

## Predicting value of HE4 and CA125 markers for optimal cytoreductive surgery in ovarian cancer patients

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### Abstract

We conducted a cross-sectional study to evaluate the role of serum levels of CA125 and HE4 in predicting optimal cytoreductive surgery. Eligible women who had been diagnosed with ovarian cancer based on both clinical and imaging criteria were enrolled in this study. Serum levels of CA 125 and HE4 were checked before surgery and all patients underwent complete surgical staging. After completion of the pathological evaluation, data were entered in SPSS version 23. One hundred and ten individuals were enrolled in our study. We divided cases between two groups: stage I to III b and stage IIIc to IV. Serum level of HE4 >170 pmol/L can predict optimal cytoreductive surgery before operation. (sensitivity:80% and specificity 70%) and serum level of CA 125 > 320 UI/mL can predict optimal cytoreductive surgery before operation. (sensitivity:80% and specificity 70%). Our data demonstrated a negative predictive value of about 80% for both HE4 and CA125. Based on these cut-off, unnecessary surgery can be avoided in many cases, however, it is unwise to ignore clinical performance and radiological findings. Nevertheless, we can say the evaluation of tumor markers is feasible and helpful in predicting optimal surgery.

**Key Words:** HE4; CA 125 Ovarian neoplasm; optimal cytoreduction.

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Ovarian cancer is the second most common gynecologic cancer in developed countries with incidence and mortality rate 9.1 and 5 per 100.000 respectively. It is the third most common gynecologic cancer in developing countries with incidence and mortality rate 5 and 3 per 100.1000 respectively.<sup>1</sup> It is assumed that the overall survival in ovarian cancer is related to the stage of the disease. Five-year-overall survival for stage I, II, III, IV, are roughly 90%, 80%, 40%, and 35% respectively.<sup>2</sup> Based on a prevailing consensus, optimal cytoreductive surgery is one of the most crucial and determinative factors of the fatality rate in ovarian cancer. Every 10 % increase in cytoreduction, surges the overall survival about 5.5%.<sup>3</sup> Several factors contribute to the difficulty in proving the value of cancer screening and tumor markers such as Cancer Antigen 125 (CA 125) and Human Epididymis Protein 4 (HE4) and Risk of Ovarian Malignancy Algorithm (ROMA) index in ovarian cancer. But experts tried to use them for predicting optimal cytoreductive surgery. HE4 is a new tumor marker which increases in malignant epithelial

ovarian cancer and although its role has not been known completely, is introduced as a helpful marker in recurrence of ovarian cancer.<sup>4</sup> A multi-centric study composed of 387 cases demonstrated the superiority of HE4 over CA125 in diagnosis of epithelial ovarian cancer.<sup>5</sup> In 2009 ROMA index was introduced. ROMA is an algorithm composed of CA125 and HE4 and menopausal status for detecting malignancy rate of ovarian neoplasm before surgery.<sup>6</sup> Recently, some study claimed that there is no difference between specificity of CA125 and ROMA in diagnosing malignancy in ovarian neoplasm (92.5%).<sup>7</sup> Another study revealed that although ROMA index had more sensitivity than HE4, (96.7 versus 73.3) its specificity is less than HE4 (98.6% versus 80%).<sup>8</sup> It seems that CA 125 and HE4 are more helpful than ROMA index in detecting malignancy of ovarian neoplasm before surgery. A substantial body of opinion supports this idea that HE4 serum level can predict malignancy in ovarian cancer before surgery with sensitivity 76%.<sup>9</sup> The difficulties of management of advanced ovarian cancer led to a new definition in cytoreductive surgery in which, the size of maximum

residual tissue < 2 cm changed into no macroscopic residual tumor.<sup>10</sup> Advanced ovarian cancer has raised a multitude of questions about contemplating the best procedure and taking some drastic measures. There is no consensus among experts. Several studies shed some light on the matter of performing laparoscopy in advanced ovarian cancer, but laparoscopy is an invasive procedure with its own risks.<sup>11</sup> Abdominal pelvic Computerized Tomography (CT) has been used profusely to reveal omental cake, liver metastasis, retroperitoneal lymphadenopathy but there is no consensus that CT scan may predict whether the tumor is operable or not.<sup>12</sup>

Because all those previous studies suggest to find a cut-off level for pre-surgical diagnosis, we designed a cross-sectional study to evaluate the role of serum levels of CA125 and HE4 in predicting cytoreductive surgery.

## Materials and Methods

### Study Design

We conduct a cross-sectional study in a tertiary center hospital in Tehran, Iran, between 2015 – 2020. In this study, codes of ethics were obtained and general guidelines of ethics in medical science research were followed. This proposal has been approved by the ethical committee in our research center with the code of IR.IUMS.FMD.REC.1399. 843. The project was approved by the research department of the Faculty of Medicine. Informed consent was obtained from patients. One hundred and ten patients with ovarian neoplasm were enrolled in this study. All of them were referred from other centers with the diagnosis of ovarian neoplasm made by transvaginal sonography (TVS) or CT scan. Just for the matter of giving transparency in the diagnosis process to build up trust, we performed TVS again in our center as conceivable imaging to confirm pre-surgical diagnosis of ovarian neoplasm.

### Inclusion and exclusion criteria

The inclusion criteria were as follows: individuals between 20-80 years old of age who were diagnosed with ovarian neoplasm based on clinical and pathological characteristics, eligible for complete staging surgery or cytoreductive surgery composed of unilateral cystectomy/oophorectomy for benign neoplasm and hysterectomy, bilateral salpingo-oophorectomy, omentectomy and retroperitoneal lymphadenectomy in malignant ovarian neoplasm. Exclusion criteria included smokers, history of hepatic, cardiac, or renal insufficiency, history of prior malignancy at other parts of the body, patients who did not have acceptable performance before surgery and took neo-adjuvant chemotherapy, and patients with thromboembolism.

### Method description and data collection

For all cases, serum levels of CA 125 and HE4 were checked one week before surgery just in one laboratory. The blood sample was analyzed through

chemiluminescent micro-particle immunoassay specific mean for CA125 (ARCHITECT CA125II assay; Abbott GmbH, Wiesbaden, Germany) or HE4 (ARCHITECT HE4 assay; Abbott GmbH Wiesbaden, Germany). After completion of the surgery, all ovarian neoplasms were evaluated by one pathologist who was an expert in Gynecology Oncology. Several variables such as benign or malignant morphology, stage of malignancy, histological type of tumor, grade of tumor, and lymph node involvement were collected.

### Statistical analysis

Data were gathered and then entered SPSS version 23. Numerical variables were evaluated by Mean  $\pm$  Standard Deviation (SD) and categorical variables by count & percentage. T-test and Chi-2 (or Exact Fisher) test were used for quantitative and qualitative variables, respectively. ANOVA and T-tests were used for evaluating the association between serum levels of tumor markers and clinic-pathological factors after surgery. To assess the predictive value (sensitivity, specificity, positive, and negative predictive values) of tumor markers, a cut-off of serum level of each one was extracted for prediction of optimal surgery, using the ROC curve (Receiver Operating Characteristic curve) considering its AUC (area under the curve), and  $p < 0.05$  was considered significant.

## Results

A total of 110 patients were enrolled in this study. They were between 20-80 years old. The mean and standard deviation for age was  $49.1 \pm 13.8$ . The mean for CA125 serum level was  $732.82 \text{ UI/mL} \pm 1293.29$ , and the mean for HE4 serum level was  $597.78 \text{ pmol/L} \pm 1049.25$ .

Table 1 shows clinicopathological factors of patients' and their association with serum levels of HE4 and CA125. The serum level of HE4 was significantly higher in malignancies with lymph node involvement ( $p = 0.003$ ), omental involvement ( $p = 0.001$ ), and in papillary serous tumors ( $p = 0.001$ ) and in higher stage ( $p = 0.005$ ), while there was no significant association between HE4 level with histopathological grade ( $p = 0.015$ ). There was no significant association between CA125 level with lymph node involvement, omental involvement, stages, grade and type of tumor. Among all 110 women enrolled in our study, 9 patients (8.2%) had benign ovarian neoplasm, 7 patients (6.4%) had a borderline ovarian cancer and 94 patients (85.5%) had malignant ovarian neoplasm. Patients with benign ovarian neoplasms were excluded and we carried out the analysis on 101 cases. Based on the tumor type, in 94 cases with malignant neoplasm, 54 cases had papillary serous subtype, 9 cases had endometrioid adenocarcinoma, 8 cases had clear cell carcinoma and the rest of the cases had other types of ovarian cancer.

Given the abundant evidence, unlike women with stage I to IIb, in patients with stage IIIc or stage IV, optimal cytoreductive surgery may be out of reach. Therefore, it

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**Table 1.** Clinic-pathologic factors and their association with serum level of HE4 and CA 125.

Variables	Number	Mean± SD		
		HE4	CA 125	
Age:	< 50	48	338.96 ± 518.80	739.96 ± 1681.06
	≥ 50	53	832.17 ± 1325.17	726.35 ± 813.76
	P-value		<b>0.018</b>	0.958
Tumor Type:	Papillary	54	917.04 ± 1317.94	906.64 ± 1087.37
	serous			
	Other types	47	230.97 ± 367.94	533.12 ± 1482.41
P-value		<b>0.001</b>	0.149	
Grade:	1	22	231.78 ± 280.68	410.09 ± 616.02
	2	7	503.00 ± 497.55	962.23 ± 1196.37
	3	72	718.82 ± 1203.80	809.13 ± 1441.94
	P-value		0.158	0.402
Lymph node involvement:	Positive	41	970.65 ± 1465.17	943.66 ± 1134.26
	Negative	60	342.98 ± 497.94	588.74 ± 1382.27
	P-value		<b>0.003</b>	0.177
Omental involvement:	Positive	47	978.27 ± 1394.84	957.59 ± 1134.23
	Negative	54	266.60 ± 385.34	537.19 ± 1308.38
	P-value		<b>0.001</b>	0.103
Stage:	I	40	203.44 ± 341.65	477.44 ± 1599.59
	II	11	365.82 ± 448.01	561.43 ± 564.20
	III	45	955.09 ± 1412.33	969.92 ± 1101.87
	IV	5	1047.00 ± 742.01	1019.00 ± 1117.37
	P-value		<b>0.005</b>	0.323

is assumed that in advanced ovarian cancer, neoadjuvant chemotherapy followed by cytoreductive surgery is more acceptable.

Thus, in Table 2 we divided cases between two groups: stage I to III b and stage IIIc to IV. This table revealed that serum level of HE4 >170 pmol/l can predict optimal cytoreductive surgery before operation. (sensitivity:80% and specificity 70%) and serum level of CA 125 >320 UI/mL can predict optimal cytoreductive surgery before operation (sensitivity: 80% and specificity 70%).

Considering the ROC curve analysis, AUC (area under the curve) and 95% CI (confidence interval) of the lower stage (I-IIIb) in comparison with the higher stage (IIIc-IV) HE4 and CA125 were 82.3% (74.1-90.5) and 79.3% (70.3-88.2), respectively (Figure 1).

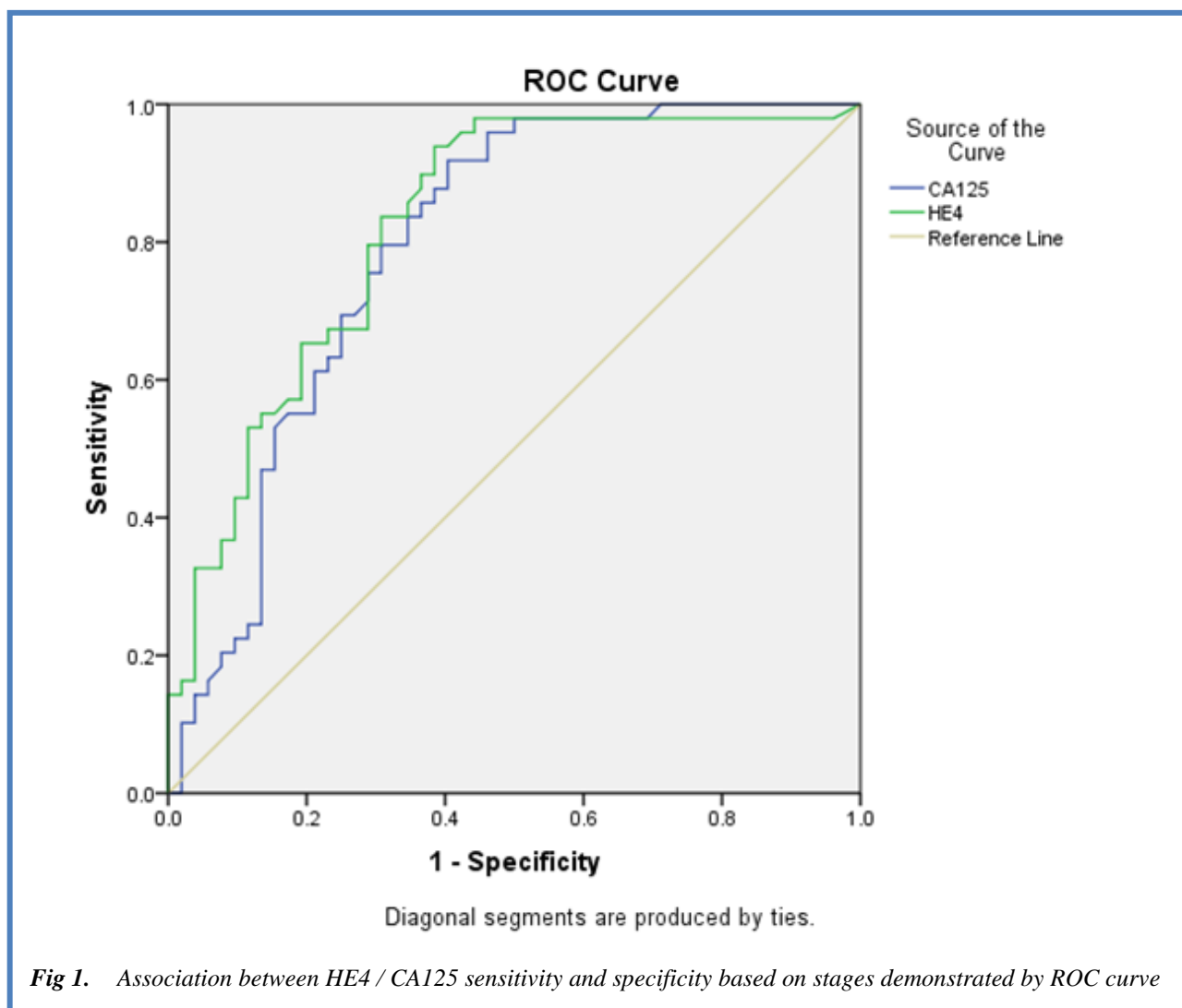
### Discussion

It is intuitively obvious and incontrovertibly true that cytoreductive surgery followed by chemotherapy is

**Table 2.** Predictive value of HE4 and CA 125 considering cut-off values for optimal cytoreductive surgery before the operation (Stage I –IIIb versus IIIc-IV).

Description	Sen	Spec	PPV	NPV	Sen	Spec	PPV	NPV	Sen	Spec	PPV	NPV
HE4 cut-off Value	70	70	70	70	140	140	140	140	170	170	170	170
	98	43	0.58	0.96	85	66	0.68	0.85	80	70	0.68	0.81
CA125 cut-off Value	320	320	320	320								
	80	70	0.71	0.82								

Sen: Sensitivity; Spec: Specificity; PPV: Positive Predictive Value; NPV: Negative Predictive Value.



considered the standard of care in ovarian cancer. However, no defined criteria have been determined so far to prove exactly who is the best candidate for optimal surgery. Finding the criteria will represent a breakthrough in the management of ovarian cancer especially in advanced cases. Optimal debulking surgery will have achieved in 80% of cases by oncologist gynecologists who have expertise in ultra-radical surgery.<sup>13</sup> Therefore, in the remaining 20% of patients, debulking surgery was not appropriate and these patient groups should initially receive chemotherapy and this intervention is a waste of time for chemotherapy. Paramount importance of timing justifies surgeons' predilection for initial chemotherapy. So the ideal timing of cytoreductive surgery has considerable significance. We sift through the evidence to find articles that addressed the prediction value of tumor markers and radiologic assessment in ovarian cancer. Some studies have suggested CT scans before surgery to evaluate operability.<sup>14,15</sup> For instance, Bristow et al. (2000) have claimed radiologic criteria with a sensitivity of 67.6% and specificity of 74% for predicting optimal surgery.

These criteria were as follows: peritoneal thickening and peritoneal implants >2 cm, bowel mesentery tumor > 2cm, suprarenal lymph node >1 cm, omental extension to the spleen, pelvic sidewall involvement, and hydro ureter.<sup>14</sup> But this method could raise concerns about clinical complexity. Some experts put diagnostic laparoscopy forward as a predicting measure. The accuracy rate was variable from 77.3% to 100%.<sup>16-18</sup> But in many oncologic centers in developing countries, facilities are inadequate for performing laparoscopy, moreover, it is an invasive procedure. On one hand, serum level of CA 125 has helped predict optimal cytoreductive surgery, on the other hand, a poor negative predictive value of serum level of CA 125 was reported.<sup>17-20</sup> Finding the most eligible criteria for predicting successful surgery in ovarian cancer has been an insurmountable problem in gynecology oncology so far, therefore, we assessed the preoperational serum level of CA 125 and HE4 to find a reliable cut-off. Firstly, we considered three cut-offs for serum level of HE4: 70, 140 and 170 Pmol/L, and our result showed that the HE4 value of 170 Pmol is the best cut-off for our main goal.

The negative predictive value is 81% which can be an acceptable cut-off. This means that in cases with ovarian cancer if the serum level of HE4 is less than 140 Pmol/L, optimal surgery can be achieved approximately 80%. and if the serum level of HE4 is more than 140 Pmol/L, postponing the surgery is logical and patients should refer to neo-adjuvant chemotherapy. In our research, we achieved the CA125 value of 320 IU/mL as the best cut-off for predicting optimal debulking. The negative predictive value is 82% which can be a reasonable cut-off. This means that in cases with ovarian cancer if the serum level of CA125 is less than 320 Pmol/L, optimal surgery can be achieved approximately 80%. and if the serum level of CA125 is more than 320 Pmol/L, postponing the surgery is logical and the patient should refer to neo-adjuvant chemotherapy. In our study, we divided cases into two groups: stage I to IIIb and stage IIIc-IV. because in advanced ovarian cancer (stage IIIc and IV), due to diffuse involvement in the peritoneal cavity, optimal cytoreductive surgery is not possible in an overwhelming majority of cases. So we designed our evaluation based on this classification. The HE4 value of 262 Pmol was achieved as the best cut-off for predicting optimal debulking in the Angioli et al. study (2013).<sup>21</sup> This data is the same as our study and reported that HE 4 is more reliable than CA 125 in predicting of poor prognosis of ovarian cancer. Moreover, the cut-off of CA 125 IU/mL was 303 and HE4 was 777 Pmol/L. Although our study had some similarities we excluded patients with the underlying disease who were not excluded in their study and it can explain the difference between the two studies.<sup>22</sup> Another study of the determination of reference intervals of serum levels of HE4 in the Chinese Journal of ovarian research reported a level of 472 Pmol/L as a cut-off for lymph node involvement in ovarian cancer. They reported that this cut-off was not associated with grade or type of tumor.<sup>23</sup> In our study higher HE4 was associated with a higher probability of lymph node involvement too. Despite our research, underlying diseases were not excluded in their study. Other studies determined a cut-off of 345 IU/mL for CA 125 and 218 Pmol/L for HE4, and a cut-off of 282 IU/mL for CA 125 and 277 Pmol/L for HE4, our study is similar to them.<sup>24,25</sup> The most considerable limitation of our study was the low sample size. But we were able to demonstrate two cut-offs for two tumor markers with acceptable negative predictive value for predicting optimal ovarian cancer surgery. Based on our study, it seems that selecting patients for successful optimal surgery or in contrast referring them to neoadjuvant chemotherapy and delaying surgery, can predict the two tumor markers at the pre-operating phase. Further studies with a larger sample size and combination of tumor markers with other clinical variables, should be carried out to achieve the best predictor criteria.

To sum up, our data claimed that preoperative serum levels of both HE4 and CA125 are a predictor for optimal debulking to avoid unnecessary surgery.

### List of acronyms

CA 125 - Cancer Antigen 125  
HE4 - Human Epididymis Protein 4  
NPV - Negative Predictive Value  
PPV - Positive Predictive Value  
ROMA - Risk of Ovarian Malignancy Algorithm  
SD - Standard Deviation  
Sen - Sensitivity  
Spec - Specificity  
TVS - Transvaginal sonography

### Contributions of Authors

ES and SN have contributed to development of the article and are responsible for conception and design of the study. ES was responsible for acquisition of data. Manuscript drafting was performed by SN. Critical revision was done by NA. Interpretation of data was done by MM. SN was responsible for revision of the manuscript. All authors have read and approved the final version of the article.

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### Conflict of Interest

The authors declare no conflict of interests.

### Ethical Publication Statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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