

# Comparison of CA 125 after three courses of chemotherapy and results of second-look surgery

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## Summary

**Objective:** To compare CA 125 levels after three courses of cisplatin-based chemotherapy and the results of second-look surgery.

**Methods and Materials:** From January 1990 to December 1996, the medical records of 72 patients diagnosed with epithelial ovarian cancer were reviewed. After initial staging surgery, all patients received cisplatin-based chemotherapy. Prior to each course of chemotherapy, patients underwent physical exams and serum CA 125 was obtained. After 6 courses of chemotherapy, if CA 125 levels were normal ( $\leq 35$  IU/ml) and there was no clinical evidence of disease, the patient was offered second-look surgery. The sensitivity, specificity, and negative predicative value of CA 125 levels after 3 courses of chemotherapy and results of second-look surgery were calculated. Survival curves were constructed using Kaplan-Meier actuarial methods.

**Results:** Seventy-two patients were enrolled in the study. After completing 3 courses of chemotherapy, 43 out of 72 patients were reported to have normal CA 125 levels and were offered second-look surgery. Forty-six out of 72 patients underwent second-look surgery, 28 patients (60%) were reported to have positive second-look surgery. Of the patients with normal CA 125 levels after 3 courses of chemotherapy, 23 patients (57.5%) had a positive second-look surgery. The sensitivity and specificity of CA 125 values after 3 courses of chemotherapy were 17.9% and 94.7%, respectively and the negative predicative value was 43.9%. Patients with normal CA 125 values after 3 courses of chemotherapy had a significantly improved survival compared to those who failed to normalize their CA 125 levels after three courses of chemotherapy.

**Conclusion:** Normalization of CA 125 after 3 courses of chemotherapy is a poor predictor of findings at second-look surgery.

## Introduction

Epithelial ovarian cancer is the second most common gynecologic malignancy among women and it is the most common cause of mortality among women with gynecologic malignancies. In the past three decades, major advances have been made in surgical techniques and chemotherapeutic regimens for the treatment of epithelial ovarian cancer [1, 2]; yet, despite these advances, the estimated ten-year survival is only 20% [3].

Noninvasive methods have been used in following patients' response to chemotherapy. CA 125 is widely accepted as a biochemical marker in assessing tumor status [4, 5]; unfortunately, CA 125's ability to detect small volume disease is limited [6]. Arguably, second-look surgery is the most accurate method in evaluating a patient's response to chemotherapy. The purpose of the current study was to evaluate whether CA 125 values after three courses of cisplatin-based chemotherapy are predicative of findings at second-look surgery.

## Materials and Methods

From January 1990 to December 1996, the medical records of 72 patients treated for epithelial ovarian cancer at Millard Fillmore Hospital, State University of New York at Buffalo, New York were reviewed. Diagnosis of epithelial ovarian cancer was confirmed by reviewing the pathologic report at the

time of the patient's original surgery. All patients initially underwent optimal cytoreductive and staging surgery. Optimal cytoreductive surgery consisted of total abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy, and resection of any gross disease; at the end of initial surgery, residual disease was less than one centimeter. Staging of ovarian cancer was performed according to the International Federation of Gynecologists and Obstetricians (FIGO) staging system [7]. After initial cytoreductive surgery, all patients underwent six courses of a cisplatin-based chemotherapy every 28 days. Prior to each course of chemotherapy, the patients underwent physical examinations and serum CA 125 was obtained.

After six courses of chemotherapy, if the patient's CA 125 level was within normal range and there was no clinical evidence of disease, the patient was offered a second-look surgery. CA 125 values less than or equal to 35 IU/ml were considered to be within normal range. Second-look surgeries were performed as either laparotomies or laparoscopies. Results of second-look surgery were divided into three categories: negative second-look demonstrated no histological or cytologic evidence of tumor; microscopic positive second-look surgery demonstrated residual disease less than 0.5 cm or positive peritoneal washings; macroscopically positive second-look surgery demonstrated residual disease greater than 0.5 cm. At the time of second-look surgery, all patients with macroscopic disease underwent further cytoreductive surgery.

In reference to the results of second-look surgery, sensitivity, specificity and negative predicative value of CA 125 levels after three courses of chemotherapy were calculated. Overall survival was defined as survival from time of diagnosis till death or last follow-up. Survival curves were constructed using the Kaplan-Meier actuarial methods [8] and survival curves were compared by the log-rank test [9].

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## Results

Table 1 lists information regarding the 72 patients with epithelial ovarian cancer. The mean age of the patients was 58.9 years. Initially, all patients underwent optimal cytoreductive surgery performed by one of us (SL). The majority of the patients (90.4%) were initially diagnosed with stage III epithelial ovarian cancer. Pathologic diagnoses were distributed as follows: 51 patients (69.9%) were diagnosed with papillary serous adenocarcinoma; nine patients (12.5%) with endometriod adenocarcinoma; seven patients (9.7%) with clear cell carcinoma; four patients with mucinous adenocarcinoma and one patient with undifferentiated carcinoma. All patients were initially treated with six courses of a cisplatin-based chemotherapy regimen: 43 patients received Cisplatin and Cytosin, 15 patients received Taxol and Cisplatin, 12 patients received Cisplatin, Adriamycin, and Cytosin and two patients received Methotrexate and Cytosin. After completing three courses of chemotherapy, 43 out of 72 patients (59.2%) were reported to have normal CA 125 values while 29 patients (40.3%) had elevated CA 125 values.

Forty-six out of 72 patients (63.9%) underwent second-look surgery: 42 patients underwent laparotomies while four patients had laparoscopies. Two patients refused second-look surgery. After six courses of cisplatin-based chemotherapy, 24 patients demonstrated clinical evidence of progressive disease: six patients underwent interval cytoreductive surgery while the remaining 18 patients refused surgery and received salvage chemotherapy. Eighteen patients (39.1%) were reported to have a negative second-look surgery. Nine patients (19.6%) had microscopically positive second-look surgery while 19 patients (41.3%) had macroscopically positive second-look surgery. Of the patients who had normal CA 125 values after completing three course of chemotherapy, 23 patients (57.5%) had a positive second-look surgery (six patients with microscopic disease and 17 patients with macroscopic disease) while 17 patients (42.5%) had a negative second-look surgery. Among the patients with an elevated CA 125 value after completing three courses of chemotherapy, five patients (83.3%) had a positive second-look surgery (three patients with microscopic disease and three patients with macroscopic disease) while one patient had a negative second-look (Table 2). With regards to the results of second-look surgery, the sensitivity and specificity of CA 125 values after three courses of chemotherapy were 17.9% and 94.7%; likewise, the negative predicative value was 43.9%.

The overall median survival for the 72 patients was 23.3 months and the mean survival was 32.83 months. As shown in Table 3, patients with normal CA 125 values after three courses of chemotherapy had a significantly improved median survival than those with elevated CA 125 levels, 30.50 months vs 17.27 months, respectively ( $p < .0001$ , Log-rank test) (Figure 1). Furthermore, regardless of the patient's CA 125 level after three courses of chemotherapy, the median survival among patients with a negative second-look surgery was not significantly

Table 1. — Patient characteristics.

	No. of patients
Total number of patients in study	72
Average age	58.9 years
Pathology	
serous	51
endometriod	9
clear cell	7
mucinous	4
undifferentiated	1
Stage	
I	0
II	4
III	66
IV	3
3rd CA 125	
$\leq 35$ U/ml	43
$> 35$ U/ml	29
Second-look surgery	
laparotomy	42
laparoscopy	4
interval cytoreductive surgery	6
not done	20
Pathology of second-look surgery	
negative	18
microscopic positive	9
macroscopic positive	15

Table 2. — 3rd CA 125\* and results of second-look surgery.

	Second-look surgery	
	(+)	(-)
3rd CA 125 abnormal	5	1
normal	23	17

\*3rd CA 125 = CA 125 after 3 courses of cisplatin-based chemotherapy.

Table 3. — Survival.

	CA 125*	
	Normal	Abnormal
Mean survival in months	42.71	19.11
95% confidence interval	(31.37, 54.06)	(14.47, 23.75)
Median survival months	30.50	17.27
95% confidence in interval	(25.66, 35.34)	(10.29, 24.24)

\*CA 125 after 3 courses of chemotherapy.

Normal =  $\leq 35$  U/ml

Abnormal =  $> 35$  U/ml

improved compared to those with a microscopically positive second-look surgery: 53.7 months vs 35.4 months ( $p = .08$ ). Of the 18 patients with a negative second-look surgery, 11 patients (61.1%) recurred with disease. The mean time for recurrence of disease was 14.3 months.

## Discussion

The role of second-look surgery in the routine management of patients with epithelial ovarian cancer is controversial. Proponents for second-look surgery argue that it is the only method which accurately provides cytologic

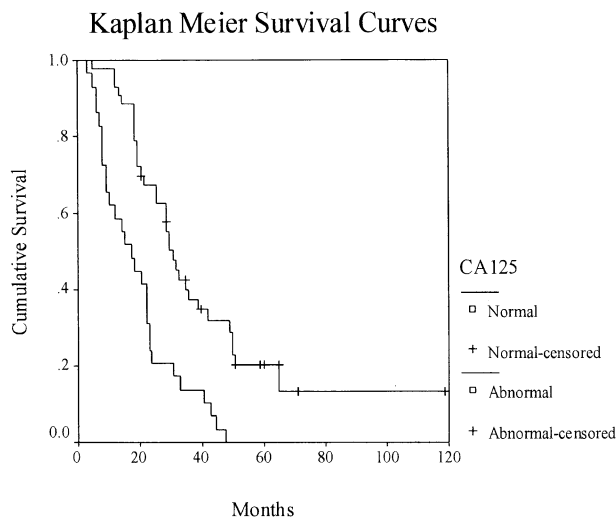


Figure 1. — Kaplan-Meier Survival Curve comparing patients with normal CA 125 values with those with elevated CA 125 values after 3 courses of chemotherapy.

and pathologic data with regards to a patient's response to chemotherapy. Since less than 30% of patients with complete clinical remission are confirmed by second-look surgery, those patients who do not undergo second-look surgery may have their chemotherapy terminated prematurely [10, 11]. Conversely, opponents to second-look surgery argue that the overall complication rate among patients undergoing second-look surgery ranges from 8% to 67% [12, 13]; furthermore, second-look surgery has not been demonstrated to significantly improve patients' survival [14, 15]. In a multicenter study of 192 ovarian cancer patients with advanced ovarian cancer and pathologic complete response at second-look surgery, Gadducci *et al.* [16] reported that 48.9% of the patients developed recurrent disease after a median time of 18 months. Likewise, Cohen *et al.* [17] failed to demonstrate any survival advantage among those patients who underwent second-look surgery versus those who were not eligible for the procedure. Consequently, non-invasive methods have been used in the evaluation of a patient's response to chemotherapy.

While CT scans have routinely been used in evaluating a patient's response to chemotherapy, the major limitation of computed tomography lies in its failure to identify lesions less than 2 cm in size [6]. In a study of 47 patients who were in complete clinical remission from ovarian cancer, Clarke-Pearson *et al.* [18] correlated CT scan results to surgical findings and demonstrated that CT scans had a sensitivity and specificity of 32% and 77%, respectively, with a negative predictive value of 30%. Furthermore, in the study by Clarke-Pearson *et al.*, CT scan only detected 7% of tumor nodules 1 cm or less and only 37% of nodules more than 1 cm. Likewise, De Rosa and colleagues [19] also demonstrated that CT scans failed to reliably predict the results of second-look surgery.

Serum CA 125 levels obtained prior to second-look surgery have also failed to reliably identify patients with persistent disease [20-22]. In a study comparing serum CA 125 levels and findings at second-look surgery, Rubin *et al.* [23] reported that 62% of patients with normal CA 125 levels (< 35 U/ml) were identified as having persistent disease at surgery. Likewise, in a study of 125 patients with ovarian cancer who underwent cytoreductive surgery, cisplatin-based combination chemotherapy and second-look surgery, Pastner *et al.* [24] reported that 92% of patients with negative second-look surgery had normal pre-second-look serum CA 125 levels; however, 75% of patients with normal pre-second-look CA 125 values had a positive second-look surgery.

The prognostic value of serum CA 125 levels during chemotherapy has been evaluated in several studies. Redman *et al.* [25] reported that patients with CA 125 levels less than or equal to 35 U/ml after two courses of chemotherapy were more likely to have a better prognosis and achieve complete remission than those patients who had levels greater than 35 U/ml. Moreover, Redman and colleagues suggested that it is questionable to continue active chemotherapy for those patients with elevated CA 125 levels after two courses of chemotherapy. Likewise, Lavin *et al.* [5] reported that all patients with CA 125 greater than 35 U/ml after three courses of chemotherapy demonstrated persistent disease at second-look surgery while only 35.7% of those with normal CA 125 levels after three courses of chemotherapy demonstrated persistent disease. The results of this current study agree with those of Lavin *et al.* [5]; 57% of patients with normal CA 125 levels after three courses of chemotherapy demonstrated persistent disease at second-look surgery while 83.3% of patients with elevated CA 125 levels after three courses of chemotherapy demonstrated a positive second-look surgery. Interestingly, the results of this current study shows that patients who normalize their CA 125 levels after three courses of chemotherapy survive significantly longer than those who fail to normalize their CA 125 levels after three courses of chemotherapy.

In conclusion, normalization of CA 125 (< 35 U/ml) after three courses of cisplatin-based chemotherapy does not reliably indicate a negative second-look surgery. However, survival among those patients who normalized their CA 125 after three courses of chemotherapy is significantly improved over those who did not have normalized CA 125.

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