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RESEARCH ARTICLE

COMPARISON OF SERUM HE4 AND CA125 LEVELS IN THE DETECTION OF RECURRENT OVARIAN CANCER

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ABSTRACT

Human Epididymis Protein (HE4) is a new promising biomarker in detecting recurrent ovarian cancer. In this study, we investigated the role of serum HE4 in comparison to CA125 in the detection of recurrent disease in patients during follow-up.615 ovarian cancer patients treated at Shandong Provincial Tumor Hospital between 2008 and 2014 were included in the retrospective study. Serum HE4 and CA125 were analyzed during follow-up using the ARCHITECT assay. 131 patients developed recurrent disease. Results showed that a serum HE4 level of 70pmol/L was associated with a sensitivity of 76.3%, a specificity of 89.6%, a negative predictive value of 93.3% and a positive predictive value of 66.6% when assessing for recurrent ovarian cancer whereas CA125 was associated with a sensitivity of 54.9%, a specificity of 79.3%, negative predictive value of 86.6% and a positive predictive value of 41.8%. However, combining CA125 and HE4 at a cut-off of 70pmol/L, the sensitivity, specificity, negative predictive value and positive predictive value increased to 83.9%, 90.9%, 95.4% and 71.4% respectively. These data suggest HE4 is a more sensitive and specific predictor of recurrent disease and should therefore be incorporated with CA125 in detection of recurrent ovarian cancer.

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INTRODUCTION

Ovarian cancer is the fifth leading cause of cancer death in women. Of all the gynecological cancers it has the highest mortality (Bertone-Johnson, 2005). Estimated new cases of ovarian cancer in the US in 2014 were 21 980, estimated deaths from ovarian cancer in the US in 2014 were 14 270 (Cancer statistics, 2014). As a result of improved surgery and combination chemotherapy with carboplatin and paclitaxel, the 5-year survival rates have improved significantly from 37% in the 1970s to 45% at the turn of the century (Archana *et al.,* 2013).While over 80% of advanced stage ovarian epithelial cancer patients attain clinical remission with standard platinum/paclitaxel based chemotherapy (Chemotherapy, 2000), the vast majority of them relapse within two to five years (Ozols *et al.,* 2013; Cannistra, 2004). CA125 elevation often precedes clinical evidence of relapse by imaging or physical examination in roughly 80% of patients with ovarian cancer (Rustin *et al.,* 2001; Tuxen *et al.,* 2000; Bridgewater *et al.,* 1999). While CA125 has proved helpful in detecting recurring ovarian cancer, its low specificity, particularly in premenopausal women, as it could also be elevated above normal in a number of benign gynecological conditions and in other malignancies (Buamah, 2006) calls for the need of a new biomarker for ovarian cancer. CA125 levels are also elevated in both benign and malignant tumors, as well as other inflammatory conditions of the peritoneum, pleura and pericardium (Buamah, 2006). Ovarian cancer, like diabetes and hypertension, is a chronic illness. The paucity and insidious onset of symptoms of recurring ovarian cancer make it difficult to diagnose and manage the disease. Human Epididymis Protein 4 (HE4), highly expressed in the human epididymis, is a secreted protein over expressed in patients with endometrioid epithelial ovarian cancer and uterine cancers. HE4 is emerging as a promising biomarker in addressing the unmet clinical needs in recurring ovarian cancer. When four biomarkers, CA125, HE4, MMP-7 and mesothelin were monitored in patients with advanced stage ovarian cancer following surgery and chemotherapy, HE4 rose prior to recurrence with a lead -

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time of 4.5 months. HE4 was elevated prior to the rise of CA125 in some patients. For a fraction of patients whose CA125 and imaging were negative, HE4 levels stayed at or above cut off (Schummer *et al.,* 2012). A recent prospective controlled study showed that HE4 was able to detect recurrent ovarian cancer with 74% sensitivity and 100% specificity at a cut off of 70pmol/L. A combination of HE4 and CA125 increased overall sensitivity to 76% (Plotti *et al.,* 2012). In a study of 80 ovarian cancer patients, Allard et al. found HE4 to compare well to CA125 for recurrence detection, including patients where CA125 was of no utility (Allard *et al.,* 2008). In a study of 31 ovarian cancer patients, Anastasi *et al.* found HE4 to rise 5-8 months before CA125 (Anastasi *et al.,* 2010). A combination of CA125 and HE4 may offer better lead times and sensitivity for the detection of recurrent ovarian cancer. HE4 has emerged as a promising biomarker in complementing CA125. This study was aimed at studying HE4 marker levels and to determine its effectiveness in complementing CA125 in monitoring patients with recurrent ovarian cancer.

MATERIALS AND METHODS

Study population

The study population consisted of 615 female patients (age range, 41-74 years). They had been treated at the Gynecology department of Shandong Provincial Cancer Hospital between 2008 and2014.They were entered onto the study at the time of their diagnosis or during a return visit within 6 years of initial diagnosis. The patients were selected based on the availability of medical records and consecutive blood samples, pre and post confirmation of recurrence, for those admitted for recurrence. Medical records were reviewed for CA125 levels, chemotherapy status, disease status and period free interval over a multi-year period.40% of the patients' first initial surgery was performed in our hospital by gynecologic oncologists, followed by 6 to 8 cycles of adjuvant chemotherapy(carboplatin/paclitaxel or carboplatin/docetaxel), then remission. The extent of surgery depended on the disease stage, risk classification and ability of patient to withstand surgery. Surgery included at least total hysterectomy, bilateral salpingo–oophorectomy, bilateral adnexectomy, total omentectomy including supracolic omentum, appendicectomy, debulking of tumor masses and dissection of pelvic lymph nodes. Patient follow-up was performed once every three months for the first 3 years, once every six months from year 3 to 5 and afterwards, once every year. They were followed up by frequent CT scans, blood tests, CA125 and HE4 and thereafter, grouped into two groups, recurrent and non-recurrent. Recurrent group included those whom after a disease free interval of 3or more months, physical examination and /or imaging (CT,PET or MRI) resulted in the subsequent detection of a recurring mass even and especially when the CA125 levels remained within normal range 0-35 U/ml. Name, age, disease stage, histology, grade, treatment, date of recurrence were recorded. Informed consent and agreement was taken to have additional testing for new markers. This study was approved by our Institution Review Board. 131patients (21.3%) developed recurrence, 484(80.3%) remained disease free. Recurrent disease was defined as a histo-pathologically confirmed disease after a disease free interval of 3 or more months. Median follow up time was 4 years. Histological characteristics of the 131 patients are outlined below (Table 1) Histological classification was in accordance to WHO criteria and the stage of disease was in accordance with FIGO guidelines.

Table 1. Histology and staging of 615 patients

Characteristic	Value
Age in years, median	58
Range	36-79
Histological type(n)	
Serous adenocarcinoma	264(42.9%)
Endometrioid adenocarcinoma	152(24.7%)
Mucinous adenocarcinoma	113(18.4%)
Clear cell adenocarcinoma	86(14.0%)
FIGO stage at diagnosis	
I	151(24.6%)
II	244(39.7%)
III	136(22.1%)
IV	84(13.6%)

Abbreviations: FIGO (International Federation of Gynecology and Obstetrics)

Statistical analyses

Statistical analyses were performed using IBM SPSS Statistics version 22.0.The relative serum tumor marker levels were compared using the Wilcoxon signed-rank test as they did not follow a normal distribution, A p value <0.05 was considered statistically significant. The threshold for positive diagnosis by CA125 was set at 35U/mL,as is routinely used in our hospital. There is no recommended cut-off value for HE4. In apparently healthy females, a cut-off value of 70 pmol/L has been suggested (Francesco Plotti *et al.,* 2012; Shin Hye Chung *et al.,* 2013; Gadducci *et al.,* 2004). However the values change depending on the study population. For the purposes of our study, serum HE4 at a cut-off point of 70pmol/L was considered. Receiver operator curves (ROC) were used to compare the ability of HE4 and CA125 to identify patients with recurring disease.

RESULTS

615 patients were included in our study. 496（78.7%） patients remained disease free. 131（21.3%） developed recurrence. 72 out of the 131（54.9%） had elevated CA125. 99 out of 131(75.6%) had elevated serum HE4 using 70pmol/L as the cut-off. Patients with recurrence were older and more likely had late stage carcinoma at presentation. No significant histological differences were noted between patients who developed recurrent disease in comparison to those who remained disease free (Table 2). From the medical records, we noted that mean serum HE4(219.6 pmol/L; 95% CI) was significantly elevated in the recurrent group compared to the disease free group (59.4 pmol/L; 95% CI). There was also a significant difference between mean serum CA125 (392.4U/mL; 95% CI) in the recurrent group as compared to the non-recurrent group(26.4U/mL; 95% CI) (Figure 1a and 1b). The serum levels of the biomarkers were evaluated by the receiver operator characteristic curves (ROC). The ROC curve of HE4 was located closer to the theoretical 100% sensitivity and specificity value than the ROC curve of CA125.For all patients, area under the curve (AUC) analysis of HE4

vs.CA125 measured during follow-up revealed an increased AUC for HE4(AUC 0.83; 95%)compared to CA125 (AUC 0.78; 95%), suggesting clinical usefulness of both markers for diagnosing recurrence (Figure 2). The two biomarkers both rose prior to recurrence and dropped after subsequent surgery and adjuvant treatment. CA125 is the gold standard biomarker used to detect recurrence.

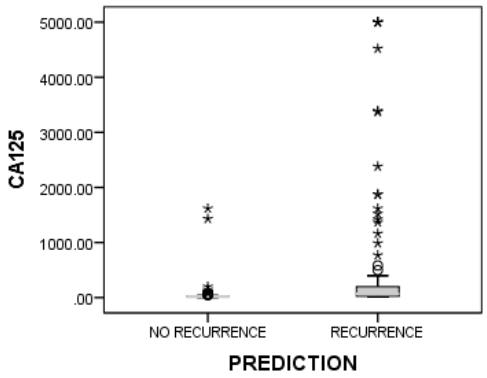

Figure 1a.

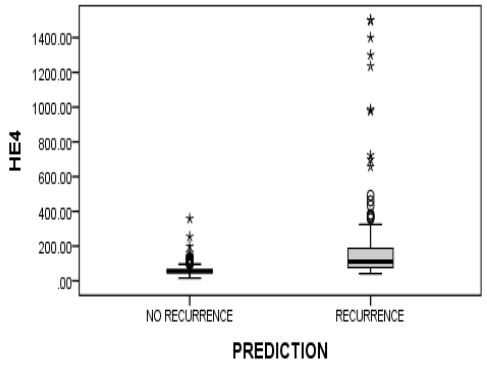

Figure 1b.

Figure 1. Box plots of HE4 and CA125 levels with bars demonstrating 95% confidence intervals demonstrating behavior of the two biomarkers in patients who developed recurrent disease (n=131) and those who remained disease free (n=484)

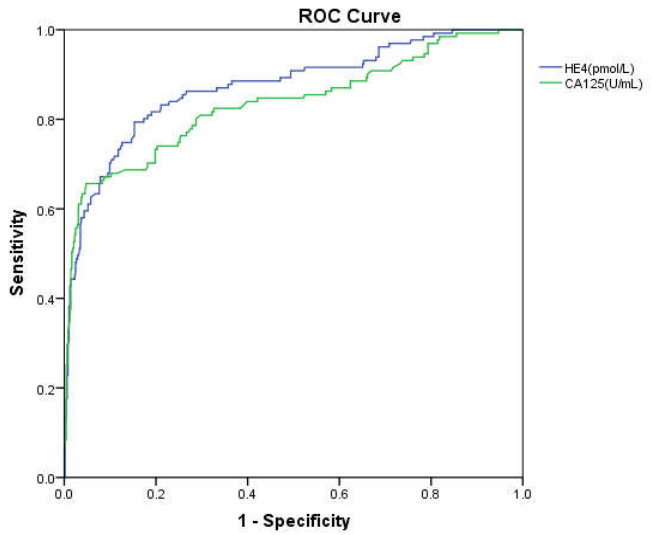

Figure 2. Receiver operator characteristic curve of HE4 and CA125 in patients with recurrent ovarian cancer. The ROC curve of HE4 was located closer to the theoretical 100% sensitivity and specificity value than the ROC curve of CA125

In 59(45.0%) of the cases with recurrence though, we noted that CA125 did not elevate to indicate recurrence. 23(38.9%) of those cases had an elevated serum HE4 using 70pmol/L as the cut-off point. On the other hand, in 32(24.4%) of the cases with recurrence, HE4 stayed within normal limits whereas CA125 in 12(37.5%) of those cases indicated recurrence. These show that the two biomarkers should both be incorporated in the diagnosis of recurrent cancer so that they complement each other.

Table 2. Patient characteristics based on recurrence status

	No recurrence	Recurrence	P value
Age in years, median	58	58	0.4
Range	36-76	38-79	
FIGO Stage			
I	126(26.7%)	22(16.8%)	<0.001
II	196(40.5%)	48(36.6%)	
III	112(23.1%)	24(18.3%)	
IV	47(9.7%)	37(28.3%)	
Histology			
Serous adenocarcinoma	199(41.4%)	65(49.6%)	<0.001
Endometrioid carcinoma	111(22.9%)	41(31.3%)	
Mucinous adenocarcinoma	102(21.1%)	11(8.4%)	
Clear cell carcinoma	72(14.9%)	14(10.7%)	

Table 3. Sensitivity, specificity, positive predictive values and negative predictive values of the serum biomarkers

	HE4>70	CA125>35	Combined HE4 and CA125
Sensitivity (%)	76.30%	54.9	83.9
Specificity (%)	89.60%	79.3	90.9
Positive Predictive Value (%)	66.6	41.8	71.4
Negative Predictive Value (%)	93.3	86.6	95.4

The sensitivity and specificity of HE4 to indicate recurrence during follow-up was assessed using a threshold of 70pmol/L as previously published (Francesco Plotti *et al.,* 2012; Shin Hye Chung *et al.,* 2013; Gadducci *et al.,* 2004). A serum HE4 level of 70pmol/L was associated with a sensitivity of 76.3%, a specificity of 89.6%, a negative predictive value of 93.3% and a positive predictive value of 66.6% when assessing for recurrent ovarian cancer. CA125 was associated with a sensitivity of 54.9%, a specificity of 79.3%, negative predictive value of 86.6% and a positive predictive value of 41.8%. Combining CA125 and HE4 at a cut-off of 70pmol/L, the sensitivity to detect recurrent ovarian cancer increased to 83.9%, the specificity to 90.9%, negative predictive value to 95.4% and the positive predictive value to 71.4%. (Table 3) This shows that the best results are obtained when the two biomarkers are used in conjunction.

DISCUSSION

Monitoring of ovarian cancer patients focuses on early detection of recurrent disease, which occurs in 17-21% of women, mainly 2-5 years after primary treatment. The earlier the diagnosis of recurrence, the better the prognosis. Most of the patients, however, experience no worrisome symptoms.By the time they present to the hospital, they have a higher volume of disease thereby increasing mortality and morbidity. There is need therefore for a quick, affordable diagnostic test for recurrent ovarian cancer. A serum biomarker to identify

recurrent disease would be of immense clinical value. In the present study, HE4 displayed some advantages over CA 125 for predicting a recurrence. In some cases, the HE4 was elevated but the CA 125 caused no alarm. Further examinations proved a recurrence. In some few cases though, CA125 was elevated, HE4 was not but imaging studies and/or physical examination confirmed a recurrence. HE4 showed some advantages over CA125 in detecting recurrence but the best results were obtained when it was used in association with CA125(sensitivity and specificity increased to 83.9% and 90.9% respectively). Similar results have been cited in non-Chinese populations (Anastasi *et al.,* 2010; Francesco Plotti *et al.,* 2012). HE4 threshold of 70pmol/L was chosen to identify recurrence as it has been previously used by others to identify recurrent disease (Francesco Plotti *et al.,* 2012; Shin Hye Chung *et al.,* 2013; Gadducci *et al.,* 2004) and has proved to be more sensitive and specific at that threshold. These data suggest that HE4 may be an effective biomarker in post treatment surveillance of ovarian cancer especially when used with CA125.Further studies are required to validate the 70pmol/L threshold and to investigate the importance of dynamic changes in HE4 over time. The strengths of the study include the fact that this is one of the first few studies comparing HE4 and CA125 in recurrent ovarian cancer to use such a relatively large cohort. Also, most of our patients were surgically staged and serum samples were managed in a relatively standardized version. This study had some limitations. Some patients were not cooperative and often missed their clinic times. Furthermore, it was a single institutional study and we only had access to samples at two to three time points and were thus unable to assess dynamic changes in HE4 and CA125 as predictors of recurrence. In addition, no statistical analysis was performed according to the histological subtype. Finally, the age was not included and this could have influenced the serum HE4 level.

Conclusion

In conclusion, this data is a preliminary description of HE4 in comparison to CA 125 and suggest it might be clinically relevant in proving recurrent ovarian cancer and that elevated HE4 levels even in the absence of elevated CA 125, should not be ignored. The two biomarkers should be used in conjunction to effectively diagnose recurrences.

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