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Doubling time of serum CA125 is an independent prognostic factor for survival in patients with ovarian cancer relapsing after first-line chemotherapy

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ABSTRACT

Introduction: Confirmed doubling of CA125 value is one definition of progression in ovarian cancer patients. If asymptomatic, the management of these patients is unclear. To provide information which may assist in therapeutic decision making, we set out to determine the independent prognostic significance for the rate of rise in CA125 during surveillance in ovarian cancer patients as measured by CA125 doubling time.

Patient and methods: Clinical information was obtained through a 2-staged chart review of ovarian cancer patients treated in our department from 1994 to 2003. We searched for patients who met criteria for CA125 progression and doubling during surveillance following first-line therapy.

Results: A total of 296 patients were initially identified. During surveillance, the median doubling time of CA125 was 40 d and the median survival for patients with a CA125 doubling time of $\leqslant$40 d was 10.6 months compared to 22.1 months for those with doubling time > 40 d. In a univariate analysis, age, high-grade, suboptimal cytoreduction, short CA125 doubling time, short time to progression and high CA125 at progression were significantly associated with poor survival, but in a multivariate analysis, a short CA125 doubling time of $\leqslant$40 d and a short time to disease progression ($\leqslant$180 d) were the only independent adverse prognostic factors ($p = 0.001$). Second stage review identified 28 new patients who provided a confirmatory set that supported the adverse survival trend for patients with short CA125 doubling time.

Discussion: The rate of rise of CA125 during surveillance carries independent prognostic significance, and should be considered when making therapeutic decisions.

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1. Introduction

In western countries, ovarian carcinoma is the leading cause of death from gynaecologic cancer, and worldwide, it accounts for 4.2% of all cancer deaths.[1] Most ovarian cancers are diagnosed when the disease has spread beyond the pelvis.[2,3] The 5-year survival, as a result, is only 30%, despite the fact that most patients initially have chemo-sensitive disease and may achieve a complete remission with aggressive surgical cytoreduction and platinum-based chemotherapy.[4] Many clinicians believe that prompt recognition of recurrence is a key part of patient care, and for that reason, careful surveillance is an integral part of ovarian cancer management.

As a part of this approach, monitoring of serum CA125 is generally recognised as the cornerstone of epithelial ovarian cancer surveillance. Increasing CA125 levels have been shown to predate clinical or radiological evidence of relapse in approximately 70% of patients with ovarian cancer by a median of 4 months.[5] Therefore, a rising CA125 is increasingly accepted as an early indicator of disease recurrence. Furthermore, several reports have recently indicated that it may be possible to define the risk of relapse and death by dividing patients that have achieved a complete biochemical and radiological response after primary treatment into distinct groups based on the CA125 nadir.[6]

Several definitions of progression according to CA125 have been proposed, following the initial observation that increases of 50–100% predicted disease relapse.[7] Two simpler definitions have also been proposed: the North Thames Ovary Group study found that a confirmed increase of CA125 more than twice the upper limit of normal during follow-up after first-line chemotherapy predicts tumour relapse with a sensitivity of 84% and a false-positive rate of less than 2%.[8] A similar definition is based on patients whose CA125 levels remain persistently elevated during and/or after first-line chemotherapy. In this group, a confirmed doubling of CA125 from its nadir level predicted progression with a sensitivity of 94% and almost 100% specificity.[9]

While the measurement of a rising CA125 as an indicator of ovarian cancer recurrence has been widely accepted, the appropriate action to take clinically has been less clear. However, a recently completed randomised trial has revealed that early re-treatment on the basis of rising CA125 alone in the absence of symptoms confers no survival benefit, nor proves to be advantageous in quality of life. The authors concluded that there is no value in routine measurement of CA125 during surveillance after achievement of complete response post frontline therapy.[10] These results may have a significant impact; however, it is likely that many clinicians will continue to utilise CA125 as a routine surveillance tool, with increasing focus being placed on the issue of the timing of re-treatment.

Intuitively, a parameter which clinicians may well consider to be important is the rate of rise of CA125. Therefore, we set out to determine the independent adverse prognostic significance of CA125 kinetics during surveillance after completion of frontline treatment. This is the first study to systematically examine the rate of rise in CA125, measured by CA125 doubling time, as an approach to achieve risk-stratification sufficient to justify its inclusion in the factors which influence therapeutic decision making.

2. Patients and methods

2.1. Patients

Data collection regarding patient clinicopathologic information was performed in two stages. During the first stage, chart review was performed in 01/2007 to identify all patients with ovarian cancers at The Royal Marsden Hospital London and Surrey, United Kingdom who received first-line chemotherapy between 01/1994 and 12/2003, and in whom full clinical information was available. For patients with post-treatment CA125 within normal limits (<35 u/mL), the first date of any subsequent reading greater than the upper limit of normal (>35 u/mL) was recorded as the date of CA125 progression (pD). For patients with abnormal post-treatment CA125, the first recorded date at which CA125 had increased to at least 20% of nadir was recorded as the date of CA125 progression. The value on this date is referred to as the progression value (pV), and CA125 doubling date (dD) is therefore defined as the first time CA125 rose to at least twice the progression value. The value at this time is the doubling value (dV). Thus, the CA125 doubling time (dT) is calculated by the:

$$dT = \ln(2)/b, \text{ where } b = [\ln(dV) - \ln(pV)]/[dD - pD]$$

Using the above-mentioned criteria for CA125 doubling, a total of 296 patients were identified.

A subsequent review was then performed in 07/2009 that served to identify an additional 28 new patients who met the criteria for CA125 doubling since the first review and also to update survival information on the previous 296 patients. We obtained permission and complied with requirements of our home's institutional review board for the protection of human subjects.

2.2. Clinicopathologic data

Patient charts were reviewed for data regarding age, diagnosis, grade, International Federation of Gynaecologists and Obstetricians (FIGO) stage, cytoreducibility, time to progression, CA125 measurements through diagnosis, surveillance and recurrence and demise. Optimal cytoreduction was defined as <2 cm of residual disease following surgery. All patients were surgically staged in accordance to FIGO standards. A gynaecologic pathologist reviewed the pathology of all patients. Serum CA125 levels were determined using a commercially available immuno-assay kit (Abbot Diagnostics, Maidenhead, UK).

2.3. Confirmatory set

The additional 28 new patients who met the criteria for CA125 doubling served as an independent test set to confirm the findings from our original set consisting of the 296 patients. All clinicopathologic data were collected in a similar fashion to the original test.

2.4. Statistical analyses

The continuous CA125 data were summarised as median and range. A univariate model was constructed to examine the hazard ratio of established clinical variables and factors related to disease recurrence such as CA125 and time to progression. A multivariate Cox regression model was used to determine independent prognostic factors for death from disease by a forward stepwise selection method with an alpha of 0.05 as criteria for inclusion and removal. Overall survival was estimated using the Kaplan–Meier product limit method. Furthermore, a univariate log-rank test was utilised in the test set to confirm the influence of CA125 doubling time on overall survival. A p-value <0.05 was considered significant. All testing employed the two-tailed method. All calculations were performed using SPSS statistical software (SPSS Inc., Chicago, IL, USA).

3. Results

3.1. Patient characteristics

The characteristics of the initial 296 patients with documented CA125 doubling while under surveillance are described in Table 1. The median age of the group was 61 years. At diagnosis, the majority had high stage (stages III and IV) and high grade (grade 2 and 3) disease. Nearly half of these patients underwent optimal cytoreduction, and nearly all were treated with platinum-based chemotherapy. Post-treatment CA125 levels reached a nadir within normal limits (<35 u/mL) in 73% of the patients, while 27% had CA125 levels above 35 u/mL. The overall median value was 9.5 u/mL (Table 2).

Table 2 – CA125 values at disease progression.

CA125 (u/mL)	Median	Range
Nadir post first-line treatment	9.5	(3–82)
At first progression	77	(36–13, 480)
At first doubling	291	(75–44, 574)

3.2. Measured parameters at disease progression

CA125 data before and at disease progression are given in Table 2, and progression intervals are listed in Table 3. The median progression value for CA125 (as defined in the Section 2) was 77 u/mL, and the median time from completion of front-line therapy to first diagnosed progression was 180 d. For the 296 patients in whom doubling time was confirmed, the median CA125 doubling value was 291 u/mL. The median days required for CA125 to double were 40 d from the time of first progression.

3.3. Influence of CA125 doubling time on survival

With a median follow-up of 4.2 years (range 0.4–8.7 years), a total of 258 deaths were noted out of this group of 296 patients. Patients who experienced a short CA125 doubling

Table 1 – Patient characteristics.

Characteristic	Number of Patients (N = 296)	%
Age	61 (Median)	31–86 (Range)
Stage		
Low (I, II)	43	14
High (III, IV)	253	86
Grade		
Low (1)	8	3
High (2, 3)	259	87
Unknown	29	10
Cytoreduction		
Optimal	146	49
Suboptimal	139	47
Unknown	11	4
First-line chemotherapy		
Platinum alone	148	50
Platinum + Taxane	144	49
Other	4	1
Best first-line response		
CR	70	24
PR	40	14
SD	33	11
PD	10	3
Unknown	143	48
CA125 nadir post-treatment		
<35 u/mL	216	73
⩾35 u/mL	80	27

Table 3 – Disease progression intervals.

Progression intervals (days)	Median	Range
Time to first CA125 progression	180	(7–2, 560)
Time to first CA125 doubling	40	(2–1, 675)

(⩽40 d, median value) had a significantly shorter survival (10.6 months versus 22.1 months for patients with a doubling time >40 d). The result of the univariate analysis, which incorporated age, stage, grade, extent of surgery, time to progression, CA125 level at progression as well as CA125 doubling time is given in Table 4.

All factors, except disease stage, were significantly associated with survival. After adjusting for age ($p = 0.06$), grade ($p = 0.1$), cytoreducibility ($p = 0.6$) and progression value ($p = 0.4$) in a multivariate Cox regression model, a short CA125 doubling time of ⩽40 d and a short time to progression of ⩽180 d were the only factors associated with poor survival ($p = 0.001$ and $p < 0.001$, respectively, Table 5). Furthermore, when CA125 doubling time was further stratified into quartiles time frames, a significant association with overall survival was noted ($p < 0.001$; Fig. 1A): there was an incremental increase in the length of overall survival based on CA125 doubling time. For patients who achieved a CA125 doubling time of ⩽23 d, the median overall survival was 9.5 months versus patients with a doubling time >23 and ⩽40 d who lived 13.2 months. While patients with a CA125 doubling time >40 and ⩽81 d lived 23.2 months, more than twice as long as the group of patients with rapid biomarker doubling time of ⩽23 d. Lastly, for the last group of patients with known CA125 doubling time of >81 d, the overall median survival was 34.5 months, almost four-times as long as those in the rapid biomarker progressing group (Fig. 1A).

In order to assess the clinical relevance of CA125 doubling time, we conducted a test set using the additional 28 patients identified during the second stage review. With 20 deaths reached, we found that overall the patient characteristics of this test set are comparable to those from the original population. The median age for this group was 57 years (range 29–82), with 61% diagnosed with high stage (stages III and IV) disease, and 64% found to have high grade (grades 2 and 3) tumours. Moreover, 32% underwent optimal cytoreduction, and all received a platinum-based chemotherapy. Overall, 89% of these patients achieved a CA125 nadir of <35 u/mL. The median overall survival for this test set of patients was 16.8 months. A broadly similar survival disadvantage for patient with short CA125 doubling time is seen in this confirmatory set, although due to small numbers, the *p*-value approaches significance at 0.08 (Fig. 1B).

4. Discussion

The predictive and prognostic values of CA125 are well described in all phases of epithelial ovarian cancer management. For example, its value after the completion of frontline therapy predicts progression-free survival (PFS) incrementally based on its nadir. Thus, if the CA125 nadir is less than 10 u/mL, the PFS was found to be 17 months versus 13 months for nadirs of 11–20 u/mL or 8 months for nadirs of above 20 u/mL.[6] In addition, the rate of CA125 normalisation during primary chemotherapy also predicts patient survival such that patients who achieve normalisation of this biomarker after three cycles of chemotherapy are found to have significantly longer PFS and overall survival than their counterparts who fail to reach normalisation (19 months versus 6 months, and 48 months versus 27 months, respectively).[11] Studies examining pretreatment CA125 levels revealed that they are independent predictors of PFS in patients with advanced epithelial ovarian cancer who subsequently receive standard platinum-based chemotherapy.[12,13] These findings are consistent with previously published data where preoperative CA125 value is associated with poor survival.[14] The predictive value of CA125 extends beyond survival to ovarian cancer surgical cytoreducibility: preoperative levels greater than 500 u/mL predict the inability to achieve optimal

Table 4 – Univariate analysis of survival.

Characteristic	Hazard ratio	95% Confidence interval (CI)	*p*-Value
Age	1.55	(1.21, 1.98)	0.001
High stage (III and IV)	1.31	(0.91, 1.88)	0.144
High grade (2 and 3)	2.77	(1.14, 6.73)	0.025
Suboptimal cytoreduction	1.44	(1.12, 1.86)	0.004
Short CA125 doubling time (⩽40 d)	1.83	(1.43, 2.36)	<0.001
Short time to progression (⩽180 d)	2.56	(1.98, 3.32)	<0.001
High CA125 at progression (⩾77 u/mL)	1.45	(1.13, 1.85)	0.003

Table 5 – Multivariate analysis of survival.

Characteristics	Hazard ratio	95% confidence interval (CI)	*p*-Value
Short CA125 doubling time (⩽40 d)	1.56	(1.21, 2.12)	0.001
Short time to progression (⩽180 d)	2.26	(1.70, 3.01)	<0.001

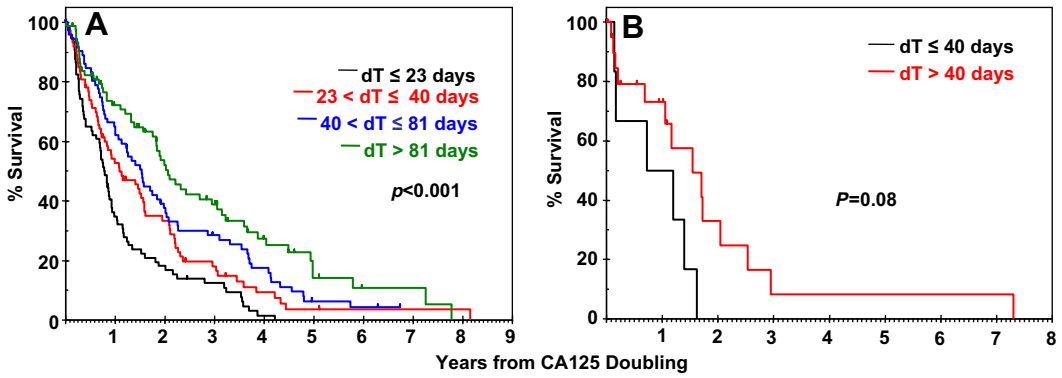

Fig. 1 – (A) Kaplan–Meier estimates of the probability of survival: in patients with CA125 doubling time of ⩽23 d (solid line), median survival was 9.5 months (HR = 1); for patients with CA125 doubling time of >23 and ⩽40 d (dotted line), the median survival was 13.2 months (HR = 0.64); for patients with CA125 doubling time of >40 and ⩽81 d (dotted/dashed line), the median survival was 23.2 months (HR = 0.49) and for patients with CA125 doubling time of >81 d (dashed line), the median survival was 34.5 months (HR = 0.34). All $p < 0.001$. (B) Kaplan–Meier estimates for the 28 patients in the test set grouped as patients with short CA125 doubling time (⩽40 d, solid line) versus long CA125 doubling time (>40 d, dotted line) where *p*-value approached significance at 0.08.

cytoreduction.[15] Therefore, singular CA125 values at these salient time points in ovarian cancer management can provide prognostic insight.

The rate of rise of CA125 during surveillance has been much less studied. One study which provided relevant information was a randomised, placebo-controlled maintenance study using a monoclonal antibody against CA125.[16] A total of 145 patients were recruited for this trial, and the velocity of CA125 rise at relapse was found to be a significant predictor of survival. However, this was not quantified in terms of CA125 doubling time. The doubling time of a biomarker such as prostate specific antigen (PSA) has been studied in prostate cancer[17,18], however, this is the first study in ovarian cancer in which the clinical significance for the rate of rise of CA125, specifically as measured by doubling time, during surveillance has been elucidated.

Despite a general recognition of the clinical relevance of a rising CA125 in patients with treated ovarian cancer, there remains considerable uncertainty over the timing of subsequent clinical management, particularly when patients are asymptomatic. Some clinicians, frequently influenced by patients' anxiety, will initiate a second line chemotherapy without delay. Others, including ourselves, will pursue a policy of careful observation with regular assessments. This debate has recently been informed by the results of the MRC-OVO5/EORTC55955 trial in which 1442 patients with relapsed ovarian cancer were randomised to either early treatment based on a rising CA125 alone or to treatment only after the development of clinical signs or symptoms of progression.[10] With a median follow-up of 49 months there was no evidence of any difference in survival between the two arms (HR 1.01; $p = 0.91$).[10]

Not surprisingly, this study has attracted substantial commentary not only from our own clinicians but also the public media. Clearly the impact of the study on clinical practice will vary according to existing policies, but it is likely that careful observation will be increasingly practiced. We acknowledge that our study provides no data to indicate that at present, early re-introduction of any specific form of treatment based on the rate of rise of CA125 will influence outcome. However, systemic treatment of ovarian cancer is in a rapid state of evolution, and a number of promising therapeutic avenues based on novel targeted agents are now being identified.[19] It is therefore conceivable that maximum benefit for these new treatments may be observed when tumour volume is limited, in contrast to cytotoxic chemotherapy that was the only effective systemic treatment available in the era of the MRC/EORTC trial. As the Society of Gynaecologic Oncologists (SGO) pointed out in response to this study, continued CA125 monitoring in relapsed disease is integral "to a philosophy of active management that includes participation in trials of novel therapy."[20]

In this study, we determined that the median CA125 doubling time for patients undergoing surveillance for ovarian cancer is 40 d, and that patients with a doubling time ⩽40 d have a significantly shorter survival than those whose doubling time is >40 d (10.6 months versus 22.1 months). Importantly, this correlation is independent of the time to disease progression. The appropriate management approach for patients with an asymptomatic first relapse of ovarian cancer will require increased individualised discussion between patients and clinicians, and the knowledge of the rate of rise of CA125 (i.e. doubling time) could be a key factor in making that decision.

Conflict of interest statement

None declared.

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