

# The Importance of CA125 Normalization During Neoadjuvant Chemotherapy Followed by Planned Delayed Surgical Debulking in Patients With Epithelial Ovarian Cancer

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## Abstract

**Objectives:** To examine the prognostic significance, in patients with ovarian cancer, of normalization of CA125 levels in serum during neoadjuvant chemotherapy treatment combined with delayed primary surgical debulking.

**Methods:** We carried out a retrospective chart review to identify ovarian cancer patients treated between 1997 and 2005 with neoadjuvant chemotherapy and delayed surgical debulking. Serum levels of CA125 were measured at baseline, prior to each cycle of chemotherapy, and before surgery. "CA125 normalization" was defined as a reduction in serum CA125 levels, in patients with elevated levels at diagnosis, to less than 35 kU/L. Cox proportional hazard models were built to model progression-free survival and overall survival.

**Results:** Ninety patients met the inclusion criteria. Sixteen patients (17.8%) had CA125 normalization before surgery, and 52 patients (57.8%) had normalization at the conclusion of all primary chemotherapy. Cox regression showed that CA125 normalization from neoadjuvant chemotherapy before surgery did not significantly predict survival. Patients who failed to normalize CA125 after finishing primary chemotherapy had shortened progression-free survival (HR 3.1; 95% CI 1.9–5.1,  $P < 0.001$ ) and overall survival (HR 2.6; 95% CI 1.0–6.9,  $P < 0.05$ ). The estimated median survival was 72 months (95% CI 64.6–79.40) in patients with normal CA125 at the end of chemotherapy, whereas in those with persistently elevated CA125 the corresponding estimated median survival was 46.8 months (95% CI 38.2–55.3).

**Conclusion:** CA125 normalization after neoadjuvant chemotherapy is not an independent predictor of either progression-free or overall survival. Patients with persistently elevated CA125 after completing primary treatment had significantly inferior survivals compared with those who normalized CA125.

**Key Words:** CA125 normalization, neoadjuvant chemotherapy, ovarian cancer

Competing Interests: None declared.

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## Résumé

**Objectifs :** Examiner l'importance pronostique, chez les patientes atteintes d'un cancer de l'ovaire, de la normalisation des taux sériques de CA125 au cours de la chimiothérapie néoadjuvante, conjointement avec le report de la chirurgie de réduction tumorale primaire.

**Méthodes :** Nous avons mené une analyse de dossiers rétrospective en vue d'identifier les patientes atteintes d'un cancer de l'ovaire qui ont été traitées, entre 1997 et 2005, au moyen d'une chimiothérapie néoadjuvante et d'une chirurgie de réduction tumorale différée. Les taux sériques de CA125 ont été mesurés d'entrée de jeu, avant chaque cycle de chimiothérapie et avant la chirurgie. La « normalisation des taux de CA125 » a été définie comme le passage, chez les patientes qui présentaient des taux élevés au moment du diagnostic, à des taux sériques de CA125 inférieurs à 35 kU/L. Des modèles des risques proportionnels de Cox ont été conçus pour modéliser la survie sans progression et la survie globale.

**Résultats :** Quarante-vingt-dix patientes ont satisfait aux critères d'inclusion. Seize patientes (17,8 %) ont connu une normalisation des taux de CA125 avant la chirurgie et 52 patientes (57,8 %) ont connu une normalisation à la fin de tous les traitements de chimiothérapie primaire. Le modèle de régression de Cox a indiqué que la normalisation des taux de CA125 attribuable à la chimiothérapie néoadjuvante avant la chirurgie ne permettait pas de prédire la survie de façon significative. Les patientes qui n'ont pu connaître une normalisation des taux de CA125 après avoir terminé la chimiothérapie primaire présentaient une survie sans progression (DI, 3,1; IC à 95 %, 1,9–5,1,  $P < 0,001$ ) et une survie globale (DI, 2,6; IC à 95 %, 1,0–6,9,  $P < 0,05$ ) moindres. La survie médiane estimée était de 72 mois (IC à 95 %, 64,6–79,40) chez les patientes présentant des taux normaux de CA125 à la fin de la chimiothérapie, alors que chez celles qui présentaient des taux obstinément élevés de CA125, la survie médiane estimée correspondante était de 46,8 mois (IC à 95 %, 38,2–55,3).

**Conclusion :** La normalisation des taux de CA125 à la suite de la chimiothérapie néoadjuvante ne constitue pas un prédicteur indépendant, que ce soit en matière de survie sans progression ou de survie globale. Les patientes qui présentaient des taux obstinément élevés de CA125 à la suite du traitement primaire ont connu des taux de survie significativement inférieurs, par comparaison avec celles qui ont connu une normalisation des taux de CA125.

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## INTRODUCTION

Standard management of metastatic epithelial ovarian cancer frequently involves a combination of aggressive surgical tumour debulking with platinum- and taxane-based chemotherapy.<sup>1</sup> The ideal sequence of surgery and chemotherapy to optimize oncologic outcomes and patients' quality of life and to minimize perioperative morbidity after initial diagnosis has not been clearly defined. Traditionally, surgical debulking has been performed first to confirm the diagnosis of ovarian cancer and to allow maximal debulking of metastatic tumour masses. Initial maximal cytoreduction has been strongly advocated, because having minimal residual tumour after surgery has been proven in many retrospective and prospective studies to improve a patient's prognosis significantly.<sup>2</sup> More recently, neoadjuvant chemotherapy administered prior to an attempt at surgical debulking has been reported in a number of retrospective case series in patients deemed to be poor surgical candidates.<sup>3-5</sup> These reports have demonstrated oncologic outcomes comparable to those of a similar historical patient cohort treated in the traditional manner, but with lower postoperative mortality and morbidity and shorter duration of hospitalization. The European Organization for Research and Treatment of Cancer (EORTC) is currently evaluating the role of neoadjuvant chemotherapy in a prospective randomized controlled clinical trial (EORTC protocol 55971) that has recently completed accrual.<sup>6</sup> The final results of this trial are not expected for several years while survival data are maturing.

Unfortunately, many patients with advanced ovarian cancer will subsequently have a recurrence of their disease despite an excellent clinical response to initial surgery and chemotherapy. It is important to be able to predict future disease behaviour reliably so that individualized follow-up plans, as well as consideration for consolidation treatment or further chemotherapy, can be rationally planned. The half-life of CA125 and its early normalization prior to the third cycle of adjuvant chemotherapy have both been established as independent prognostic factors for the achievement of pathologic complete response and survival in patients treated with primary surgery.<sup>7-10</sup> To our knowledge, few prior published studies have considered the importance of CA125 normalization patterns in patients treated with neoadjuvant chemotherapy.<sup>11,12</sup> Because neither the pattern of CA125 response nor its significance has been established for patients with ovarian cancer who are undergoing neoadjuvant chemotherapy followed by interval surgery, we studied the normalization of CA125 in these women during neoadjuvant chemotherapy in relation to standard oncologic outcomes.

## METHODS

We carried out a retrospective review of the charts of patients with epithelial ovarian cancer to identify those who were treated between 1997 and 2005 with neoadjuvant chemotherapy, with the intention of performing delayed primary surgical debulking. This time period was chosen to allow for sufficient maturation of survival data. At our institution, all patients who had clinical and radiographic findings consistent with intra-abdominal or extra-abdominal metastatic ovarian or peritoneal cancer, and who had no indication for urgent surgical intervention, underwent an ultrasound-guided core biopsy of the most accessible tumour mass and had a baseline serum CA125 measurement. Once a diagnosis consistent with primary gynaecologic malignancy was confirmed on histology and immunohistochemistry, three treatment cycles of carboplatinum (AUC 6) and paclitaxel (175 mg/m<sup>2</sup>) were administered intravenously at three week intervals. Debulking surgery was carried out approximately four weeks after the last cycle of chemotherapy, regardless of the response to neoadjuvant treatment. All surgery was performed by gynaecologic oncologists. After surgery, patients were given three more cycles of a similar chemotherapy regimen as soon as their postoperative recovery progress would allow it. Serum CA125 measurements were performed at the time of diagnosis, prior to each cycle of chemotherapy, and prior to debulking surgery.

Relevant patient demographics, together with disease characteristics, treatment details, CA125 levels, and survival outcome were abstracted from patients' clinic charts, with cross-reference made to hospital clinical databases to ensure accuracy and the most recent clinical information. CA125 normalization was defined as having occurred when a value of < 35 kU/L was reached in patients who had had an elevated CA125 level at the time of diagnosis.

Descriptive statistics and cross-tabulations were used as appropriate to summarize demographic data and to test for associations between categorical variables. Cox proportional hazard regression models were built to model time to first clinical progression and overall survival using predictor variables of age, cancer stage, tumour grade, residual disease status (< 1 cm vs. > 1 cm), and CA125 normalization either before surgery or at the conclusion of all primary treatment. A backwards conditional variable selection strategy was used to identify the most significant predictive variables of survival outcomes. All *P* values less than 0.05 were considered statistically significant. Data analysis was performed using SPSS version 15 for Windows (SPSS Inc., Chicago IL).

## RESULTS

We identified 101 patients who were treated with a neoadjuvant chemotherapy protocol between 1997 and 2005. Ninety patients with complete CA125 data were included in this study cohort. Unlike patients in most other reports of the use of neoadjuvant chemotherapy, none of our patients had major contraindications to primary surgery, and 71% had no significant concurrent medical comorbidities. The median age of these patients was 65.4 years (range 36–87). Most of our patients (93%) had stage 3 or 4 disease at the time of diagnosis, based on radiographic assessments. Patients with apparent measurable disease localized to the pelvis were assigned as having stage 2 disease. All patients tolerated neoadjuvant chemotherapy with no significant complications or delays and all proceeded with planned surgical debulking after three cycles of chemotherapy. No progressive disease was observed during the neoadjuvant treatment period. Eighty-seven percent of patients had serous histology, and 73% had grade 3 tumours based on the final pathology documented at the time of surgical debulking. No non-gynaecologic malignancy was diagnosed at the time of debulking surgery. The distribution of tumour characteristics in the study cohort is summarized in Table 1.

Sixteen patients (17.8%) had normalization of CA125 before surgery, and 52 patients (57.8%) had normalization at the conclusion of all chemotherapy. Optimal debulking (< 1 cm residual) was achieved in 54% of all patients in the study. Of the 74 patients who failed to normalize CA125 preoperatively, 51% (38/74) had suboptimal debulking, compared with a suboptimal debulking rate of 19% (3/16) in patients with a normal CA125 after three cycles of neoadjuvant chemotherapy. Thirty-four of the 74 patients with persistent abnormal CA125 after neoadjuvant chemotherapy (45.3%) had an elevated CA125 after debulking surgery and further chemotherapy. These patients were followed up for signs of clinical disease progression. At a median follow-up interval of 27 months (range 6.2 months–83.7 months), 75 patients (83%) had progressed, and 18 patients (20%) had died from disease progression. Disease progression and survival status of the study cohort at the latest follow up, stratified by CA125 normalization status after three cycles of neoadjuvant chemotherapy and at the completion of all primary treatment, are summarized in Tables 2 and 3. Of the patients with progressive disease, 25 (33%) were less than six months from their last platinum-based chemotherapy treatment. There was no significant association between CA125 normalization after three cycles of neoadjuvant chemotherapy and platinum sensitivity status at time of first recurrence ( $P = 0.28$ ). There was a significant association between CA125 normalization

**Table 1. Distribution of disease characteristics (N = 90)**

Tumour characteristics	Patients, N	Study group, %
<b>Stage</b>		
2	6	6.7
3	74	82.2
4	10	11.1
<b>Grade</b>		
I	4	4.5
II	20	22.2
III	66	73.3
<b>Final histology</b>		
Serous	78	86.7
Mucinous	1	1.1
Endometrioid	6	6.7
Clear cell	3	3.3
Mixed histologies	2	2.2

at the end of primary treatment and platinum-sensitive recurrent disease ( $P < 0.001$ ). The distribution of platinum sensitivity status stratified by CA125 normalization at the end of all primary treatment is shown in Table 4.

Cox regression analysis revealed two significant variables predictive of time to first clinical progression: older age (HR 0.97; 95% CI 0.95–0.99,  $P = 0.01$ ) and suboptimal residual disease (HR 1.67; 95% CI 1.03–2.72,  $P = 0.04$ ). Normalization of CA125 after neoadjuvant chemotherapy prior to surgery was not significantly predictive in this model, nor in the model predicting overall disease-specific survival using a similar set of predictors. When the normalization of CA125 after neoadjuvant chemotherapy was replaced by the normalization of CA125 at the end of chemotherapy treatment in the two models predicting progression-free and overall survival, different results were obtained. With respect to progression-free interval, both age (HR 0.98; 95% CI 0.96–0.99,  $P = 0.03$ ) and lack of CA125 normalization at the conclusion of primary treatment were significantly predictive (HR 3.11; 95% CI 1.88–5.14,  $P < 0.001$ ). Patients who failed to normalize CA125 after completing chemotherapy had a significantly shortened overall survival (HR 2.6; 95% CI 1.0–6.9,  $P < 0.05$ ).

The estimated median survival for the group was 67.7 months (95% CI 60.9–74.6). The estimated median survival was 72 months (95% CI 64.6, 79.40) in patients with normal CA125 at the end of chemotherapy, but in those with a persistently elevated CA125 level, the estimated median survival was only 46.8 months (95% CI 38.2–55.3). The estimated Kaplan Meier survival curves for the two groups are shown in the Figure.

**Table 2. Progression status stratified by CA125 normalization after 3 cycles of neoadjuvant chemotherapy and at conclusion of primary treatment (N = 90)**

		Progressed, n (%)	
		No	Yes
Preoperative serum CA125	normal	5 (31.2)	11 (68.8)
	elevated	10 (13.5)	64 (86.5)
Post primary treatment serum CA125	normal	12 (23.1)	40 (76.9)
	elevated	3 (8.3)	33 (91.7)

**Table 3. Survival status stratified by CA125 normalization after 3 cycles of neoadjuvant chemotherapy and at conclusion of primary treatment (N = 90)**

		Survival status, n (%)	
		Alive	Dead
Preoperative serum CA125	normal	13 (81.2)	3 (18.8)
	elevated	59 (79.7)	15 (20.3)
Post primary treatment serum CA125	normal	44 (84.6)	8 (15.4)
	elevated	27 (75)	9 (25)

**Table 4. Distribution of CA125 normalization at the end of primary treatment and platinum sensitivity status (N = 90)**

	Platinum sensitive	Platinum resistant
Serum CA125 normalized	13	3
Serum CA125 elevated	50	24

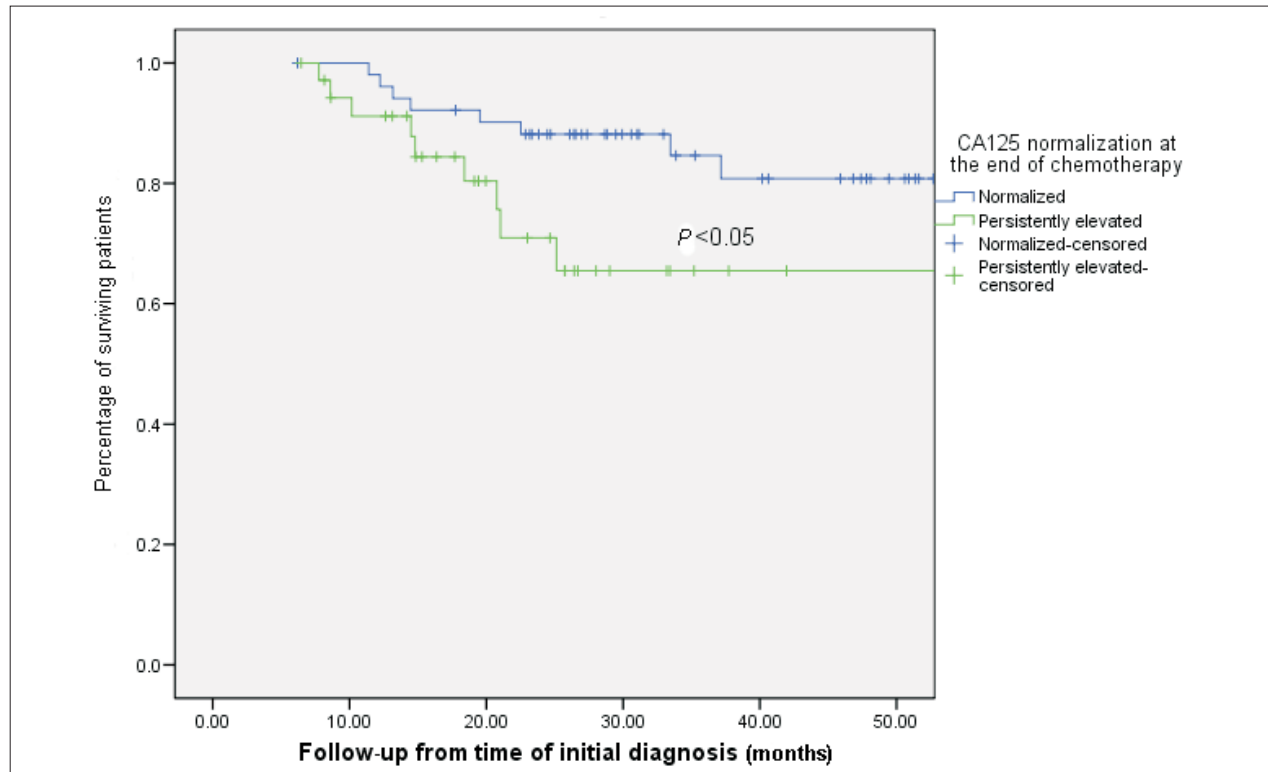
## DISCUSSION

The current study examines in detail the normalization pattern of CA125 during neoadjuvant chemotherapy followed by delayed primary surgical debulking. We chose the normalization of CA125 as a study variable because of the high reproducibility of the test and the ease of measuring this variable in most laboratories. Unlike patients in other reports,<sup>13–15</sup> our patient cohort had no relative contraindications for initial surgical exploration, thereby minimizing the possibility of selection bias. In contrast to other studies<sup>4,7</sup> examining the prognostic significance of the rate of CA125 regression in patients primarily managed surgically, we observed no significant association between CA125 normalization after three cycles of neoadjuvant chemotherapy before surgical debulking and progression-free or overall survival. Markman et al.<sup>7</sup> examined the serum CA125 values

from 101 patients with advanced ovarian cancer who participated in a trial comparing the systemic delivery of cisplatin/cyclophosphamide versus carboplatin/cyclophosphamide (both delivered every 28 days for six cycles) in suboptimal residual stage III and IV ovarian cancer. In this trial, CA125 values were measured for at least eight weeks following initiation of chemotherapy; although pretreatment CA125 values did not predict survival, the CA125 level at eight weeks after initiation of therapy was a powerful independent prognostic factor. The median survival for patients with a serum CA125 < 35 kU/L at eight weeks was 26 months, compared with 15 months in patients with a level > 35 kU/L ( $P < 0.001$ ). Similarly, Riedinger et al.<sup>9</sup> studied 494 patients with advanced epithelial ovarian cancer in order to assess the predictive and prognostic value of CA125 half-life and CA125 time to normalization during induction chemotherapy after surgery. CA125 normalization before the third cycle of chemotherapy was significantly associated with complete pathological response by univariate ( $P < 0.001$ ) and multivariate ( $P = 0.042$ ) analysis. Furthermore, CA125 normalization before the third cycle ( $P = 0.014$ ) and age ( $P = 0.032$ ) were independent prognostic factors for overall survival. As changes in CA125 levels during chemotherapy can accurately reflect tumour response to chemotherapy, it is logical to assume that, after surgical debulking, patients with tumours responding better to adjuvant chemotherapy would have a better prognosis.<sup>16–18</sup> However, when neoadjuvant chemotherapy is used, the tumour response kinetic could be different because large tumour masses have not been debulked. The potential benefits of debulking surgery include removal of large tumour masses with poor blood supply that contain cells in the Gompertzian growth cycle with a slow mitotic rate, leaving smaller tumour masses with higher growth rate<sup>19,20</sup> and making them potentially more sensitive to chemotherapy<sup>21</sup>; decreasing the risk of spontaneous evolution of chemotherapy-resistant clones<sup>22</sup>; and returning bowel function to normal by removing serosal metastases, thereby improving nutritional status and well-being. Gynaecologic oncologists are becoming increasingly aggressive in tumour debulking, employing radical pelvic and upper abdominal debulking procedures in order to minimize the chance of leaving behind significant tumour bulk. This change in surgical practice has been shown to improve survival.<sup>23,24</sup> In patients treated with primary neoadjuvant chemotherapy, the beneficial interaction between chemotherapy and surgery has not been fully exploited, so a lack of CA125 normalization before surgery would not be expected to carry as much prognostic significance as in patients who had undergone surgical debulking.

Our findings contrasted with those of Tate et al.,<sup>11</sup> who examined the association between CA125 regression

## Kaplan Meier survival estimates stratified by CA125 normalization at the end of all chemotherapy treatment



patterns in response to neoadjuvant chemotherapy (NAC) and prognosis in 50 patients with ovarian cancer. The patients in that study received NAC and did not undergo significant cytoreductive surgery. The CA125 regression coefficient was calculated using all the CA125 levels measured from the first day of NAC until the day of CA125 normalization ( $< 35$  kU/L) or the day of interval surgery. Responders were defined as patients with a regression coefficient of  $-0.039$  or greater, and non-responders as patients with a regression coefficient of less than  $-0.039$ , using the same patients' collected dataset. Univariate analysis identified the regression coefficient of CA125 as a significant prognostic factor for overall survival ( $P = 0.012$ ). However, the definition of response using a CA125 regression coefficient was not a standard one and was difficult to reproduce. In addition, the majority of patients in that study did not undergo any attempt at significant cytoreductive surgery, making a direct comparison to our study difficult. Furthermore, multivariate analysis was not reported to adjust for other potential confounders in that report.

In our study, CA125 normalization at the completion of a primary chemotherapy protocol, including interval surgical debulking, was found to be significantly associated with platinum-sensitive recurrent disease. This finding probably accounted for the independent significant value of CA125 normalization at the end of primary chemotherapy protocol in predicting progression-free and overall survival. Patients

who failed to normalize CA125 after finishing primary chemotherapy had a risk of dying from disease that was almost three times higher than patients with normal CA125 at the conclusion of primary chemotherapy and surgery. This finding is consistent with the other report<sup>25</sup> studying the rate of CA125 regression in patients treated with primary surgery followed by adjuvant chemotherapy. Our finding confirms the additive beneficial interaction between cytoreductive surgery and chemotherapy in the initial management of advanced epithelial ovarian cancers. This emphasizes the need to include attempts at radical tumour debulking in all patients treated with neoadjuvant chemotherapy, regardless of the initial degree of response to neoadjuvant treatment; this was suggested by our previous report on this topic<sup>12</sup> and a recent report showing that optimal residual disease is significantly associated with a lower chance of developing platinum resistance subsequently.<sup>26</sup> As shown in our study, more than one half of the patients with persistently abnormal CA125 levels after neoadjuvant chemotherapy eventually normalized CA125 after surgical debulking and further platinum based chemotherapy, supporting the incorporation of surgery in this subgroup of patients.

The limitations of this study lie in its retrospective nature, which is associated with unavoidable selection bias, and the incompleteness of CA125 data in some patients. Nevertheless, this series is one of the larger studies to date of

relatively healthy patients with advanced ovarian cancer treated with neoadjuvant chemotherapy. Thus there should be reduced selection bias compared with other studies using neoadjuvant chemotherapy.

On the basis of our results, we recommend stratifying patients on the basis of their CA125 normalization status at the end of primary treatment in future research into maintenance or consolidation chemotherapy strategies in the treatment of ovarian cancer. The significance of the serum CA125 value at the end of primary therapy in predicting progression-free and overall survival in patients treated with consolidation intraperitoneal chemotherapy has been outlined by Juretzka et al.<sup>27</sup> This easily obtainable and interpretable variable might serve to identify patients with a different tumour biology and prognosis so that individualized treatment can be instituted in an appropriate and timely fashion. Lastly, patients with persistently elevated CA125 levels at the end of treatment should be closely monitored because of their high risk of early progressive disease, so that a discussion about reinstating salvage treatment and appropriate counselling can be initiated at the first sign of disease progression.

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