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Systematic Review of Monitoring Criteria to Interpret CA125 Increments during First-Line Chemotherapy and the Subsequent Follow-Up Period among Patients with Advanced Epithelial Ovarian Cancer

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Abstract

Background: Optimal clinical management of ovarian cancer patients requires prompt and accurate determination of whether primary or recurrent disease is responding to chemotherapy. If CA125 is to fill this need, we must understand the design and outcomes of clinical trials that have established a correlation between CA125 levels and growth or shrinkage of tumor burden. It is particularly important to define the magnitude of changes in CA125 concentrations that indicate cancer growth and prompt cessation of ineffective therapy.

Objective: To review clinical trials which test the ability of CA125 to monitor ovarian cancer growth during chemotherapy for primary disease and detection of recurrence.

Methods: The Medline and Embase databases were searched for original articles published in English between January 1982 and May 2014 that evaluated the utility of CA125 for monitoring ovarian cancer growth.

Results: CA125 was evaluated in 13 reports during primary therapy and in eight reports during subsequent follow-up. CA125 sensitivity for detecting tumor growth was not reported consistently, but could be calculated from data provided in the articles. During primary therapy, the median sensitivity for recurrence was 60% (range 33%-95%) and during follow-up the median sensitivity was 85% (range 62%-93%).

Conclusion: Consistent criteria for indicating disease progression with CA125 could not be defined due to differences in trial design and selection of patients. The most promising criteria should be re-evaluated under similar and standardized conditions. Computer simulation models and change point algorithms may aid in identifying CA125 assessment criteria to be further validated in prospective clinical trials.

Keywords: Monitoring; Ovarian cancer; CA125; CA125 increments; CA125 progression criteria

Introduction

Worldwide, ovarian cancer is the leading cause of death from gynecological malignancies [1]. In advanced epithelial ovarian cancer, numerous small peritoneal metastases may be difficult to detect with traditional methods such as gynecological examinations, transvaginal ultrasonography, CT and MR scans. Given the cost, inconvenience and limited sensitivity of imaging investigations, there is a need for reliable and easily performed quantitative biochemical tests that can accurately reflect tumor burden and provide an early signal of tumor growth. The reliability of the test must be sufficiently high to allow clinical decision making in terms of continuing or ending treatment and initiating new therapy. The serum cancer biomarker CA125 has been proposed as a supplement to non-invasive diagnostic procedures among patients with advanced disease because concentrations may increase with growing tumor burden [2,3]. In the last decades several criteria have been proposed to detect increments in serial CA125 concentrations [4-24]. Recent guidelines have been proposed by the European Group on Tumor Markers for the design of cancer biomarker monitoring trials [25]. However, challenges remain on how to define changes in CA125 concentrations that reliably correlate with increasing tumor burden in the individual patient. The purpose of this study was to perform a systematic review of the literature on clinical monitoring trials involving CA125 with focus on the assessment criteria proposed to detect increasing concentrations during primary therapy and subsequent follow-up.

Methods

The PRISMA [Preferred Reporting Items for Systematic Reviews and Meta-analyses] statement was used as a guide to conduct and reporting of the review [26]. The peer-reviewed literature in English published up to August 2014 was searched using the Medline (since 1982) and Ovid versions of EMBASE with Mesh Terms ((cancer antigen 125) AND ovarian neoplasms) AND (increments OR rising CA125 concentrations OR monitoring OR progression criteria), and with limits Human Subjects and English. Two reviewers (SH; GS) evaluated the title and abstract of all the identified records to assess whether they were relevant to the aim of the study. Then by evaluating the complete article the reviewers determined whether the report should be excluded or included for the systematic review following the recommendations

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of the QUADAS-2 Group [27]. Original articles were excluded in the following instances: case reports, observational studies and reviews; other cancer biomarkers than CA125; other gynecological diseases than epithelial ovarian cancer and articles that only reported on criteria to interpret decrements of CA125 concentrations. Original articles were included if they met following requirements: women with ovarian cancer; and presentations of criteria that interpreted increments of CA125concentrations during therapy or follow-up period.

The following data were extracted from the included papers: criteria to interpret increasing CA125 concentrations, number of true positive signals, false negative signals, false positive signals, and true negative signals as well as lead-times (time interval between CA125 increment and tumor growth). Based on the extracted data we calculated/recalculated the sensitivities (percentage of patients with tumor growth detected by CA125 increments), false positive rates (percentage CA125 increments among patients without tumor growth), and false negative rates (percentage missing CA125 increments among patients with tumor growth). The 95% confidence intervals (95% CI) were calculated according to Geigy formula 771 and 772 [28]. CA125 assessment criteria were drawn in figure format according to the descriptions provided in the reviewed original articles [29].

Results

The search strategy retrieved a total of 422 citations. After evaluation, 39 relevant studies were chosen for detailed evaluation. Among these 21 original articles were identified describing criteria to interpret increments of CA125 concentrations. Thirteen individual reports addressed criteria and their monitoring performance during primary therapy and eight individual reports addressed criteria and their monitoring performance during the subsequent follow-up period. All patient populations were scrutinized according to clearly stated inclusion and exclusion criteria. However, most studies did not clearly report whether consecutive or only the eligible patients were included. One study reported that they included consecutive patients [12]. Four studies included eligible patients [15,20,22,23].

CA125 assessment criteria

Some early studies suggested that CA125 signaled progressive disease during first-line chemotherapy when concentrations increased 50% or 100% from values below 20 U/ml – 65 U/ml [4-8,10-13, 16,17]. Others suggested criteria that were valid during follow-up when concentrations during primary therapy had decreased below 35 U/ml [9,14,15] or 25 U/ml [6]. The monitoring performance of criteria applied in the early studies has been reviewed previously [30,31].

The most extensive investigations of criteria to assess increasing CA125 concentrations during monitoring of patients with advanced epithelial ovarian carcinoma have been reported by Rustin et al. 1992-2011 (Figure 1-5), (Figure 6) [18-21,32-37], Tuxen et al. (Figure 7) [22,23,38-40], and Liu et al. (Figure 8) [24]. Rustin et al. tested several sets of criteria to monitor therapy and follow-up, respectively. Some criteria required a defined percent of rise from below to above different cut off levels (Figure 1a, Figure a-b, Figure 3a-b, Figure 4a-e, Figure 5a-b, and Figure 6a) [18-21]. Others required an increment starting above a set cut-off to higher levels (Figure 1b, Figure 2c, and Figure 6b) [18-21]. The evolution of their criteria is presented in Figure 9 [18-21,35-37,41-55]. Tuxen et al. used the same criteria during first-line chemotherapy and the subsequent follow-up period. There was a considerable overlap of their patient groups, because the patients investigated by Rustin et al. and by Tuxen et al. were allocated to The North Thames Ovary Trial [18-20,22,23]. The patients investigated by Rustin et al. received first-line chemotherapy at Mount Vernon Hospital [21]. Liu et al. focused their criteria, named Early Signal of Progressive Disease (EPD), on the follow-up period after first-line chemotherapy [24].

CA125 in detecting tumor growth during primary therapy

The reports were mostly based on small patient populations and heterogeneous sampling intervals as well as study design. The performances of the CA125 assessment criteria are listed in Table 1. The number of included patients were 903 (median 41, range 13-173) and the number of assessable patients were 784 (median 41, range 13-173). Tuxen et al. [22] applied two sets of criteria (Figure 7a-c and Figure 7d-e) to the same group of patients. Thus, the number of events became higher than the investigated number of patients. Accordingly, the number of included CA125 events were 1071 (median 42, range 13-173) and the number of assessable CA125 events were 952 (median 41, range 13-173). The sensitivity frequently remained unreported but was calculable from the data provided (median 60%, range 33%-95%). Also the lead time was mostly not reported. The calculated false positive and false negative rates were in median 4% (range 0%-40%) and 14.5% (range 4%-100%), respectively.

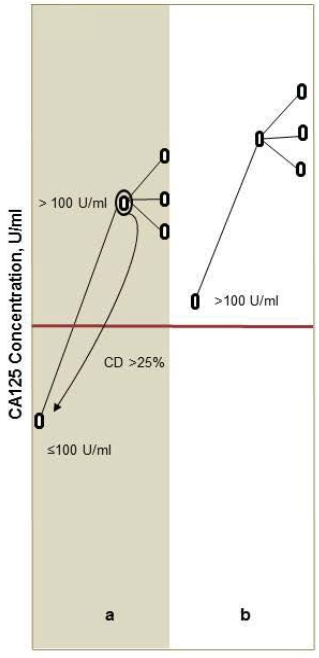

Figure 1: CA125 progression criteria proposed by Rustin et al. in 1992 to detect increments during chemotherapy among patients with ovarian cancer (FIGO stage III-IV) [18]. CD denotes the required critical difference. Points connected by solid lines indicate consecutive measurements. The red solid line indicates the applied cutoff in the individual criteria.
a The criterion was based on three consecutive measurements. The first concentration was ≤100 U/ml with an increment of >25% to >100 U/ml for the second concentration. The third concentration remained >100 U/ml and could be higher, equal to, or less than 50% lower than the second concentration. The time interval of the criterion from the first to the third sample was ≥56 days [18].
b The criterion was based on three consecutive measurements with all concentrations >100 U/ml. The second concentration was higher than the first concentration. The third concentration could be higher, equal to or less than 50% lower than the second concentration. The time interval of the criterion from the first to the third sample was ≥56 days [18].

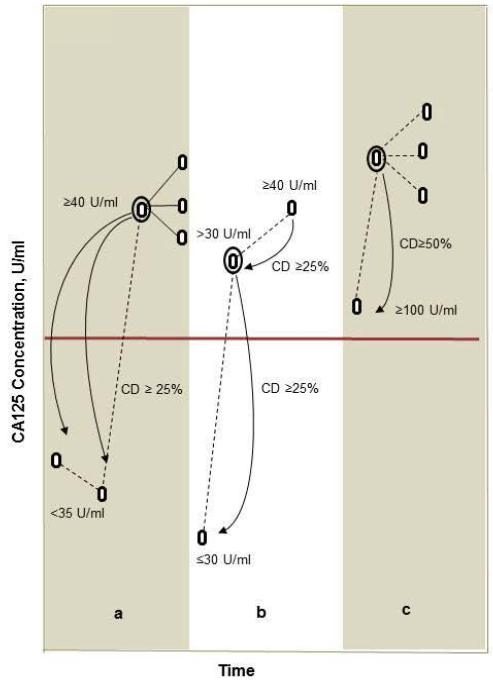

Figure 2: CA125 progression criteria proposed by Rustin et al. in 1993 to detect increments among patients with ovarian cancer. It was not specified whether the criteria were used to monitor therapy or follow-up. FIGO stage was not specified [19]. CD denotes the required critical difference. Points connected by dashed lines indicate measurements that are not necessarily consecutive. Points connected by solid lines indicate consecutive measurements. The red solid line indicates the applied cutoff in the individual criteria.

a The criterion was based on at least four measurements. The first and second concentrations were <35 U/ml with an increment ≥25% to ≥40 U/ml for the second latest concentration. The latest concentration could be higher, equal to or less than 10 % lower than the second latest concentration. Intervening concentrations between concentration two and the second latest concentration could decrease ≤10 % as compared to concentration two. The time interval between the first and the second latest concentration was ≥56 days, and the time interval between the second latest and the latest concentration was ≥28 days [19].

b The criterion was based on at least three measurements. The first concentration was ≤30 U/ml with an increment ≥25% to >30 U/ml of the second concentration as compared to the first concentration. The third concentration increased ≥25% to ≥40 U/ml as compared to the second concentration. Intervening concentrations between the first and the second concentration and between the second and the third concentration could decrease <10%. The time interval of the criterion from the first to the third concentration was ≥56 days [19].

c The criterion was based on at least three measurements and all concentrations were ≥100 U/ml. The second concentration was ≥50% of the first concentration. The third concentration could be higher, equal to or less than 10% lower than the second concentration. Intervening concentrations should be >100 U/ml and decrease ≤50% as compared to the first concentration. The time interval of the criterion from the first to the third sample was ≥56 days [19].

CA125 in detecting tumor growth during follow-up after primary therapy

Like the trials correlating CA125 with primary therapy, the monitoring studies correlating CA125 with tumor growth during follow-up were mostly based on small patient populations and heterogeneous sampling intervals as well as study design (Table 2). The number of included patients were 1084 (median 112, range 30-300) and the number of assessable patients were 814 (median 81, range 30-204). Rustin et al. [20] applied several sets of CA125 assessment criteria (Figures 3a-b, 4a-4e, and 5a-5b) to the same group of patients as did Tuxen et al. [23] (Figure 7a-c and Figure 7d-e). Thus, the number of results in terms of CA125 events became higher than the investigated number of patients. The number of included CA125 events were 2882 (median 203, range 30-300) and the number assessable CA125 events were 1958 (median 124, range 30-24). The sensitivity was not reported in some studies; however, it could be calculated from data provided in the articles (median 85%, range 62%-93%). Also the lead times were reported inconsistently. The calculated false positive and false negative rates were in median 5% (range 0%-18%) and 24% (range 5%-100%), respectively.

Rustin et al. tested several CA125 assessment criteria at different time points during a period of 18 months [20]. The first analysis was performed two months after closure of the trial, the second analysis was performed after 81 confirmed relapses, and the third analysis was performed one year later. Two criteria were applied for the first analysis (Figure 3a-b), five criteria for the second analysis (Figure 4a-e), and two criteria for the third analysis (Figure 5a-b) [20]. The number of patients was not identical in the three analyses, because new patients were included during the study period, and patients with recurrent disease were excluded from follow-up before the second and third

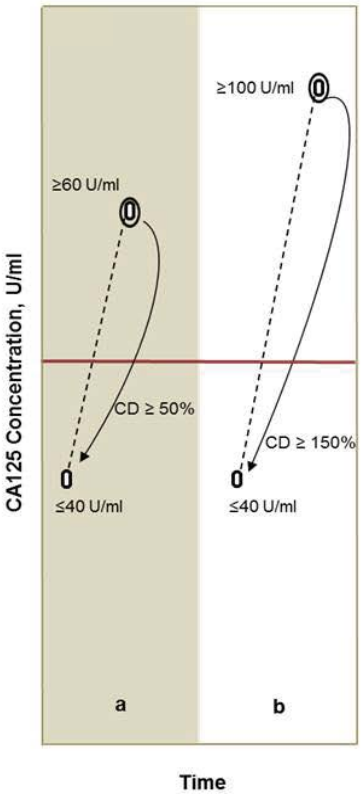

Figure 3: CA125 progression criteria proposed by Rustin et al. in 1996 to detect increments among patients with FIGO stage IC-IV ovarian cancer during follow-up after first-line chemotherapy. The criteria were applied for the analysis performed 2 months after closure of the trial [20]. CD denotes the required critical difference. Points connected by dashed lines indicate measurements that are not necessarily consecutive. The red solid line indicates the applied cutoff in the individual criteria.

a The criterion was based on at least two measurements. The first concentration was ≤40 U/ml with an increment to ≥60 U/ml. The time interval of the criterion varied from <1 month to >6 months [20].

b The criterion was based on at least two measurements. The first concentration was ≤40 U/ml with an increment to ≥100 U/ml. The time interval of the criterion varied from <1 month to >6 months [20].

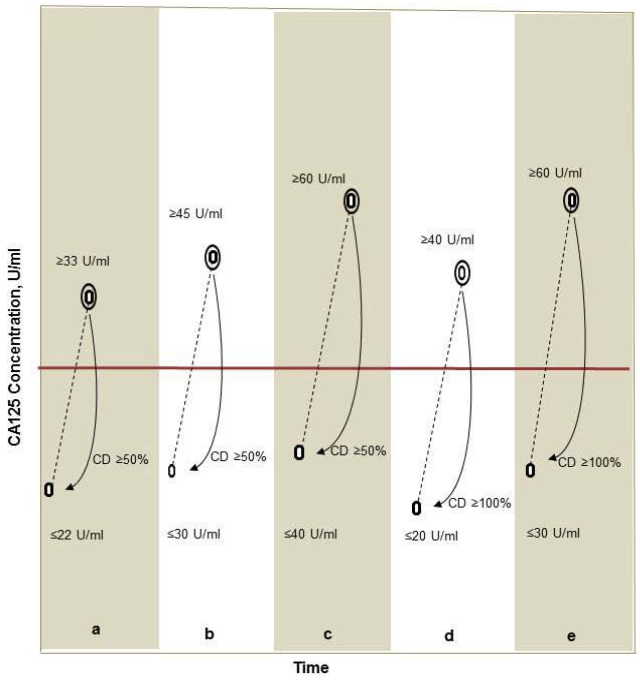

Figure 4: CA125 progression criteria proposed by Rustin et al. in 1996 to detect increments among patients with FIGO stage IC-IV ovarian cancer during follow-up after first-line chemotherapy. The second analysis was performed after 81 confirmed relapses [20]. CD denotes the required critical difference. Points connected by dashed lines indicate measurements that are not necessarily consecutive. The red solid line indicates the applied cutoff in the individual criteria.

a The criterion was based on at least two measurements. The first concentration was ≤22 U/ml with an increment to ≥33 U/ml. The time interval of the criterion varied from <1 month to >6 months [20].

b The criterion was based on at least two measurements. The first concentration was ≤30 U/ml with an increment to ≥45 U/ml. The time interval of the criterion varied from <1 month to >6 months [20].

c The criterion was based on at least two measurements. The first concentration was ≤40 U/ml with an increment to ≥60 U/ml. The time interval of the criterion varied from <1 month to >6 months [20].

d The criterion was based on at least two measurements. The first concentration was ≤20 U/ml with an increment to ≥40 U/ml. The time interval of the criterion varied from <1 month to >6 months [20].

e The criterion was based on at least two measurements. The first concentration was ≤30 U/ml with an increment to ≥60 U/ml. The time interval of the criterion varied from <1 month to >6 months [20].

analyses. The number of patients investigated at each time point also differed, because patients were excluded if the CA125 concentrations did not fulfill the requirements of the individual criterion, i.e. patients with baseline levels above 22 U/ml were excluded from assessment in the criterion provided in (Figure 4a), but included for assessment in the criterion provided in Figure 4e. Rustin et al. 1996 based all their criteria on CA125 increments from below a defined lower interval limit to above an upper limit specified for each criterion and the performance for each criterion was reported separately. The high sensitivities were obtained from selected subpopulations without considering all eligible patients. For example, for the criterion provided in (Figure 4c), the monitoring performance was based on 145 patients with sensitivity for progression of 90% and few false negative results. However, 58 (29%) of the 203 patients were excluded from the calculation because their baseline CA125 concentrations were above the lower interval limit required in the criterion.

Tuxen et al. [23] applied the same set of CA125 assessment criteria during follow-up as during monitoring of first-line chemotherapy (Figure 7a-e). They reported the combined performance of the criteria instead of reporting their individual performance. Interpretation of serial measurements was independent of the applied cutoff level of 35 U/ml because a simultaneous use of their criteria ensured that all concentrations were eligible for assessment irrespective of the baseline.

The sensitivities among non-selected patients calculated from Rustin et al. (72%) (Figure 6a-b) and Tuxen et al. (75% and 76%) (Figure 7a-e) tended to be lower than the sensitivities among selected patients calculated from Rustin et al. 1996 (81% - 93%) (Figure 3a-5b). Accordingly, the calculated false negative rates were highest for Rustin et al. 2001 (92%) (Figure 6a-b) followed by Tuxen et al. (54%) (Figure 7a-e) and Rustin et al. (7%-25%) (Figure 3a-5b).

Liu et al. [24] investigated the two EPD criteria among patients who achieved complete clinical response according to The Response Evaluation Criteria in Solid Tumors (RECIST) and CA125 concentrations ≤35 U/ml. Patients who subsequently developed progression according to RECIST or CA125 progression according to Rustin et al. (Figure 6a) were compared with patients who achieved CA125 progression according to the EPD criteria (Figure 8a-b). Liu et al. reported that the EPD criteria predicted progressive disease among more than 50% of the patients and at the same time yielded a low false-

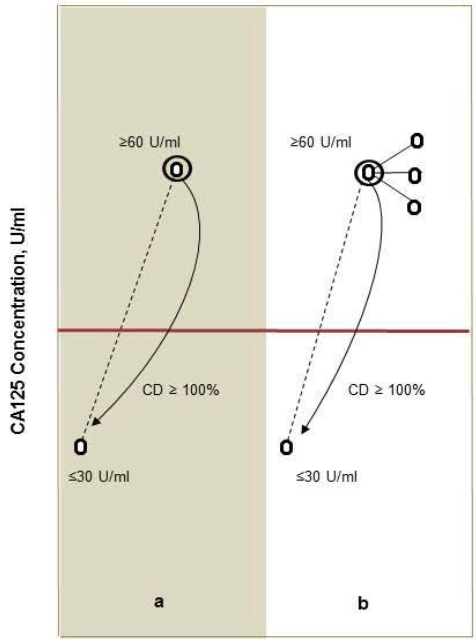

Figure 5: CA125 progression criteria proposed by Rustin et al. in 1996 to detect increments among patients with FIGO stage IC-IV ovarian cancer during follow-up after first-line chemotherapy. The third analysis was performed one year later [20]. CD denotes the required critical difference. Points connected by dashed lines indicate measurements that are not necessarily consecutive. Points connected by solid lines indicate consecutive measurements. The red solid line indicates the applied cutoff in the individual criteria.

a The criterion was based on at least two measurements. The first concentration was ≤30 U/ml with an increment to ≥60 U/ml. The time interval of the criterion varied from <1 month to >6 months [20].

b The criterion was based on at least three measurements. The first concentration was ≤30U/ml with an increment to ≥60 U/ml. The latest concentration was ≥60U/ml and could be higher, equal to or lower than the second latest concentration. The time interval of the criterion varied from <1 month to >6 months [20].

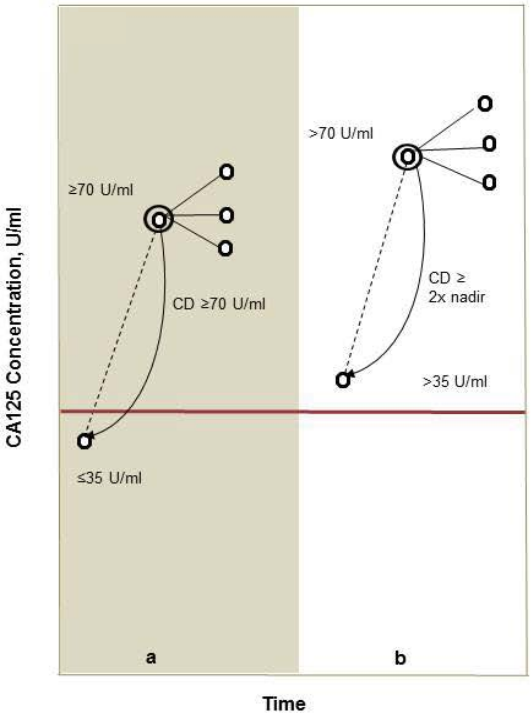

Figure 6: CA125 progression criteria proposed by Rustin et al. in 1996 and in 2001 to detect increments among patients with FIGO stage IC-IV ovarian cancer during follow-up after first-line chemotherapy [20;21]. CD denotes the required critical difference. Points connected by dashed lines indicate measurements that are not necessarily consecutive. Points connected by solid lines indicate consecutive measurements. The red solid line indicates the applied cutoff in the individual criteria.
a The criterion was based on at least three measurements. The first concentration was ≤35 U/ml with an increment to ≥70 U/ml confirmed by an additional measurement. The latest concentration was higher, equal to or lowers than the second latest concentration and ≥70U/ml [20].
b The criterion was based on at least three measurements. The nadir concentration was >35 U/ml with an increment to ≥2 times the nadir concentration. The latest concentration was higher, equal to or lowers than the second latest concentration and ≥2 times the nadir concentration [21].

positive rate. However, the false negative and true negative CA125 events were not reported.

Discussion

Monitoring performance of CA125 during primary therapy

The purpose of CA125 guided surveillance is to detect treatment failure and to abandon ineffective therapy. Thus, false negative CA125 progression signals are likely to have less importance than false positive signals because false positive signals of progression would lead to abandoning a useful treatment.

The early studies reported sensitivities of 40%-95% frequently without reporting the lead times (Table 1). The range of the calculated false negative rates was 4%-100%. Thus, Vergote et al. included 53 patients, 19 of whom had the mucinous type of epithelial ovarian cancer associated with low CA125 expression which may explain the false negative rate of 100% [17]. Some of the reported false negative rates could also be explained by the large CA125 increments (50%-100%) required to cross the applied cut-off. The false positive rates were <11% except in two studies reported by Fioretti et al. (33% and 40%, respectively) and may be ascribed to small populations where a few false positive CA125 signals may cause a relatively high false positive rate. Additionally, elevated concentrations frequently observed in benign gynecological conditions may cause false positive signals [56]. Overall, estimation of the monitoring performance of the early criteria was impossible due to heterogeneous study design and missing data [4,5,7,8,10-13,16,17].

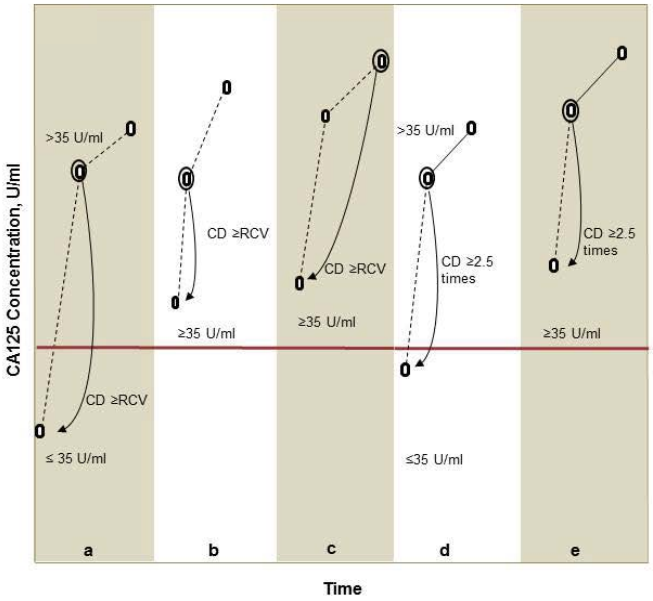

Figure 7: CA125 progression criteria proposed by Tuxen et al. in 2001 and in 2002 to detect increments among patients with FIGO stage IC-IV ovarian cancer during first-line chemotherapy and follow-up, respectively [22;23]. CD denotes the required critical difference. RCV denotes the reference change value. Points connected by dashed lines indicate measurements that are not necessarily consecutive. Points connected by solid lines indicate consecutive measurements. The red solid line indicates the applied cutoff in the individual criteria.
a The criterion was based on at least three measurements. The first concentration was ≤35 U/ml. The second and the third concentrations were >35 U/ml, where the third concentration was higher than the second concentration without requirement for the magnitude of the difference. The CD between the second and the first concentration was ≥RCV. The time interval between the first and the second concentration and between the second and the third concentration was ≥28 days [22,23].
b The criterion was based on at least three measurements. All concentrations were ≥35 U/ml. The third concentration was higher than the second concentration and the second concentration was higher than the first concentration. The CD between the second and the first concentration was ≥RCV. The time interval between the first and the second concentration and between the second and the third concentration was ≥28 days [22;23].
c The criterion was based on at least three measurements. All concentrations were ≥35 U/ml. The third concentration was higher than the second concentration without requirement for the magnitude of the difference. The CD between the third and the first concentration was ≥RCV. The time interval between the first and the second concentration and between the second and the third concentration was ≥28 days [22;23].
d The criterion was based on at least three measurements. The first concentration was ≤35 U/ml. The second latest and the latest concentrations were >35 U/ml where the latest concentration was higher than the second latest concentration. The second latest concentration was ≥2.5 times the first concentration. The time interval between the first and the second latest concentration and between the second latest and the latest concentration was ≥28 days [22;23].
e The criterion was based on at least three measurements. All concentrations were ≥35 U/ml. The latest concentration was higher than the second latest concentration without requirements for the difference. The second latest concentration was ≥2.5 times the first concentration. The time interval between the first and the second latest concentration and between the second latest and the latest concentration was ≥28 days [22,23].

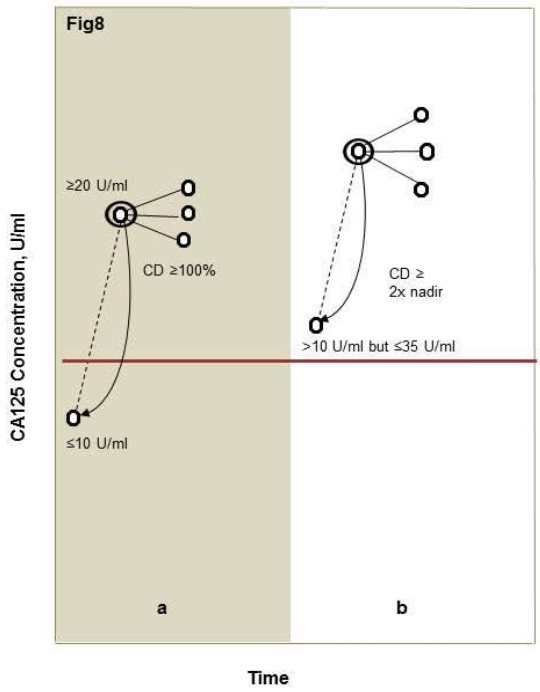

Figure 8: Early signals of CA125 progression criteria proposed by Liu et al. in 2007 to detect increments among ovarian cancer patients receiving maintenance treatment after complete clinical response to primary therapy [24]. CD denotes the required critical difference. Points connected by dashed lines indicate measurements that are not necessarily consecutive. Points connected by solid lines indicate consecutive measurements. The red solid line indicates the applied cutoff in the individual criteria.
a The criterion was based on at least three measurements. The first concentration was ≤10 U/ml. The second latest concentration was ≥20 U/ml. The latest concentration was higher, equal to or lowers than the second latest concentration and ≥20 U/ml. The time interval between the first and the second latest concentration and between the second latest and the latest concentration was ≥28 days [24].
b The criterion was based on at least three measurements. The first concentration was >10 U/ml but ≤35 U/ml [nadir value]. The second latest concentrations was ≥two times the nadir concentration. The latest concentration was higher, equal to or lowers than the second latest concentration and ≥two times the nadir concentration. The time interval between the first and the second latest concentration and between the second latest and the latest concentration was ≥28 days [24].

Rustin et al., Rustin et al. and Tuxen et al . did not specify the sensitivity, lead time, false positive rate, and false negative rate of their individual criteria but only reported their combined performance. The criteria by Rustin et al. (Figure 1a-b and Figure 2a-c) indicated higher sensitivities for progression as compared to Tuxen et al. (Figure 7a-c and Figure 7d-e) (60% and 73% vs. 33.3% and 45.8%, respectively). The results may be due to the composition of their criteria which signaled CA125 progression if three concentrations were ≥100 U/ml (Figure 1b and 2c). Overrepresentation of patients with elevated baseline concentrations may have influenced the frequency of progression signals. However, the criteria by Tuxen et al. (Figure 7d-e) tended to provide lower false positive rates thus being more robust against false positive signals of progression as compared to Rustin et al. (0% versus 8%) (Figure 1a-b and Figure 2a-c). All reports suggested that CA125 is unreliable to exclude clinical progression during treatment owing to a relatively high rate of false negative information provided by their combined criteria, 14% and 24% by Rustin et al. vs. 8% and 10% by Tuxen et al.

In summary, only Rustin et al. and Tuxen et al. reported results on all performance parameters listed in Table 1. As both authors reported the combined performance of more criteria, assessment of their individual performances was impossible. However, the 95% CIs of their combined sets of criteria were overlapping suggesting a similar monitoring performance.

Monitoring performance of CA125 during follow-up after primary therapy

The purpose is to detect recurrence and initiate an early effective treatment. Thus, false negative CA125 signals are likely to have less importance than false positive signals because false positive signals may lead to unnecessary therapy.

Among the early studies the calculated sensitivities for recurrent disease were 62%-90%, and the calculated false positive rates were <2% except in the study reported by Krebs et al. (18%), the differences being due to small and selected patient groups [6,9,14,15] (Table 2). The calculated false negative rates varied considerably (5-100%) probably depending on i) the baseline concentration, ii) the magnitude of the required increment, and iii) the number of patients with mucinous epithelial ovarian cancer.

The sensitivities for recurrence reported by Rustin et al. appeared slightly higher than those reported by Tuxen et al., most likely because the results reported by Rustin et al. were based on selected patients at three interim analyses (Table 2). However, when their studies had a comparable design the sensitivity for recurrence reported by Rustin et al 2001 was similar to the sensitivities reported by Tuxen et al. The criteria proposed by Rustin et al. (Figure 3a-b, 4a-e, and Figure 5a-b) and Rustin et al. (Figure 6a-b) suggested a shorter lead time potential as compared to the criteria proposed by Tuxen et al. (Figure 7a-e) (Table 2). However, there was a major difference as regards how marker lead times exceeding 12 months should be interpreted. Rustin et al. classified lead times exceeding 12 months as false positive information in terms of recurrence, whereas, Tuxen et al. accepted all positive lead times irrespective of length as true positive signals of recurrence. The approach by Rustin et al. may have failed to detect the CA125 kinetics with slow rates of increase resulting in delayed detection of recurrence. Additionally, both Rustin et al. (Figure 5b) (Figure 6a-b), and Tuxen

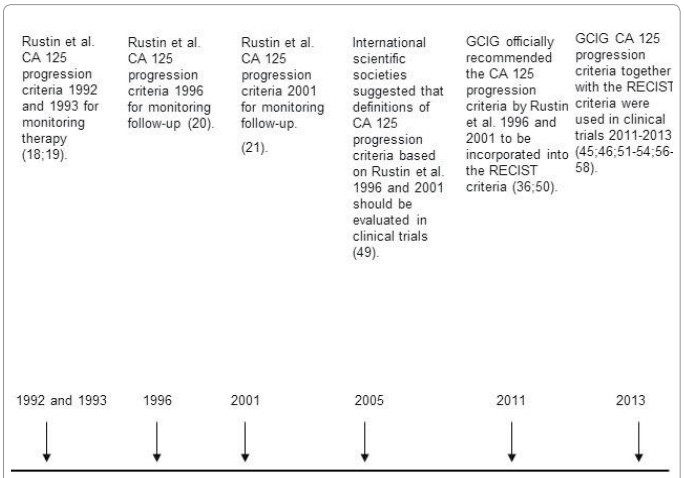

Figure 9: Timeline of CA125 progression criteria developed by Rustin et al. and GCIG during 1992-2013. GCIG denotes The Gynecologic Cancer Intergroup. RECIST denotes The Response Evaluation Criteria in Solid Tumors.

Authors, year (Reference)	Criteria as an increase of concentration in % or in figure format	No. of patients assessable for CA125 increments	Reported number of TP, FP, FN and TN	Reported sensitivity%	Reported lead time, months, median (Range)	Calculated sensitivity, % (95% CI)	Calculated false positive rate, % (95% CI)	Calculated false negative rate, % (95% CI)
[a] Bast et al. [4]	100%	38 /38 (100%)	17 TP, 0 FP, 2 FN, 19 TN	NR	NR	89% (70–98%), 17 TP, 2 FN,	0% (0–18%), 0 FP, 17 TP	10% (2–28%) 2 FN, 19 TN
[a] Bast et al. [5]	100%	41/41 (100%)	19 TP, 0 FP, 1 FN, 21 TN	NR	NR	95% (76–100%), 19 TP, 1 FN	0% (0–16%), 0 FP, 19 TP	4% (0-21%) 1 FN, 21 TN
[c] Fioretti et al. [7]	100%	13/24 (54%)	2 TP, 1 FP, 3 FN, 7 TN	NR	NR	40% (7–82%), 2 TP, 3 FN	33% (1–88%), 1 FP, 2 TP	30% (9–61%) 3 FN, 7 TN
[b] Fioretti et al. [8]	100%	21/21 (100%)	3 TP, 2 FP, 2 FN, 14 TN	NR	+3.5 (+3– +4)	60% (18–93%), 3 TP, 2 FN	40% (7–82%), 2 FP, 3 TP	12% (2–35%) 2 FN, 14 TN
[c] Vergote et al. [10]	100%	101/112 (90%)	49 TP, 0 FP, 8 FN, 44 TN	NR	+3 (+1– +8)	86% (76–93%), 49 TP, 8 FN	0% (0-–6%), 0 FP, 49 TP	15% (8–26%) 8 FN, 44 TN
[b] Altaras et al. [12]	50%	41//41 (100%)	11 TP, 0 FP, 4 FN, 26 TN	NR	NR	73% (49–90%), 11 TP, 4 FN	0% (0–26%), 0 FP, 11 TP	13% (5–28%), 4 FN, 26 TN
[c] Panza et al. [11]	100%	13/13 (100%)	3 TP, 0 FP, 4 FN, 6 TN	NR	NR	43% (13–78%), 3 TP, 4 FN	0% (0–66%), 0 FP, 3 TP	40% (15-70%), 4 FN, 6 TN
[b] Gadducci et al. [13]	100%	27/27 (100%)	8 TP, 1 FP, 7 FN, 11 TN	NR	NR	53% (30–76%), 8 TP, 7 FN	11% (0–44%), 1 FP, 8 TP	39% (20–61%) 7 FN, 11 TN
[c] Fioretti et al. [16]	100%	35/43 (81%)	10 TP, 1 FP, 11 FN, 13 TN	NR	+5 (+1– +14)	48% (29–67%), 10 TP, 11 FN	9% (0–38%), 1 FP, 10 TP	46% (28–64%) 11 FN, 13 TN
[a] Vergote et al. [17]	50%	53/135 (39%)	43 TP, 0 FP, 10 FN, 0 TN	NR	NR	81% (70–90%) 43 TP, 10 FN	0% (0–7%) 0 FP, 43 TP	100% (72–100%) 10 FN, 0 TN
[a] Rustin et al. [18]	Figures 1a-b	71/71 (100%)	12 TP, 1 FP, 8 FN, 50 TN	60.0%	+3 (0– +12)	60% (39–78%), 12 TP, 8 FN	8% (0–33%), 1 FP, 12 TP	14% (7–24%), 8 FN, 50 TN
[a] Rustin et al. [19]	Figures 2a-c	157/164 (96%)	11 TP, 1 FP, 22 FN, 71 TN	NR	NR	73% (64–81%), 59 TP, 22 FN	8% (3–16%), 5 FP, 59 TP	24% (17–32%), 22 FN, 71 TN
[a] Tuxen et al. [22]	Figures 7a-c	173/173 (100%)	11 TP, 1 FP, 13 FN, 148 TN	45.8%	+1.4 (0– +2.6)	46% (28–64%), 11 TP, 13 FN	8% (0–35%), 1 FP, 11 TP	8% (5–15%), 13 FN, 148 TN
[a] Tuxen et al. [22]	Figures 7d-e	168/168 (100%)	8 TP, 0 FP, 16 FN, 144 TN	33.3%	+1.2 (0– +2.3)	33% (18–52%), 8 TP, 16 FN	0% (0–33%), 0 FP, 8 TP	10% (6–15%), 16 FN, 144 TN

CI= Two sided 95% Confidence Interval (%), FP= false positive CA125 events, FN= false negative CA125 events, TP= true positive CA125 events, TN=true negative CA125 events, NR= Not reported.
Rustin et al. 1992, Rustin et al. 1993 and Tuxen et al. 2001 did not specify the sensitivity, false positive rate and false negative rate of the individual criteria, but only reported their combined performance.
[a] The study used clinical and radiological examination as a gold standard for clinical evaluation.
[b] The study used second look operation as a gold standard for clinical evaluation.
[c] The study used a combination of second look operation and clinical and radiological examination as a gold standard for clinical evaluation.
[d] Tuxen et al. investigated the same patient population (n=173) with two different sets of criteria.

Table 1: Ability of CA125 to detect tumor growth during primary therapy.

et al. (Figure 7a-e) may have overestimated the lead time potential of their criteria because they used the second latest instead of the latest measurement as the basis for the calculation. Most of the criteria elaborated by Rustin et al. tended to provide higher false positive rates of recurrence than the criteria elaborated by Tuxen et al. All the criteria generated by Rustin et al. (Figure 3-5a) except one (Figure 5b) were based upon at least two measurements whereas all of the criteria provided by Tuxen et al. (Figure 7a-e) were based upon at least three measurements. It seems reasonable to assume that it is more difficult to fulfill a criterion if an increment has to be confirmed by an additional measurement. However, neither the criteria proposed by Rustin et al. nor those proposed by Tuxen et al. could exclude tumor growth during follow-up because clinical recurrence without marker increments occurred frequently (high false negative rate).

Liu et al. suggested that their criteria may be suitable for surveillance among patients with low CA125 concentrations by early detection of increments within the normal range (≤35 U/ml) or increments from within to slightly above the normal range [24,57,58]. However, the ability to exclude tumor growth remains unknown due to lack of information on true negative and false negative information (false negative rate).

While rising CA125 can detect recurrent disease, the clinical value of detecting recurrence earlier in asymptomatic patients has been challenged. In 2010 Rustin et al. published results from a large prospective randomized trial conducted by the UK-based Medical Research Council (MRC) and the EORTC [24,36]. They enrolled 1442 women in complete remission after first-line platinum based chemotherapy and a normal CA125 concentration below 35 U/ml. They compared the outcome following initiation of treatment of relapsed ovarian cancer based on rising CA125 levels from below cut-off (≤35 U/ml) to twice the upper limit of normal (>70 U/ml) alone (Figure 6a) vs. initiation of treatment commencing at clinical or symptomatic relapse [36]. The patients were enrolled from 59 centers across Europe, Russia, and South Africa during a decade. In the early CA125 guided treatment arm second-line chemotherapy started a median 4.8 months earlier and third-line chemotherapy a median 4.6 months earlier as compared to the treatment arm where therapy was delayed until clinically indicated. Remarkably, earlier treatment neither improved survival nor quality of life. The authors concluded that monitoring for recurrence with CA125 could be avoided altogether and patients could be reassured that i) there is no benefit from early detection of relapse by routine CA125 measurements, and ii) even if CA125 rises, chemotherapy can be delayed until signs or symptoms of tumor recurrence. It was suggested

Authors (Reference)	Criteria as an increase of concentration in % or in figure format	No. of patients assessable for CA125 assessment	Reported number of TP, FP, FN and TN	Reported sensitivity %	Reported lead time, months, median (Range)	Calculated sensitivity, % (95% CI)	Calculated false positive rate, % (95% CI)	Calculated false negative rate, % (95% CI)
[c] Alvarez et al. [9]	100%	30/30 (100%)	24 TP, 0 FP, 6 FN, 0 TN	NR	Median NR (+0.2– +6)	80% (64–91%) 24 TP, 6 FN	0% (0–13%) 0 FP, 24 TP	100% (58–100%) 6 FN, 0 TN
[b] Krebs et al. [6]	50%	65/65 (66%)	18 TP, 4 FP, 2 FN, 41 TN	NR	NR	90% (71–98%), 18 TP, 2 FN	18% (6–37%), 4 FP, 18 TP	5% (0–14%), 2 FN, 41 TN
[c] Hørding et al. [14]	50%	57/57 (100%)	37 TP, 0 FP, 7 FN, 13 TN	NR	+2 (+1– +4)	84% (72–92%), 37 TP, 7 FN	0% (0–9%), 0 FP, 37 TP	35% (18–56%), 7 FN, 13 TN
[a] Cruickshank et al. [15]	100%	74/74 (100%)	40 TP, 1 FP, 25 FN, 8 TN	NR	NR	62% (51–72%), 40 TP, 25 FN	2% (0–12%), 1 FP, 40 TP	76% (60–87%), 25 FN, 8 TN
[a] Rustin et al. First analysis [20]	Figure 3a	124/203 (61%)	68 TP, 7 FP, 5 FN, 44 TN	93.2-93.6%	+2.1 (-2.6– +11.7)	93% (86–97%), 68 TP, 5 FN	9% (5–17%), 7 FP, 68 TP	10% (4–21%), 5 FN, 44 TN
[a] Rustin et al. First analysis [20]	Figure 3b	124/203 (61%)	60 TP, 4 FP, 14 FN, 46 TN	81.1-82.1%	+1.0 (-3.5– +8.2)	81% (70–89%), 60 TP, 14 FN	6% (2–15%), 4 FP, 60 TP	23% (13–36%), 14 FN, 46 TN
[a] Rustin et al. Second analysis [20]	Figure 4a	119/203 (59%)	53 TP, 10 FP, 4 FN, 52 TN	93.0%	+2.9 (-7.2– +11.9)	93% (83–98%), 53 TP, 4 FN.	16% (8–27%), 10 FP, 53 TP	7% (2–17%), 4 FN, 52 TN
[a] Rustin et al. Second analysis [20]	Figure 4b	135/203 (67%)	65 TP, 6 FP, 7 FN, 57 TN	90.3%	+2.5 (-7.2– +12)	90% (81–96%), 65 TP, 7 FN	8% (3–17%), 6 FP, 65 TP	11% (5–21%), 7 FN, 57 TN
[a] Rustin et al. Second analysis [20]	Figure 4c	145/203 (71%)	73 TP, 4 FP, 8 FN, 60 TN	90.1%	+2.2 (-2.6– +12)	90% (81–96%), 73 TP, 8 FN	5% (1–13%), 4 FP, 73 TP	12% (5–22%), 8 FN, 60 TN
[a] Rustin et al. Second analysis [20]	Figure 4d	115/203 (57%)	52 TP, 6 FP, 4 FN, 53 TN	92.9%	+2.5 -7.2– +12)	93% (83–98%), 52 TP, 4 FN	10% (4–21%), 6 FP, 52 TP	7% (2–17%), 4 FN, 53 TN
[a] Rustin et al. Second analysis [20]	Figure 4e	135/203 (67%)	66 TP, 4 FP, 8 FN, 57 TN	89.2%	+2.2 (-2.6– +12)	89% (80–95%), 66 TP, 8 FN	6% (2–14%), 4 FP, 66 TP	12% (5–23%), 8 FN, 57 TN
[a] Rustin et al. Third analysis [20]	Figure 5a	131/131 (100%)	73 TP,4 FP, 12 FN, 42 TN	85.9%	+2.1 (-2.6– +12)	86% (77–92%), 73 TP, 12 FN	5% (1–13%), 4 FP, 73 TP	22% (12–36%), 12 FN, 4 2 TN
[a] Rustin et al. Third analysis [20]	Figure 5b	119/130 (92%)	62 TP, 1 FP, 14 FN, 42 TN	83.9%	+2.1 (-2.6– +12)	82% (71–90%), 62 TP, 14 FN	2% (0–9%), 1 FP, 62 TP	25% (14–38%), 14 FN, 42 TN
[a] Rustin et al. [21]	Figures 6a-b	88/300 (29%)	61 TP, 1 FP, 24 FN, 2 TN	79.0%	+2.4 (-10– +12)	72% (61–81%), 61 TP, 24 FN	2% (0–9%), 1 FP, 61 TP	92% (75–99%), 24 FN, 2 TN
[a] Tuxen et al. [23]	Figures 7a-c	149/149 (100%)	94 TP, 1 FP, 29 FN, 25 TN	76.4%	+3.3 (0– 34.5)	76% (70–83%), 94 TP, 29 FN	1% (0–5%), 1 FP, 94 TP	54% (42–65%), 29 FN, 25 TN
[a] Tuxen et al. [23]	Figures 7d-e	144/144 (100%)	88 TP, 1 FP, 30 FN, 25 TN	74.6%	+2.6 (0– +32.5)	75% (67–81%), 88 TP, 30 FN	1% (0–6%), 1 FP, 88 TP	54% (43–66%), 30 FN, 25 TN
[a] Liu et al. [24]	Figures 8a-b	204/204 (100%)	135 TP, 9 FP, FN (NR), TN (NR)	NR	≤2 (≤2– >6)	135 TP, FN (NR)	6% (3–11%), 9 FP, 135 TP	FN (NR), TN (NR)

CI= Two sided 95% Confidence Interval (%), FP= false positive CA125 events, FN= false negative CA125 events, TP= true positive CA125 events, TN=true negative CA125 events, NR= Not Reported.
Rustin et al., Rustin et al. and Tuxen et al. did not specify the sensitivity, false positive rate and false negative rate of the individual criteria, but only reported their combined performance.
[a] The study used clinical and radiological examination as a gold standard for clinical evaluation.
[b] The study used second look operation as a gold standard for clinical evaluation.
[c] The study used a combination of second look operation and clinical and radiological examination as a gold standard for clinical evaluation.

Table 2: Ability of CA125 to detect tumor growth during follow-up after primary therapy.

that women should be informed about the most common symptoms prompting an appointment with a specialist and rapid access to CA125 testing [36,44,48]. The study, however, has several limitations [59]. The two groups may not have been balanced for optimal cytoreduction; imaging for residual disease was not performed consistently with the most sensitive techniques available; and secondary cytoreduction was not often undertaken based on rising CA125. Possibly of greater importance, only a quarter of patients received optimal therapy promptly with a combination of a platinum compound and a taxane. Although the groups were well balanced, the study has demonstrated that suboptimal therapy by today's standards at an earlier interval is ineffective. As regard the CA125 related issues, the measurements were decentralized to numerous local laboratories without information on the quality of measurements. Moreover, the large increment requiring a doubling of CA125 concentrations from within to outside the normal range may have delayed detection of increasing concentrations (Figure

6a). The ESGO has advised against universally abandoning CA125 in the routine follow-up of all patients with ovarian cancer based on this single randomized trial [60]. Also the European Society for Medical Oncology has advised against abandoning CA125 monitoring during follow-up because there is no doubt that regular measurements of CA125 will diagnose recurrence well before symptoms occur in most patients, it is possible that earlier treatment in selected patients may delay the onset of cancer-related symptoms [59,61].

Using each patient's own baseline, might detect recurrent disease at an even earlier interval. An algorithm, The Risk of Ovarian Cancer Algorithm (ROCA) based on serial CA125 measurements has been developed by Steven Skates to detect primary ovarian cancer at an earlier interval [62]. ROCA has been implemented in several screening trials as UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS) and the Normal Risk Ovarian Screening Study (NROSS). Preliminary results have shown that ROCA may have a role in detecting ovarian cancer. However, as yet, the ROCA has not been investigated among patients monitored during primary therapy and follow-up. Computer based simulation studies may be relevant to evaluate this approach [62]. Computer-simulation models have already shown considerable potential enabling comparison of different criteria where their respective advantages and disadvantages can be investigated under standardized conditions [63-66]. The model system may be useful for preclinical development of new biomarker assessment criteria and to optimize already existing criteria. However, it is important to emphasize that computer-simulation studies cannot replace clinical studies. Preclinical investigations may be a supplement to clinical investigations and only relevant if they provide reliable estimates of basic performance characteristics i.e. sensitivity, lead time potential, false positive and false negative rates of marker increments. It may take a year to develop the model system but it will take a large multicenter study several decades to generate the same amount of data.

A limitation of this review could be an incomplete identification of all relevant publications, which could lead to reporting bias. However, we are confident that all major studies were identified. Most studies did not clearly state their inclusion and exclusion criteria i.e. whether consecutive or eligible patients were included.

In summary, the criteria by Rustin et al. (Figure 6a-b) and Tuxen et al. (Figure 7d-e) are easy to use in clinical practice simply stating that an increment should exceed an arbitrarily high set cut-off level confirmed by an additional measurement. However, the required increments may be too large reducing the sensitivity and lead time potential of CA125. It may take unduly long time for increments with slow rates of increase to fulfill the criteria. The EPD criteria suggested by Liu et al. (Figure 8a-b) offer options to detect increments within the normal range. However, their ability to exclude tumor growth remains unknown due to lack of information on true negative and false negative CA125 information.

Conclusions

The serological cancer biomarker CA125 has the potential to be a relevant and important monitoring tool in the clinical management of patients with epithelial ovarian cancer. A high sensitivity with a low false positive rate is required for CA125 guided change of treatment during therapy or initiation of a new treatment during follow-up. The requirements for sensitivity may be lower when CA125 is used to guide intervention in terms of supplementary imaging methods. In both situations the sensitivity needed should be balanced with the clinical situation of the individual patient. However, the precise role of CA125 monitoring remains undefined owing to uncertainty as regards interpretation of serial measurements. At this stage it is difficult to recommend one approach for the other. The required increment in some of the criteria by Rustin et al. and Tuxen et al. may be too large, reducing the sensitivity and lead time potential. The ability of the criteria by Liu et al. to exclude tumor growth remains unknown due to lack of information on the false negative rate of CA125 information. We suggest that the monitoring performance of the criteria proposed by Rustin et al., Tuxen et al., and Liu et al. should be explored and validated under standardized conditions i.e. in computer-simulation models allowing assessment of their individual advantage and drawbacks at different below cutoff baseline concentration, nadir concentration above cut off, intra-individual biological variation of CA125, and rate of CA125 increase. The utility of the individual criteria may depend on the base-line concentration and kinetics of CA125 and thus on the clinical situation of the individual patient.

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Conflict of Interests

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