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Full length article

## Perioperative change in CA125 is an independent prognostic factor for improved clinical outcome in advanced ovarian cancer

M. Timmermans<sup>a,b,\*</sup>, N. Zwakman<sup>c</sup>, G.S. Sonke<sup>d</sup>, K.K. Van de Vijver<sup>e</sup>, M.J. Duk<sup>f</sup>,  
M.A. van der Aa<sup>a</sup>, R.F. Kruitwagen<sup>b</sup>

<sup>a</sup> Department of Research, Netherlands Comprehensive Cancer Organization (IKNL), Utrecht, the Netherlands

<sup>b</sup> Department of Obstetrics and Gynecology, Maastricht University Medical Centre, Maastricht, The Netherlands, GROW - School for Oncology and Developmental Biology, Maastricht, the Netherlands

<sup>c</sup> Department of Obstetrics and Gynecology, VieCuri Medical Center, Venlo, the Netherlands

<sup>d</sup> Department of Medical Oncology, The Netherlands Cancer Institute, Amsterdam, the Netherlands

<sup>e</sup> Department of Pathology, Ghent University Hospital, Cancer Research Institute Ghent (CRIG), Ghent, Belgium

<sup>f</sup> Department of Obstetrics and Gynecology, Meander Medical Center, Amersfoort, the Netherlands



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### ABSTRACT

**Objective:** Despite being the most important prognostic factor for prolonged overall survival in epithelial ovarian cancer (EOC), the measurement of residual disease is hampered by its subjective character. Additional assessment tools are needed to establish the success of cytoreductive surgery in order to predict patients' prognosis more accurately. The aim of this study is to evaluate the independent prognostic value of perioperative CA125 change in advanced stage EOC patients.

**Study design:** We identified all patients who underwent primary cytoreductive surgery for advanced stage (FIGO IIB-IV) EOC between 2008 and 2015, from the Netherlands Cancer Registry. The relative perioperative change in CA125 was categorized into four groups; increase, <50% decline, 50–79% decline and ≥80% decline. Overall survival (OS) was analyzed using Kaplan-Meier survival curves and multivariable cox regression models.

**Results:** We included 1232 eligible patients with known pre- and postoperative CA125 serum levels. Patients with a decline of ≥80% in CA125 levels experienced improved OS compared to those with a decline of <50% (univariable Hazard Ratio (HR) 0.45, 95%CI 0.36–0.57). The prognostic effect of perioperative CA125 change was independent of patient- and treatment characteristics, such as the extent of residual disease after cytoreductive surgery (multivariable HR<sub>≥80%</sub> 0.52(0.41–0.66)).

**Conclusions:** This study shows that the perioperative change in CA125 is an independent prognostic factor for overall survival after primary surgery for EOC patients. This pleads for the use of a combined model, consisting of perioperative CA125 change and the outcome of residual disease, in order to predict the prognosis of EOC patients more accurately.

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### Introduction

Epithelial ovarian cancer (EOC) is the leading cause of death from gynecological tumors [1]. Since 1999, the five-year overall survival (OS) rates have hardly changed, resulting in an OS of 35% [2–5]. Management of advanced stage ovarian cancer consists of surgical cytoreduction and (neo)adjuvant platinum-based

chemotherapy. The timing of surgery depends on patient characteristics and extensiveness of the tumor in relation to the ability of achieving maximal cytoreduction [6,7].

Despite being the most important prognostic factor for prolonged OS in EOC patients, measurement of the extent of residual disease is hampered by several factors [8–10]. First, it is based on the surgeons' intraoperative assessment, and is therefore subject to inter- and intra-observer variability [11,12]. Second, it can be difficult to distinguish viable residual tumor from fibrotic lesions, particularly after neoadjuvant chemotherapy (NACT). Third, residual disease does not account for the number of lesions but only for the largest lesion in maximum diameter, and is therefore a crude measure of the residual cancer burden.

\* Corresponding author at: Department of Research - Netherlands Comprehensive Cancer Organization (IKNL), Godebaldkwartier 419, 3511 DT, Utrecht, the Netherlands.

E-mail address: [m.timmermans@iknl.nl](mailto:m.timmermans@iknl.nl) (M. Timmermans).

Additional assessment tools are needed to establish the success of cytoreductive surgery in order to predict patients' prognosis more accurately [12,13].

In search of new prognostic factors, it is suggested that initial disease burden influences the prognosis of patients, regardless of successful surgery [14,15]. This implies that disease presentation should be incorporated into new prognostic factors. The perioperative change in CA125 is an objective measurement which includes initial disease presentation, and may be a better marker for residual cancer burden after cytoreductive surgery (and therewith disease-specific survival), than the surgeons' estimation of residual tumor volume. Prior studies evaluating the prognostic value of perioperative CA125 decline were limited by a small sample size, precluding optimal multivariable adjustments [16–18]. Nevertheless, a decline in CA125 < 50% was associated with higher crude disease-specific mortality [16,19–21].

The aim of this study is to establish the independent prognostic value of perioperative CA125 change in advanced EOC patients who underwent primary cytoreductive surgery. In addition, we aim to provide insight into the association between perioperative CA125 change and the outcome of cytoreductive surgery.

## Methods

Patients were identified from the Netherlands Cancer Registry (NCR), which is a nationwide cancer registry with coverage of all newly diagnosed malignancies in the Netherlands since 1989. Information on vital status and date of death were obtained from the municipal demography registries. The study design, data abstraction process and storage protocols were approved by the NCR review board.

### Study population

For this study, we identified all consecutive patients diagnosed with EOC, including primary peritoneal and fallopian tube carcinoma (ICD-O codes C48.2, C56.9 and C57.0) [22], between 01.01.2008 and 31.12.2015 in the Netherlands. We selected all advanced stage patients (FIGO IIB–IV) who underwent primary cytoreductive surgery. FIGO stage (2014) was derived from the registered Tumor Nodal Metastasis (TNM) staging system [23].

Dedicated registration clerks from the NCR reviewed all medical files of eligible patients to extract additional clinical data for this

study. We collected all available CA125 values from date of diagnosis until the first CA125 value after the last treatment date. Furthermore, additional information about treatment protocol (details of chemotherapy and surgery), patient characteristics (i.e. Charlson Comorbidity Index and volume of ascites) and follow-up (disease progression) were collected [24].

### Definitions

Patients were eligible for analysis if CA125 values were recorded pre- and postoperatively, and if postoperative CA125 was determined before the initiation of adjuvant chemotherapy. If more than one preoperative value was documented (n = 260), the value closest to the date of cytoreductive surgery was used. For patients with more than one postoperative value before the initiation of adjuvant chemotherapy (n = 137), the lowest value was chosen as this probably reflects the effect of surgery best. Patients with normal preoperative CA125 values (<35U/mL) were excluded (S1).

In order to compare our results to previous studies, CA125 decline was categorized within the same groups; <50% decline, 50–79% decline and ≥80% decline. Patients with an increase in CA125 levels were, however, analyzed as a separate group in our study as it was expected that these patients may have a worse prognosis.

The outcome of cytoreductive surgery was defined as complete (no macroscopic residual disease), optimal (largest tumor nodule ≤1 cm in maximal diameter) or suboptimal (largest tumor nodule >1 cm in maximal diameter). Patients with an unknown amount of residual disease were excluded (S1).

### Statistical analyses

Categorical variables were expressed as percentages, and chi-square tests were used to identify differences between groups. Continuous variables were expressed as the mean with a standard deviation if they were normally distributed, or as geometric mean with a confidence interval if skewed. Absolute CA125 levels showed a positively skewed distribution and were therefore log<sub>e</sub>-transformed for further analyses in this study. Uni- and multivariable linear regression analyses were used to compare perioperative change in CA125 levels by the outcome of cytoreductive surgery.

**Table 1**

Association between CA125 levels and the outcome of surgery.

	CA125 level (U/ml)	CA125 level (U/ml)	Model I		Model II	
	Geometric mean (95%CI)	Log <sub>e</sub> mean (SD)	β-coefficient	p-value <sup>a</sup>	β-coefficient	p-value <sup>b</sup>
<b>Preoperative CA125</b>						
Suboptimal	540 (443–656)	6.29 (1.25)	Reference		Reference	
Optimal	504 (447–568)	6.11 (1.31)	−0.07 (−0.30, 0.17)	0.566	0.01 (−0.22, 0.24)	0.960
Complete	380 (342–422)	5.94 (1.32)	−0.35 (−0.58, −0.12)	<b>0.003</b>	−0.06 (−0.29, 0.18)	0.645
			<b>Linear trend</b>	<b>&lt;0.001</b>	<b>Linear trend</b>	0.520
<b>Postoperative CA125</b>						
Suboptimal	232 (186–288)	5.45 (1.40)	Reference		Reference	
Optimal	148 (132–166)	5.00 (1.26)	−0.45 (−0.67, −0.23)	<b>&lt;0.001</b>	−0.31 (−0.51, −0.11)	<b>0.002</b>
Complete	76 (70–83)	4.34 (1.11)	−1.11 (−1.32, −0.90)	<b>&lt;0.001</b>	−0.68 (−0.88, −0.47)	<b>&lt;0.001</b>
			<b>Linear trend</b>	<b>&lt;0.001</b>	<b>Linear trend</b>	<b>&lt;0.001</b>
<b>Decline (absolute)</b>						
Suboptimal	293 (225–383)	5.68 (1.54)	Reference		Reference	
Optimal	340 (291–397)	5.83 (1.60)	0.15 (−0.17, 0.46)	0.363	0.21 (−0.10, 0.52)	0.186
Complete	299 (261–342)	5.70 (1.60)	0.02 (−0.29, 0.32)	0.912	0.29 (−0.03, 0.61)	0.074
			<b>Linear trend</b>	0.639	<b>Linear trend</b>	0.092

Bold values: <0.05.

<sup>a</sup> Model I: crude regression model.

<sup>b</sup> Model II: regression model with adjustment for age, FIGO stage, the amount of ascites and the time between CA125 and surgery (preoperative CA125) or surgery and CA125 (postoperative CA125).

Progression free survival (PFS) was defined as the time between date of diagnosis and progression or death, whichever occurred first. Progression was defined as clinical signs of tumor growth, i.e. increase in CA125 and/or visible lesions on imaging techniques (either regrowth of pre-existing lesions or new lesions), combined with the clinical judgment of the treating physician (medical oncologist or gynecologist). Patients who were alive without record of progressive disease were censored at the date of their last hospital visit. OS was defined as the time between date of diagnosis and death or last follow-up for patients who were alive (01.02.2018). PFS and OS were analyzed using Kaplan-Meier survival curves and multivariable cox regression models. A  $P$ -value  $< 0.05$  was considered statistically significant and statistical analyses were performed using STATA/SE (version 14.1; STATA CORP., College Station, Texas, USA).

## Results

We identified 2113 eligible advanced stage EOC patients who underwent primary cytoreductive surgery of whom 881 patients were excluded (S1). Patients who were excluded were slightly older, more often had non-serous types of tumors and less often had an optimal debulking. The FIGO stage distribution was comparable between in- and excluded patients (S2). A total of 1232 patients was included for analyses and baseline characteristics, stratified by the perioperative CA125 change, are listed in the supplementary material (S3). As can be appreciated from Table S3, patients that had a decrease of  $> 80\%$  were slightly younger, and were less often diagnosed in FIGO stage IV. The median time between the last preoperative CA125 value and cytoreductive surgery was 22 days (IQR 14–33), and the median time between cytoreductive surgery and the postoperative CA125 value was also 22 days (IQR 16–29).

### Perioperative change in CA125 levels

The preoperative CA125 values for patients with no macroscopic residual disease after cytoreductive surgery were significantly lower compared to patients with  $\leq 1$  cm residual disease ( $P = 0.001$ ) or  $> 1$  cm residual disease ( $P = 0.003$ , Table 1)). The preoperative CA125 values did not differ significantly between an optimal or suboptimal result during cytoreductive surgery ( $P = 0.566$ , Fig. 1). Moreover, after adjustment for age, FIGO stage, the amount of ascites and the time between CA125 measurement and surgery, preoperative CA125 levels did not differ between any of the groups ( $P = 0.520$ , Table 1).

The postoperative CA125 levels were significantly lower after complete cytoreductive surgery compared to patients with macroscopic residual disease, also after adjustment for the listed variables above (Fig. 1, Table 1). In addition, postoperative CA125 levels after an optimal cytoreduction were also significantly lower when compared to patients with  $> 1$  cm of residual disease.

The absolute decline in CA125 was not associated with the outcome of cytoreductive surgery (Table 2). The relative CA125 decline, however, differed significantly between patients with complete, optimal and incomplete cytoreductive surgery ( $P < 0.001$ ). Patients with no residual disease experienced more often a decrease  $\geq 80\%$  compared to patients with any macroscopic residual disease (Fig. 2).

### Prognostic effect of perioperative CA125 change

The relative CA125 decline is a prognostic factor for OS ( $P < 0.001$ , Fig. 3). Patients with a decline of  $\geq 80\%$  in CA125 levels experienced improved crude OS compared to patients with a decline of 50–79% (Hazard Rate (HR) 0.55, 95%CI 0.45–0.67) and to patients with a decline of  $< 50\%$  (HR 0.45(0.36–0.57)), also when adjusted for patient- and tumor characteristics including the amount of residual disease and the histological subtype (adjusted HR's in Table 2). In addition, patients with an increase in perioperative CA125 experienced worse OS compared to patients with a decline of  $< 50\%$  (HR 1.49(1.15–1.93)). The prognosis of patients with a decline of 50–79% was comparable to those with a decline of  $< 50\%$  (HR 0.94(0.76–1.17)). These effects were also observed for PFS (Table 2).

### Survival analyses stratified by the outcome of surgery

In stratified analyses based on the outcome of surgery, the same patterns were observed. For example, when only patients with a complete cytoreduction were selected, the perioperative CA125 decline was still a prognostic factor for OS (S5). Again, the same patterns were observed for progression-free survival (Table 2).

### Sensitivity analyses

Patients with a preoperative CA125 level between 35–160U/mL (lowest 25% of our studied population), were less likely to experience a decline of  $\geq 80\%$  compared to those with higher baseline CA125 levels ( $P < 0.001$ ). Therefore, we performed a sensitivity analysis in which we included the baseline CA125 level in our multivariable analyses. Trends in survival did not differ from our previous multivariable model (HR $_{\geq 80\% \text{-CA125 decline}}$  0.50(0.39–

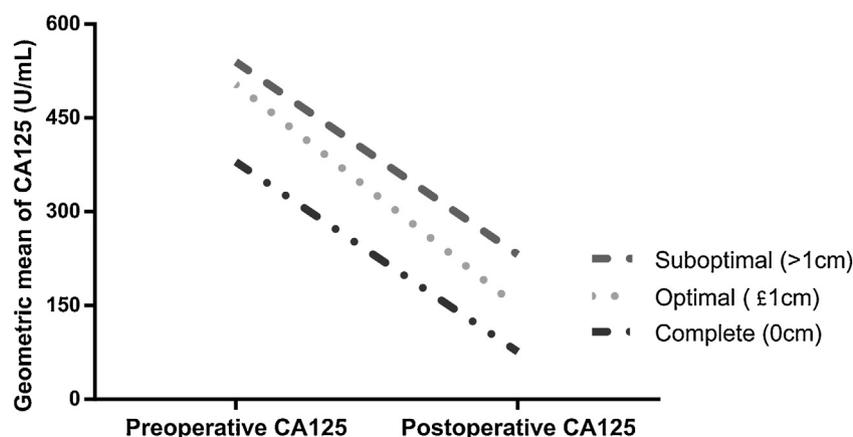


Fig. 1. Perioperative CA125 decline stratified by the outcome of surgery.

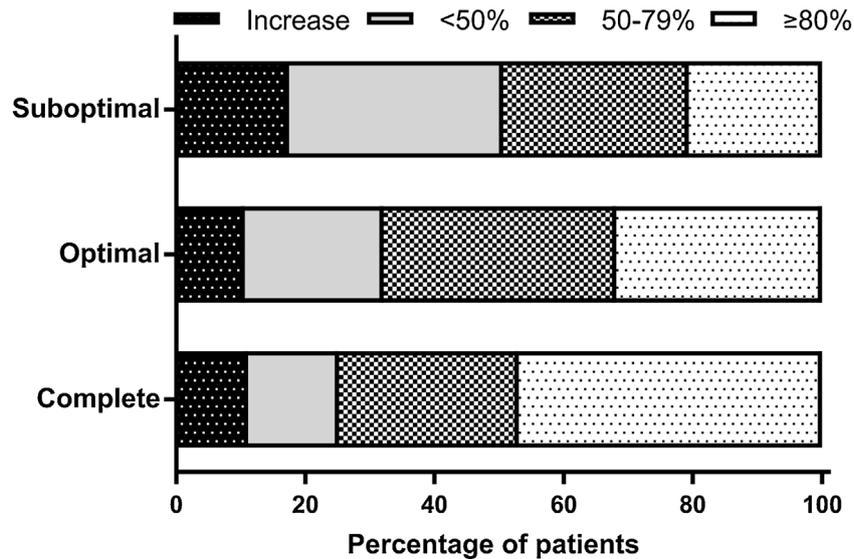
**Table 2**  
Multivariable cox regression models for overall- and progression-free survival.

	All patients (HR, 95% CI) <sup>a</sup>	Complete debulking (HR, 95% CI) <sup>b</sup>	Optimal debulking (HR, 95%CI) <sup>b</sup>	Suboptimal debulking (HR, 95% CI) <sup>b</sup>
<b>Overall survival</b>				
Increase	<b>1.49 (1.15-1.93)</b>	<b>1.85 (1.18-2.89)</b>	1.38 (0.90-2.11)	1.00 (0.56-1.80)
<50% decrease	Reference	Reference	Reference	Reference
50-79% decrease	0.94 (0.76-1.17)	0.79 (0.52-1.21)	1.03 (0.74-1.42)	1.10 (0.67-1.78)
≥80% decrease	<b>0.52 (0.41-0.66)</b>	<b>0.49 (0.32-0.73)</b>	<b>0.55 (0.38-0.80)</b>	<b>0.44 (0.24-0.78)</b>
<b>Progression-free survival</b>				
Increase	<b>1.24 (1.00-1.57)</b>	<b>1.71 (1.16-2.52)</b>	1.02 (0.70-1.50)	0.97 (0.57-1.68)
<50% decrease	Reference	Reference	Reference	Reference
50-79% decrease	0.87 (0.72-1.06)	0.83 (0.59-1.18)	0.92 (0.69-1.22)	1.11 (0.68-1.81)
≥80% decrease	<b>0.58 (0.47-0.71)</b>	<b>0.59 (0.42-0.83)</b>	<b>0.63 (0.46-0.86)</b>	<b>0.39 (0.22-0.67)</b>

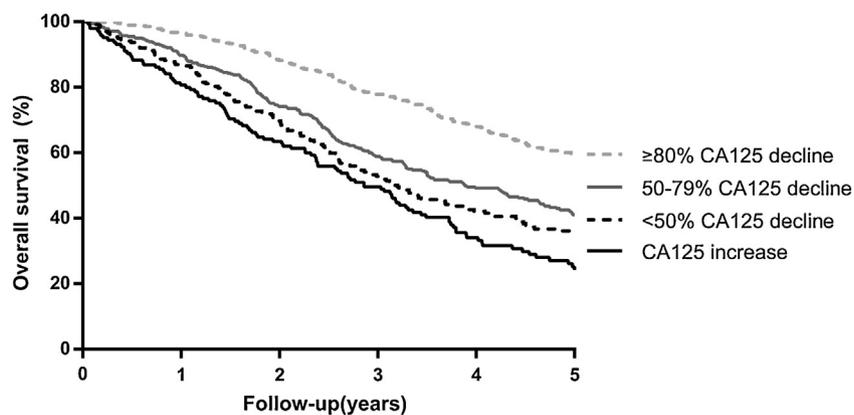
Bold values: <0.05.

<sup>a</sup> Adjusted for age, FIGO stage, histological subtype, differentiation grade, outcome of surgery, amount of ascites (<500 ml or ≥500 mL), and chemotherapy alterations.

<sup>b</sup> Adjusted for age, FIGO stage, histological subtype, differentiation grade, amount of ascites (<500 ml or ≥500 mL), and chemotherapy alterations.



**Fig. 2.** Categorized perioperative CA125 change stratified by the outcome of surgery.



**Fig. 3.** Overall survival of EOC patients stratified by the relative CA125 change.

0.64), HR<sub>50-79%-CA125decline</sub> 0.92 (0.74–1.15) and HR<sub>CA125increase</sub> 1.52 (1.17–1.98) compared to a CA125 decline of <50%.

**Discussion**

In this population-based study, we observed that the relative perioperative change in serum CA125 is an independent prognostic

factor for prolonged OS in advanced ovarian cancer. This prognostic effect was therefore also observed in patients with the same amount of residual disease, suggesting the need for a complementary model to predict clinical outcome more accurately in advanced ovarian cancer patients.

Both perioperative change in CA125 and the outcome of cytoreductive surgery were independent prognostic factors, so the

association between the two factors needs to be addressed. Patients who underwent an optimal or suboptimal cytoreductive surgery had similar CA125 levels in the preoperative setting, while preoperative CA125 levels were significantly lower in the group of patients without macroscopic residual disease after surgery. However, after adjustment for FIGO stage and the presence of ascites, the height of the preoperative CA125 was similar in all groups despite differences in residual disease. These results suggest that FIGO stage and the presence of ascites are closely correlated to the serum level of CA125 preoperatively. CA125 is expressed on the ovarian tumor cell surface, and biological functions include, among others, the mesothelial cell adhesive interaction on peritoneal surfaces and modulation of tumor cell growth [25–30]. So, CA125 might play a role in the initial adhesion and subsequent implantation on the peritoneum, which enforces findings that the height of CA125 is associated with the tumor burden [25,26].

As the perioperative change in CA125 is closely associated with the outcome of cytoreductive surgery, it is not surprising that this decline is a prognostic factor for both PFS and OS [16–18]. But, even after adjustment for residual disease, the perioperative CA125 change remains an independent prognostic factor. A previous Dutch study showed that the perioperative CA125 change was a stronger predictor than postoperative residual disease [16]. In contrast, in the present study we found that both factors are important to establish the prognosis of patients. The discrepancy between the two studies is most likely caused by the larger cohort of this study. Moreover, it underlies the prognostic value of CA125 besides the outcome of residual disease.

Multiple studies confirmed that residual disease after surgery is the most important prognostic factor for prolonged OS [8,10]. The current method for determining residual disease after surgery relies on clinical intraoperative assessment. Several studies investigated the correlation between the surgeons' operative assessment and the amount of residual disease identified on postoperative computed tomography scans. These studies showed only a 46–60% correlation between the two different methods, with a higher probability in underestimating the amount of residual disease than overestimating it [12,31,32]. Moreover, tumor measurements in individual patients by different surgeons are highly variable [11]. However, while searching for better prognostic factors to predict clinical outcomes in ovarian cancer, no factor seems to be more valuable than the amount of residual disease after surgery. We suggest designing a complementary model, which combines the outcome of surgery assessed by the surgeon and the perioperative CA125 change to make a more reliable prediction for both OS and PFS.

What pleads for such a combined prognostic model is the additional prognostic information of relative CA125 change besides the outcome of surgery. This could be explained by the abovementioned variability in the assessment of tumor residue by gynecologists. But also by heterogeneity within the groups of patients with a certain amount of residual disease. The optimal group, for example, is defined by  $\leq 1$  cm of residual disease in maximum diameter, and therefore contains patients with only one tumor spot but also patients with hundreds of these spots as is the case in some patients with peritoneal carcinomatosis. Moreover, the outcome of surgery does not incorporate the initial disease burden, while this influences clinical outcome [14,15]. When using a combined model, a more specific prognosis could be made based on the outcome of surgery and CA125 levels.

Besides the perioperative decline, some patients experienced a postoperative increase in CA125 levels. The size of the present cohort enabled us to analyze this patient group separately, while

most studies included these patients in their lowest group. Patients with an increase in CA125 experienced worse OS and PFS, especially those who had no residual disease after cytoreductive surgery. In studies on the physiological behavior of CA125, it was shown that CA125 increases within the first two weeks after surgery, which is possibly caused by the surgery induced peritoneal damage [33,34]. Hereafter, it is expected to drop again. In our study, we found that the mean time between surgery and the postoperative CA125, was shorter in the group with a postoperative increased CA125 compared to those with a decline (21 vs. 28 days,  $P=0.005$ ). Even though time may explain the increase, it cannot explain the worse OS of these patients. Moreover, we found that patients with a postoperative increase had a lower CA125 at diagnosis. This could not be explained by differences in FIGO stage, tumor grade or histologic subtype, but we found that patients with an increase in CA125 were less often diagnosed with a large amount of ascites ( $\geq 500$  mL). However, the presence of ascites is an unfavorable prognostic factor [35,36]. Therefore, it remains unclear why these patients experience worse OS. Nevertheless, the abovementioned results seem to confirm the added value of the perioperative change in CA125 as prognostic factor.

The present study has several limitations, of which its retrospective nature is the most important. Therefore, a substantial number of patients was excluded from analyses due to missing CA125 values. Another limitation may be the inclusion of different histological subtypes of EOC, such as endometrioid and clear-cell EOC. As known from earlier studies, CA125 is most highly expressed in serous ovarian cancers, and predominantly in high grade serous ovarian cancer [37–39]. This may raise the question if our results are applicable to other histologic subtypes. We observed, however, the same prognostic effects in these tumor types as well (data not shown). In addition, serum CA125 levels were measured on different moments after surgery. We adjusted for the time between surgery and CA125 levels in our multivariable models, however this may have influenced the rate of postoperative decline. Moreover, the prognostic effect was based on chosen thresholds based on earlier studies, this threshold could potentially be optimized. And finally, the amount of residual disease is judged by several gynecologists, which could have led to suboptimal interpretation of actual residual disease and may biased our results.

In conclusion, this study confirmed that the perioperative CA125 change is a prognostic factor for improved clinical outcomes in EOC patients. Newly found are the prognostic differences between the CA125 groups in patients with the same outcome of cytoreductive surgery. This pleads for the use of a combined model, consisting of perioperative CA125 change and the outcome of residual disease, in order to predict the prognosis of EOC patients more accurately.

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## Declaration of Competing Interest

None.

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## Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.ejogrb.2019.07.010>.

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