategies for surveillance of ovarian cancer recurrence are not standardized. Since it was first described more than 25 years ago, the CA125 serum antigen has been used routinely in the surveillance for recurrent ovarian cancer. In the USA, most clinicians use a combination of serial physical examinations, CA125 evaluation typically every 3 months during the first years after primary treatment, and potentially cross-sectional imaging such as CT or MRI, on the assumption that early detection of recurrence would translate into more effective second-line treatment [2]. Our usual routine follow-up procedures include pelvic examination and tumor marker (CA125 and HE4) evaluation every 4 months for 2 years, then every 6 months until the fifth year according to National Comprehensive Cancer Network 2011 and European Society for Medical Oncology 2010 recommendations, and a total body CT scan or PET/CT annually.

Rustin and his colleagues found that increasing CA125 levels can precede signs and symptoms of recurrence by

Table 1 The clinical characteristics of recurrent ovarian cancer group and control group

	Recurrent ovarian cancer group	Control group
Median age and range	53 (38–67)	37 (31–74)
FIGO stage; *n* (%)		
IB	2(5.9)	–
IC	2(5.9)	–
IIIA	2(5.9)	–
IIIB	8(23.5)	–
IIIC	20(58.8)	–
Median time of recurrence (Months)	14.7	–
Histology; *n* (%)		
Serous	30 (88.2): 20 High grade (67) and 10 Low grade (33)	–
Endometrioid	2(5.9)	–
Clear cell	2(5.9)	–
Endometrioma cyst	–	14(41.2)
Ovarian serous cystadenoma	–	12(35.3)
Simple ovarian cyst	–	8(23.5)
Type of surgery; *n* (%)		
Optimal (Residual Tumor=0)	34 (100)	–
Suboptimal (Residual Tumor>1 cm)	0 (0)	–
Laparoscopic mono or bilateral salpingo-oophorectomy	–	4 (11.8)
Laparotomic mono or bilateral salpingo-oophorectomy	–	5 (14.7)
Laparotomic ovarian cyst removal	–	3 (8.8)
Laparoscopic ovarian cyst removal	–	22 (64.7)
Radiologic recurrence; *n* (%)		
Computed tomography	28 (82.3)	–
Magnetic resonance imaging	4(11.8)	–
Positron Emission Tomography	2(5.9)	–
Therapy Strategy; *n* (%)		
Neoadjuvant Chemotherapy+Radical Surgery	5 (15)	–
Primary Radical Surgery+Adjuvant Chemotherapy	29 (85)	–

3–5 months in up to 70 % of cases, and predict disease progression with 80–90 % sensitivity [11, 12].

Although serial monitoring following initial chemotherapy can lead to the early detection of recurrent disease, the clinical value of this lead time is unclear. In fact, the only randomized controlled, multi-center trial in ovarian cancer looking at early treatment of disease relapse based on CA125 level alone versus delayed treatment based on conventional clinical indicators showed no statistically differences in terms of overall survival. A criticism that can be moved against this study is that chemotherapy was the only treatment option and patients were not evaluated for secondary cytoreduction [13]. Moreover there are some limitations of serum biomarker surveillance with CA125 reported in literature. In fact, CA125 antigen is not exclusively expressed in ovarian cancer tumor cells, but its concentration is also grossly increased in non-malignant conditions resulting in a reduction of specificity [14]. Furthermore, other difficulties the physician faces happened when patients show pretreatment CA125 concentrations in

Table 2 Test accuracy in detecting malignant disease

	N (34)	Mean	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
CA125>35 U/mL	12	29.68	35.29	58.82	46.15	47.62
HE4>70 pmol/L	25	144.56	73.53	100	100	79.07
HE4>150 pmol/L	9		26.47	100	100	57.63

PPV Positive Predictive Value, *NPV* Negative Predictive Value

Table 3 Analysis of the data series for CA125 and HE4

		Benign	Malignant	Comparison of marker values related to diagnoses
CA125 (UI/mL)	Mean	36.17	29.68	*t* Test, Welch test (assuming unequal variances)
	Median	31.00	30.65	$P=0.30$
Kolmogorov–Smirnov test for Normal distribution		Accept Normality ($P=0.08$)	Accept Normality ($P=0.76$)	
HE4 (pmol/L)	Mean	41.29	144.56	Mann-Withney test (independent samples) $P<0.0001$
	Median	41.98	122.26	
Kolmogorov–Smirnov test for Normal distribution		Accept Normality ($P=0.98$)	Reject Normality ($P=0.02$)	

the normal range or with increased pretreatment CA125 concentrations that never normalize. CA125 is the ovarian cancer marker against which new markers for this malignancy such as HE4 should be judged. In this new view, the role of novel biomarkers and its usefulness in the follow up of advanced ovarian cancer to detect relapse or progression of disease could be important.

HE4 has the highest sensitivity as a single marker in detecting early-stage malignancy (76,9 %), followed by CA125 [8]. The expression of HE4 is higher in endometrioid and serous ovarian cancer, possibly enabling one to distinguish among several tumor types [15].

Another reported benefit is that HE4 has less false positives, especially in non-malignant ovarian diseases, and possessing a similar sensitivity as CA125 among blinded serum studies of women with non-malignant disease [5, 16].

The HE4 has been recently approved by the FDA to monitor recurrence or progressive disease in epithelial ovarian cancer in conjunction with CA125. Concerning the role of HE4 in recurrence of ovarian cancer, only two studies have been published in literature until now.

Havrilesky et al. [4], monitoring 27 patients who experienced recurrent ovarian cancer, found that sensitivity in predicting the recurrence was 100 % considering a biomarker panel, specifically HE4, MMP7 and Glycodelin, and 96 % for CA125 alone. At least one of the panel biomarkers elevated before (range 6–69 weeks) the CA125 and prior to clinical evidence of recurrence in 14/27 (52 %) patients [4].

The other study of Anastasi et al., performed in five patients with recurrent ovarian cancer showed that HE4 expression began 5–8 months before the CA125 one[10].

Both these studies suggest that HE4 potentially could be an important early indicator of the recurrent ovarian cancer, even if they do not define the HE4 sensitivity and specificity alone in this case.

This is the third study in literature studying the role of HE4 in recurrent ovarian cancer. Therefore, this is the first prospective controlled one with the aim of evaluating the

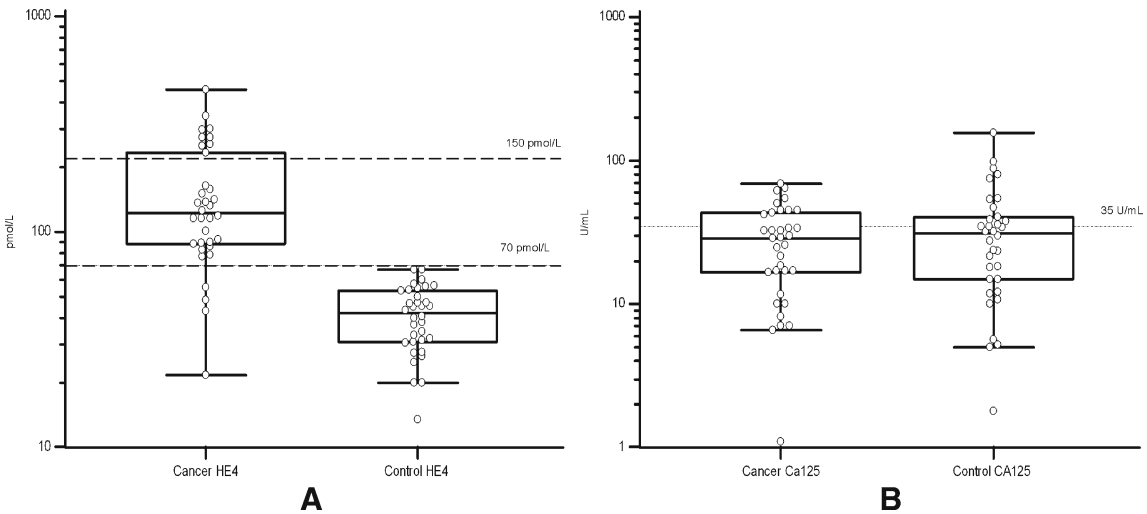

Fig. 1 **a** Comparison among control group and recurrent ovarian cancer patients HE4 serum levels. **b** Comparison among control group and recurrent ovarian cancer patients CA125 serum levels

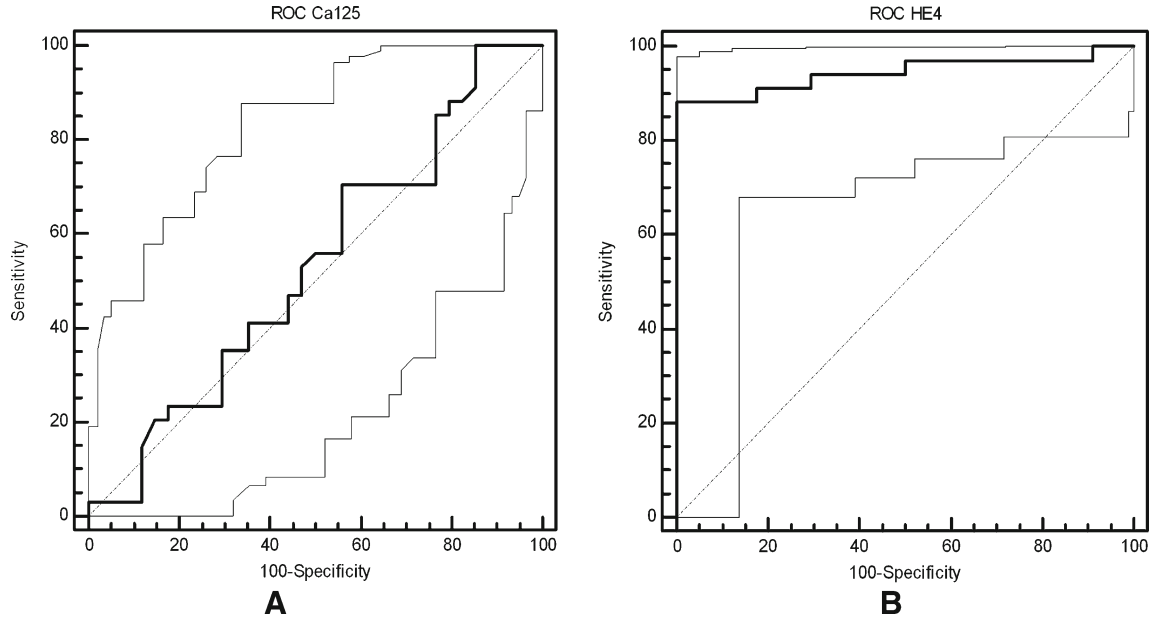

Fig. 2 **a** CA125 statistical specificity and sensitivity analysis studied in the two selected groups of patients showed that the area under the ROC curve was 0.519 (95 %; CI 0.395–0.642). **b** HE4 statistical specificity and sensitivity analysis studied in the two selected groups of patients showed that the area under the ROC curve was 0.874 (95 %; CI 0.771–0.942)

sensitivity and specificity of HE4 and CA125 in detecting recurrent ovarian cancer.

In recurrent ovarian cancer patient group, CA125 levels above the cut-off are detected in 12/34 (35.29 %) patients, achieving 35.29 % of sensitivity.

If we compare our data with the study of Havrilesky et al., we find that their sensitivity is higher (96 %). However, if we look at literature data CA125 sensitivity, based on 38 articles, using 35 U/mL as a cut-off level, is 65 %, with a median lead time of 3 months (range, 1–7 months) [17].

In recurrent ovarian cancer patient group, the sensitivity of HE4 is 73.53 and 26.47 % for 70 and 150 pmol/L cut-off, respectively. The analysis of the specificity shows that HE4 is more effective than CA125 in identifying patients with malignant disease. Furthermore, the specificity and positive predictive value equal to 100 %. Even when analyzing the not neoplastic patients, the HE4 results, above all using the cut-off of 70 pmol/L, show a higher power to not include them if compared with the CA125 with a PPV of 100 % and NPV equal to 79.07 and 57.63 % for the 70 and 150 pmol/L cut-off, respectively.

There are no data in literature about the sensitivity and specificity of HE4 in recurrence of ovarian cancer for comparing our results. In fact, Havrilesky et al. [4] studied the sensitivity in predicting recurrence using a biomarker panel, including HE4, but not considering this marker alone in recurrent ovarian cancer. They also found that in 6/12 patients with positive second look procedures, the biomarker panel predicted residual disease in 50 % compared to 0 % for CA125 [4]. These results are preliminary and further evaluations are needed to confirm them.

Table 4 CA125+HE4 accuracy in detecting recurrent ovarian cancer

	Sensitivity (%)	Specificity (%)
Ca125>35 U/mL+HE4>70 pmol/L	76.47	100
Ca125>35 U/mL+HE4>150 pmol/L	44.11	100

A lot of studies are trying to define the characteristics of HE4 and its applications. In particular, an important problem is to determine HE4 cut-off that provides the best accuracy, in terms of minimal false-negative and false-positive results [18–20].

Havrilesky et al. [4] considered a level of HE4>1.8 ng/mL, as cut-off achieving 82.7 % sensitivity in detecting early stages and 92.5 % sensitivity in detecting advanced stages. Anastasi et al. used 150 pmol/L as HE4 cut-off with 96.9 % sensitivity for patients with OC and 3.7 % sensitivity for patients with other pathologies [10].

On the other hand, Moore et al. used 70 pmol/L as HE4 cut-off, with 72.9 % sensitivity at the specificity of 95 % for detecting early ovarian cancer [18]. On the contrary, Montagnana et al. found that sensitivity and specificity of HE4 using a cut-off of 30 pmol/L were 98 and 100 %, respectively, in patients with early ovarian cancer [19].

In our study, we considered two cut-off: normal values less than 150 pmol/L, according to the manufacturer's indications, and also less than 70 pmol/L, as suggested by Moore et al. [6].

The problem of HE4 cut-off is still open, and more data are needed in order to draw definitive conclusions. Even if a

standard cut-off point has not been determined, this study suggested that HE4 can be a more sensible and specific marker for recurrent ovarian cancer than CA125. According to our ROC curve, the best HE4 cut-off value to detect recurrence of ovarian cancer is 67.1 pmol/L.

The combination of CA125 with HE4 at cut-off of 70 pmol/L can allow us to obtain an assessment of the recurrence of ovarian cancer with a sensitivity of 76.47 % and a specificity of 100 %.

Our study suggests a useful clinical application of HE4 in strategies for surveillance of ovarian cancer recurrence. In particular, HE4 can be used probably to detect recurrent ovarian cancer earlier than CA125 and to have a more effective second-line treatment, even if there are no data about the consequent benefit in terms of overall survival and disease-free survival. Another point of interest of this new serum biomarker HE4 is to evaluate if it can correlate with the amount or disease volume found during the surgery of the recurrence and if it could predict also the respectability. This topic will be object of our future research.

Therefore, this new biomarker can be used to monitor patients with negative CA125 values at first ovarian cancer diagnosis.

In conclusion, the absolute specificity of HE4 may be crucial to select patients at high risk for ovarian cancer recurrence in order to avoid unnecessary explorative surgery and\or radiologic examinations and to be able to refer them to highly specialized oncology centers.

Conflicts of interest None

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