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RESEARCH ARTICLE

The role of novel biomarker HE4 in endometrial cancer: a case control prospective study

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Abstract The aim of the study was to explore the clinical value of serum human epididymis secretory protein E4 (HE4) and CA125 in endometrial carcinoma. From January 2010 to April 2012, serum specimens were collected from consecutive cases of endometrial carcinoma and from cases of uterus benign disease (control group). The CA125 normal value is considered less than 35 U/mL. Two HE4 cutoff are considered: less than 70 pmol/L and less than 150 pmol/L. The specificity analysis was performed using the Mann–Whitney test for the CA125 and HE4 series. The level of statistical significance is set at $p<0.05$. The sensitivity of CA125 in detecting endometrial cancer is 19.8 %, whereas the sensitivity of HE4 is 59.4 and 35.6 % for 70 and 150 pmol/L cutoff, respectively. Thus the specificity of HE4 is 100 % (positive predictive value=100 %, negative predictive value=71.52 and 61.31 % considering the two HE4 cutoff, respectively), whereas the CA125 specificity is 62.14 % (positive predictive value=33.9 %, negative predictive value=44.14 %) in detection of endometrial cancer. Combining CA125 and HE4, the sensitivity to detect endometrial cancer is 60.4 and 34.6 %, at HE4 cutoff of 70 and 150 pmol/L, respectively, with a specificity of 100 %. HE4 may be a new tool for preoperative evaluation and postoperative surveillance of endometrial cancer patients, with a positive predictive value=100 %. HE4 at cutoff of 70 pmol/L yields the best sensitivity and specificity.

Keywords CA125 · HE4 · Endometrial cancer

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Background

In developed countries, endometrial cancer represents the most common gynaecologic cancer [1]. In the USA, approximately 42,160 cases are diagnosed annually; 7,780 deaths occur and over 4,000 new cases are diagnosed in Italy yearly [2]. The diagnosis is usually performed in an early stage and this results in better prognosis, with a 5-year overall survival rate of 80–85 % and a cancer-specific survival rate of 90–95 % [3, 4]. Abnormal bleeding from the uterus after menopause is the most common and early developed symptom of endometrial cancer. However, almost 15 % of endometrial cancers occur in women without vaginal bleeding [5].

The role of tumor markers in endometrial cancer is still debated. However, some serum tumor markers have been studied during recent years. CA15-3 and CA125 have been found to be elevated in only 36 % [6] and 24.6 % [7] of endometrial cancer patients, respectively. Elevated CA125 levels have been demonstrated to correlate with advanced disease [8]. Thus the challenge to find a preoperative tool for endometrial cancer diagnosis and staging is still open.

Human epididymis protein 4 (HE4) is a novel tumor marker that circulates in the bloodstream and is overexpressed in patients with serous and endometrioid epithelial ovarian carcinomas and recurrent ovarian cancer [9, 10]. However, only few studies on HE4 in endometrial cancer exist in literature up

to now. Moore has been the first to investigate the role of HE4 in endometrial cancer, demonstrating an improvement in sensitivity compared with that of CA 125, even if just in endometrioid endometrial cancer [7, 11].

The aims of this prospective comparative study are:

- To evaluate HE4 sensitivity and specificity in all histotypes of consecutive endometrial cancer patients;
- To correlate the preoperative HE4 levels with different prognostic factors: stage of disease, myometrial and cervical invasion, lymph node status, and histotypes.

Materials and methods

Starting January 2010 to April 2012, all patients with endometrial cancer at prior endometrial biopsy, referred to the Division of Gynaecologic Oncology of 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; (2) presence of a secondary malignancy; (3) concomitant benign and/or malignant adnexal pathologies.

All patients had radiologic imaging by pelvic ultrasound. Concerning operative features, all patients diagnosed with endometrial cancer at prior endometrial biopsy underwent surgery consisting in hysterectomy and bilateral salpingo-oophorectomy with complete surgical staging. Staging included also pelvic washing, bilateral pelvic, and/ or para-aortic lymph node dissection. Only patients with complete surgical staging and a pathologically confirmed endometrial cancer were considered in the study. The control group, consisted of age-matched patients with benign uterine disease, received vaginal, laparoscopic, or laparotomic hysterectomy.

The day before surgery, blood samples were obtained. All sera were acquired following a standard collection protocol. Briefly, samples were collected in a red top vacutainer, clotted 60–90 min and centrifuged for 10 min at 1,300×*g*. 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, noncompetitive 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. 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. 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. Several studies are trying to determine for HE4 the cutoff point that provides the best accuracy, in terms of minimal false-negative and false-positive results. For this study, we consider two cutoff: 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. [7].

Using the statistical software MedCalc Software Version No. 11.6.1.0, we firstly analyzed the chance to describe the collected values as normal distributions. The series of CA125 and HE4 values detected in the carcinoma patients did not satisfied the Kolmogorov–Smirnov test for normal distribution. So we performed the analysis using the non-parametric test (Mann–Whitney for independent samples) for comparing the CA125 and HE4 series. The level of statistical significance was set at $p<0.05$. In terms of diagnostic accuracy of the assays, the performance was assessed on the estimation of receiver operating characteristic (ROC) curve for endometrial cancer cases versus uterine benign cases. The area under the ROC curve (AUC) was calculated by MedCalc Software Version No. 11.6.1.0.

Results

Starting January 2010 to April 2012, serum samples were obtained from 101 patients with surgically staged endometrial cancer (study group) and from 103 patients with benign uterine disease (control group). Patients of both groups matched for age (64.9 versus 63 years, not statistically significance), performance status (1 versus 1, not statistically significance), and BMI (23.7 versus 24.2, not statistically significance).

Concerning preoperative blood samples, mean preoperative CA125 plasma concentration for cancer patients is 39.26±57 U/mL (range 1.8–300.5) and mean preoperative HE4 plasma concentration for cancer patients is 128.07± 120 pmol/L (range 12.52–734.12). In this group, CA125 levels above the cutoff are detected in 20/101 (19.8 %) patients, HE4 levels above the cutoff of 70 pmol/L are detected in 60/101 (59.4 %) patients, while HE4 levels above the cutoff of 150 pmol/L are detected in 36/101 (35.6 %) cancer patients.

Table 1 Test accuracy in detecting malignant endometrial disease

	Number (n=101)	Mean	Sensitivity %	Specificity %	PPV * (%)	NPV ** (%)
Ca125>35 U/mL	20	39.27	19.8	62.1	33.9	44.1
HE4>70 pmol/L	60	128.07	59.4	100	100	71.5
HE4>150 pmol/L	36		35.6	100	100	61.3

* Positive predictive value

** Negative predictive value

Mean preoperative CA125 plasma concentration in control group is 36.4±46.04 U/mL (range 3.2–381.7) and mean preoperative HE4 plasma concentration for control group is 40.16±13.99 pmol/L (range 11–59.28). In control group, CA125 levels above the cutoff are detected in 37/103 (35 %) patients; HE4 levels above the cutoff of 70 and of 150 pmol/L are never detected.

The sensitivity of CA125 in detecting cancer patients is 19.8 % whereas the sensitivity of HE4 is 59.4 and 35.6 % for 70 and 150 pmol/L cutoff, respectively. In both cases the specificity of HE4 is absolute (100 %), whereas the CA125 has a lower specificity of 62.14 % with a positive predictive value of 33.9 %. These data are summarized in Table 1.

Comparing CA125 and HE4 levels in the two groups, we did not find a statistically significant difference (p=0.3879) of CA125 levels, but we found a statistically significant difference of HE4 levels (p<0.0001). Distributions of the CA125 and HE4 values in cancer and control groups have been drawn in two graphs (Fig. 1). In Fig. 1a, the 35-U/mL threshold has been drawn to highlight that the majority of carcinoma patients lie below this level.

In Fig. 1b, the HE4 cutoff of 70 and 150 pmol/L have been traced to underline that all control patients remain below the lowest cutoff chosen in this work. HE4 statistical specificity and sensitivity analysis studied in the two selected groups of patients showed that the area under the ROC curve was 0.864 (95 % CI 0.809–0.908) (Fig. 2a).

CA125 statistical specificity and sensitivity analysis studied in the two selected groups of patients showed that the area under the ROC curve was 0.546 (95 % CI 0.475–0.616) (Fig. 2b).

Statistically significant difference has been found (p< 0.0001) comparing CA125 and HE4 ROC-AUC (Fig. 3). Combining CA125 and HE4, the sensitivity to detect endometrial cancer is 60.4 and 34.6 %, at HE4 cutoff of 70 and 150 pmol/L, respectively, with a specificity of 100 %.

Within the 101 patients with surgically staged endometrial cancer, 50 (49 %) were diagnosed with stage I disease, 12 (12 %) with stage II disease, 36 (36 %) with stage III disease, and 3 (3 %) with stage IV disease. Operative features of the two study groups are exposed in Table 2.

Concerning analysis of HE4 values according to prognostic factors, we found a mean serum HE4 value of 85.8 pmol/L for Stage I, 147.8 pmol/L for Stage II, 140.4 pmol/L for Stage III, and 588.3 pmol/L for Stage IV.

Analyzing stage I, patients with stage IA disease (<50 % myometrial invasion) have a significantly lower median serum HE4 value than patients with stage IB disease (>50 % myometrial invasion; 63.4 vs 108.7 pmol/L; p= 0.012). Moreover, we found a statistically significant difference comparing median HE4 value in patients with Stage I versus Stage II (p=0.0011) and in patients with Stage III versus patients with Stage IV (p<0.001) (Table 3).

Concerning the histology, endometrioid cancer patients have a median HE4 value of 130.7 pmol/L comparing with non-endometrioid cancer patients with a median HE4 value of 56.8 pmol/L (p<0.001).

Discussion

Endometrial carcinoma is generally considered a malignancy with favorable prognosis because the majority of patients show their disease early by postmenopausal bleeding and therefore can be diagnosed at the first stage. However,

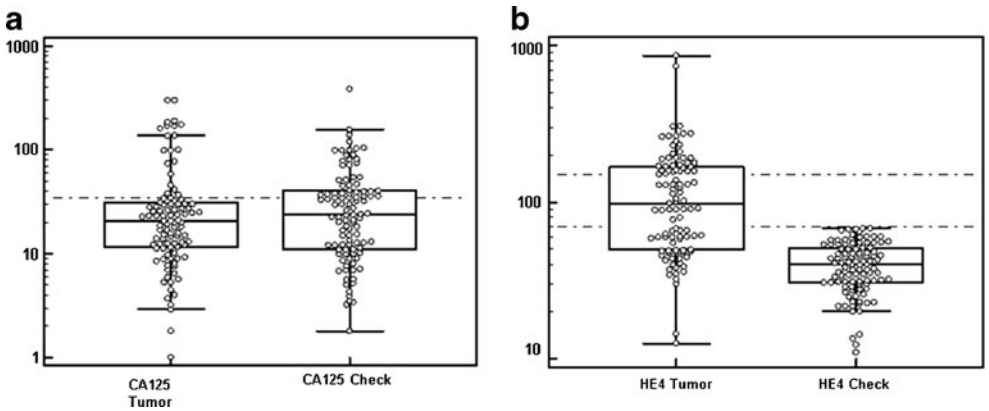

Fig. 1 **a** Comparison among control and carcinoma patients CA125 serum levels. **b** Comparison among control and carcinoma patients HE4 serum levels

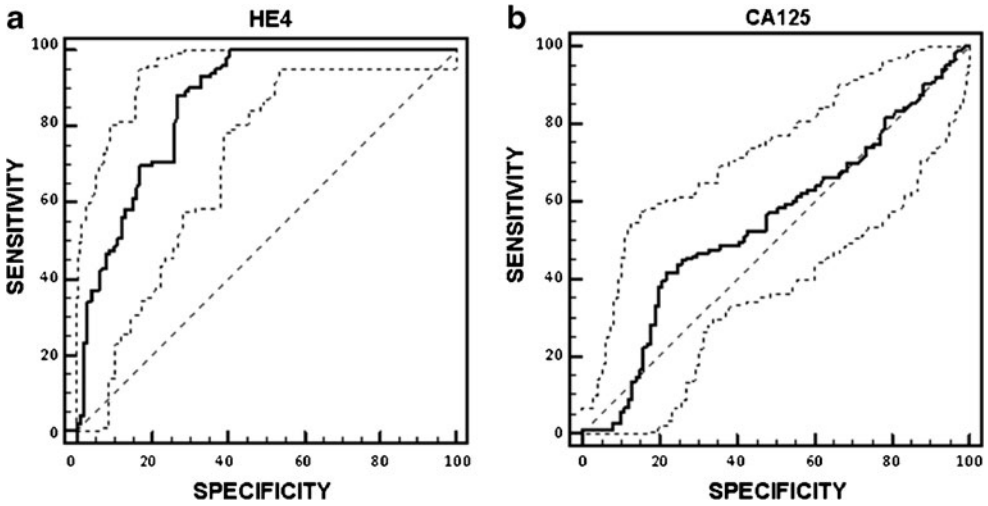

Fig. 2 **a** HE4 ROC curve was 0.864 (95 % CI 0.809–0.908). **b** CA125 ROC curve was 0.546 (95 % CI 0.475–0.616)

almost 15 % of endometrial cancers occur in women without vaginal bleeding [5].

The role of tumor markers in endometrial cancer is still debated, and the challenge to find a preoperative tool for endometrial cancer diagnosis and staging is still open.

In literature, several studies have investigated the role of different serum markers in endometrial cancer such as CEA, CA72.4, CA19.9, CA15.3, and M-CSF, resulting elevated in only 20 % to 30 % of patients [7, 12–18]. The most commonly used tumor marker in endometrial cancer is CA125. Presurgical CA 125 levels were shown to be related to the stage of the disease, myometrial invasion depth, peritoneal cytology, and lymph node metastasis [15, 16, 19–23]. However, another study reports that only 10 % of patients with stage I and II disease have elevated CA125 levels [14]. In addition, Beck et al. demonstrated that only 15 % of stage I uterine cancer patients, 33 % of stage II, and 62 % of stage III patients have elevated CA125 levels [24]. Furthermore, serum CA 125 levels are often elevated in disease-free endometrial cancer patients who have undergone abdominal radiation [25].

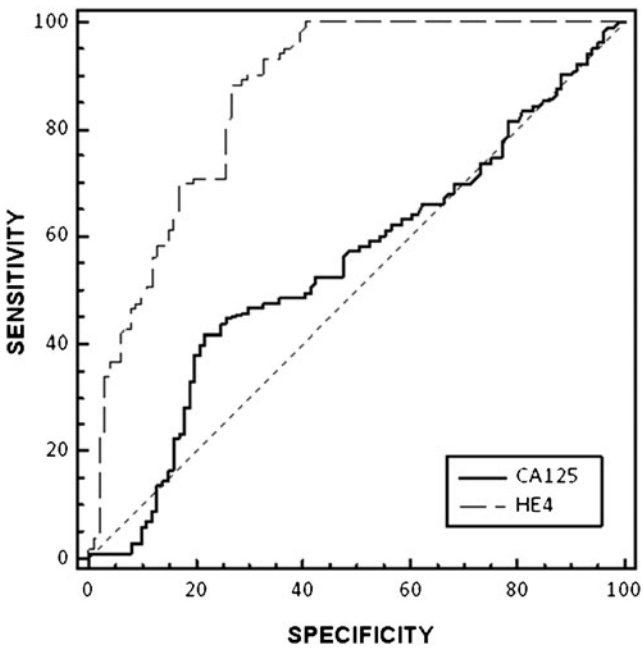

Fig. 3 Comparison of CA125 and HE4 ROC curves

In our study, CA125 sensitivity and specificity in detecting endometrial cancer is 19.8 and 62.1 % respectively, considering all stages. Other serum markers for endometrial cancer, such as HE4, are now under investigation. HE4 is a novel tumor marker that circulates in the bloodstream and it is overexpressed in patients with serous and endometrioid epithelial ovarian carcinomas [9].

In literature, only two studies investigated the HE4 role in endometrial cancer diagnosis. Moore found that HE4 provided 46 % sensitivity for endometrioid adenocarcinoma of the endometrium in all stages at 95 % specificity [7]. Bignotti et al. found that HE4 had a sensitivity of 67 % at a specificity of 95 % compared with CA125 alone, considering all endometrial cancer stages [8]. Moore and Bignotti considered only endometrioid endometrial cancer and used as control group healthy postmenopausal women. Our study is the first in literature that includes all endometrial cancer histotypes and a surgical control group. In the present study, HE4 sensitivity in detecting endometrial cancer is 59.4 % (using 70 pmol/L as cutoff), with a specificity of 100 %.

Concerning the HE4 role in endometrial cancer staging, there are only two studies up to now in literature. Moore et al. found that HE4 differentiated women with less than 50 % myometrial invasion (stage I A) from those with more than 50 % myometrial invasion (stage I B) with 94 % sensitivity and a negative predictive value (NPV) of 97 %. These findings suggest that serum HE4 concentrations greater that 70 pmol/l can be helpful in identifying almost 95 % of patients with stage I disease who ultimately need surgical

Table 2 The clinical characteristics of the study group and control group patients

	Endometrial Cancer Group (n=101)	Control Group (n=103)
Median age (range)	64.9 (34–85)	63.8 (31–74)
FIGO stage		
I	50 (49 %)	–
II	12 (12 %)	–
III	36 (36 %)	–
IV	3 (3 %)	–
Histology		
Endometrioid adenocarcinoma G1	3 (3 %)	–
Endometrioid adenocarcinoma G2	50 (49 %)	–
Endometrioid adenocarcinoma G3	42 (42 %)	–
Non-endometrioid carcinoma	6 (6 %)	–
Benign uterine disease	–	103(100 %)
Type of surgery		
Pelvic lymphadenectomy	101 (100 %)	–
Para-aortic lymphadenectomy	56 (56 %)	–
Vaginal hysterectomy	–	48 (47 %)
Laparotomic hysterectomy	70 (70 %)	32 (31 %)
Laparoscopic hysterectomy	31 (30 %)	23 (22 %)
Myometrial Invasion		
≤1\2	49(48 %)	–
≥1\2	54(52 %)	–
Cervical Involvement		
Negative	65 (64 %)	–
Positive	36 (36 %)	–
Adnexal metastasis		
Negative	95 (94 %)	–
Positive	6 (6 %)	–

staging while excluding more than 95 % of patients who do not [26]. Kalogera et al. found that HE4 is elevated in a high proportion of EC patients and it is correlated with myometrial invasion (>50 %, p<0.001) [27].

Our data confirm the preliminary results of Moore and Kalogera. In fact, in our cancer group, median serum HE4 value is 85.8 pmol/L for Stage I, 147.8 pmol/L for Stage II, 140.4 pmol/L for Stage III, and 588.3 pmol/L for Stage IV. In addition, patients with stage IA disease (<50 % myometrial invasion) have a significantly lower median serum HE4 value than patients with stage IB disease (>50 % myometrial invasion; 63.4 vs 108.7 pmol/L; p=0.012). Moreover, we found a statistically significant difference comparing median HE4 value in patients with Stage I versus Stage II (p=0.0011) and in patients with Stage III versus patients with Stage IV (p<0.001).

We also found that the lymph node status correlates with the HE4 values. In fact, there is a statistical significant difference comparing stage I versus stage III (p<0.001).

These findings suggest that HE4 could be useful as a preoperative indicator to identify patients suitable for pelvic and para-aortic lymphadenectomy. This is further corroborated by a recent study by Kamei et al. who showed that HE4 expression was closely associated with lymph node involvement in breast cancer patients [28].

Moreover, concerning the histology, endometrioid cancer patients have a median HE4 value of 130.7 pmol/L comparing with non-endometrioid cancer patients with a median HE4 value of 86.8 pmol/L (p<0.001). These results are in accordance with the literature evidence of HE4 overexpression in patients with endometrioid histotype in epithelial ovarian carcinomas [9].

In conclusion, our results confirm that HE4 is an accurate and sensitive serum marker for detection of endometrial cancer patients, exhibiting a better diagnostic performance compared to CA125. In particular, HE4 cutoff of 70 pmol/L yields the best sensitivity and specificity, with a positive predictive value of 100 % and NPV equal to 71.52 % for the 70 pmol/L cutoff. We also found that HE4 marker was never increased in patients with benign disease, differently from the CA125 results. Combining CA125 and HE4, the sensitivity to detect endometrial cancer is 60.4 % at HE4 cutoff of 70 pmol/L with a specificity of 100 %.

Our data suggest that serum HE4 may offer preliminary risk stratification prior to definitive surgery. Large prospective clinical studies are certainly necessary to support these findings and to assess the potential of HE4 as a new tool for preoperative evaluation and postoperative surveillance of endometrial cancer patients.

Table 3 Mean HE4 levels and stage correlation

	STAGE I		STAGE II	STAGE III	STAGE IV	p	
MEAN HE4 (pmol/L)	85.8		147.8	140.3	588.3	Stage IA vs IB	p<0.05
	I A	I B				Stage I vs II	p<0.05
	63.4	108.7				Stage II vs III	p=0.07
						Stage III vs IV	p<0.05

Conflicts of interest None

References

1. Bray F, Dos Santos Silva I, Moller H, Weiderpass E. Endometrial cancer incidence trends in Europe: underlying determinants and prospects for prevention. Cancer Epidemiol Biomarkers Prev. 2005;14(5):1132–42.
2. Jemal A, Siegel R, Ward E, Hao Y, Xu J, Thun MJ. Cancer statistics, 2009. CA Cancer J Clin. 2009;59(4):225–49.
3. Creutzberg CL, van Putten WL, Koper PC, Lybeert ML, Jobsen JJ, Wárlám-Rodenhuis CC, et al. Surgery and postoperative radiotherapy versus surgery alone for patients with stage-1 endometrial carcinoma: multicentre randomised trial. PORTEC Study Group. Post Operative Radiation Therapy in Endometrial Carcinoma. Lancet. 2000;355(9213):1404–11.
4. Papanikolaou A, Kalogiannidis I, Goutzioulis M, Misailidou D, Makedos A, Vergote I, et al. Pelvic lymphadenectomy as alternative to postoperative radiotherapy in high risk early stage endometrial cancer. Arch Gynecol Obstet. 2006;274(2):91–6.
5. Smith-Bindman R, Weiss E, Feldstein V. How thick is too thick? When endometrial thickness should prompt biopsy in postmenopausal women without vaginal bleeding. Ultrasound Obstet Gynecol. 2004;24(5):558–65.
6. Scambia G, Benedetti Panici P, Baiocchi G, Perrone L, Greggi S, Mancuso S. CA 15–3 as a tumor marker in gynecological malignancies. Gynecol Oncol. 1988;30(2):265–73.
7. Moore RG, Brown AK, Miller MC, Badgwell D, Lu Z, Allard WJ, et al. Utility of a novel serum tumor biomarker HE4 in patients with endometrioid adenocarcinoma of the uterus. Gynecol Oncol. 2008;110(2):196–201.
8. Bignotti E, Ragnoli M, Zanotti L, Calza S, Falchetti M, Lonardi S, et al. Diagnostic and prognostic impact of serum HE4 detection in endometrial carcinoma patiens. Br J Cancer. 2011;104:1418–25.
9. Drapkin R, von Horsten HH, Lin Y, et al. Human epididymis protein 4 (HE4) is a secreted glycoprotein that is overexpressed by serous and endometrioid ovarian carcinomas. Cancer Res. Kobel M, Kalloger SE, Boyd N, et al. Ovarian carcinoma subtypes are different diseases: implications for biomarker studies. PLoS Med. 2008;5:e23.
10. Plotti F, Capriglione S, Terranova C, Montera R, Aloisi A, Damiani P, Muzii L, Scaletta G, Benedetti-Panici P, Angioli R. Does HE4 have a role as biomarker in the recurrence of ovarian cancer? Tumour Biol. 2012 Aug 9.
11. Duk IM. CA125: a useful marker in endometrial carcinoma. Am J Obstet Gynaecol Oncol. 1994;54(3):321–6.
12. Gadducci A, Ferdeghini M, Caenaro GF, Prontera C, Malagnino G, Annichiarico C, et al. Immunoacid protein (IAP) as marker for cervical and endometrial carcinoma: alone and in comparison with CA 125 and SCC. Cancer J. 1992;5:272–8.
13. Sawada M, Okudaira Y, Matsui Y, Shimizu Y. Immunosuppressive acidic protein in patients with gynecologic cancer. Cancer. 1984;54 (4):652–6.
14. Takeshima N, Shimizu Y, Umezawa S, Hirai Y, Chen JT, Fujimoto I, et al. Combined assay of serum levels of CA125 and CA19-9 in endometrial carcinoma. Gynecol Oncol. 1994;54(3):321–6.
15. Scambia G, Gadducci A, Panici PB, Foti E, Ferdeghini M, Ferrandina G, et al. Combined use of CA 125 and CA 15–3 in patients with endometrial carcinoma. Gynecol Oncol. 1994;54 (3):292–7.
16. Cherchi PL, Dessole S, Ruiu GA, Ambrosini G, Farina M, Capobianco G, et al. The value of serum CA 125 and association CA 125/CA 19–9 in endometrial carcinoma. Eur J Gynaecol Oncol. 1999;20(4):315–7.
17. Hareyama H, Sakuragi N, Makinoda S, Fujimoto S. Serum and tissue measurements of CA72-4 in patients with endometrial carcinoma. J Clin Pathol. 1996;49(12):967–70.
18. Gadducci A, Ferdeghini M, Prontera C, Giordano P, Cristofani R, Bianchi R, et al. A comparison of pretreatment serum levels of four tumor markers in patients with endometrial and cervical carcinoma. Eur J Gynaecol Oncol. 1990;11(4):283–8.
19. Hakala A, Kacinski BM, Stanley ER, Kohorn EI, Puistola U, Risteli J, et al. Macrophage colony-stimulating factor 1, a clinically useful tumor marker in endometrial adenocarcinoma: comparison with CA 125 and the aminoterminal propeptide of type III procollagen. Am J Obstet Gynecol. 1995;173(1):112–9.
20. Peters-Engl C, Buxbaum P, Ogris E, Sevelda P, Medl M. TATI (tumor associated trypsin inhibitor) and cancer antigen 125 (CA 125) in patients with early-stage endometrial cancer. Anticancer Res. 1998;18(6B):4635–9.
21. Ginath S, Menczer J, Fintsi Y, Ben-Shem E, Glezerman M, Avinoach I. Tissue and serum CA125 expression in endometrial cancer. Int J Gynecol Cancer. 2002;12(4):372–5.
22. Sood AK, Buller RE, Burger RA, Dawson JD, Sorosky JI, Berman M. Value of preoperative CA 125 level in the management of uterine cancer and prediction of clinical outcome. Obstet Gynecol. 1997;90(3):441–7.
23. Hsieh CH, ChangChien CC, Lin H, Huang EY, Huang CC, Lan KC, et al. Can a preoperative CA 125 level be a criterion for full pelvic lymphadenectomy in surgical staging of endometrial cancer? Gynecol Oncol. 2002;86(1):28–33.
24. Beck EP, Wagner M, Anselmino L, Xu F, Bast Jr RC, Jaeger W. Is OVX1 a suitable marker for endometrial cancer? Gynecol Oncol. 1997;65(2):291–6.
25. Carpenter PM, Gamboa GP, Dorion GE, Ramsinghani NS, Aïssi AM, Manetta A. Radiation-induced CA 125 production by mesothelial cells. Gynecol Oncol. 1996;63(3):328–32.
26. Moore RG, Miller CM, Brown AK, Robison K, Steinhoff M, Lambert-Messerlian G. Utility of tumor marker HE4 to predict depth of myometrial invasion in endometrioid adenocarcinoma of the uterus. Int J Gynecol Cancer. 2011;21(7):1185–90.
27. Kalogera E, Scholler N, Powless C, Weaver A, Drapkin R, Li J, et al. Correlation of serum HE4 with tumor size and myometrial invasion in endometrial cancer. Gynecol Oncol. 2012;124 (2):270–5. Epub 2011 Oct 28.
28. Kamei M, Yamashita S, Tokuishi K, Hashioto T, Moroga T, Suehiro S, et al. HE4 expression can be associated with lymph node metastases and disease-free survival in breast cancer. Anticancer Res. 2010;30:4779–83.