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CA-125 AUC as a predictor for epithelial ovarian cancer relapse

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Abstract. *Purpose:* The aim of the present work was to evaluate the usefulness of CA-125 normalized in time area under the curve (CA-125 AUC) to signalise epithelial ovarian cancer relapse.
Patients and Methods: Data from a hundred and eleven patients were submitted to two different approaches based on CA-125 AUC increase values to predict patient relapse. In *Criterion A* total CA-125 AUC normalized in time value (AUC_i) was compared with the immediately previous one (AUC_{i-1}) using the formulae $AUC_i \geqslant F * AUC_{i-1}$ (several F values were tested) to find the appropriate close related increment associated to patient relapse. In *Criterion B* total CA-125 AUC normalised in time was calculated and several cut-off values were correlated with patient relapse prediction capacity.
Results: In *Criterion A* the best accuracy was achieved with a factor (F) of 1.25 (increment of 25% from the previous status), while in *Criterion B* the best accuracies were achieved with cut-offs of 25, 50, 75 and 100 IU/mL. The mean lead time to relapse achieved with *Criterion A* was 181 days, while with *Criterion B* they were, respectively, 131, 111, 63 and 11 days.
Conclusion: Based on our results we believe that conjugation and sequential application of both criteria in patient relapse detection should be highly advisable. CA-125 AUC rapid burst in asymptomatic patients should be firstly evaluated using *Criterion A* with a high accuracy (0.85) and with a substantial mean lead time to relapse (181 days). If a negative answer was obtained then *Criterion B* should performed to confirm the absence of relapse.

Keywords: Ovarian cancer, CA-125, CA-125 kinetics, follow-up, relapse, recurrence

1. Introduction

Ovarian cancer has the highest mortality among all invasive cancers of the female gynaecological system in the western world. In addition, without a routine generalized screening test, the majority of patients with ovarian cancer present an advanced stage of disease at the time of diagnosis [1–3].

Despite the developments in first line cytoreductive surgery [4] and chemotherapy [5,6], most women with the disease at an advanced stage suffer recurrence, making ovarian cancer a disease with a poor prognosis. Approximately 10%–50% of patients who receive surgery for treatment of early stage ovarian cancer also have a recurrence [7]. Since curative therapy for a recurrence of the disease may not be possible, attempts to prolong progression-free (PFS) and overall survival, relieve symptoms, and extend quality of life become the alternative goals [8,9]. The treatment options for patients with recurrent ovarian cancer include additional chemotherapy and, in some particular cases, surgery and radiation therapy [10,11].

Several drugs and regimens can be used in relapsed ovarian cancer [12]: for instance, carboplatin alone [13] or together with paclitaxel [14,15] in sensitive patients, topotecan [16–18], doxorubicin, and gemcitabine, among others for resistant patients.

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Past available data do not supply a conclusive role for surgery in the treatment of relapsed ovarian cancer [20]. More recent studies suggest that secondary cytoreduction may improve patient survival [21,22], especially in patients that recur at least six months after first-line treatment [23].

In practice, radiation therapy is rarely used due to the amount of radiation that abdomen organs can safely receive. Nevertheless, radiation therapy for advanced ovarian cancer was reported to be more positive than second- and third-line chemotherapy in terms of response, survival and tolerance [24] and therapy with involved field radiation is effective in controlling localized recurrences, particularly after optimal debulking [25].

Although in many cases the treatment objective is to prolong survival, the majority of women with ovarian cancer prefer continuing to treat their cancer aggressively, regardless of poor outcomes and the quality of life becomes secondary [26]. Approximately half of patients without any symptoms of relapse (and the corresponding physicians) want early chemotherapy for a rising CA-125, even with the increase of toxicity [27].

There are several surveillance options to manage ovarian cancer patients. These include second-look laparotomy, regular physical examination, regular imaging, and CA-125 measurement [7].

Described by Bast et al. [28], CA-125 has an important role in analyzing ovarian cancer follow-up. Numerous studies indicate that a continuous rise in serum CA-125 precedes the clinical detection of recurrence [29,30] and CA-125 may have an important role to play in the design of clinical trials, from prognosis to follow-up [31,32].

Several authors tested alternative CA-125 progression criteria to predict ovarian cancer recurrence. Rustin et al. state that a confirmed rise in CA-125 serum concentration to more than twice the normal upper limit during follow-up after first-line chemotherapy accurately predicts relapse [33]. Tuxen et al. reported that analytical imprecision and intra-individual biological fluctuation considerably influence the variation in CA-125 results [34], and developed several progression criteria that could provide early information about ovarian cancer recurrence [35].

Instead of using the absolute tumour marker concentration itself, the use of tumour marker kinetic parameters seems to be a more rational approach. Indeed, the serum CA-125 kinetic behaviour has an important role in describing the course of the disease. Parameters such as the CA-125 half-life can be used to evaluate the clinical response to the first-line treatment of patients [36], while doubling time (DT) can be used as a predictive factor for ovarian cancer recurrence [37]. Moreover, the intrinsic value of the recently, so called 'normalized in time area under the curve (CA-125 AUC) kinetic parameter' as a prognostic factor and as a primary treatment efficacy outcome, has already been described [38].

The objective of the present work was to evaluate the potential usefulness of CA-125 AUC kinetic parameter to signal ovarian cancer relapse before (and anticipating) any clinical detection.

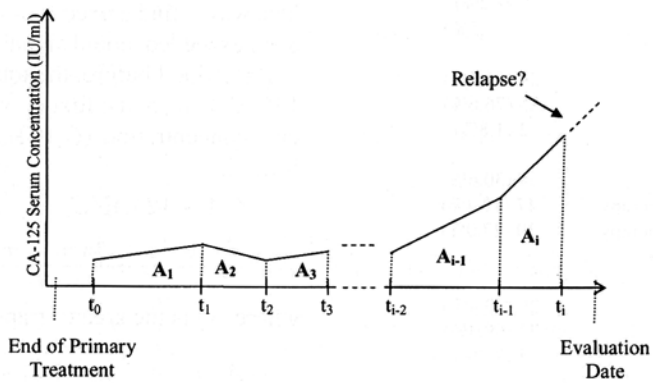
2. Patients and methods

Retrospective clinical information was gathered on patients diagnosed in the late 80 s and 90 s with epithelial ovarian cancer from the Gynaecology Service of Coimbra University Hospital (HUC) main database. CA-125 serum levels of these patients were obtained from the Pathology Service (HUC – Hormonology & Drug Monitoring Laboratory) database. Patients with a minimum of three CA-125 serum concentrations between the end of primary treatment and the evaluation date were included in the study. The end of treatment was determined as the date of curative surgery if the patient did not receive any chemotherapy, or the date of conclusion of primary (adjuvant) chemotherapy, or the end of consolidation chemotherapy if the patient received it after the primary chemotherapy. In patients with an early stage (I-IIa) the surgery includes a total abdominal hysterectomy, bilateral salpingo-oophorectomy, infra-colic omentectomy, multiple biopsys of the abdominal cavity and peritoneal lavage cytology. In rare cases pelvic lymphadenectomy was performed. For advanced stages (IIb-IV) cytoreduction surgery was performed with the attempt of resection of lesions smaller than 2 cm.

During the follow up period, beginning at the end of primary treatment, data was appropriately recorded in the patient clinical file database. Relapse was first determined by physical examination in most cases, by imaging and, in few cases, by biopsy. It should be emphasised that no patients were treated for relapse based on CA-125 information alone. Due to the fact that CA-125 analysis only became standard practice at the beginning of the 90s, not all patients presented CA-125 levels immediately after the end of primary treatment. Therefore, for data analysis purpose and to ensure the same starting conditions for all of them, the

Table 1
Increase factors (F) used in *Criterion A*

Factor	
1.10	AUC_i greater or equal than AUC_{i-1} in more than 10%
1.25	AUC_i greater or equal than AUC_{i-1} in more than 25%
1.50	AUC_i greater or equal than AUC_{i-1} in more than 50%
1.75	AUC_i greater or equal than AUC_{i-1} in more than 75%
2.00	AUC_i greater or equal than AUC_{i-1} in more than 100%
2.50	AUC_i greater or equal than AUC_{i-1} in more than 150%
3.00	AUC_i greater or equal than AUC_{i-1} in more than 200%



Criterion B
Search a concentration/time (Ci/t_i) where:

$$CA\ 125\ AUC = \frac{A_1 + A_2 + A_3 + \ldots + A_{i-1} + A_i}{t_i - t_0} \geq \textbf{Cut - Off (IU/ml)}$$

Criterion A
Search a concentration/time (Ci/t_i) where
CA 125 AUC to $t_i \geq$ *Factor* * CA 125 AUC to t_{i-1}

Fig. 1. Hypothetical CA-125 evolution after primary treatment of patient with ovarian cancer.

first available CA-125 level (C_0) after the end of primary treatment had to be under 35 IU/mL (baseline). Four patients that only had CA-125 levels after relapse detection and one patient with only one CA-125 level between primary treatment conclusion and relapse were withdrawn from the study. Thus, a hundred and eleven patients were included in the present study where two different methodological approaches were tested in order to get the best value from the CA-125 tumour marker to predicted epithelial ovarian cancer relapse.

2.1. Criterion A

The aim of this approach was to find in what way a rapid increase in CA-125 AUC could signal patient relapse. For this purpose the overall CA-125 AUC for two consecutive CA-125 sampling times were calculated and the increment between them evaluated.

Mathematically, in this criterion the overall CA-125 AUC normalized in time to C_i/t_i (AUC_i) was compared to the previous one, i.e. the total CA-125 AUC normalized in time to C_{i-1}/t_{i-1} (AUC_{i-1}). AUC_i and AUC_{i-1} were determined using the following formulae:

$$AUC_i = \frac{A_1 + A_2 + A_3 + \ldots + A_i}{t_i - t_0}$$

$$AUC_{i-1} = \frac{A_1 + A_2 + A_3 + \ldots + A_{i-1}}{t_{i-1} - t_0}$$

where in both cases A_j is the area of trapezoid j, calculated by:

$$A_j = \frac{C_{j-1} + C_j}{2}(t_j - t_{j-1})$$

$$\begin{cases} j \in \{1, 2, 3, \ldots, i\} \text{ in } AUC_i \\ j \in \{1, 2, 3, \ldots i-1\} \text{ in } AUC_{i-1} \end{cases}$$

Table 2
Summary of patient characteristics

FIGO Stage	Patient Count (%)
I	50 (45.1%)
II	12 (10.8%)
III	42 (37.8%)
IV	3 (2.7%)
Missing	4 (3.6%)
Tumor Grade	
1	27 (24.3%)
2	20 (18.0%)
3	8 (7.2%)
Missing	56 (50.5%)
Residual Disease (>2 cm)	
Yes	24 (21.6%)
No	85 (76.6%)
Missing	2 (1.8%)
Primary Treatment	
Surgery	34 (30.6%)
Surgery + Adjuvant Chemotherapy	47 (42.4%)
Surgery + Adjuvant Chemotherapy + Consolidation Chemotherapy	30 (27.0%)
Relapse	
Yes	26 (23.4%)
No	77 (69.4%)
Missing	8 (7.2%)
Patient Final State	
Deceased	30 (27.0%)
Alive	81 (73.0%)

Therefore, the calculated AUCs were compared accordingly the following rational: $AUC_i \geqslant F * AUC_{i-1}$ with F equal to 1.10 ($AUC_i \geqslant AUC_{i-1}$ in more than 10% of AUC_{i-1}), 1.25 ($AUC_i \geqslant AUC_{i-1}$ in more than 25% of AUC_{i-1}), 1.50 ($AUC_i \geqslant AUC_{i-1}$ in more than 50% of AUC_{i-1}), 1.75 ($AUC_i \geqslant AUC_{i-1}$ in more than 75% of AUC_{i-1}), 2.00 ($AUC_i \geqslant AUC_{i-1}$ in more than 100% of AUC_{i-1}), 2.50 ($AUC_i \geqslant AUC_{i-1}$ in more than 150% of AUC_{i-1}) or 3.00 ($AUC_i \geqslant AUC_{i-1}$in more than 200% of AUC_{i-1}) (Table 1). If the condition $AUC_i \geqslant F * AUC_{i-1}$ was true the test was considered positive. Otherwise the test was considered negative.

In order to build our model and due to the fact that this was a retrospective study, a forward stepwise approach was implemented using the following strategy for each patient dataset. Exemplifying with a patient having ten CA-125 levels obtained after the end of primary treatment (all patients should have a minimum of three CA-125 levels), the CA-125 AUC was calculated from C_0 to C_3 (AUC_i) and compared to CA-125 AUC from C_0 to C_2 (AUC_{i-1}); subsequently CA-125 AUC was calculated from C_0 to C_4 (AUC_i) and compared to CA-125 AUC from C_0 to C_3(AUC_{i-1}), and so on, until CA-125 AUC from C_0 to C_{10} (AUC_i) was calculated and compared to CA-125 AUC from C_0 to C_9 (AUC_{i-1}). The stepwise procedure stopped when the CA-125 AUC to a certain concentration/time fulfilled the started condition ($AUC_i \geqslant F * AUC_{i-1}$) (positive test) or when the started condition was not reached at all for the complete dataset (negative test).

2.2. Criterion B

While with the *Criterion A* we were looking for rapid increases in CA-125 AUC, the *Criterion B* aimed to look for sustained increases that could potentially be associated to a relapse. Therefore, in this approach the idea was to find a fixed CA-125 AUC cut-off value that, once exceeded, could signal patient relapse.

As defined before, the total normalised in time CA-125 AUC from the first concentration (C_0/t_0) to a certain concentration (C_i/t_i) was determined using the formula:

$$CA-125AUC_i = \frac{A_1 + A_2 + A_3 + ... + A_{i-1} + A_i}{t_i - t_0}$$

where A_j is the area of trapezoid j, calculated by:

$$A_j = \frac{C_{j-1} + C_j}{2}(t_j - t_{j-1}), j \in \{1, 2, 3, ...i\}.$$

In order to find the best cut-off and due to the fact that this was a retrospective study, a forward stepwise approach was carried out for each patient dataset. In fact, for each patient the corresponding CA-125 AUC were calculated and compared with several cut-off values: 15; 25; 50; 75; 100; 150; 200; 400; 600 and 1000 IU/mL. If the CA-125 AUC values were equal or superior to a considered cut-off value the test was considered positive. Otherwise the test was considered negative.

Using the example with a patient having ten CA-125 levels obtained after the end of primary treatment, the CA-125 AUC was calculated from C_0 to C_3 (all patients should have a minimum of three CA-125 levels), then from C_0 to C_4 and so on, until reaching CA-125 AUC from C_0 to C_{10}. The test stopped when the CA-125 AUC to a certain concentration (for instance C_6) exceeded the considered cut-off value (positive test) or when the overall CA-125 AUC (i.e. C_0 to C_{10} in the present example) did not exceeded the selected cut-off value (negative test).

For both criteria (A and B) sensitivity, specificity, the positive predictive value (PPV), negative predictive value (NPV) and best accuracy for predicting relapse was calculated. In all true-positive tests, the lead time to relapse was measure from t_i to the relapse date (t_r) recorded in the patient clinical file (Fig. 1). A positive lead time indicates that the increase criteria occur before the relapse while a negative time indicates that the increase criteria occur after the relapse.

Table 3
Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), false positives (FP %), false negatives (FN %) and accuracy achieved for each criterion ($N = 103$ due to missing values)

Criterion A										
Test CA-125 AUC to $t_i \geqslant$ F *AUC to t_{i-1}		Relapse Yes	Relapse No	Sensitivity	Specificity	PPV	NPV	Accuracy	FP (%)	FN (%)
$F = 1.10$ (10%)	Positive	22	26	0.85	0.66	0.46	0.93	0.71	25.2	3.9
	Negative	4	51							
$F = 1.25$ (25%)	Positive	19	8	0.73	0.90	0.70	0.91	0.85	7.8	6.8
	Negative	7	69							
$F = 1.50$ (50%)	Positive	15	4	0.58	0.95	0.79	0.87	0.85	3.9	10.7
	Negative	11	73							
$F = 1.75$ (75%)	Positive	12	2	0.46	0.97	0.86	0.84	0.84	1.9	13.6
	Negative	14	75							
$F = 2.00$ (100%)	Positive	10	1	0.38	0.99	0.91	0.83	0.83	1.0	15.5
	Negative	16	76							
$F = 2.50$ (150%)	Positive	6	0	0.23	1.00	1.00	0.79	0.81	0.0	19.4
	Negative	20	77							
$F = 3.00$ (200%)	Positive	6	0	0.23	1.00	1.00	0.79	0.81	0.0	19.4
	Negative	20	77							
Criterion B										
Test CA-125 AUC $\geqslant C$ [IU/mL]		Relapse Yes	Relapse No	Sensitivity	Specificity	PPV	NPV	Accuracy	FP (%)	FN (%)
$C = 15$ IU/mL	Positive	25	25	0.92	0.68	0.49	0.96	0.74	24.3	1.9
	Negative	2	52							
$C = 25$ IU/mL	Positive	19	12	0.73	0.84	0.61	0.90	0.82	11.7	6.8
	Negative	7	65							
$C = 50$ IU/mL	Positive	13	4	0.50	0.95	0.76	0.85	0.83	3.9	12.6
	Negative	13	73							
$C = 75$ IU/mL	Positive	13	2	0.50	0.97	0.87	0.85	0.85	1.9	12.6
	Negative	13	75							
$C = 100$ IU/mL	Positive	13	1	0.50	0.99	0.93	0.85	0.86	1.0	12.6
	Negative	13	76							
$C = 150$ IU/mL	Positive	10	1	0.38	0.99	0.91	0.83	0.83	1.0	15.5
	Negative	16	76							
$C = 200$ IU/mL	Positive	8	1	0.31	0.99	0.89	0.81	0.82	1.0	17.5
	Negative	18	76							
$C = 400$ IU/mL	Positive	5	1	0.19	0.99	0.83	0.78	0.79	1.0	20.4
	Negative	21	76							
$C = 600$ IU/mL	Positive	5	1	0.19	0.99	0.83	0.78	0.79	1.0	20.4
	Negative	21	76							
$C = 1000$ IU/mL	Positive	2	1	0.08	0.99	0.67	0.76	0.76	1.0	23.3
	Negative	24	76							

3. Results

The mean age at diagnostic time was found to be 54.2 (17.2–83.8; S.E. = 1.4) years. At evaluation date the mean overall survival was 6.4 (0.6–19.4; S.E. = 0.4) years with thirty (27.0%) patients deceased. Fifty (45.1%) patients had FIGO stage I, twelve (10.8%) had stage II, forty-two (37.8%) had stage III, three (2.7%) had stage IV and in four (3.6%) patients this information was missing. Twenty-seven (24.3%) patients had a tumour grade 1, twenty (18.0%) a tumour grade 2, eight (7.2%) had a tumour grade 3 and fifty-six (50.5%) patients had no tumour grade information. Twenty-four (21.6%) patients had a residual tumour greater than 2 cm after surgery. In thirty-four (30.6%) patients the primary treatment consisted of surgery only, in forty-seven (42.4%) cases the patients were also given adjuvant chemotherapy and in thirty (27.0%) the primary treatment included consolidation chemotherapy. The mean duration of treatment for patients that only received adjuvant chemotherapy was 4.1 (1.4–11.5; S.E. = 0.2) months while for patients that received both types of chemotherapy was 7.7 (2.6–39.1; S.E. = 1.3) months. The mean follow-up time between the first and the last CA-125 level was 54.3 (1.4–110.0; S.E. = 3.1) months, in which a mean of 12.9 (3–40; S.E. = 0.7) CA-125 serum levels were obtained per patient with a mean of 141.9 (10.5–521.2; S.E. = 8.7) days between samples. The mean follow-up time between the end of primary treatment and the evaluation date was 69.6

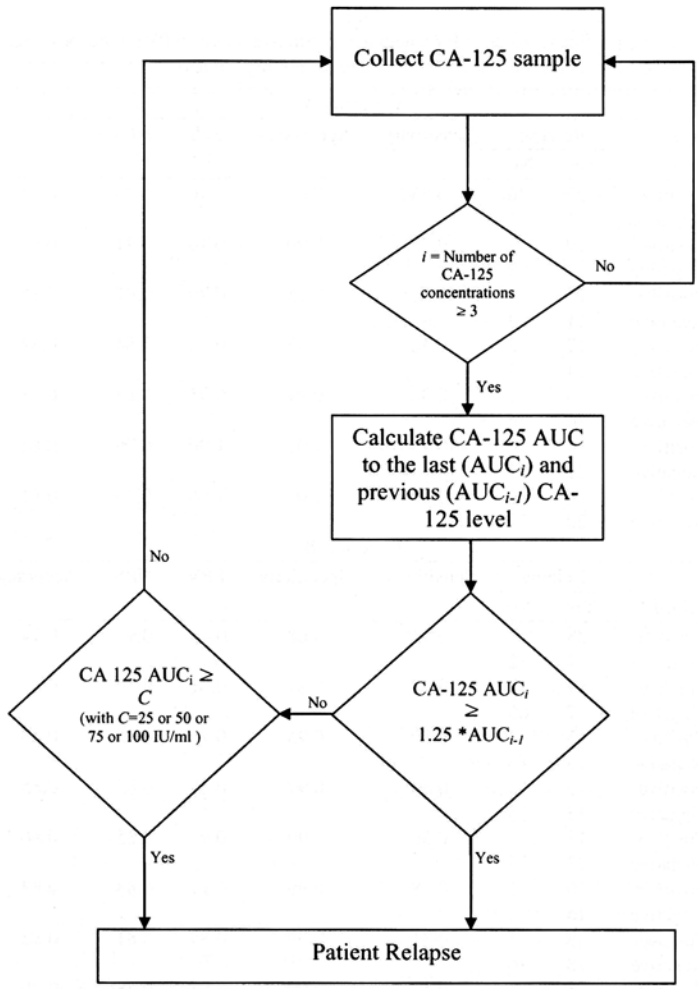


Fig. 2. Algorithm for implementation of both criteria (A and B) in clinical practice.

months (5.1–229.8; S.E. = 4.4). In that time twenty-six (23.4%) patients had a recorded relapse, seventy-seven (69.4%) had no recorded relapse and in eight (7.2%) this information was unavailable. Relapse was recorded in eight (20.7%) patients with FIGO stage I/II against seventeen (65.3%) patients with FIGO stage III/IV (the FIGO stage was missing in one patient with relapse). The mean time from the conclusion of treatment to relapse detection was 27.0 (5.1–89.4; S.E. = 3.9) months (Table 2).

In *Criterion A* the best accuracy (0.85) was achieved for both F values of 1.25 (25%) and 1.50 (50%), and start decreasing with F value equal or greater then 1.75 (75%). For *Criterion B* the accuracy start to increase above 80% with a cut-off of 25 IU/mL (0.82) achieving a maximum with a cut-off of 100 IU/mL (0.86) (Table 3).

The mean time difference between t_i and t_{i-1} obtained with*Criterion A* ($F = 1.25$) was 5.6 (1.1–16.0; S.E. = 0.7) months and the mean lead time to relapse achieved was 181.0 (−37 to 843; S.E. = 56.3) days. The mean lead time to relapse achieved with *Criterion B* was 131 (−270 to 644; S.E. = 55.9) days with a cut-off of 25 IU/mL, 111 (−103 to 530; S.E. = 51.1) days with a cut-off of 50 IU/mL, 63 (−292 to 507; S.E. = 54.9) days with a cut-off of 75 IU/mL, and 11 (−377 to 264; S.E. = 44.8) days with a cut-off of 100 IU/mL cut-off (Table 4).

4. Discussion

From a clinical point of view, earlier relapse detection might have no impact on overall survival since it will be depend on the success of second line treatments.

Table 4
Lead time to recurrence using the best accuracies for each criterion

Test	Mean lead time to relapse (t_i to relapse) [days]	Range [days]	Standard Error [days]	Standard Deviation [days]
Criterion A				
CA-125 AUC to $t_i \geqslant$ 1.25 *AUC to t_{i-1}	181	−37 to 843	56.3	245.6
Criterion B				
CA-125 AUC to $t_i \geqslant$ 25 IU/mL	131	−270 to 644	55.9	243.7
CA-125 AUC to $t_i \geqslant$ 50 IU/mL	111	−103 to 530	51.1	184.1
CA-125 AUC to $t_i \geqslant$ 75 IU/mL	63	−292 to 507	54.9	197.9
CA-125 AUC to $t_i \geqslant$ 100 IU/mL	11	−377 to 264	44.8	161.6

Nevertheless, it may have an immediate impact on patient follow-up scheme (number and frequency of the physician's visits, and the request for additional diagnostic tools including CA-125 serum levels). However, it should be recognized that powerful relapse detection tools associated with other advances in therapeutic options could increase survival and/or improve the patient's quality of life in the short term.

Although currently there is no evidence that earlier chemotherapy is superior to administering chemotherapy at clinical detection of recurrence, it should be stressed that a prospective, randomised trial on this issue is currently being carried out by the European Organization for Research and Treatment of Cancer (EORTC) [8]. If incoming studies demonstrate an increased overall survival for asymptomatic patients receiving chemotherapy based on a CA-125 tumour marker information, the sooner the relapse is detected the greater the chances of being able to catch the tumour at an earlier stage of evolution. Working with this scenario, earlier relapse detection will play a fundamental role in ovarian cancer patient follow-up. In addition, earlier relapse detection could also be relevant in the design of clinical trials for new anti-cancer agents.

If any test wants to be classified as suitable for predicting ovarian cancer relapse, the minimal requirement is to accurately signal the relapse in asymptomatic patients. As it can be seen from the results obtained in our population, both approaches (A and B) allow it with interesting accuracy values (above 80%). If *Criterion A* is adopted, an increase of 25% between two consecutive CA-125 AUCs suggests, with a substantial mean lead time to the event (181 days), that a relapse is ongoing (accuracy of 85%). Otherwise, if *Criterion B* is adopted, cumulative CA-125 AUCs values between 25 IU/mL and 100 IU/mL indicates the presence of relapse (accuracy above 80%). Obviously, increasing the cut-off from 25 IU/mL to 100 IU/mL imply a small rise of accuracy (from 82% to 86%), but an important decrease regarding the mean lead time to relapse from 131 days (with 25 IU/mL) to 11 days (with 100 IU/mL).

Technically speaking, *Criterion A* (in comparison with *Criterion B*) presents the advantage of not considering the upper normal limit or even nadir values, while in both approaches (in comparison with other methods) the use of all available CA-125 serum levels during the follow-up period decrease the residual error (analytical imprecision and intra-individual biological fluctuation of CA-125). In fact, for each CA-125 AUC normalized in time value, a carry-over effect can be observed (cumulative effect), which promote the dilution of marginal errors. An important issue concerning the present methodological approach is that the mean lead time might be influenced by the CA-125 sampling scheme (more precisely by the interval between any two consecutive samples). Therefore the interval between any two consecutive CA-125 samples might influence the way a particular CA-125 criterion signals the relapse. To be explicit, the negative lead times to relapse must be considered false negatives, corrupting the accuracy. This is more notorious in the case of *Criterion B*, since the number of patients with a negative lead time to relapse would make the accuracy fall when compared with *Criteria A*. Due to the study design constrains (retrospective study without any pattern), the interval between CA-125 samples was not standardised (between and within-patients). Therefore, in some cases the rapid tumour burst occurred between CA-125 samples if the interval between samples was too extended. Nevertheless, the false negatives and false positives in *Criterion A* were below 10% while in *Criterion B*, as the cut-off value increase from 25 to 100 IU/mL, the false positive rate decreased from 11.7% to 1.0% while the false negative rate changed from 6.8% to a stable 12.6%, which are encouraging results for clinical practice. Anyway, as a general rule, the interval between samples must be balanced not only for technical, but also for economic and psychological reasons (many patients reported CA-125 anxiety) [12].

In accordance with the results obtained with our population, the major advantage of *Criterion A* is that it can predict patient relapse far sooner than *Criterion B* (and even sooner than other known criteria using the CA-125 levels). However the *Criterion A* is especially useful if patient experience a rapid increase in CA-125 AUC. Otherwise *Criterion B* should be implemented because under some circumstances (i.e. when patients experienced a long term sustained increase of CA-125 tumour marker) relapses can occur even when differences between consecutive CA-125 AUC are less than 25%. For this reason, we strongly recommend the use of both criteria in conjugation. Firstly, *Criterion A* should be applied to evaluate the situation. If a negative answer occurs *Criterion B* should be attempted to confirm the absence of relapse. The algorithm of implementation of both criteria in clinical practice is appropriately illustrated in Fig. 2.

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