

CAN PREOPERATIVE CA-125 PREDICT RESECTABILITY OF TUMOR IN PATIENTS WITH ADVANCED EPITHELIAL OVARIAN CARCINOMA?

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Abstract- Larger tumor burden leads to higher serum CA-125 levels and the ability to perform optimal tumor cytoreduction of advanced ovarian cancer is also a function of tumor bulk. The purpose of this study was to identify the ability of preoperative serum CA-125 to predict possibility of optimal primary tumor cytoreduction in epithelial ovarian carcinoma (EOC). A total of 90 patients with EOC were evaluated in a prospective study from 2000 to 2002. Preoperative serum CA-125 levels were determined, using a solid phase immunoassay. We used a receiver operating characteristic curve to identify the CA-125 level with the maximal prognostic power in predicting optimal versus suboptimal debulking. The median CA-125 level for the 90 patients was 500 U/ml (range 13 to 5000 U/ml). Seventy patient (78%) had stage III or IV based on staging system of the International Federation of Gynecology and Obstetrics (FIGO) for ovarian carcinoma. Optimal cytoreduction (diameter of largest residual tumor less than 1 cm) was obtained in 44 patients (62.9%) with stage III-IV. Preoperative CA-125 value less than 450 U/ml had a positive predictive value for optimal cytoreduction of 78%, but a poor negative predictive value of 50% in advanced EOC. In patients with advanced EOC, at a cutoff 450 U/ml, 78% underwent optimal debulking, whereas 50% of patients with preoperative CA-125 level above 450 U/ml were still able to undergo optimal debulking. Preoperative CA-125 does not seem to be a reliable predictor of optimal cytoreduction.

Acta Medica Iranica, 42(6): 419-423; 2004

Keywords: Preoperative CA-125, Resectability, Epithelial ovarian carcinoma

INTRODUCTION

Advanced epithelial ovarian cancer represents the greatest clinical challenge in gynecology oncology. In 1983, Bast *et al.* developed a monoclonal antibody, CA-125, which detects an antigen

present in peripheral blood (1); this antigen was called CA-125. Since its introduction, the serum CA-125 assay has been used in the screening of ovarian cancer, as a tool to differentiate benign from malignant ovarian masses, and as an indicator of tumor status during and after chemotherapy (2-6).

Over the past 25 years, it has become established, largely through retrospective analysis, that optimal resection of metastatic epithelial ovarian cancer has profound impact on the survival of patients with advanced stages (7-10). It has been reported that serum CA-125 is elevated (>35 U/ml) in 90% of International Federation of Gynecology and

Received: 17 Jun. 2003, Revised: 21 Sep. 2003, Accepted: 12 May 2004

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Obstetrics (FIGO) advanced-stage epithelial ovarian cancers, while less than 50% of patients with stage I disease have abnormal levels (11). It seems that perhaps a larger tumor burden leads to higher serum CA-125 levels. If the amount of serum CA-125 elevation depends on the tumor load and the ability to perform optimal tumor cytoreduction for advanced ovarian cancer is also a function of tumor bulk (along with other factors) (12), then the question arises, “is there a threshold serum CA-125 level above which optimal cytoreduction for patients with advanced stage of ovarian cancer would probably not be achieved?”.

The purpose of this study was to determine the ability of preoperative serum CA-125 to predict optimal primary tumor cytoreduction in patients with advanced epithelial ovarian carcinoma.

MATERIALS AND METHODS

A total of 90 patients with epithelial ovarian cancer, who were treated at Vali-e-asr Gynecology-Oncology Center, were evaluated in a prospective study from 2000 to 2002.

Serum CA-125 levels were determined by a commercially available radioimmunoassay that remained the same throughout the study period. The primary surgeons in all surgeries were a staff gynecologic oncologist and a fellow.

Patients were evaluated for their preoperative CA-125 levels, age at the time of surgery, operative findings, operative procedure performed, residual disease at the completion of the procedure and final histopathologic diagnosis. Optimal tumor cytoreduction was defined as less than 1cm residual disease (distinct nodules) after cytoreductive surgery, in accordance with studies published by the Gynecologic Oncology Group (9).

To determine the ability of preoperative serum CA-125 level to predict optimal cytoreduction, the sensitivity was defined as the percentage of suboptimally cytoreduced patients who had preoperative serum CA-125 levels above various given cutoff values. The false positive rate (one minus specificity) was defined as the percentage of optimally cytoreduced patients who had a

preoperative serum CA-125 above the given cutoff value.

Receiver operating characteristic (ROC) curves methodology was used to determine the CA-125 level with the maximum prognostic power in predicting optimal versus suboptimal debulking. ROC curve plots the true positive rate along the y-axis and the false positive rate along the x-axis for the various cutoff points. The area under the ROC curve is a measure of predictive accuracy where a value of 1 corresponds to a perfect predictor and 0.5 to a coin toss.

RESULTS

The mean age of the 90 patients in this study was 50 years (range: 19-78 years). Seventy patients (78%) had stage III-IV disease. Sixty eight patients (75.6%) had papillary serous and 22 patients (24.4%) had non serous tumor histology.

Using the definition of optimal cytoreduction as cases in which the diameter of the largest residual tumor nodule measured less than or equal to 1 cm, optimal tumor cytoreduction was obtained in 64 cases (71.1%) of total patients and in 44 (62.9%) of patients with stage III-IV disease.

The median serum CA-125 level for the 90 patients was 500 U/ml, (range 5-5000 U/ml). The level was elevated (>35 U/ml) in 49% of patients with stage I-II compared with 93% of patients with stage III or IV disease.

The sensitivity and specificity of various threshold serum CA-125 levels for predicting suboptimal debulking for all patients with cancer are shown in table 1.

Figure 1 shows the ROC curve generated by the data. The curve progression from the lower left-hand corner to the upper right-hand corner corresponds to successively lower cutoff CA-125 levels and a resultant increase in both the true-positive and the false-positive rates. The ideal test would have a true-positive rate of 100% with a false-positive of 0% and it would be located at the left upper corner of the graph. The point on the curve closest to the left upper corner corresponds to a threshold CA-125 serum level of 450 U/ml and had maximum true-positive rate of 73% and minimum false-positive rate of 35%.

Table 1. Prediction of suboptimal cytoreduction in all patients at different cutoff CA-125 levels*

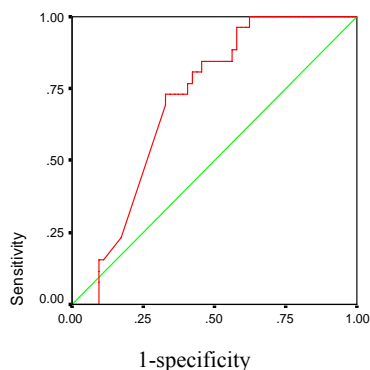
CA125(U/ml)	Sen	Spe	PPV	NPV
≤60	100	32	37	100
100	90	39	39	96
160	84	44	37	89
200	84	48	40	88
300	84	53	42	88
350	80	56	42	87
400	76	59	43	86
450	73	65	47	86
500	23	82	35	72
550	15	89	36	72
600	15	89	36	72
750	15	90	40	72
1000	11	90	33	71
1500	7	90	25	70

Abbreviations: Sen, sensitivity; Spe, specificity; PPV, positive predictive value; NPV, negative predictive value.

* Data are given as percent.

At a cutoff 450 U/ml, 86% of all patients with a lower CA-125 were optimally cytoreduced. Of those with a level higher than 450 U/ml, 52% were still able to undergo optimal surgical cytoreduction. (Table 2)

The sensitivity and specificity for predicting suboptimal debulking at different cutoff CA-125 levels in patients with advanced stages are shown in figure 2 and table 3.

**Fig.1.** Receiver operating characteristic curve showing the relationship between true positive rate (sensitivity) and false positive rate (1- specificity) for all patients, using each serum CA-125 level as a cutoff point.**Table 2.** Preoperative serum CA-125 level and type of cytoreduction in all patients (n=90)*

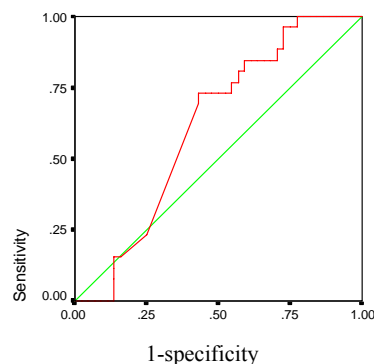
CA-125 (U/ml)	Optimal cytoreduction	Suboptimal cytoreduction
<450	43(86)	7(14)
>450	21(52.5)	19(47.5)
Total	64(71.1)	26(28.9)

*Data are given as number (percent).

Of patients with advanced stages with CA-125<450 U/ml, optimal cytoreduction was achieved in 25 patients (78.1%), while of those with a level higher than 450 U/ml, 50% were still able to undergo optimal surgical cytoreduction (Table 4); therefore at a threshold level of 450 U/ml, for predicting optimal versus suboptimal debulking, preoperative CA-125 levels have a high positive rate (78.1%), but a low negative predictive value (50%).

DISCUSSION

Since laparotomy with suboptimal debulking has not been shown to offer a survival advantage (13), many studies have been done to determine value of preoperative serum level of CA-125 for predicting the optimal versus suboptimal debulking. The results could be used to modify the primary surgical approach or approach after the standard sequence of cytoreductive surgery and chemotherapy (14-16).

**Fig .2.** Receiver operating characteristic curve showing the relationship between true positive rate and false positive rate for advance-stage disease using each serum CA-125 level as a cutoff point.

Preoperative CA-125 and respectability of tumor

Table 3. Predicting of suboptimal cytoreduction in advanced stage III-IV at different cutoff CA-125 levels*

CA-125 (U/ml)	Sen	Spe	PPV	NPV
≤60	100	18	41	100
100	96	22	42	90
160	84	29	41	76
200	84	34	43	78
300	84	38	44	80
350	80	40	44	78
400	76	45	45	76
450	73	54	49	78
500	23	75	35	62
550	15	84	36	62
600	15	84	36	62
750	15	86	40	63
1000	11	86	33	62
1500	7	86	25	61

Abbreviations: Sen, sensitivity; Spe, specificity; PPV, positive predictive value; NPV, negative predictive value.

*Data are given as percent.

Previous studies have shown that preoperative CA-125 is a significant predictor of type of surgery in patients with epithelial ovarian carcinoma. Chi *et al.* evaluated the ability of preoperative CA-125 levels to predict optimal cytoreduction in patients with stage III epithelial ovarian cancer (16). They found that at a cutoff 500 U/ml, 73% of patients with a preoperative CA-125 level lower than this value underwent optimal cytoreduction, whereas only 22% of patients with a higher preoperative CA125 level were optimally cytoreduced. They concluded that the probability of performing optimal cytoreduction in patients with stage III ovarian carcinoma and a preoperative CA-125>500 U/ml is approximately one in five and these patients may be candidates for

Table 4. Preoperative serum CA-125 level and type of cytoreduction in patients with advanced stage III-IV (n=70)*

CA-125(U/ml)	Optimal cytoreduction	Suboptimal cytoreduction
<450	25(78.1)	7(21.9)
>450	19(50)	19(50)
Total	44(62.9)	26(37.1)

*Data are given as number (percent).

initial laparoscopic evaluation to obtain a confirmatory tissue diagnosis and to determine resectability.

Conversely, in another study by Cooper *et al.* 74% of all patients who had stage III or IV cancers, with preoperative CA-125 levels less than 500 U/ml were optimally cytoreduced, whereas 51% of patients with levels above 500 U/ml were optimally cytoreduced. They concluded that preoperative CA-125 does not appear to be a reliable predictor of optimal cytoreduction (17).

In our study 86% of all patients with preoperative CA-125 levels less than 450 U/ml underwent optimal debulking, whereas 52% of patients with preoperative CA-125 levels above 450 U/ml were optimally cytoreduced. When evaluating only those patients who had stage III or IV disease, we found that 78% of those with preoperative CA-125 levels less than 450 U/ml underwent optimal debulking, whereas 50% of patients with levels above 450 U/ml were optimally cytoreduced, thus preoperative CA-125 does not have enough specificity to predict resectability of tumor in patients with epithelial ovarian carcinoma. In summery, this study should be viewed as a provocative analysis that should lead to more prospective studies to determine the applicability of CA-125 to predict resectability.

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