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Preoperative Predictors for Residual Tumor after Surgery in Patients with Ovarian Carcinoma

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Key Words
Albumin · CA 125 · Ovarian carcinoma · Prediction model · Primary surgical debulking · Residual tumor

Abstract
Objectives: Suboptimal debulking (>1 cm residual tumor) results in poor survival rates for patients with an advanced stage of ovarian cancer. The purpose of this study was to develop a prediction model, based on simple preoperative parameters, for patients with an advanced stage of ovarian cancer who are at risk of suboptimal cytoreduction despite maximal surgical effort. ***Methods:*** Retrospective analysis of 187 consecutive patients with a suspected clinical diagnosis of advanced-stage ovarian cancer undergoing upfront debulking between January 1998 and December 2003. Preoperative parameters were Karnofsky performance status, ascites and serum concentrations of CA 125, hemoglobin, albumin, LDH and blood platelets. The main outcome parameter was residual tumor >1 cm. Univariate and multivariate logistic regression was employed for testing possible prediction models. A clinically applicable graphic model (nomogram) for this prediction was to be developed. ***Results:*** Serum concentrations of CA 125 and blood platelets in the group with residual tumor >1 cm were higher in comparison to the optimally cytoreduced group ($p < 0.0001$ and <0.01, respectively). Serum albumin and hemoglobin levels were lower in the group with residual tumor ($p < 0.0001$ and <0.05, respectively). The frequency of preoperative ascites was higher in the group with residual tumor ($p < 0.0005$). The prediction model, consisting of CA 125 and albumin, for remaining with residual tumor showed an area under the receiver operating characteristics curve of 0.79. A nomogram for probability of residual tumor >1 cm based on serum levels of CA 125 and albumin was established. ***Conclusion:*** Postoperative residual tumor despite maximal surgical effort can be predicted by preoperative CA 125 and serum albumin levels. With a nomogram based on these two parameters, probability of postoperative residual tumor in each individual patient can be predicted. This proposed nomogram may be valuable in daily routine practice for counseling and to select treatment modality.

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Introduction

Ovarian cancer is the second most frequent gynecological cancer in developed countries. It is the fourth most common cause of cancer-related death in women worldwide, accounting for 5% of all cancer deaths in women [1]. Efficient and cost-effective screening tools for ovarian cancer are currently unavailable [2–5]. As a result of the insidious onset of ovarian cancer, at least two thirds of cases remain undetected before disease progression to an advanced stage [6]. Common features of patients with advanced ovarian cancer are ascites, a decreased Karnofsky performance status (PS), thrombocytosis, anemia, and elevated serum levels of cancer antigen 125 (CA 125) and lactate dehydrogenase (LDH) [7–11]. In addition, transvaginal sonography or computed tomography may disclose enlarged ovaries [12], pelvic mass, ascites, lymphadenopathy, omental cake and peritoneal implants [13].

In the Netherlands, the mean 5-year survival rate of women with epithelial ovarian cancer is 43%; however, up to 65% will eventually die from the disease [14]. Current standard management of ovarian cancer patients consists of surgical staging in early-stage disease [International Federation of Gynecology and Obstetrics (FIGO) IA–IIA]. In case of an advanced stage of ovarian cancer (FIGO IIB–IV), staging is followed by upfront debulking in a maximal effort to achieve an optimal cytoreduction. Without exception, these patients are subsequently treated with chemotherapy [15, 16]. However, in a subset of patients, this might not be the most effective approach since optimal cytoreduction may not be achieved in all patients by upfront surgical debulking [17–21].

Prior to surgery, identification of patients with an advanced stage of epithelial ovarian carcinoma with a low chance of optimal cytoreduction is highly desirable. It has been suggested that in patients with preoperative CA 125 levels >586 IU/l, residual tumor may be present postoperatively despite upfront debulking [8]. In addition, the parameters hemoglobin, blood platelets, albumin and LDH may help to identify patients who benefit most from primary surgical cytoreduction [9, 22–24].

This observational longitudinal study was designed to identify preoperative predictors of patients with ovarian cancer remaining with residual tumor despite maximal surgical effort. In addition, with the prediction model, a clinically simple tool for predicting the chance of residual tumor in each individual patient was to be designed.

Patients and Methods

Selection of Patients and Study Design

By power analysis, based on previous studies and an incidence in ovarian carcinoma of 1,138 new cases/year in the Netherlands, a minimum of 151 patients was required to enter the study [8, 25]. Subsequently, between January 1998 and December 2003, 187 consecutive patients with ovarian cancer initially treated by surgical staging and upfront surgical debulking were retrieved from the Ovarian Cancer Database. Eligibility criteria for inclusion in this study were clinical suspicion of advanced-stage ovarian cancer in patients undergoing surgical staging followed by an upfront surgical debulking procedure. The clinical staging of patients was based on clinical characteristics, radiodiagnostics (CT scans and/or ultrasound) and laboratory results. All identified patients underwent primary surgical staging and subsequent cytoreduction by qualified gynecologic oncologists in three affiliated specialized centers. Patients with a chance finding of ovarian carcinoma, previous neoadjuvant chemotherapy, benign ovarian disease and those with a coexistence or history of cancer were excluded from analysis. This study was approved by the Medical Ethical Committee and informed consent of the patients was obtained. In addition, this study was performed according to the standards outlined in the Declaration of Helsinki.

Preoperative Workup and Surgical Procedure

In this analysis, age was defined as age at the time of diagnosis. Clinical condition of the patients was scored by means of the PS. Patients underwent physical examination and transvaginal sonography. CT scans were electively made at the discretion of the attending physician. Blood samples for the determination of serum CA 125, blood platelet count, hemoglobin, albumin and LDH were taken prior to surgery. CA 125 levels were assessed by enzyme immunoassay (Roche E170) using a sandwich method with chemiluminescence (Roche Diagnostics, Almere, The Netherlands). The inter- and intra-assay coefficients of variation were 2.8 and 0.2%, respectively. Serum levels of LDH and albumin were assessed by a Hitachi 917 system (Roche, Mannheim, Germany). The blood platelet count and hemoglobin were assessed using a Sysmex XE 2100 system (Sysmex, Kobe, Japan).

Surgical staging and upfront debulking was performed by an abdominal midline incision with sampling of any ascitic fluid, total hysterectomy, bilateral salpingo-oophorectomy and omentectomy. When indicated, tumor bulk was resected in addition to biopsy samples of suspicious areas. Blind samples of the paracolic and parahepatic peritoneum were taken. Bowel and lymph node dissections were performed if required to achieve an optimal cytoreduction, defined as residual tumor <1 cm [26].

Staging and Tumor Assessments

The stage of the disease was described as defined by FIGO [27]. Tumors were histologically classified as serous, serous papillary, mucinous, endometrioid, clear cell, undifferentiated tumor and miscellaneous (leiomyosarcoma, mixed Müllerian sarcoma, Brenner tumor and granulosa tumor), respectively. Differentiation was classified as well (grade 1), moderately (grade 2), and poorly differentiated (grade 3) [28]. Data regarding size and location of postoperative residual tumors, FIGO staging and histological grading were collected.

Statistical Analysis

The characteristics of the patients according to group are presented as means ± SD. The unpaired Student t test was utilized for comparison of blood platelet count, serum hemoglobin, LDH, albumin and logarithmic-transformed CA 125 levels between the group with an optimal and suboptimal surgical debulking procedure, respectively. The χ^2 test was performed for comparison of the presence of preoperative ascites between the previously mentioned groups. These results were exploited for the detection of initial predictive parameters between the group of patients with an optimal and that with a suboptimal surgical cytoreduction, respectively. Subsequently, univariate and multivariate analyses by logistic regression with regard to the presence of residual tumor after the surgical intervention were performed. Backward stepwise elimination was utilized for the multivariate logistic analysis to predict patients remaining with residual tumor of >1 cm with $p < 0.05$ as cutoff level for elimination of non-significant predictors from the prognostic model. The area under the receiver-operating characteristic (ROC) curve (AUC) was exploited to assess the discriminative ability of the logistic models. The AUC generates the proportion of pairs (each pair consisting of 1 patient without and the other patient with the presence of residual tumor after surgery) in which the model predicts a higher probability of postoperative residual tumor of >1 cm. A nomogram was generated by combining the calculated predictive parameters in the entire population with the model predicting the postoperative result. In addition, the χ^2 test was utilized for comparison of the secondary outcome parameters, i.e. FIGO stage, histological classification and grading, respectively. $p < 0.05$ was considered to represent a statistically significant difference. The software package SPSS (SPSS, Chicago, Ill., USA) was employed for data analysis.

As a result of the selection and estimation of eight potential predictors on a dataset with 85 events (patients with a suboptimal debulking procedure), correction for overfitting was performed [29]. The internal validity of the prognostic model was tested by a bootstrapping method in which the selection and estimation process was repeated 200 times. Each of these repetitions consisted of creating a new dataset (bootstrap sample) by drawing cases with replacement from the original data. The backward stepwise elimination process was performed on this dataset, yielding a set of selected predictors and parameter estimates [29, 30]. Resulting model estimates of each bootstrap sample were evaluated on the original data, and a shrinkage factor was estimated to correct for statistical overoptimism. The Hosmer-Lemeshow goodness-of-fit test was used to check for lack of fit of the final model [31].

Results

Recruitment and Demographic Characteristics of the Patients

Of the 187 patients enrolled in the study, 8 patients were not eligible for the study due to a history of breast cancer (n = 2), ovarian carcinoma as chance finding (n = 2), previous neoadjuvant chemotherapy (n = 2), or the diagnosis of a borderline tumor (n = 1) or colon carcinoma (n = 1; fig. 1). In total, 179 patients with the clinical suspicion of advanced ovarian cancer undergoing a primary surgical cytoreduction procedure were analyzed. The median age of the patients was 61 (range 36–85) years and did not differ between the group with optimal cytoreduction and the group with a residual tumor >1 cm. In 94 patients (53%), an optimal cytoreduction has been achieved. Among the 179 patients who were initially clinically staged as ovarian cancer at advanced stage, 36 patients were surgically staged as early-stage ovarian cancer (FIGO stage IA–IIA). Further details are listed in table 1.

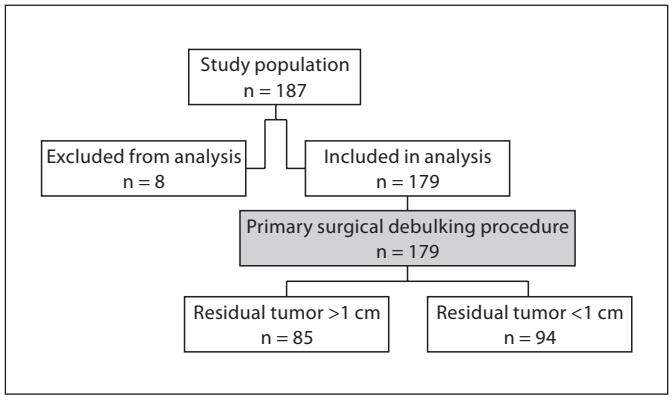

Fig. 1. Flow chart of the study population consisting of 187 patients with a suspected diagnosis of advanced-stage ovarian cancer (FIGO stage IIB–IV). Eight patients were excluded from the analysis. Optimal cytoreduction, defined as residual tumor <1 cm, was established in 53% of the patients.

Preoperative Parameters

The PS was comparable in both groups. However, the presence of ascites was increased in the suboptimally cytoreduced group (68 cases; 80%) compared to the optimally cytoreduced group (47 cases; 50%; $p < 0.0005$, table 1). The mean serum concentration of logarithmically transformed CA 125 was higher in the group of patients with postoperative residual tumor compared to the optimally cytoreduced group (2.88 ± 0.68 vs. 2.51 ± 0.71 kU/l; $p < 0.0001$, respectively). Serum albumin concentrations were lower in the suboptimally cytoreduced group in comparison to the optimally cytoreduced group (30.5 ± 8.1 vs. 36.6 ± 5.8 g/l; $p < 0.0001$, respectively; fig. 2). Serum hemoglobin was lower and blood platelets were higher in the group remaining with a residual tumor >1 cm compared to the group with residual tumor <1 cm (7.64 ± 0.99 vs. 7.95 ± 0.79 mmol/l, respectively,

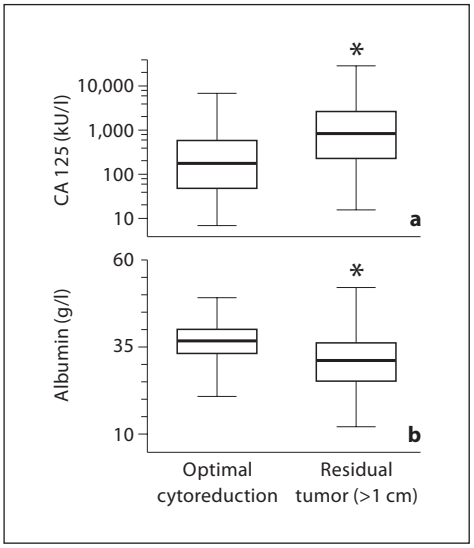

Fig. 2. Box and whisker plots of preoperative serum levels of CA 125 (**a**) and albumin (**b**), in 94 optimally cytoreduced patients and 85 patients with postoperative residual tumor >1 cm. Optimal surgical cytoreduction is defined as <1 cm residual tumor [26]. * $p < 0.0001$.

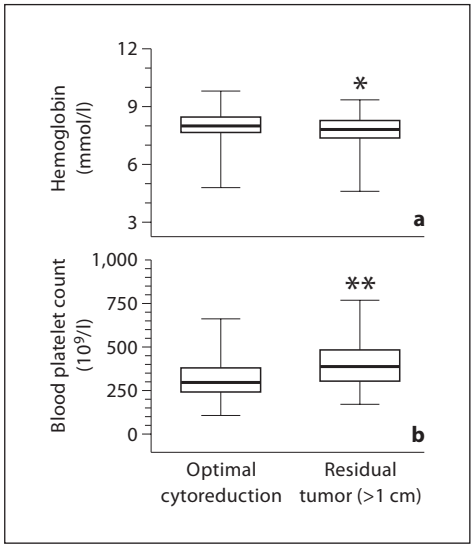

Fig. 3. Box and whisker plots of preoperative serum levels of hemoglobin (**a**) and blood platelets (**b**) in 94 optimally cytoreduced patients and 85 patients with postoperative residual tumor >1 cm. Optimal surgical cytoreduction is defined as <1 cm residual tumor [26]. * $p < 0.05$; ** $p < 0.01$.

Table 1. Characteristics of the study population consisting of patients with suspected advanced-stage ovarian cancer

Characteristics	Study group	Residual tumor ≥1 cm	Residual tumor <1 cm	p (χ^2 test)
Patients	179	85 (47%)	94 (53%)	
Age, years	62 ± 13	64 ± 12	61 ± 13	NS
Karnofsky PS, %	95 ± 7	94 ± 9	96 ± 5	NS
Ascites	115 (64%)	68 (80%)	47 (50%)	<0.0005
Serum parameters				
log CA 125, kU/l	2.70 ± 0.70	2.88 ± 0.68	2.51 ± 0.71	<0.0001
Albumin, g/l	33.5 ± 7.1	30.5 ± 8.1	36.6 ± 5.8	<0.0001
Hemoglobin, mmol/l	7.81 ± 0.89	7.64 ± 0.99	7.95 ± 0.79	<0.05
Blood platelets, $\times 10^9$/l	357 ± 123	396 ± 121	325 ± 126	<0.01

Means ± SD or absolute numbers. Significant differences were assessed between the group with residual tumor ≥1 cm and the group with residual tumor <1 cm.

and 396 ± 121 vs. 325 ± 126 × 10^9/l; $p < 0.05$ and <0.01, respectively; fig. 3). Serum LDH concentrations were comparable in both groups.

Multivariate Analysis

The variables ascites, log CA 125, albumin, hemoglobin and blood platelets were statistically significantly different between both groups. Multivariate logistic regression, utilizing a backward elimination procedure, resulted in the subsequent elimination of blood platelets, hemoglobin and ascites from the prediction model (table 2). As a consequence, the AUC of the ROC curve consisting of a combination of log CA 125 and albumin was 0.79 compared to the AUC of the ROC curve of 0.73 of each of both parameters individually (fig. 4). The shrinkage factor of 0.78 was estimated from the boot-

Table 2. Backward stepwise elimination procedure of potential prognostic parameters

Variable	Model log likelihood	Model in –2 log likelihood	d.f.	Significance of difference
Step 1				
Blood platelets	–79.51	0.03	1	0.86
Hemoglobin	–80.34	1.70	1	0.20
Ascites	–80.64	2.30	1	0.13
Albumin	–84.82	10.66	1	<0.01
log CA 125	–83.70	8.43	1	<0.01
Step 2				
Hemoglobin	–80.40	1.77	1	0.18
Ascites	–80.72	2.43	1	0.12
Albumin	–85.18	11.34	1	<0.01
log CA 125	–84.13	9.26	1	<0.01
Step 3				
Ascites	–81.66	2.54	1	0.11
Albumin	–87.07	13.34	1	<0.01
log CA 125	–85.33	9.87	1	<0.01
Step 4				
Albumin	–90.31	17.29	1	<0.01
log CA 125	–88.93	14.53	1	<0.01

Logistic regression with backward elimination procedure of the potential predictive parameters blood platelets, hemoglobin, ascites, albumin, and CA 125. With step 4 the predictive parameters albumin and CA 125 for the prediction model are generated.

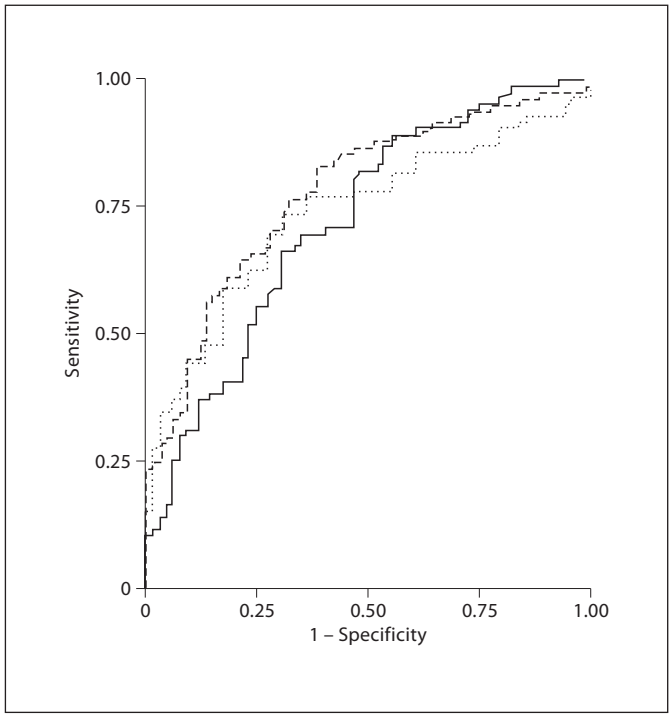

Fig. 4. ROC curves of preoperative CA 125 (——; AUC = 0.73) and albumin (·····; AUC = 0.73) serum levels. – – – = The ROC curve of the prediction model consisting of both preoperative CA 125 and albumin serum levels (AUC = 0.79).

strap procedure. This indicates that in case of replication of this analysis, the resulting coefficients of the final model are on average 22% smaller. The Hosmer-Lemeshow goodness of fit showed no lack of fit of the final model to the data ($p < 0.05$). The generated nomogram, consisting of CA 125 and albumin, for the probability of remaining with residual tumor >1 cm is depicted in figure 5.

FIGO Stage and Histology

In the group with residual tumor >1 cm, a higher FIGO stage was observed when compared to the optimally cytoreduced group ($\chi^2 = 56.7$, d.f. 6; $p < 0.0001$). The tumors of the patients in the suboptimally cytoreduced group appeared to be less differentiated in comparison to the optimally cytoreduced group ($\chi^2 = 7.4$, d.f. 2; $p < 0.05$). In addition, a different histogenetic classification of the tumor between both groups was observed ($\chi^2 = 18.6$, d.f. 6; $p < 0.005$). Table 3 provides secondary outcome parameters.

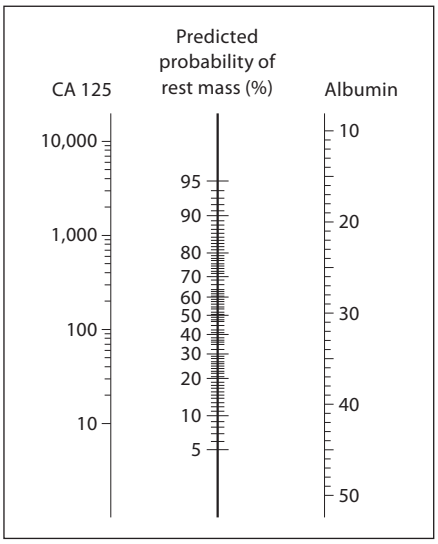

Fig. 5. Nomogram for the prediction of postoperative residual tumor, defined as >1 cm [26]. The left axis represents the preoperative CA 125 serum level, the right axis represents the preoperative albumin serum level. A straight line drawn between the preoperative CA 125 and the serum albumin level indicates the probability of postoperative residual tumor for an individual patient with ovarian cancer.

Table 3. Secondary outcome parameters (absolute numbers) of the study population consisting of patients with suspected advanced-stage ovarian cancer

Parameters	Study group	Residual tumor ≥1 cm	Residual tumor <1 cm	Significance
FIGO stage				56.7, d.f. 6 $p < 0.0001$
IA–IIA	36	0	36	
IIB	2	0	2	
IIC	3	1	2	
IIIA	7	1	6	
IIIB	7	3	5	
IIIC	93	55	37	
IV	31	25	6	
Total	179	85	94	
Histologic grade				6.9, d.f. 2 $p < 0.05$
I	15	3	12	
II	46	19	27	
III	114	61	53	
Total	175[a]	83[b]	92[c]	
Histologic classification				18.6, d.f. 5 $p < 0.01$
Serous	112	62	50	
Mucinous	15	6	9	
Clear cell	14	2	12	
Endometrioid	10	0	10	
Undifferentiated	22	12	10	
Miscellaneous	6	3	3	
Total	179	85	94	

Significant differences between the group with residual tumor ≥1 cm and the group with residual tumor <1 cm were assessed by χ^2 tests with d.f. representing the degrees of freedom.

[a] In 4 patients histologic grading was not performed.

[b] Two patients with a granulosa tumor.

[c] One patient with a mixed Müllerian tumor and 1 patient with a leiomyosarcoma.

Discussion

The median age of 61 years at the time of diagnosis in the study population was consistent with previous studies reporting a median age ranging from 56 to 61 years; the distribution of histological characteristics and FIGO stage of ovarian carcinoma was also in agreement with previous studies [8, 10, 32–35]. Based on preoperative criteria, all 179 patients were clinically suspected for an advanced stage of ovarian cancer (FIGO stage IIB–IV). Postsurgical data differed in 36 patients who were surgically staged as early-stage ovarian cancer (FIGO stage IA–IIA).

In addition to the considerable number of patients who were in early and not advanced stage of the disease, a small number of patients had non-epithelial ovarian cancer according to postsurgical data. The concept of optimal debulking in epithelial ovarian cancer is solely validated in the advanced stage. Histological data and surgical staging of ovarian cancer according to FIGO criteria [27] were only assessed postoperatively. Including these (postsurgical) parameters aiming at establishing a preoperative prediction model for optimal debulking in ovarian cancer may be considered as a contradictio in terminis. Consequently, FIGO stage and histology, although important in the prognosis of ovarian cancer, were not considered as parameters in this analysis. A more accurate estimation of clinical staging, including histology, may be obtained by a preceding diagnostic laparoscopy [36]. However, these data were not available for the population studied.

PS and age in the group of patients with postoperative residual tumor and the group of optimally cytoreduced patients were comparable. After primary surgery, 53% of our study patients, including those in the early stages of disease, were considered to be optimally cytoreduced (<1 cm residual tumor). Although consistent with other studies [8, 32–35], the optimal debulking rate achieved in this study may be low compared to other centers [37]. Surgical techniques utilized in the study population are considered as standard of care. However, ultra-aggressive cytoreduction including splenectomy and low anterior en bloc resection was subject to unfamiliarity [38, 39]. This may at least partly explain the lower optimal cytoreduction rate observed. Alternatively, feasibility and supplementary benefit of these aggressive techniques are unclear, and data of prospective randomized trials addressing these issues are lacking.

In the group of optimally surgically cytoreduced patients, serum levels of CA 125 were lower compared to the suboptimally cytoreduced group. Indeed, previous studies demonstrated serum CA 125 levels may predict the cytoreducibility of ovarian cancer in patients with an advanced stage of the disease [8, 32, 33, 35, 40]. They appeared to be elevated in case of tumor implants in the peritoneum [41]. However, sensitivity and specificity of serum CA 125 levels in the diagnosis of ovarian malignancies may be limited. In addition, the relationship between tumor load and serum levels of CA 125 is inconclusive [42–44].

Serum albumin levels were significantly lower in the group of patients with postoperative residual tumor in comparison to optimally surgically cytoreduced patients.

Albumin might be predictive for survival in patients with an advanced stage of ovarian carcinoma [23, 45]. In addition, a preoperative serum albumin level <35 g/l may indicate a poor prognosis in terms of survival [23]. Consequently, serum levels of albumin may be a predictor for cytoreducibility of ovarian cancer. A possible explanation for this feature is that in case of disseminated disease, intra-abdominal tumor cells may preclude the resorption of peritoneal fluid, resulting in hypoalbuminemia [46]. In this study, the preoperative presence of ascites may indicate the cytoreducibility of patients with ovarian cancer in case the backward stepwise elimination in the multivariate logistic analysis was lacking serum albumin. Indeed, the presence of ascites is in turn related to serum albumin levels [23]. Previous studies demonstrated that the presence of ascites is related to the survival of patients with an advanced stage of ovarian cancer [10, 23].

This study showed decreased preoperative hemoglobin levels in the group of patients with postoperative residual tumor in comparison to the optimally cytoreduced group. In addition, blood platelet count was elevated in the group with residual tumor. Although various studies demonstrated that low hemoglobin serum levels are related to poor survival in patients with ovarian cancer, a causal relationship remains to be established [11, 22, 47]. However, a relatively low serum level of hemoglobin may contribute to induction of angiogenesis and proliferation of tumor cells, reflecting an advanced stage of disease [48]. In addition, thrombocytosis might be an independent prognostic factor for the progression of disease and outcome of second-look laparotomy [9]. Serum LDH levels were comparable in the patients with suboptimal and optimal cytoreduction. Although LDH may have a predictive value for the prognosis of ovarian carcinoma, the relationship between LDH and the result of the surgical intervention was absent in this study [10, 49].

In accordance with previous studies, a multivariate analysis was employed to identify parameters predicting cytoreducibility of ovarian carcinoma [8, 10, 47]. Of all potential parameters, solely the preoperative serum levels of CA 125 and albumin were able to predict the chance of an optimal surgical cytoreduction (when analyzed by multivariate logistic regression with backward elimination procedure). The AUC of the ROC curve for these parameters combined was approximately 80%. These two parameters were the independently predictive factors in the analysis, and the eliminated parameters may be mutually related. As suggested before, serum albumin and the presence of ascites are related in ovarian cancer. However, albumin is the stronger predictor when analyzed in these terms.

In addition to the multivariate analysis, a nomogram based on these two parameters was generated according to a previously published method [50]. With the nomogram, the risk of postoperative residual tumor can be estimated for each individual patient. When optimal cytoreduction may be at stake, alternative treatments may be considered [51]. These data should be interpreted with caution. Although the proposed nomogram was internally validated, an external validation remains mandatory to apply the nomogram routinely in a wider context. In addition, bias related to inclusion and exclusion criteria could not be ruled out. A total of 3 patients, receiving a regimen of neoadjuvant chemotherapy, were not included in the trial. The nomogram is designed to select particularly patients eligible for an alternative approach. However, the ongoing EORTC 55971 trial, comparing neoadjuvant chemotherapy to upfront surgical cytoreduction in patients with an advanced stage of ovarian carcinoma, may establish the viability of such an alternative approach [52].

Upfront debulking in advanced epithelial ovarian cancer remains the standard of care until non-inferiority trials demonstrate that a regimen of neoadjuvant chemotherapy may lead to similar results in terms of survival. Survival rates in patients with postoperative residual tumor <1 cm are higher compared to those with >1 cm residual tumor [26, 28]. However, radical surgery is associated with higher morbidity rates that may subsequently result in lower survival rates [53]. Hence, a regimen of neoadjuvant chemotherapy might be considered in ASA 1 and 2 patients with an approximately 80% predicted chance of residual tumor while neoadjuvant chemotherapy may be an acceptable alternative in ASA 3 and 4 patients with a much lower chance of residual tumor [54].

In conclusion, differences in preoperative serum levels of CA 125, albumin, hemoglobin and blood platelets were established between patients with postoperative residual tumor and those with an optimal surgical cytoreduction, as was the presence of ascites. In addition, serum CA 125 levels combined with serum albumin were strong preoperative predictors for tumor resectability in patients with ovarian cancer. In each individual patient with a suspected diagnosis of advanced-stage ovarian cancer, the proposed nomogram could be applied to inform the patient and to select the most effective treatment modality.

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