

# Is postoperative CA125 level in patients with epithelial ovarian cancer reliable to guess the optimality of surgery?

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## Summary

**Introduction:** Cytoreductive surgery is a pivotal component of primary treatment in patients with ovarian epithelial cancer (OEC) and several studies have shown better outcomes of optimal debulking. The aim of this prospective study was to determine if optimum versus suboptimal cytoreductive surgery predicts CA125 levels two weeks after surgery. **Material and Methods:** Sixty patients with epithelial ovarian cancer scheduled for cytoreductive surgery in Imam Khomeini Hospital, Tehran, Iran were enrolled in this study. Two groups of patients were to undergo optimal or suboptimal cytoreductive surgery. Optimal cytoreduction was defined as the largest volume of residual disease < 1 cm in maximal dimension. CA125 levels were measured in all patients preoperatively and at two, seven and 14 days after surgery. CA125 levels were converted to a log scale. **Results:** The distribution of staging, grading and types of tumors in each group were statistically equal but insignificant (chi square). The difference in mean of CA125 before and two weeks after surgery was statistically significant (paired t-test;  $p = 0.0001$ ) but the grade, stage and type of tumors did not have any impact on CA125 regression. However, regression of CA125 two weeks after the operation did not differ statistically between the optimal and suboptimal cytoreduction groups (repeated measure ANOVA). **Conclusion:** Although, postoperative CA125 decreased significantly in two weeks after tumor cytoreduction in patients with epithelial ovarian cancer, its regression did not differ according to optimal or suboptimal groups.

**Key words:** Ovarian cancer; CA125; Cytoreductive surgery; Optimal; Iran.

## Introduction

Ovarian cancer is the fourth cause of cancer-related death in women. Cytoreductive surgery represents a pivotal component of primary treatment [1]. Several studies have shown the better outcomes of optimal debulking and amount of residual tumor following cytoreductive surgery is inversely proportional to survival [1-3]. Even complete pathological responses to chemotherapy depends on optimal or suboptimal surgery and may vary, respectively, 50% to 20% [1, 4, 5].

CA125 is an antigen expressed by tissue derived from celomic epithelium (mesothelial cells of the pleura, pericardium, and peritoneum) and mullerian epithelium (tubal, endometrial, and endocervical). The surface epithelium of normal fetal and adult ovaries does not express CA125 unless an inclusion cyst, metaplasia, and or papillary excrescences are present [6]. The CA125 level is elevated (> 35 U/ml) in 90% of advanced-stage epithelial ovarian cancers, while less than 50% of patients with Stage I disease have abnormal levels [7]. A correlation has been reported between tumor biology and CA125 levels; tumors that tend to be poorly differentiated or present with wide metastatic disease have higher levels of serum CA125 [8].

The extent of residual tumor after primary cytoreductive surgery has been proven to be an important prognostic factor of survival [9]. Although a number of potential tumor markers have been identified in ovarian cancer, by far the greatest interest has been attracted by CA-125.

Surgical cytoreduction improves survival only if the patient is optimally cytoreduced. The definition of optimal cytoreduction has evolved over time and is currently residual disease measuring 1 cm [10]. Survival is superior when EOC is surgically debulked by a gynecological oncologist presumably because greater cytoreduction can be achieved by surgeons more experienced in resecting the disease [11, 12].

In general, patients with tumor regression present with a decline in CA125 levels. We expected this decrease in CA125 level would be prominent in patients undergoing optimal debulking in comparison with suboptimal surgery, so this study was designed to verify this hypothesis.

## Material and Methods

This prospective study was carried out at Imam Khomeini Hospital, Tehran, Iran. Sixty epithelial ovarian cancer patients admitted for cytoreductive surgery were enrolled. Patients in this study were operated without any previous chemotherapy, and adjuvant chemotherapy was performed 14 days after surgery. Two groups of patients were defined as undergoing optimal or suboptimal cytoreductive surgery. Optimal cytoreduction was defined as the largest volume of residual disease < 1 cm in the maximal dimension. CA125 levels were measured in all patients preoperatively and at the 2<sup>nd</sup>, 7<sup>th</sup> and 14<sup>th</sup> days after surgery. All patients gave informed consent and the study was approved by Tehran University Ethical Committee. All blood samples were taken using conventional venipuncture with minimal stasis. Separation was performed by centrifugation for 15 min, and immediately thereafter serum was stored frozen at -80°C until analysis. All serum samples from one patient were assayed in the same run and by the same analyst.

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### Statistics

CA125 levels were logarithmically transformed before the statistical analyses due to a large variation. Preoperative CA125 level and age of patients were analyzed using an independent t-test; categorical data such as grading, staging, type of tumors and vascular space involvement were analyzed by the chi square test or Fisher's exact test, if needed. The regression of CA125 in both groups (optimal versus suboptimal cytoreductive surgery) and according to different time points (preoperatively, 2, 7 and 14 days after surgery) were analyzed by repeated measure ANOVA; a *p* value less than 0.05 was considered significant. All analyses were performed by SPSS-16.

### Results

The mean  $\pm$  SD of age in the optimal (*n* = 30) and suboptimal (*n* = 30) cytoreduction groups were respectively, 49.7  $\pm$  9 and 49.5  $\pm$  12 years (t-test; *p* = 0.91). Preoperative serum levels of CA125 were elevated (> 35.0 IU/ml) in all patients. The mean of CA125 before surgery in the optimal group was 952 u/ml and for the suboptimal group 1784 u/ml (log scale was compared by t-test; *p* = 0.81). Most of the ovarian tumors were papillary serous (33/55%) followed by serous (15/25%), endometroid (9/15%), poorly differentiated (2/3.3%), and mucinous (1/1.7%). Grade 2 tumors were reported in 28 patients (46.7%), grade 3 in 19 (31.7%) and grade 1 in 13 (21.7%) patients. Also, Stage IIIC was reported in 41 patients (68.3%) in comparison with only IIA and IIB in two patients (3.4%); and finally, vascular space involvement was seen in 45 patients (75%).

The difference in CA125 level between the preoperative and 14<sup>th</sup> day after surgery was positive in all cases, except for one patient (1.7%) in the suboptimal group in which the value was negative. Thus, in spite of CA125 regression in this period of time for nearly all subjects, none reached less than 35 IU/ml.

Another form of analysis showed that four out of 30 patients in the optimal group and five out of 30 in the suboptimal group had more than 50% reduction in CA125 level, 14 days after surgery (chi<sup>2</sup> test, *p* = 0.71).

The comparison of age, tumor pathology characteristics and mean of log transformed CA125 levels (preoperative, 2, 7 and 14 days postoperation) between two groups of cytoreduction surgery (optimal vs suboptimal) are summarized in Table 1. As shown, the mean age and CA125 levels (preoperative, 2, 7 and 14 days postoperation) did not differ significantly according to the two groups of cytoreduction surgery (optimal vs suboptimal).

Also, the distribution of stage, grade and vascular space involvement were equivalent in both groups. However mucinous (1; 3.3%) and poorly differentiated tumors (2; 6.7%) were found only in the suboptimal group and endometroid tumors were prominently located in the optimal group (8; 26.7% vs 1; 3.3%) (Table 1).

Although the linear regression of CA125 two weeks after surgery was statistically significant relative to preoperative values (repeated measure ANOVA; *p* = 0.001), it did not differ statistically between optimal and suboptimal cytoreduction groups (repeated measure ANOVA). Finally, the grade and stage, and type of tumor lesions did not have any impact on CA125 regression as a whole.

Table 1. — Comparison of tumor and patient characteristics in the two types of cytoreductive surgery.

Variables		Cytoreductive surgery		p value
		Optimal	Suboptimal	
Age (years)	Mean $\pm$ SD (min-max)	49.7 $\pm$ 9 (33-70)	49.5 $\pm$ 12 (20-77)	0.94
CA125 (U/ml)	Preoperative	2.73 $\pm$ 0.48	2.71 $\pm$ 0.56	0.91
	2 days later	2.65 $\pm$ 0.48	2.63 $\pm$ 0.53	0.81
	7 days later	2.59 $\pm$ 0.48	2.57 $\pm$ 0.53	0.92
	14 days later	2.52 $\pm$ 0.49	2.51 $\pm$ 0.53	0.93
Stage	II or III	27 (90%)	24 (80%)	0.47
	IV	3 (10%)	6 (20%)	
Grade	1	7 (23.3%)	6 (20%)	0.71
	2	15 (50%)	13 (43.3%)	
	3	8 (26.7%)	11 (36.7%)	
Vascular space involvement	Positive	20 (66.7%)	25 (83.3%)	0.13
	Negative	10 (33.3%)	5 (16.7%)	
Types of tumor	Serous	9 (30%)	6 (20%)	–
	Papillary serous	13(43.3%)	20 (66.7%)	
	Endometroid	8(26.7%)	1 (3.3%)	
	Mucinous	0	1 (3.3%)	
	Poorly differentiated	0	2 (6.7%)	

### Discussion

In this longitudinal study, postoperative CA125 levels decreased significantly in a short-term follow-up of women with epithelial ovarian cancer. Although statistical analysis did not prove any significant difference in CA125 regression in the two cytoreductive groups (optimal vs suboptimal) in a period of 14 days, it has been shown in different studies that optimal surgical debulking as an independent factor appears to improve the prognosis of patients with even Stage IV epithelial ovarian cancer (EOC) [13-16].

Since the original work by Griffiths [17] in 1975, numerous retrospective studies have reported the benefits of tumor cytoreduction for advanced ovarian carcinoma [18]. However, the Gynecologic Oncology Group (GOG) has demonstrated that tumor debulking improves overall survival only if optimal residual disease status can be attained. Pooled data of reports from numerous institutions suggest that optimal primary cytoreduction can be achieved in approximately 30-40% of patients with advanced ovarian carcinoma [19]. Therefore, the traditional approach to laparotomy and attempted tumor cytoreduction does not significantly benefit the majority of patients with advanced disease. In contrast, withholding attempts at cytoreduction may deprive a substantial number of patients from a procedure that could potentially double their median survival [19]. A structured review of 81 cohorts involving 6,885 patients reported that an average 42% of patients were declared optimally debulked using the standard definition at the time of the individual report; however, in "centers with a particular interest and expertise in cytoreductive surgery", optimal debulking (OD) was achieved for 75% of patients [20]. The utility of preoperative computed tomography (CT) scans [21, 22] and serum CA125 to predict OD for patients with EOC has been examined. The performance

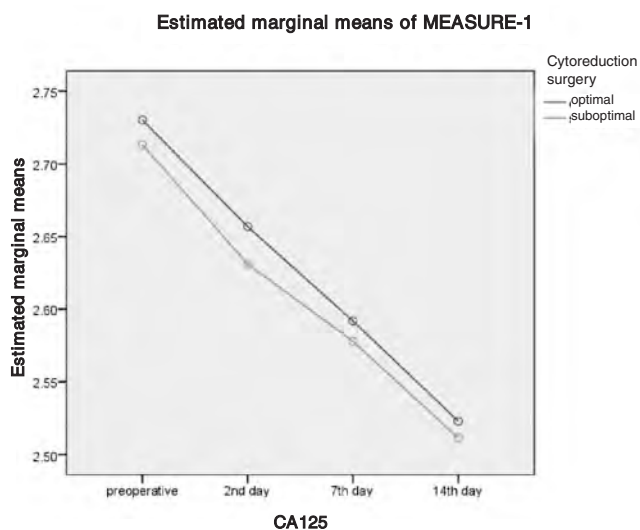


Figure 1. — The regression line of CA125 according to different time points for both surgery groups produced by repeated measure ANOVA.

of preoperative CA125 exhibited a sensitivity for predicting OD in patients with Stage III-IV EOC ranging from 55% to 78% and a specificity from 54% to 73% [23, 24]. Chi *et al.* [23] reported that the probability of OD was only one in five for those with CA125 greater than 500. CA125 is an antigen expressed by tissue derived from celomic epithelium (mesothelial cells of the pleura, pericardium, and peritoneum) and mullerian epithelium (tubal, endometrial, and endocervical). The surface epithelium of normal fetal and adult ovaries does not express CA125 unless an inclusion cyst, metaplasia, and or papillary excrescences are present [25]. CA125 level is elevated (> 35 U/ml) in 90% of advanced-stage EOC, while less than 50% of patients with Stage I disease have abnormal levels [26]. A correlation has been reported between tumor biology and CA125 levels; tumors that tend to be poorly differentiated or present with wide metastatic disease present with higher levels of serum CA125 [27].

Age of patients and postoperative pathologic results such as stage, grade and vascular space involvement were evenly distributed in both groups (optimal vs suboptimal). However mucinous and poorly differentiated types of tumors were found only in the suboptimal group; in contrast, endometrioid tumors were more commonly reported in optimal debulking. However as verified by statistical analysis, none of the mentioned variables (age, stage, grade, vascular space involvement and tumor type) had any impact on overall CA125 regression 14 days after operation nor on each subtype of cytoreductive surgery, separately. Rustin *et al.* [28] used a method that defined treatment response on the basis of CA125 decrease; in the present study, only four out of 30 patients in the optimal group and five out of 30 in suboptimal group had more than 50% CA125 level decrease in 14

days. The suboptimal group seemed to have better treatment response but it was not proven by statistical analysis. However, it seems strange to believe this conflict because it has been shown that CA125 levels reflect volume of disease and the correlation between residual tumor and CA125 levels has been verified [29-35]. Albeit, it is worthy to say that CA125 remains elevated by tissue damage after surgery, potentially taking weeks to return to normal [13]. Thus, further CA125 level measurement is required in longer durations of time to determine if there is any significant CA125 difference in two groups, as seen in Munstedt *et al.*'s [30] study where treatment response was defined by dividing CA125 value after chemotherapy by CA125 value at four weeks after surgery.

Finally, we were able to determine if optimal cytoreductive surgery predicts CA125 levels two weeks after operation, but no decrease in CA125 due to the effect of optimal debulking could be found in this study.

In conclusion, although, postoperative CA125 decreased significantly in two weeks after tumor cytoreduction in patients with epithelial ovarian cancer, its regression did not differ according to optimal or suboptimal groups.

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