Nomogram for Suboptimal Cytoreduction at Primary Surgery for Advanced Stage Ovarian Cancer

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Abstract. *Aim: Maximal cytoreduction to minimal residual tumor is the most important determinant of prognosis in patients with advanced stage epithelial ovarian cancer (EOC). Preoperative prediction of suboptimal cytoreduction, defined as residual tumor >1 cm, could guide treatment decisions and improve counseling. The objective of this study was to identify predictive computed tomographic (CT) scan and clinical parameters for suboptimal cytoreduction at primary cytoreductive surgery for advanced stage EOC and to generate a nomogram with the identified parameters, which would be easy to use in daily clinical practice. Materials and Methods: Between October 2005 and December 2008, all patients with primary surgery for suspected advanced stage EOC at six participating teaching hospitals in the South Western part of the Netherlands entered the study protocol. To investigate independent predictors of suboptimal cytoreduction, a Cox proportional hazard model with backward stepwise elimination was utilized. Results: One hundred and fifteen patients with FIGO stage III/IV EOC entered the study protocol. Optimal cytoreduction was achieved in 52 (45%) patients. A suboptimal cytoreduction was predicted by preoperative blood platelet count (p=0.1990; odds ratio (OR)=1.002), diffuse peritoneal thickening (DPT) (p=0.0074; OR=3.021), and presence of ascites on at least two thirds of CT scan slices (p=0.0385; OR=2.294) with a for-optimism corrected c-statistic of 0.67. Conclusion: Suboptimal cytoreduction was predicted by preoperative platelet count, DPT and presence of ascites. The generated nomogram can, after external validation, be used to estimate surgical outcome and to identify those patients, who might benefit from alternative treatment approaches.*

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Worldwide, each year approximately 200,000 women are diagnosed with ovarian cancer. Ovarian cancer accounts for 5% of cancer-related death in women (1). Cytoreductive surgery and paclitaxel platinum chemotherapy are the cornerstone of treatment for advanced stage epithelial ovarian cancer (EOC). Maximal cytoreduction to no macroscopic residual tumor is the most important determinant of prognosis (2-4). Patients with residual disease >1 cm after cytoreductive surgery are generally believed to have limited survival benefit from this extensive procedure and are probably candidates for an alternative treatment approach with neoadjuvant chemotherapy followed by interval cytoreduction (3-9).

Optimal cytoreduction rates range from 40-90%, with a higher rate of optimal cytoreduction in patients treated by gynecologic oncologists and when surgery is performed in high-volume institutions (2, 10). It is suggested that outcome could be improved by referral of all patients with suspected EOC to high-volume centers.

Ovarian cancer has an insidious onset and heterogeneous presentation, and the vast majority of patients will present in a regional, low volume hospital. In order to prevent undertreatment of a substantial number of patients, an accurate preoperative assessment on resectability and operative risk is therefore essential to guarantee proper decision making and management of these patients (9, 11-12).

Several studies identified CT scan parameters predictive for suboptimal cytoreduction at primary cytoreduction for advanced stage EOC(13-17). Accuracy of prediction using such parameters ranges between 71 and 93% (14-16). Each study identifies a different set of CT scan predictors in relatively small single- center data sets with retrospective study designs, resulting in a disappointing predictive performance if applied to other patient cohorts (15, 18). In order to determine the actual value of CT scan and clinical predictors, we decided to perform a prospective multi-institutional study on prediction of suboptimal cytoreduction at primary cytoreductive surgery for advanced stage EOC. With this study, we aimed to identify CT scan and clinical predictors and to generate a nomogram for suboptimal cytoreduction which would be easy to use in daily clinical practice.

Materials and Methods

Selection of patients and study design. Between October 2005 and December 2008, all patients with primary surgery for suspected advanced stage EOC at six participating teaching hospitals in the South Western part of the Netherlands entered the study protocol. All patients had a Risk of Malignancy Index (RMI) >200, based on CA125 level, ultrasound examinations and menopausal status(19). Only patients with a histological diagnosis of FIGO stage III/IV EOC who underwent primary cytoreductive surgery were eligible for this study.

During the study period, neoadjuvant chemotherapy was not the standard of care and was only reserved for patients unable to withstand extensive surgical procedures due to a poor physical condition or with extensive extraabdominal disease.

Preoperative assessments. Demographic data, laboratory results, surgical findings and results were registered in our prospectively maintained ovarian cancer database.

Standard preoperative work-up of the patients consisted of patient history, physical examination, transvaginal sonography (TVS) and abdominopelvic CT scan. CT scans were carried out within 4 weeks prior to surgery. A standard CT scanning protocol was used. With oral and intravenous contrast, images with a 5 mm collimation area through the abdomen and pelvis were obtained. Two study radiologists systematically reviewed all CT scans. The radiologists were blinded to the surgical findings and outcome. Discrepancies between the two radiologists were discussed until consensus was reached.

To accurately estimate logistic regression coefficients without overestimation and improve predictive performance of our prediction model, we selected a set of earlier reported predictors for suboptimal cytoreduction (20).

From previously published CT scan studies on prediction of suboptimal cytoreduction at primary cytoreduction for advanced stage EOC, four CT scan parameters with the best predictive performance were chosen: diffuse peritoneal thickening (DPT), large bowel mesentery implants (LBMI), ascites on two thirds of CT scan slices and diaphragmatic disease (13-17).

DPT was defined as peritoneal thickening to ≥4 mm involving at least two out of the five following areas: lateral colic gutters, lateral conal fascia, anterior abdominal wall, diaphragm, and pelvic peritoneal reflections, as described by Dowdy *et al*. (16).

Blood samples for measurement of CA125, blood platelet count, and albumin serum concentrations were drawn within four weeks prior to surgery. CA125 was assessed by enzyme immunoassay (Roche E170) using a sandwich method with chemoluminescence (Roche Diagnostics BV, Almere, the Netherlands). The blood platelet count and albumin were assessed by a Sysmex XE 2100 system (Sysmex Corporation, Kobe, Japan). Performance status was defined according to WHO criteria (21).

Treatment regimen. Primary cytoreductive surgery was performed by a gynecologic oncologist using an abdominal midline incision and included total hysterectomy, bilateral salpingo-oophorectomy, omentectomy and resection of all visible and palpable bulky tumor. The aim of this procedure was to resect all macroscopic tumor or at least to lesions ≤1 cm. Bowel resection, splenectomy, diaphragmatic stripping, partial liver resection and lymphadenectomy were performed if warranted to achieve an optimal cytoreduction, defined as residual disease ≤1 cm.

Histopathological assessment. Histology was classified as serous, mucinous, endometrioid, clear cell, and undifferentiated adenocarcinoma. Differentiation was classified as grade 1 to 3, according to the Silverberg criteria (22). Subsequently, stage of the disease was determined according to FIGO guidelines (23).

Study parameters and outcome measures. Parameters for analysis were the earlier described CT scan parameters, WHO performance status, CA125, albumin concentration and blood platelet count .

Primary outcome measure was suboptimal cytoreduction, defined as residual tumor >1 cm.

Data analysis. Data analysis, utilizing the software package SPSS 14.0 (SPSS, Chicago, IL, USA), was performed on all patients fulfilling in- and exclusion criteria of the study. The Student-t-test was utilized to compare preoperative serum concentrations of CA125, blood platelet, and albumin between the group of patients with suboptimal cytoreduction and those patients with optimal cytoreduction. Chi- square tests were used to compare the preoperative WHO performance status, FIGO stage, presence on CT scan of DPT, LBMI, ascites and diaphragmatic disease between the groups of patients with residual disease >1 cm to the group of patients with residual disease ≤1 cm. $P<0.05$ was considered as statistically significant. We accounted for missing values by multiple imputation (24).

Based on the univariate analysis, initial predictive parameters for suboptimal cytoreduction with $p<0.30$ were selected to be assessed by multivariate Cox regression analysis with backward stepwise elimination (20). The selected parameters were entered into a prognostic model. The discriminative ability of the prognostic model, or the ability to distinguish patients with suboptimal cytoreduction from those with optimal cytoreduction was expressed by means of the c-statistic (25). The internal validity of the 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 (25-26). The resulting model estimates of each bootstrap sample were evaluated

on the original data, and a shrinkage factor was estimated to correct for statistical over optimism. In addition, a correction for optimism in the c-statistic was derived from the bootstrap method. A nomogram was then generated with the identified predictive parameters.

Results

Recruitment and demographic characteristics of the patients. Between October 2005 and December 2008, 140 patients who underwent primary cytoreductive surgery for suspected advanced stage EOC were included. Eighteen patients were excluded because the final histology was different from EOC. (benign ovarian neoplasm (N=6), borderline ovarian tumor (N=7), other primary tumor (N=5)). Subsequently, seven patients with early-stage disease were also excluded. Finally, 115 patients with advanced stage EOC were eligible.

The median age patient was 62.4 years (range 15.9-83.6 years), with 37 patients (32%) aged ≥70 years at time of surgery. Twenty-seven patients (23.5%) underwent cytoreduction to no macroscopic residual disease; cytoreduction to residual disease <1 cm was achieved in another 25 patients (21.7%).

Five patients were diagnosed with FIGO stage IIIA, 10 with FIGO stage IIIB, 79 with FIGO stage IIIC (extensive peritoneal disease) and 21 with stage IV disease. Further patient characteristics are given in Table I.

Initial predictive parameters for suboptimal cytoreduction. Median preoperative platelet count differed markedly between patients with residual disease ≤1 cm and those with residual disease >1 cm: 341±144.5 *versus* 419.0±177.7 $\times 10^9$/l (p=0.033), respectively. WHO performance status, preoperative serum CA125 level and albumin were comparable in both groups (Table I).

The CT scan parameters DPT, diaphragmatic disease and ascites were different between patients with suboptimal and those with optimal cytoreduction, respectively: 42 (66.7%) *versus* 19 (36.5%) (p=0.001), 23 (36.5%) *versus* 9 (17.3%) (p=0.022) and 36 (57%) *versus* 15 (28.8%) (p=0.002) (Table II).

Multivariate analysis of predictors for suboptimal cytoreduction. The results of the univariate analyses are given in Table III. The variables with p<0.30 in the univariate analysis were assessed by multivariate Cox regression, utilizing a backward elimination procedure. A suboptimal cytoreduction was predicted by preoperative blood platelet count (p=0.1990, odds ratio=1.002), DPT (p=0.0074, OR=3.021) and presence of ascites (p=0.0385, OR=2.494) with a c-statistic of 0.74. In other words, our model accurately discriminated patients with from those without suboptimal cytoreduction 74% of the time. Because our model was developed and evaluated on the same data, the performance of the model is too optimistic. To correct for the optimism in discriminative ability, the steps taken in Cox regression were internally validated by 200 random bootstrap samples. The for-optimism corrected c-statistic was 0.67. A shrinkage factor of 0.69 was estimated from the bootstrap procedure. This indicates that in case of replication of this analysis, the resulting coefficients of the final model are on average 0.69 smaller. The generated nomogram, consisting of blood platelet count, DPT and ascites, for the probability of suboptimal cytoreduction is depicted in Figure 1.

Table I. *Patient characteristics of the study population.*

	Study population	Residual disease	
		≤1 cm	>1 cm
Number of patients, n (%)	115	52 (45.2)	63 (54.8)
Age (years), n (%)			
<50	15 (13.0)	6 (11.5)	9 (14.3)
50-59	31 (27.0)	18 (34.6)	14 (22.2)
60-69	32 (27.8)	17 (32.7)	15 (23.8)
>70	37 (32.2)	11 (21.2)	26 (41.3)
WHO performance, n (%)			
0-1	106 (92.2)	51 (98.0)	55 (87.3)
2	5 (4.3)	0 (0)	5 (7.9)
>2	4 (3.5)	1 (2.0)	3 (4.8)
FIGO stage, n (%)			
III	94 (81.7)	46 (88.4)	48 (76.2)
IV	21 (18.3)	6 (11.5)	15 (23.8)
Histologic grade, n (%)			
1	25 (21.7)	10 (19.2)	15 (23.8)
2	29 (25.0)	13 (25.0)	16 (25.4)
3	61 (53.0)	29 (55.8)	32 (50.8)
Histologic classification, n (%)			
Serous	83 (72.2)	38 (73.1)	45 (71.4)
Other	32 (27.8)	14 (26.9)	18 (28.6)
Operative procedure, n (%)			
TH-BSO	91 (79.1)	52 (100)	39 (61.9)
Omentectomy	93 (80.9)	50 (96.1)	36 (57.1)
Pelvic lymphadenectomy	3 (2.6)	2 (3.8)	1 (1.6)
Para-aortic lymphadenectomy	3 (2.6)	3 (5.8)	0
Pelvic peritoneum stripping	6 (5.2)	4 (3.5)	0
Small bowel resection	5(4.3)	4 (3.5)	1 (1.5)
Large bowel resection	10 (8.7)	4 (3.5)	6 (9.5)

TH-BSO, Total hysterectomy and bilateral-salpingo-oophorectomy.

Discussion

In the current study, we identified predictors for suboptimal cytoreduction at primary cytoreductive surgery for advanced stage EOC. Preoperative platelet count, DPT and the presence of ascites on two thirds of the CT scan slices were predictive

Table II. *Predictive parameters for suboptimal cytoreduction in patients with advanced-stage epithelial ovarian cancer. Differences, if any, between the group of patients with residual disease ≤1 cm and those with residual disease >1 cm were tested with Student t- and Chisquare tests. Data is presented as median with standard deviation or in absolute numbers, when applicable.*

	Residual disease		Significance *P*-value
	≤1 cm	>1 cm	
Number of patients	52	63	
WHO performance, n (%)			
0	26 (50.0)	25 (39.7)	0.140
1	25 (48.1)	30 (47.6)	
≥2	1 (1.9)	8 (12.7)	
Platelet count ($\times 10^9$/l)	341.0±144.5	419.0±177.7	0.033
Log Ca125 (kU/l)	2.53±3.32	2.80±4.20	0.375
Albumin (g/l)	32±17.0	29.0±15.9	0.453
CT scan parameters, n (%)			
DPT	19 (36.5)	42 (66.7)	0.001
LBMI	14 (26.9)	27 (42.9)	0.076
Ascites on two thirds of CT scan slices	15 (28.8)	36 (57.1)	0.002
Diaphragmatic disease	9 (17.3)	23 (36.5)	0.022

DPT, Diffuse peritoneal thickening; LBMI, large bowel mesentery implants.

of residual disease >1 cm. With these parameters, we generated a nomogram to predict suboptimal cytoreduction in the individual patient.

Multiple retrospective studies have shown the prognostic importance of maximal attempt to achieve cytoreduction to minimal tumor residue (2-3).

Recent data support an alternative management with neoadjuvant chemotherapy followed by interval cytoreductive surgery for patients with extensive disease or diminished performance status and who are at increased operative risk (4). Preoperative selection of those patients in whom complete resection can be achieved could guide treatment decisions.

Many investigators attempted to identify accurate predictors of irresectable disease.

Predictive models based on radiographic characteristics show accuracy rates ranging from 71 to 93% (14-16, 27-30). However, accuracy drops when these models are extrapolated to other patient populations (15, 18).

Our nomogram accurately predicted surgical outcome in 74% of the patients. This confirms the limited accuracy of currently available predictors. Nevertheless, we do believe predictive models could be of value in the management of this heterogeneous patient population. In contrast to a subjective offhand assessment of suboptimal cytoreduction and operative risk, prediction models are reproducible and could support multidisciplinary discussions on optimal treatment for the individual patient. Future research should be directed at identifying more accurate predictors of surgical outcome (31).

Our study is, to our knowledge, the second large prospective study on CT scan predictors of suboptimal cytoreduction ever conducted. Nevertheless, 115 patients is still a small data set; for this reason, we considered a limited selection of earlier described predictors found in other studies (13-17). With this design we were able to generate a model with identical predictors as these described by Dowdy *et al*. (16). In a recent multicenter validation study on CT predictors of suboptimal cytoreduction, the predictive model of Dowdy *et al*. based on DPT and ascites showed the best predictive performance. Although external validation of our model has to be performed to determine the applicability of our nomogram to other patient populations, these data support the predictive importance of these CT predictors for

Table III. *Univariate analysis of predictors of suboptimal cytoreduction. interval.*

Variable	Significance (*P*-value)	OR (95% CI)
WHO performance status	0.1513	1.248 (0.582-2.68)
Platelet count	0.0107	1.004 (1.001-1.010)
Log CA 125	0.1357	1.206 (0.943-1.540)
Albumin level	0.0709	0.952 (0.902-1.000)
CT scan parameters		
DPT	0.0015	3.474 (1.608-7.500)
LBMI	0.0779	2.036 (0.924-4.490)
Ascites	0.0028	3.289 (1.507-7.180)
Diaphragmatic disease	0.3197	2.042 (0.500-8.330)

CT, Computed tomographic scan; DPT, diffuse peritoneal thickening; LBMI, large bowel mesentery implants; OR, odds ratio; NS, not significant; CI, confidence.

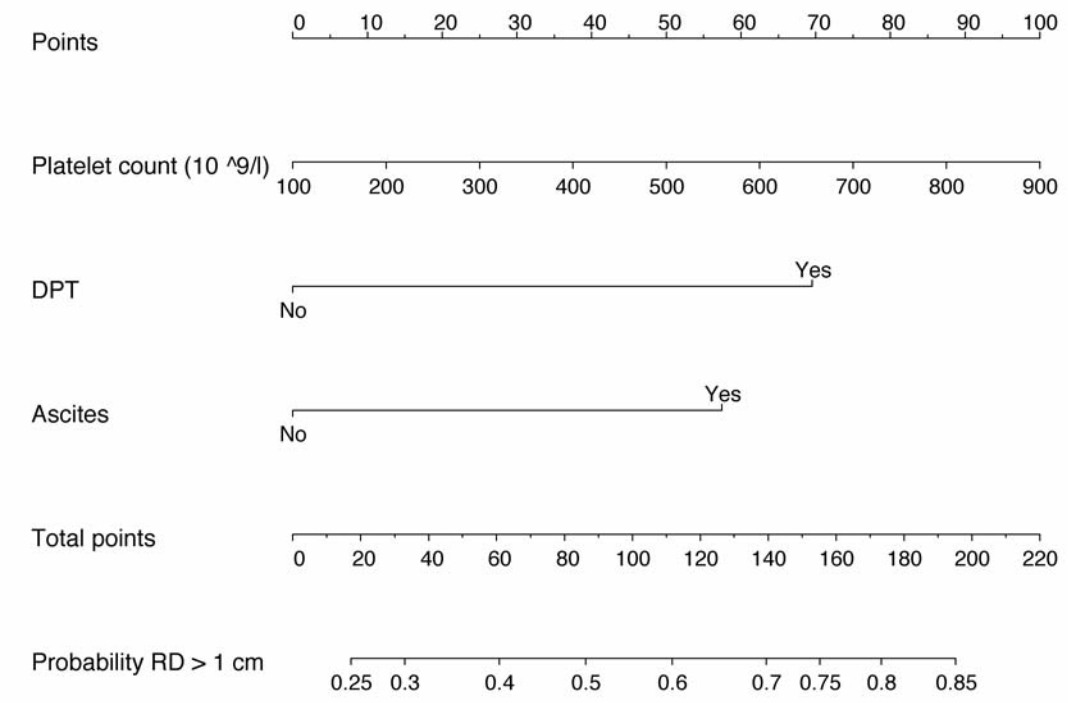

Figure 1. *Nomogram for prediction of suboptimal cytoreduction. For each predictive factor there are a number of corresponding points allocated form the point scale at the top. By adding the points for each parameter, the total points can be calculated. This number represents the probability of suboptimal cytoreduction. For example for a patient with a preoperative platelet count of 300 [25 points], DPT [70 points] and ascites on two thirds of the CT scan slices (34), the total score is 152 points (25+70+57) representing a 74% chance of suboptimal cytoreduction. RD, Residual disease; DPT, diffuse peritoneal thickening.*

patients with an advanced-stage EOC. In contrast to earlier described predictive models, we aimed to generate a simple model which is easy to use in daily clinical practice (32). The annotation in a nomogram facilitates convenient clinical utilization.

Nevertheless, our current study has several limitations that must be recognized and considered in interpreting these data. Firstly, the optimal cytoreduction rate at 45%, although within the range of other reports, is relatively low, this could reflect a less aggressive philosophy. Unfortunately, our study population was too small to determine the impact of individual surgeon's skills and philosophy on surgical outcome. The impact of surgeon capacity and philosophy could possibly be embedded in future prediction models by calculating a personal optimal cytoreduction rate. Including optimal cytoreduction rate in future prediction models could also correct for differences between institutions.

Secondly, we developed a predictive model for patients with suspected advanced-stage EOC. Other studies restrict their analyses to patients with bulky disease, defined as FIGO stage IIIC (with extensive peritoneal disease) and IV disease, reflecting a clear need for a revised subclassification of advanced-stage disease (33).

Finally, our nomogram was internally validated by bootstrapping. However, before applying the nomogram in daily clinical practise, the nomogram needs to be externally validated.

In conclusion, we developed and internally validated a nomogram predicting suboptimal cytoreduction at primary cytoreductive surgery for advanced-stage EOC. Preoperative platelet count, DPT and the presence of ascites on two thirds of the CT scan slices were predictive of residual disease >1 cm.

The generated nomogram can, after external validation, be used to estimate surgical outcome for each individual patient and be valuable for counseling and electing tailored treatment strategies.

Conflict of Interest Statement

The Authors declare that there are no conflicts of interest.

Ethics Approval

The study was approved by the Medical Ethical Committee of the Erasmus University Medical Center (May 2005, MEC-2005-135) and was performed according to the standards outlined in the Declaration of Helsinki.

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