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ORIGINAL ARTICLE

The diagnostic, prediction of postoperative recurrence and prognostic value of HE4 in epithelial ovarian cancer

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Summary

Purpose: *To explore the clinical value of the level of human epididymis protein 4 (HE4) in serum in the diagnosis, prediction of postoperative recurrence and prognosis of epithelial ovarian cancer (EOC).*

Methods: *A total of 103 EOC patients and 121 individuals with benign ovarian lesions were selected. All of them were admitted to our hospital between January 2013 and January 2014 as group A (EOC, n=103) and group B (benign ovarian lesions, n=121), respectively. Additionally, 106 serum samples collected from healthy people who underwent physical examination were selected as group C. The serum levels of HE4 were assessed one day before and one day after the operation to reveal differences among the three groups. In addition, we analyzed the clinical value of HE4 in the diagnosis, prediction of recurrence and progression-free survival (PFS) of EOC patients.*

Results: *In group A, the level of HE4 was significantly higher than in groups B and C ($p<0.05$), while comparison between the group B and C revealed no statistically significant difference ($p>0.05$). The sensitivity, specificity, positive predictive value and negative predictive value of HE4 in the diagnosis of EOC were 82.52, 84.46, 83.47 and 92.34%, respectively. In the prediction of recurrence of EOC, the sensitivity and specificity of HE4 alone were 87.57 and 92.45%, respectively, while the sensitivity and specificity of HE4 combined with CA-125 were 93.45 and 94.24%, respectively. In addition, the level of HE4 showed a significant negative effect on PFS ($p<0.05$).*

Conclusions: *Detection of HE4 is conducive to the diagnosis and prediction of recurrence of EOC, and HE4 in high concentration suggests poor prognosis.*

Key words: *HE4, ovarian cancer, prognosis, recurrence*

Introduction

Ovarian cancer, a common type of gynecological malignant tumor, is only second to the uterine corpus cancer and cervical cancer in terms of incidence [1]. Ovarian cancer, with the highest mortality rate in all gynecological tumors, severely affects the health and life of females [2,3]. Prone to metastasis and spread, EOC includes almost 50-70% of the ovarian cancers [1]. Based on clinical practice, early effective treatment can improve the prognosis of ovarian cancer patients, but the great obstacle in achieving better results is its silent genesis and progression. Currently, no clinical or laboratory diagnostic method of ovarian cancer in early stage exists, which frequently results in misdiagnosis and/or missed diagnosis. Therefore, most of the patients are diagnosed in advanced disease stages and the treatment will, thus, be more difficult and less efficacious. CA-125, the most common tumor marker of ovarian cancer, shows poor specificity, and its concentration is correlated with

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the tumor stage [4,5]. CA15-3, a carbohydrate antigen, shows varying expressions in ovarian cancer, but bears little significance in the early disease diagnosis for its high false negative rate [6]. In recent years, researchers have reported that HE4 is significantly highly expressed in ovarian cancer tissues, and the serum of EOC patients can be used in the early disease diagnosis utilizing HE4 as a kind of effective marker in ovarian cancer [7-9]. In this study, we investigated the clinical value of HE4 level in serum in the diagnosis, prediction of recurrence and prognosis of EOC.

Methods

General data

Group A consisted of 103 patients with EOC who were admitted to our hospital between January 2013 and January 2014. In this group, patients were aged from 20 to 76 years (mean 42.6±10.5). All patients in group A were diagnostically confirmed with EOC through pathological examination, received no radiotherapy or chemotherapy before surgery, and underwent 6 courses of platinum-containing chemotherapy after the operation. In re-examination, patients were required to have gynecological examination, detection of HE4 and CA-125 in serum one day before and one day after the operation, abdominopelvic ultrasound and computed tomography (CT) or magnetic resonance imaging (MRI) in the abdominopelvic cavity. Follow-up was terminated when recurrence appeared or patient's death, or at the end point of this study (January 2017). All the recruited patients with recurrence were required to have secondary cytoreductive surgery.

Inclusion criteria: a) patients with primary EOC; b) patients without metastasis; c) patients with single EOC and no malignant tumors in other sites; d) patients with no history of cardiac, hepatic, renal or pulmonary diseases or drug allergy. At the same period, 121 patients with benign ovarian lesions who were operated in this hospital were enrolled as group B and their mean age was 39.6±9.5 years (range 23-65). In addition, 106 serum samples were collected from healthy females who were subjected to physical examination during the same period, their mean age being 43.6±10 years (range 25-70). All patients and their families were informed of the objective and the significance of this study, and agreed to participate. This study was approved by the ethics committee of the First People's Hospital of Kashi Prefecture.

Collection and assessment of serum samples

Three mL of fasting venous blood were collected from the subjects of the three groups in the morning (for patients destined to surgery, the collection was performed at 1 day before surgery and 1 week after surgery, and no patient received chemotherapy). For patients in group A, 3 mL of fasting venous blood was additionally collected at the 1st, 3rd, 6th, 12th, 18th, 24th and 36th months after surgery. After collection, samples were centrifuged at 3000 r/min for 15 min. Ten min later, the supernatant was taken away for detecting the level of HE4 in serum using enzyme-linked immunosorbent assay (ELISA), and, simultaneously, CA-125 level was also required to be measured in group A in strict accordance with the instructions of relevant instruments and kits. The upper limits of normal of HE4 and CA-125 were defined according to the instruction of the kit, and were ≥70 pmol/L for HE4 and ≥35 IU/mL for CA-125.

Observation indexes

By comparing the HE4 level in serum among the three groups, we calculated the specificity, sensitivity, negative predictive value and positive predictive value of HE4 in the diagnosis of EOC and to analyze the specificity and sensitivity of HE4 in evaluating the postoperative recurrence of EOC. PFS was defined as the time from the day of surgery to progression of disease or patient death or termination of follow-up.

Statistics

Data analyses were performed using SPSS 19.0, Version X; IBM, Armonk, NY, USA. Qualitative data were presented as mean ± standard deviation, and t-test was carried out for intergroup comparisons. Qualitative data were presented as rates, and chi-square test was used for intergroup comparisons. Kaplan-Meier method with log-rank test were used for survival analysis. A p value <0.05 suggested that the difference was statistically significant.

Results

Comparison of serum HE4 level in patients among the three groups before surgery

The level of HE4 in group A ovarian cancer patients was obviously higher than those in the group B and C, and the difference was statistically significant ($p<0.05$). The comparison of serum HE4 level of patients between the group B and C showed no statistically significant difference ($p>0.05$; Table 1).

Table 1. Comparison of the levels of HE4 in three groups

Group	*Number of patients*	*HE4 (pmol/L) mean±SD*
Group A	103	197.87±12.34*
Group B	121	34.24±8.34§
Group C	106	35.41±9.52†
P1		0.000
P2		0.000
P3		0.573

P1: group A vs group B, P2: group A vs group C, P3: group B vs group C *Compared with group B, p<0.0001; §compared with group C, p<0.573; †compared with group A, p<0.0001

Table 2. The diagnostic efficacy of HE4 (%)

Sensitivity	*Specificity*	*Positive predictive value*	*Negative predictive value*
82.52	84.46	83.47	92.34

Table 3. Comparison of CA-125 and HE4 at different time points

Time after chemotherapy	HE4(pmol/L) mean±SD	*CA-125(IU/mL) mean±SD*	*p value*
1 month	44.23±6.34	24.35±4.23	0.0074
3 months	54.34±2.64	31.69±7.08	0.0093
6 months	71.83±5.23	32.84±4.93	0.0023
12 months	73.57±8.83	35.92±8.23	<0.001
18months	85.63±9.89	51.49±9.10	<0.001
24months	110.79±10.23	68.83±3.56	<0.001
36 months	132.82±7.45	84.19±3.58	<0.001

Table 4. Sensitivity and specificity of HE4 and/or CA-125 for the diagnosis of epithelial ovarian cancer recurrence

Markers	*Sensitivity* %	*Specificity* %
HE4	87.57*	92.4*
CA-125	75.32*	87.84*
HE4+CA-125	93.45	94.24

*compared with HE4 + CA-125, p<0.05

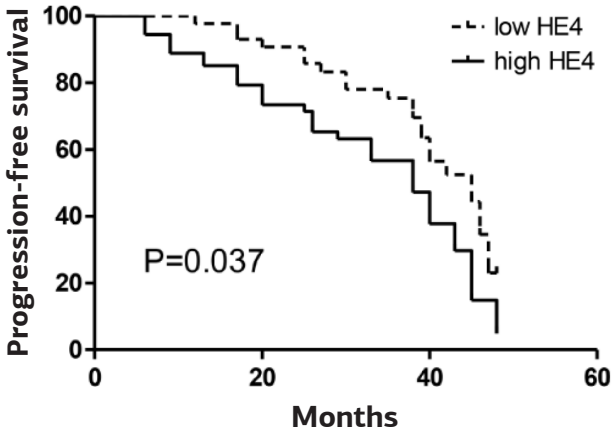

Figure 1. Kaplan-Meier progression-free survival of patients with low or high HE4. Progression-free survival was defined as the time from the day of surgery to progression of disease, death or termination of follow-up.

Diagnostic efficiency of HE4 level for EOC

The specificity, sensitivity, positive and negative predictive values of HE4 in the diagnosis of EOC were assessed through detection of serum samples collected from patients one day prior to surgery, and the sensitivity, specificity, positive predictive value and negative predictive value were 82.52, 84.46, 83.47 and 92.34%, respectively (Table 2).

Diagnostic efficiency of HE4 in postoperative recurrence of EOC

Among 103 patients in group A with primary surgery of EOC, 52 recurred. After sorting out and analyzing the levels of HE4 and CA-125 at different time points (Table 3), it was found that the increase of HE4 level was almost 6 months earlier than that of CA-125 (p=0.0023). In the diagnosis of recurrent ovarian cancer, the sensitivity and specificity of CA-125 were 75.32 and 87.84%, respectively, while those of HE4 were 87.57 and 92.45%, respectively, and those of combined diagnosis using HE4 and CA-125 93.45 and 94.24% (Table 4).

HE4 level in evaluating the prognosis of EOC

With HE4 ≤205.6 pmol/L as the low-level group, and HE4 ≥205.6 pmol/L as the high-level group, we evaluated the correlation between HE4 level and PFS. Among 103 ovarian cancer patients, there were 59 patients in the high-level group and 44 in the low-level group. In the high-level group, the mean PFS was 14.3±7.6 months, while in low-level group it was 25.3±8.2 months, with statistically significant difference (p=0.037; Figure 1).

Discussion

In the early stage, ovarian cancer usually has no significant clinical symptoms, and the complexity in embryonic development and endocrine function of the ovary, plus the interference of multiple hormones, leads to insufficient specificity in the clinical diagnosis in an early disease stage. Thus, most of the patients progress into the middle or advanced stages. With a high mortality rate, ovarian cancer has become one of the most common malignant tumors threatening the health and life of fe-

males. Hence, how to increase the early-stage diagnostic rate of ovarian cancer has become an urgent and hot problem in order to increase the patient survival rate through effective and timely intervention and therapeutic measures in clinical practice.

CA-125 serves as the preferred marker for detection of ovarian cancer for its high expression in epithelial cancer cell membrane and detecting its serum level is conducive to the diagnostic and prognostic evaluation of this disease [10]. However, the level of CA-125 changes with the occurrence, regression, proliferation and recurrence of ovarian cancer, which limits the single use of CA-125, not forgetting its poor specificity [11]. CA-125 can give frequently positive results in non-ovarian diseases, such as pelvic inflammation, gastrointestinal tumors and benign ovarian tumors, while 40-60% of ovarian cancer patients have negative CA-125. Thus, discovering a better marker in combination with CA-125 for the diagnosis of ovarian cancer is of great clinical significance for increasing the sensitivity and specificity of diagnosis [12,13]. HE4 is a newly-discovered tumor marker in ovarian cancer. Rosen et al. [11] examined 296 ovarian cancer patients by immunohistochemistry and found that CA-125 was highly expressed in ovarian cancer tissues, while HE4 was highly expressed in tissues not expressing CA-125. This result suggested that HE4 has a higher specificity in comparison with CA-125, and additionally, it can supplement the diagnosis *via* CA-125. HE4, firstly been isolated from the epididymal epithelial cells, is a kind of secretory protein in the Whey acidic protein family, and has differential expressions in ovarian cancer tissues [14] and thus can serve as diagnostic indicator of ovarian cancer. Research has confirmed that the sensitivity and specificity of HE4 in the diagnosis of ovarian cancer can be as high as 80-90%, suggesting that HE4 has a promising value in clinical diagnosis [7]. The result of this study revealed that HE level in ovarian cancer patients was significantly higher than those in groups B and C, and over 80% of patients with ovarian cancer in advanced stage gained clinical remission after regular surgical treatment and standard chemotherapy. However, within 2 to 5 years after treatment, most of the patients would suffer from recurrent disease. Therefore, proper management aiming to discovering recurrence in an early stage is necessary for those patients. At present, no unified criteria have been developed in monitoring the recurrence of ovarian cancer. Among patients suffering from recurrent ovarian cancer, abnormal increases would emerge in various tumor markers including CA-125 and HE4 within 6 to 9 weeks ahead of the appearance of clinical symptoms and positive imaging examinations. Therefore, monitoring the level of HE4 in serum can detect the recurrence earlier, thereby identifying the optimal time of secondary cytoreductive surgery to avoid the unnecessary second-look laparotomy.

From the results of this study, we could find that 6 months after surgery, the level of HE4 was increased, which was significantly earlier than that of the increase in CA-125. In this study, we also analyzed the correlation between HE4 level and the prognosis of ovarian cancer patients and found that the level of HE4 influences the prognosis of patients: in the low-level group, the median PFS was 22.3 months, significantly longer than that of 16.3 months in the high-level group, and the difference had statistical significance ($p<0.05$).

Conclusions

In conclusion, HE4 has impressive value for the diagnosis, condition-monitoring and prognostic analysis of ovarian cancer, and serves as the follow-up indicator for recurrence of this disease. Hence, with such a great clinical significance, HE4 detection is worthy of being promoted in clinical practice.

Conflict of interests

The authors declare no conflict of interests.

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