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CA-125 AUC as a new prognostic factor for patients with ovarian cancer

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Abstract

Objective. The aim of the present study was to investigate the usefulness of the CA-125 area under the curve (AUC) as a new kinetic parameter for predicting overall survival in patients with ovarian cancer. In addition, the relationship of CA-125 AUC with other prognostic factors of ovarian cancer was evaluated.

Methods. Ninety-two patients that underwent primary line chemotherapy within 4 months after submission to cytoreductive surgery were included. For each patient, CA-125 AUC was calculated and a statistical analysis was conducted to compare CA-125 AUC behavior among patients according to several covariates.

Results. The mean age at diagnostic time was found to be 55.5 (16.1–82.4) years with a mean survival of 39.2 (3.5–100.1; SE = 2.6) months. Across FIGO stage I, II, III, and IV patients had a mean CA-125 AUC of 18.2, 24.6, 147.8, and 574.6 IU/ml*days, respectively ($P < 0.05$). At the evaluation date, living patients had a mean CA-125 AUC of 40.1 in contrast to 234.1 IU/ml*days ($P < 0.05$) for deceased ones. Patients with a complete response to primary chemotherapy had a mean CA-125 AUC of 48.8, while patients with a partial response had a mean of 251.7 IU/ml*days, and patients with no response or disease progression had a mean of 316.5 IU/ml*days ($P < 0.05$). The best CA-125 AUC performance is in predicting patient complete response to chemotherapy with a cut-off of 100 IU/ml*days and an accuracy of 82%.

Conclusions. Despite CA-125 AUC high correlation with the FIGO stage, residual disease, and patient final outcome, the main interest of CA-125 AUC calculation is to evaluate the treatment efficacy and to foresee a full chemotherapy response. Further studies should be carried out before extrapolating these results to other data sets.

Keywords: CA-125 kinetics; Ovarian cancer; Prognostic factors

Introduction

Ovarian cancer, generally treated with combination first line chemotherapy after cytoreduction surgery [1,2], has the highest mortality rate of all invasive cancers of the gynecological system. Bast et al. [3] first described a radioimmunoassay that could detect CA-125 (Cancer Antigen 125) in the serum of ovarian cancer patients [3]. CA-125 serum concentration is usually adopted to evaluate the clinical situation in ovarian cancer patients and the rate of decline in CA-125 during primary chemotherapy has been an important prognostic factor in several multivariate analyses [4]. The postoperative serum CA-125 level is an independent prognostic factor in patients with invasive ovarian cancer [5], and CA-125 tumor marker half-life ($t_{1/2}$) and tumor marker doubling time (DT) are often used as kinetic parameters for the evaluation of clinical response and follow-up of patients with ovarian cancer [6]. Serum CA-125 half-life during early chemotherapy is an independent prognostic factor for both the achievement of a pathologically complete response and the survival of patients with advanced epithelial ovarian cancer [7], and several studies report that the greatest difference in progression rate was found at a $t_{1/2}$ of 20 days [8–11]. Nevertheless, although CA-125 level before the 3rd course of chemotherapy was considered the best prognostic

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indicator by Fayers et al., it was classified inaccurately for clinical use [12].

In addition to CA-125 kinetic parameters, several other prognostic factors can be used in the management of ovarian cancer: the FIGO (Fédération Internationale de Gynécologie et d'Obstrétrique) tumor stage, tumor grade, tumor biology, overexpression of the HER-2/neu oncogene, residual disease after initial cytoreductive surgery, and rate of response to chemotherapy [13].

CA-125 tumor marker kinetics are more important than the isolated value of CA-125 serum concentration for patient prognosis, and in the present work, we propose a new kinetic parameter: the CA-125 area under the curve (AUC) and its relation with the FIGO stage, patient final state, tumor grade, residual disease, and primary chemotherapy response. Additionally, the influence of this new prognostic factor to overall survival in patients with ovarian cancer was also studied in our population.

Patients and methods

Retrospective clinical information was gathered from 339 patients with a diagnosis of ovarian cancer at the Gynaecology Service of Coimbra University Hospital (CUH) main database from 1990 to 2000. In addition, CA-125 serum levels of these patients were obtained from the Pathology Service (Hormonology and Drug Monitoring Laboratory) of CUH. Only 92 patients were included in the present analysis due to the restriction of our inclusion criteria: patients that underwent primary line chemotherapy within 4 months after submission to cytoreductive surgery

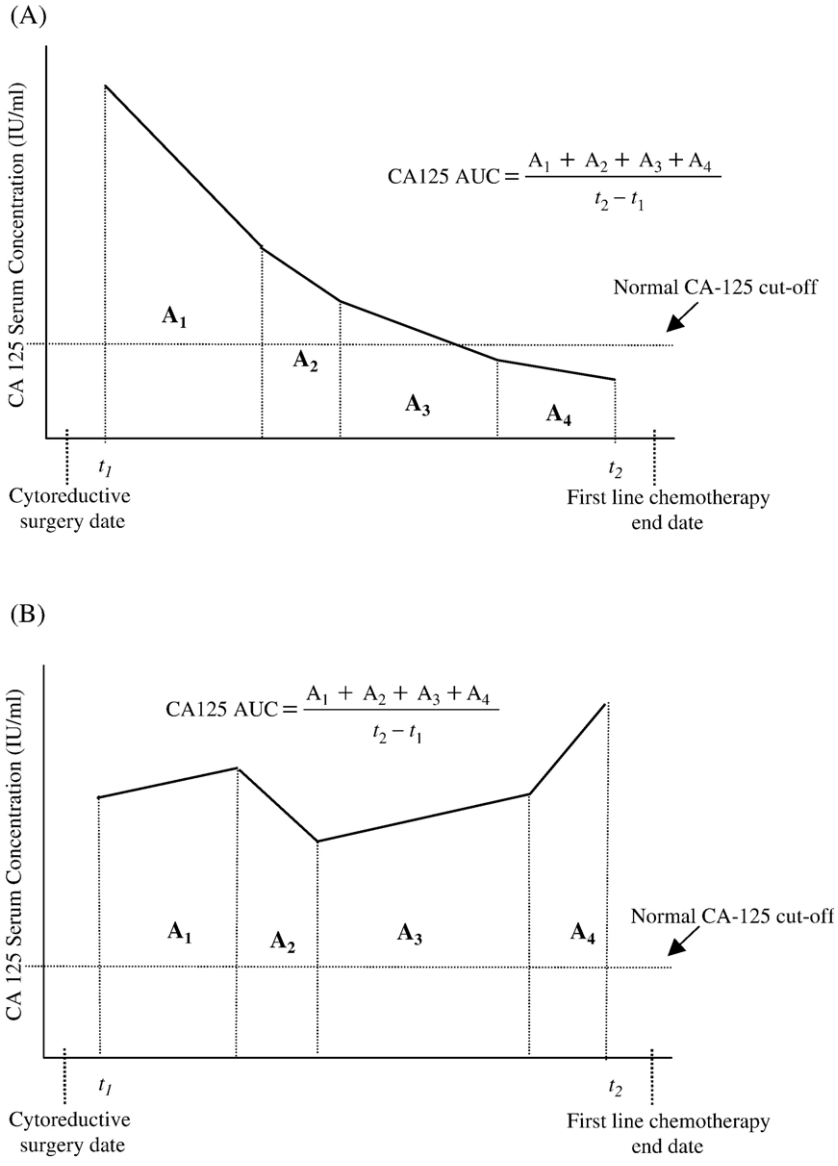

Fig. 1. CA-125 AUC hypothetical determination in a patient with ovarian cancer treated with first line chemotherapy after cytoreductive surgery; (A) patient with an optimal CA-125 serum levels evolution during treatment; (B) patient with an unstable CA-125 serum levels during treatment.

and with a minimum of three CA-125 serum concentrations between the time of surgery and the end of chemotherapy. For each patient, CA-125 AUC was calculated using the following formula:

$$\text{CA}-125\,\text{AUC} = (\text{sum of all trapezoid are as between } C_1 \text{ and } C_2)/(t_2 - t_1)$$

where C_1 is the first CA-125 serum concentration after the cytoreduction surgery and C_2 is the last CA-125 serum concentration before the end of first line chemotherapy, and t_1 and t_2 are the corresponding dates for C_1 and C_2, respectively (Fig. 1). A statistical analysis was conducted. The Mann–Whitney U test (for two groups) and Kruskal–Wallis test (for three or more groups) were used to compare the CA-125 AUC across subgroups of patients, depending on the FIGO stage, patient final state, tumor grade, histological type, residual disease (>2 cm), and response to primary chemotherapy. The area under the Receiver Operating Characteristic (ROC) curve was established for the discrimination by CA-125 AUC in predicting the patient final state, overall survival equal or superior to 1, 3, and 5 years, and a full response to chemotherapy. Sensitivity, specificity, positive predictive values (PPV), and overall accuracy were also determined for several CA-125 AUC cut-offs. In addition, a multivariant regression analysis based on the Cox proportional hazard model to test the variation of CA-125 AUC in relation to the overall survival time was also carried out. A P level ≤ 0.05 was considered significant.

Results

The mean age at diagnostic time was found to be 55.5 (16.1–82.4; SE = 1.65) years with a mean overall survival of 39.2 (3.5–100.1; SE = 2.6) months. According to the FIGO tumor stage, nineteen (20.7%) patients had stage I, eleven (11.9%) had stage II, fifty-one (55.4%) had stage III, nine (9.8%) had stage IV, and in two (2.2%) patients this information was missing. Eighty-two (89.1%) patients had epithelial ovarian cancer for histological type. Twelve (13.0%) patients had a tumor grade 1, twenty-nine (31.5%) a tumor grade 2, nine (9.8%) had a tumor grade 3, and forty-two (45.7%) patients had no tumor grade information. Thirty-six (39.1%) patients had a residual tumor greater than 2 cm after surgery. The mean duration of primary chemotherapy was 4.1 (0.7–10.2; SE = 0.15) months: fifty-two (56.5%) patients had a complete response to primary chemotherapy, twenty-two (23.9%) had a partial response, thirteen (14.1%) had no response or a disease progression, and five (5.4%) patients had missing information for the response to chemotherapy. At evaluation date, fifty (54.3%) patients were deceased while forty-two (45.7%) were alive. Eighty patients (86.9%) had at least 1 year survival, forty-four (47.8%) had at least 3 years while only twenty-one (22.8%) had more than 5 years survival (Table 1).

Table 1
Summary of patient characteristics

	Patient count (%)
FIGO stage	
I	19 (20.7)
II	11 (11.9)
III	51 (55.4)
IV	9 (9.8)
Missing	2 (2.2)
Patient final state	
Deceased	50 (54.3)
Alive	42 (45.7)
Tumor grade	
1	12 (13.0)
2	29 (31.5)
3	9 (9.8)
Missing	42 (45.7)
Histological type	
Epithelial	82 (89.1)
Other	8 (8.7)
Missing	2 (2.2)
Residual disease (>2 cm)	
Yes	36 (39.1)
No	53 (57.6)
Missing	3 (3.3)
Primary chemotherapy response	
Complete response (CR)	52 (56.5)
Partial response (PR)	22 (23.9)
Without response or disease progression (WR/DP)	13 (14.1)
Missing	5 (5.4)
Overall survival	
≥1 year	80 (86.9)
≥3 years	44 (47.8)
≥5 years	21 (22.8)

The CA-125 AUC across groups of patients is shown in Table 2. Patients with FIGO stage I, II, III, and IV had a mean CA-125 AUC of 18.2 (SE = 2.4) IU/ml*days, 24.6 (SE = 7.6) IU/ml*days, 147.8 (SE = 30.8) IU/ml*days, and 574.6 (SE = 134.6) IU/ml*days, respectively ($P < 0.05$) (Fig. 2). Patients with a tumor grade 1, 2, and 3 had a mean CA-125 AUC of 100.1 (45.5) IU/ml*days, 158.1 (43.0) IU/ml*days, and 238.8 (114.0) IU/ml*days, respectively ($P > 0.05$). Patients with residual disease (>2 cm) had a mean CA-125 AUC of 207.4 (SE = 48.3) IU/ml*days, while patients without residual disease had 97.9 (SE = 30.0) IU/ml*days ($P < 0.05$). At the evaluation date, living patients had a mean CA-125 AUC of 40.1 (SE = 10.5) IU/ml*days in contrast to deceased patients, who had a CA-125 AUC of 234.1 (SE = 44.4) IU/ml*days ($P < 0.05$). Fifty-two patients had a complete response to primary chemotherapy with a mean CA-125 AUC of 48.8 IU/ml*days (SE = 15.9) while twenty-two patients had a partial response and thirteen patients had no response or disease progression with a mean CA-125 AUC of 251.7 IU/ml*days (SE = 65.8) and a mean

Table 2
CA-125 AUC behavior among patients according to several covariates

Group	Mean CA-125 AUC (standard error) [IU/ml*days]	Median CA-125 AUC (Q_{25}–Q_{75}) [IU/ml*days]	*P* value
FIGO stage			
I	18.2 (2.4)	14.6 (12.0–20.1)	$P < 0.05$
II	24.6 (7.6)	14.4 (9.8–20.5)	
III	147.8 (30.8)	54.2 (23.5–199.5)	
IV	574.6 (134.6)	676.3 (118.6–973.3)	
Patient final state			
Deceased	234.1 (44.4)	83.2 (23.5–319.5)	$P < 0.05$
Alive	40.1 (10.5)	16.5 (12.0–34.0)	
Tumor grade			
1	100.1 (45.5)	19.8 (12.3–146.9)	NS
2	158.1 (43.0)	65.8 (16.6–230.7)	
3	238.8 (114.0)	44.8 (37.3–375.2)	
Residual disease (>2 cm)			
Yes	207.4 (48.3)	98.1 (31.3–237.9)	$P < 0.05$
No	97.9 (30.0)	16.6 (12.0–44.8)	
Primary chemotherapy response			
Complete response (CR)	48.8 (15.9)	16.8 (12.0–34.1)	$P < 0.05$
Partial response (PR)	251.7 (65.8)	98.1 (51.9–319.5)	
Without response or disease progression (WR/DP)	316.5 (107.5)	116.8 (54.2–344.3)	

of 316.5 IU/ml*days (SE = 107.5), respectively ($P < 0.05$) (Fig. 3).

For predicting the patient final state, the best accuracy (74%) was achieved at CA-125 AUC ≤ 100 IU/ml*days (ROC AUC = 0.77). To predict patient survival, the most accurate was 87% (CA-125 AUC ≤ 1000 IU/ml*days), 72% (CA-125 AUC ≤ 100 IU/ml*days), and 66% (CA-125 AUC ≤ 25 IU/ml*days) for a 1-, 3-, and 5-year overall survival, respectively (ROC AUC = 0.67, 0.75, and 0.73). In predicting a complete response to chemotherapy (ROC AUC = 0.87), the best CA-125 AUC cut-off was 100 IU/ml*days with an accuracy of 82% (Table 3). We estimated the parameters in the Cox proportional hazard model using overall survival as a dependent variable, CA-125 AUC as an independent variable, and the patient final state ("Alive" or "Deceased") as a censoring variable. FIGO tumor stage, residual disease, and primary chemotherapy response were stratification variables (Table 4). Fig. 4 shows the survival functions for different values of CA-125 AUC produced with the Cox model without any stratification variable.

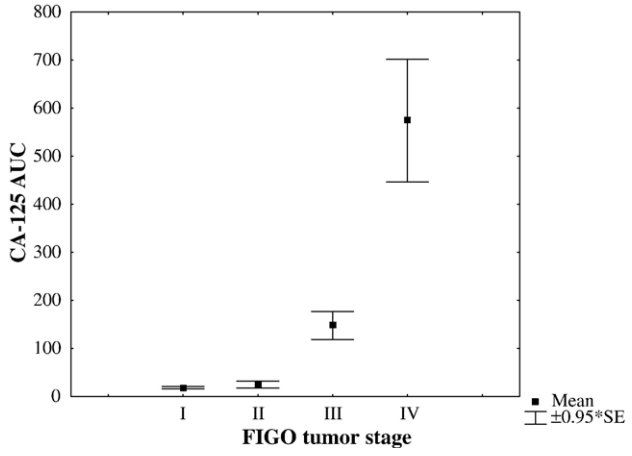

Fig. 2. CA-125 mean plot according to patients' FIGO tumor stage.

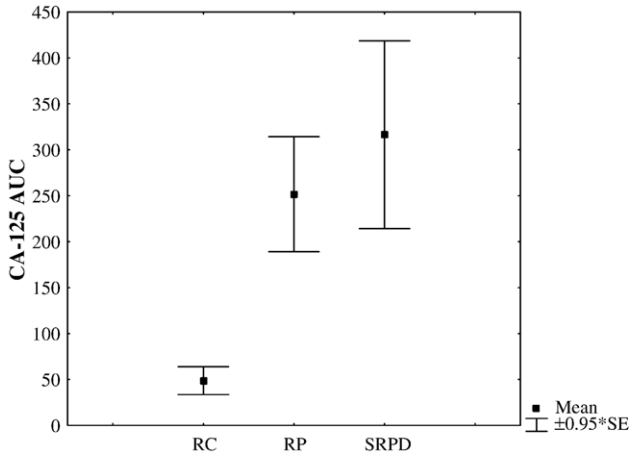

Fig. 3. CA-125 mean plot according to patient response to primary chemotherapy. (CR = complete response; PR = partial response; WRDP = without response or disease progression.)

Discussion

Many authors have studied the CA-125 kinetic in monitoring the ovarian cancer patient. Kinetic parameters prove to be more useful than rough serum concentration alone. Van der Burg et al. [8], Hawkins et al. [9], Verda et al. [10], S. Èolakoviæ et al. [11], and others used the CA-125 half-life value to evaluate patient survival, finding a $t_{1/2}$ of 20 days to be a breakpoint between a "good" and "poor" prognosis.

Buller et al. showed that the rate of decline of CA-125 in effectively treated ovarian cancer is described by an exponential model and his study suggests that it is possible to predict overall survival, which patients have residual disease at reassessment laparotomy, who will be free of disease, and who will have a recurrence [14,15].

In a review article, Jean-Michel et al. [6] accentuated the value of different serum marker kinetic parameters in the monitoring of patients in several types of cancer.

To increase the value of CA-125 kinetics as a prognostic factor in ovarian cancer, we proposed and studied a new kinetic parameter: CA-125 AUC. As can be seen in Figs. 1A/B, the CA-125 AUC calculation is independent of the shape presented by the CA-125 serum concentrations, making CA-125 AUC a more suitable kinetic parameter than CA-125 half-life (Fig. 1A). In addition, the CA-125

Table 3
Sensitivity, specificity, positive predictive value (PPV), and accuracy of several CA-125 AUC cut-offs for predicting the patient final state, overall survival, and chemotherapy complete response (SE = standard error)

CA-125 AUC [IU/ml*days]	≤25	≤50	≤100	≤200	≤300	≤400	≤500	≤600	≤800	≤1000	ROC AUC (SE)
CA-125 cut-off to predict patient final state "alive"											
Sensitivity	0.62	0.86	0.86	0.95	0.97	1.00	1.00	1.00	1.00	1.00	0.77 (0.05)
Specificity	0.72	0.64	0.64	0.32	0.30	0.20	0.20	0.14	0.08	0.04	
PPV	0.65	0.67	0.67	0.54	0.54	0.51	0.51	0.50	0.48	0.47	
Accuracy	0.67	0.74	0.74	0.61	0.61	0.57	0.57	0.53	0.50	0.48	
CA-125 cut-off to predict patient overall survival ≥ 1 year											
Sensitivity	0.48	0.63	0.63	0.81	0.84	0.90	0.90	0.94	0.98	0.99	0.67 (0.08)
Specificity	0.83	0.67	0.67	0.25	0.25	0.17	0.17	0.17	0.17	0.08	
PPV	0.95	0.93	0.93	0.88	0.88	0.88	0.88	0.88	0.89	0.88	
Accuracy	0.52	0.63	0.63	0.74	0.76	0.80	0.80	0.84	0.87	0.87	
CA-125 cut-off to predict patient overall survival ≥ 3 years											
Sensitivity	0.64	0.82	0.82	0.98	0.98	0.98	0.98	0.98	0.98	1.00	0.75 (0.05)
Specificity	0.75	0.63	0.63	0.35	0.31	0.19	0.19	0.13	0.06	0.04	
PPV	0.70	0.67	0.67	0.58	0.57	0.52	0.52	0.51	0.49	0.49	
Accuracy	0.70	0.72	0.72	0.65	0.63	0.57	0.57	0.53	0.50	0.50	
CA-125 cut-off to predict patient overall survival ≥ 5 years											
Sensitivity	0.71	0.90	0.90	1.00	1.00	1.00	1.00	1.00	1.00	1.00	0.73 (0.06)
Specificity	0.65	0.51	0.51	0.25	0.23	0.14	0.14	0.10	0.08	0.04	
PPV	0.38	0.35	0.35	0.28	0.28	0.26	0.26	0.25	0.44	0.43	
Accuracy	0.66	0.60	0.60	0.42	0.40	0.34	0.34	0.30	0.47	0.45	
CA-125 cut-off to predict patient complete response to chemotherapy											
Sensitivity	0.65	0.85	0.85	0.94	0.96	0.98	0.98	0.98	1.00	1.00	0.87 (0.04)
Specificity	0.89	0.77	0.77	0.37	0.34	0.23	0.23	0.14	0.11	0.06	
PPV	0.89	0.85	0.85	0.69	0.68	0.65	0.65	0.63	0.63	0.61	
Accuracy	0.75	0.82	0.82	0.71	0.71	0.68	0.68	0.64	0.64	0.62	

AUC is less disturbed by peak phenomena (especially after surgery) and sources of variability (i.e., intra-subject and assay variability).

In the present work, the poor correlation between CA-125 AUC and tumor grade is perhaps the consequence of the high number of patients without this information. Inversely, CA-125 AUC is highly correlated with the FIGO stage in which lower values are related with stage I and II, middle values with stage III, and higher values with stage IV. Patients with stage IV have a mean CA-125 AUC 31.6 times greater than patients with stage I. CA-125 AUC is also correlated with residual disease for patients with a residual tumor >2 cm after initial cytoreductive surgery (mean CA-125 AUC 2.1 times greater). CA-125 AUC is also correlated with patient final state in deceased patients, having a mean CA-125 AUC 5.8 times greater than living. As shown by the Cox proportional hazard model, the CA-125 AUC is an independent prognostic factor for patient overall survival and patients with a lower CA-125 AUC have a better overall survival than patients with a higher CA-125 AUC.

Concerning survival forecast, the best CA-125 AUC cut-off was 100 IU/ml*days, obtained for predicting an overall survival ≥3 years, the patient final state "alive", and the complete response to chemotherapy, with an accuracy of 72%, 74%, and 82%, respectively. In fact, it seems clear that

Table 4
Cox proportional hazard model results for CA-125 AUC as an independent factor for predicting patient overall survival

Dependent: overall survival; independent: CA-125 AUC; censoring variable: patient final state (deceased/alive)		
Stratified by:	Chi-square	*P* value
None	18.19	$P < 0.05$
FIGO tumor stage (I, II, III, IV)	6.42	$P < 0.05$
Residual disease (>2 cm)	14.80	$P < 0.05$
Primary chemotherapy response (CR, PR, WR/DP)	1.83	NS

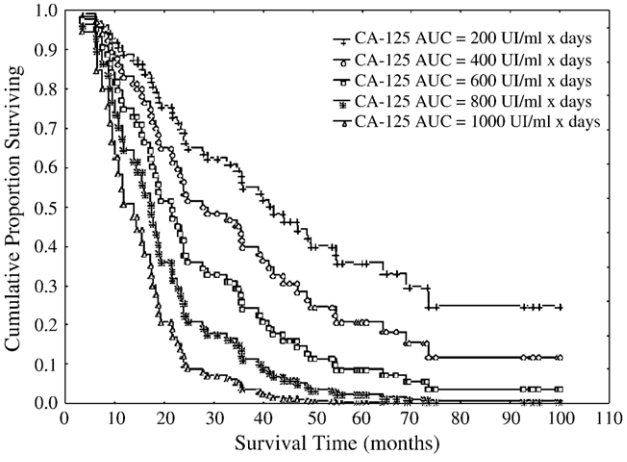

Fig. 4. Survival function for hypothetical CA-125 AUC values.

lower CA-125 AUC values are associated with a complete response, while higher values are associated with a partial response or even a disease progression. Therefore, CA-125 AUC could be a useful measure of the primary treatment efficacy, not only to evaluate the cytoreductive surgery but also the chemotherapy cocktail adopted. Regarding the CA-125 AUC kinetic, the objective of initial treatment (cytoreductive surgery and primary chemotherapy) of ovarian cancer is to produce the lowest CA-125 AUC possible. In addition, the CA-125 AUC kinetic parameter could be useful as an end-point in the development of new chemotherapy drugs or to establish new guidelines for the primary treatment of ovarian cancer.

Finally, CA-125 AUC presents some benefits over other kinetic parameters: it is easier to calculate and model-independent. Nevertheless, further studies should be carried out in order to compare CA-125 AUC with other prognostic factors used in the management of ovarian cancer patients and caution should be exercised before extrapolation of the present results to different data sets.

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