EJGO European Journal of Gynaecological Oncology

Nomogram for 30-day morbidity after primary cytoreductive surgery for advanced stage ovarian cancer

G.M. Nieuwenhuyzen- de Boer[1], C.G. Gerestein[1,2], M.J.C. Eijkemans[3], C.W. Burger[1], G.S. Kooi[4]

[1] Department of Obstetrics and Gynecology, Division of Gynecologic Oncology, Daniel Den Hoed/Erasmus MC University Medical Center, Rotterdam
[2] Department of Obstetrics and Gynecology, Meander Medisch Centrum, Amersfoort
[3] Julius Centre for Health Sciences and Primary care, University Medical Centra Utrecht, Utrecht
[4] Department of Obstetrics and Gynecology, Albert Schweitzer Hospital, Dordrecht (The Netherlands)

Summary

Purpose of investigation: Extensive surgical procedures to achieve maximal cytoreduction in patients with advanced stage epithelial ovarian cancer (EOC) are inevitably associated with postoperative morbidity and mortality. This study aimed to identify preoperative predictors of 30-day morbidity after primary cytoreductive surgery for advanced stage EOC and to develop a nomogram for individual risk assessment. *Materials and Methods:* Patients in The Netherlands who underwent primary cytoreductive surgery for advanced stage EOC between January 2004 and December 2007. All peri- and postoperative complications within 30 days after surgery were registered and classified. To investigate predictors of 30-day morbidity, a Cox proportional hazard model with backward stepwise elimination was utilized. The identified predictors were entered into a nomogram. The main outcome was to identify parameters that predict operative risk. *Results:* 293 patients entered the study protocol. Optimal cytoreduction was achieved in 136 (46%) patients. Thirty-day morbidity was seen in 99 (34%) patients. Morbidity could be predicted by age ($p = 0.033$; OR 1.024), preoperative hemoglobin ($p = 0.194$; OR 0.843), and WHO performance status ($p = 0.015$; OR 1.821) with a optimism-corrected c-statistic of 0.62. Determinants co-morbidity status, serum CA125 level, platelet count, and presence of ascites were comparable in both groups. *Conclusions:* Thirty-day morbidity after primary cytoreductive surgery for advanced stage EOC could be predicted by age, hemoglobin, and WHO performance status. The generated nomogram could be valuable for predicting operative risk in the individual patient.

Key words: Ovarian cancer; Cytoreductive surgery; 30-day morbidity; Prediction model; Operative risk.

Introduction

Treatment of patients with advanced stage epithelial ovarian cancer (EOC) is based on cytoreductive surgery and adjunctive paclitaxel/platinum-based chemotherapy. Literature shows that the prognosis for survival is most dependent on completeness of surgery. However, more extensive surgery to achieve maximal cytoreduction will be related to an increase in peri- and postoperative complications [1-4]. Postoperative morbidity after primary cytoreductive surgery for advanced stage ovarian cancer is reported inconsistently, without standard definition of postoperative morbidity. Unadjusted morbidity rates range from 11 to 67% [1-9]. Postoperative mortality (POM) rates vary between 0 and 6.7%, with a mean POM rate of 2.8% [10].

In addition to the extent of surgery, age, performance status, and co-morbidity are of importance in the prediction of postoperative complications after primary cytoreduction for advanced stage EOC [1, 11]. Risk-adjustment models can provide a more individual and accurate prediction of operative risk and corroborate the decision to withhold patients from extensive surgical procedures. Prediction models for operative risk can especially improve management in the enlarging subgroup of elderly patients by determining individual risk profiles. Unfortunately, available risk-adjustment models for patients with EOC are based on peri- and postoperative parameters.

The objective of this study was to identify preoperative predictors and develop a nomogram for individual risk assessment of 30-day morbidity after primary cytoreductive surgery for advanced stage EOC. The primary outcome measure was 30-day morbidity.

Materials and Methods

Between January 2004 to December 2007 patients with advanced stage EOC defined as International Federation of Gynecology and Obstetrics (FIGO) Stages III and IV, who underwent primary cytoreductive surgery, were eligible for this study. They were retrieved retrospectively from the Rotterdam Cancer Registry database in the South Western part of The Netherlands which serves a population of 2.4 million inhabitants.

Two clinical researchers (G.N. and C.G.) obtained all available medical data. General case notes, operation reports, and pathology reports were reviewed.

Revised manuscript accepted for publication December 15, 2014

Table 1. — *The modified Charlson Comorbidity Index* [13]

Comorbidity condition	Index
Coronary artery disease [a]	1
Congestive heart failure	1
Cerebrovascular disease	1
Peripheral vascular disease	1
Hypertension	1
Dementia	1
Diabetes (mild or moderate)	1
Pulmonary disease	1
Renal disease	1
Any prior malignant tumor	2
Hepatic disease	3

[a] Including myocardial infarction, coronary artery bypass graft, percutaneous transluminal coronary angioplasty and angina pectoris.

Table 2. — *Causes of death.*

	Age (years)	WHO	CCI	FIGO	Residual Tumor	SCS	Cause of death
1	43	1	1	IIIC	>1cm	1	Sepsis
2	81	0	0	IV	>1cm	1	Hemorrhage
3	50	1	0	IIIC	>1cm	2	VTE
4	67	0	1	IV	<1cm	1	Pulmonary failure
5	67	1	2	IIIC	<1cm	1	Pulmonary failure
6	82	0	1	IV	>1cm	1	Pulmonary failure
7	78	3	2	IIIC	>1cm	2	Progressive disease
8	76	2	2	IIIC	>1cm	1	Hemorrhage
9	78	0		IIIC	>1cm	1	Progressive disease
10	74	1	2	IV	>1cm	1	Sepsis
11	66	1	0	IIIC	>1cm	2	Anastomotic leakage
12	84	1	0	IIIC	>1cm	1	Progressive disease
13	81	1	2	IIIC	>1cm	1	Anastomotic leakage
14	70	1	0	IIIC	>1cm	1	Renal failure

CCI = Charlson Comorbidity Index; SCS = Surgery Complexity Score; VTE = Venous thromboembolism.

The Medical Ethics Committee of the Erasmus University Medical Center (May 2005, MEC 2005-135) approved the study and it was performed in accordance with the Declaration of Helsinki standards. Preoperative parameters for analysis were patients' age, clinical condition according to the WHO performance scale, comorbidity status, presence of ascites prior to surgery, and preoperative blood concentrations. Comorbidity was scored and categorized using a modification of the Charlson comorbidity index (CCI) (Table 1) [12].

Blood tests including hematology (hemoglobin and blood platelets) and CA125 were carried out within one week prior to surgery. Hemoglobin and blood platelet count were assessed by a Sysmex XE 2100 system. CA125 was assessed by enzyme immunoassay using a sandwich method with chemiluminescence. Women who underwent emergency surgery due to ovarian carcinoma were excluded from the study. Ascites was defined as the presence of pelvic fluid preoperatively, at ultrasound or CT-scan.

Primary cytoreductive surgery was performed using an abdominal midline incision and included total hysterectomy, bilateral salpingo-oophorectomy, omentectomy, and resection of all visible and palpable bulky tumor. Optimal cytoreduction was defined as residual disease less than one cm [14]. To achieve a cytoreduction with tumor lesions less than one cm, diaphragmatic stripping, partial liver resection, pancreas resection, splenectomy, bowel resection, and lymphadenectomy were performed if necessary.

Histopathology was classified as endometroid, serous, mucinous, clear cell, and undifferentiated adenocarcinoma. Differentiation was classified in Grades 1 to 3, according to the Silverberg criteria [15]. Subsequently, stage of the disease was determined according to FIGO guidelines [16].

All peri- and postoperative complications were registered. They were classified according to the definitions of the National Surgical Quality Improvement Program (NSQIP) [17, 18]. Postoperative mortality (POM) was defined as death within 30 days after surgery.

Systematic description of cause of death was performed according to the methodology of Waljee *et al*. The most serious complication in postoperative course which resulted in death, was noted as cause of postoperative mortality [18] (Table 2). Postoperative morbidity was defined as the occurrence of a serious event attributed to surgery within 30 days after surgery. This morbidity included: POM, bleeding requiring > 4 U of transfused blood, sepsis, pneumonia, venous thromboembolism (pulmonary embolus or deep venous thrombosis), any type of complication requiring re-operation, any bowel injury (leak, fistula, anastomotic leakage), prolonged ileus (> six days), urinary complications (ureteral fistula, obstruction or leak), failure to wean from the ventilator > 48 hours after operation, renal failure requiring dialysis, myocardial infarction, stroke, and unplanned intubation. The primary outcome measure was 30-day morbidity.

Analysis

Data analysis was performed utilizing the software package SPSS 14.0. The Student *t*-test was used to compare patients' age and preoperative serum concentrations of hemoglobin, blood platelets, and log CA125 between the group of patients with 30-day morbidity and those patients with an uncomplicated postoperative course. To compare the preoperative presence of ascites, WHO performance status and CCI between the two groups, Chi square tests were used.

Based on the univariate analysis, initial predictive parameters for 30-day morbidity with $p < 0.50$ were selected to be assessed by multivariate Cox regression analysis with backward stepwise elimination. To achieve a better model and in order to prevent overestimation, parameters with $p < 0.15$ were entered into the authors' prognostic model [13]. Missing values were accounted by multiple imputation according to Van Buuren *et al.* [19].

The discriminative ability of the prognostic model, or the ability to distinguish patients with poor outcome from patients with a favourable outcome, was expressed by means of the c-statistic [20]. By means of bootstrapping the internal validity of the model was tested. With this method, the model was repeated 200 times and each time the original data were replaced with data from a new created dataset (bootstrap sample). On this dataset, the backward stepwise elimination process was performed, accordance with scientific literature [20, 21]. This process provides a set of selected predictors and parameters.

After completing bootstrapping, each resulting prediction was tested again based on the original data. To correct for statistical over-optimism, a shrinkage factor was estimated. Additionally, a correction for optimism in the c-statistic was derived from the bootstrap method. A nomogram was generated with the predictive parameters for operative risk in the individual patient.

Table 3. — *Characteristics of the study population of patients with advanced stage ovarian cancer (FIGO III-IV).*

	Study Population		No complications		30-day morbidity		*p* value
	n	%	n	%	n	%	
Number of patients	293	100	194	66.0	99	34.0	
Preoperative parameters							
Age							
Median (range)	64.7 (15.9-90.5)		62.5 (31.0-90.5)		66.7 (15.9-81.1)		0.012
< 50 years	34	11.6	25	12.9	9	9.1	
50-59 years	80	27.3	60	30.9	20	20.2	
60-69 years	88	30.0	57	29.4	31	31.3	
≥ 70 years	91	31.1	52	26.8	39	39.4	
WHO performance							0.043
WHO 0	161	55.0	118	60.8	43	43.4	
WHO I	117	39.9	68	35.1	49	49.5	
≥ WHO II	15	5.1	8	4.1	7	7.1	
CCI							0.981
0	129	44.0	89	45.9	40	40.4	
1	84	28.7	55	28.3	29	29.3	
≥ 2	80	27.3	50	25.8	30	30.3	
Presence of ascites	174	59.4	109	56.2	65	65.7	0.665

Differences, if any, between the group of patients with 30-day morbidity and those with an uncomplicated postoperative course are tested with Student t- and Chi square tests, when applicable. SD = standard deviation, CCI = Charlson Comorbidity Index.

Table 4. — *Preoperative serum parameters of the study population of patients with advanced stage ovarian cancer (FIGO III-IV).*

	Study Population	SD	No complications	SD	30-day morbidity	SD	*p* value
Number of patients (n)	293		194		99		
Hemoglobin (mmol/L)	7.9	0.99	8.0	0.98	7.6	0.99	0.051
Platelet count (*109/L)	381	140	380	142	388	137	0.221
Log CA125 (kU/L)	2.80	3.90	2.67	3.98	2.98	3.40	0.459

Differences, if any, between the group of patients with 30-day morbidity and those with an uncomplicated postoperative course are tested with Student *t*- and Chi square tests, when applicable.
SD = standard deviation, CCI = Charlson Comorbidity Index.

Results

Between January 2004 and December 2007, 494 patients underwent primary surgery for EOC and 293 patients with advanced stage EOC entered the study protocol and underwent primary cytoreductive surgery. Thirteen patients with emergency surgery and 188 patients with early-stage EOC were excluded. Patient characteristics are depicted in Tables 3 and 4. At time of surgery the median age was 64.7 years with a range between 15.0 and 90.5 years. Ninety-one patients (31.1%) were aged ≥ 70 years and 161 patients (55.0%) were asymptomatic and classified as WHO performance score 0. The mean preoperative hemoglobin was 7.9 mmol/L.

Fourteen (4.8%) patients were diagnosed with FIGO Stage IIIA, 23 (7.8%) patients with FIGO Stage IIIB, 208 (71.0%) patients with FIGO Stage IIIC, and 48 (16.4%) patients with FIGO Stage IV disease. Postoperative mortality was seen in 14 patients (4.8%). Causes of death are listed in Table 2. Thirty-day morbidity was seen in 99 patients (34.0%).

Median age was lower in the group of patients without complications when compared to the group of patients with 30-day morbidity, 62.5 (SD 11.3) versus 66.7 (SD 12.2) years ($p = 0.012$). In the group of patients with an uncomplicated postoperative course, preoperative hemoglobin was higher ($p = 0.051$) and WHO performance status was better ($p = 0.043$).

Parameters comparable in both groups were co-morbidity status, presence of ascites, platelet count and serum CA125 level (Tables 3 and 4). A nomogram with predictors for 30-day morbidity was generated with the results of uni- and multivariate analyses (Tables 5 and 6).

By means of a multivariate Cox' regression, the variables with $p < 0.50$ in the univariate analysis were assessed. Operative risk could be predicted by age ($p = 0.033$; OR 1.024), hemoglobin ($p = 0.194$; OR 0.843), and WHO performance status ($p = 0.015$; OR 1.892) with a c-statistic of 0.65. This signifies that the authors' model accurately discriminated patients with and without morbidity within 30 days in 65% of the time. The model was developed and evaluated based on the same data, resulting in an initially too optimistic model. Therefore, the steps taken in Cox regression were internally validated by 200 random bootstrap samples. The optimism

Table 5. — *Univariate analysis of the potential predictors of 30-day morbidity.*

Variable	*p* value	OR	95% CI
Preoperative parameters			
Age	0.013	1.028	1.006-1.050
WHO performance status	0.018	1.977	1.191-3.280
CCI	0.913	1.173	0.654-2.110
Presence of ascites	0.947	0.976	0.480-1.990
Preoperative serum parameters			
Hemoglobin	0.062	0.976	0.952-1.000
Platelet count	0.366	1.001	0.999-1.000
Log CA125	0.430	1.069	0.905-1.260

Parameters with $p < 0.50$ were included in the multivariate Cox' regression analysis. OR = odds ratio; NS = not significant; CI = confidence interval; CCI = Charlson Comorbidity Index.

Table 6. — *Multivariate Cox' regression analysis.*

Variable	*p* value	OR	95% CI
Preoperative parameters			
Age	0.033	1.024	1.002-1.050
WHO performance status	0.015	1.892	1.131-3.160
CCI	NS		
Presence of ascites	NS		
Preoperative serum parameters			
Hemoglobin	0.193	0.843	0.651-1.090
Platelet count	NS		
Log CA125	NS		

OR = odds ratio; NS = not significant; CI = confidence interval; CCI = Charlson comorbidity index.

corrected c-statistic was 0.62. A shrinkage factor of 0.78 was estimated based on the bootstrap procedure. This indicates when replicating this analysis, the resulting coefficients of the final model are on average 0.78 smaller.

The final generated nomogram for the probability of 30-day morbidity is shown in Figure 1 and comprises preoperative parameters age, hemoglobin, and WHO performance status.

Discussion

In this study the authors identified preoperative predictors for 30-day morbidity and mortality after primary cytoreductive surgery for advanced stage EOC. Postoperative complications could be predicted by age, preoperative hemoglobin, and WHO performance status. With these parameters, a nomogram was generated to predict operative risk in the individual patient.

Although the course of disease in patients with advanced stage EOC is to some extent determined by preoperative tumor spread and biologic characteristics of the tumor, multiple studies have shown the survival benefit of maximal cytoreduction, with the best outcome in patients with no macroscopic tumor residuals after cytoreductive surgery [22].

Extensive surgical procedures are inevitably related to operative mortality and morbidity. According to unadjusted morbidity rates, approximately one out of three patients will experience a serious complication after primary cytoreductive surgery for EOC. Although overall POM is low with a

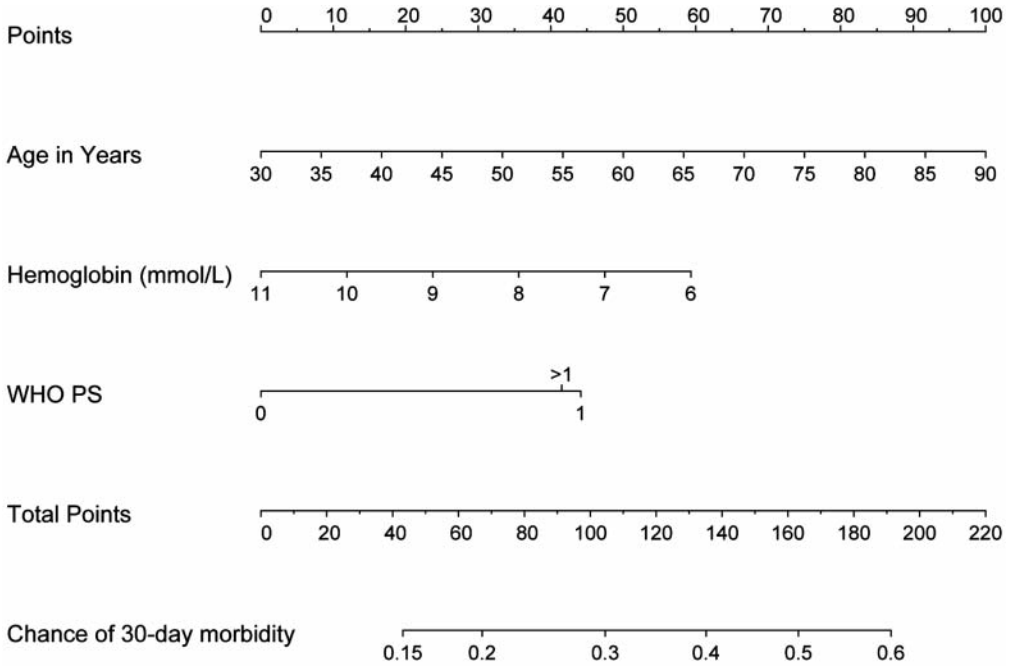

Figure 1. — Nomogram for prediction of 30-day morbidity. For each level of predictive factors, there is a number of points allocated at the point scale above. By adding the points of each parameter, the total points could be calculated. This number represents the probability of 30-day morbidity. For example in a 80-year-old patient (83 points) with respectively a WHO 0 performance status [0 points], had a hemoglobin level of 7.2 mmol/l [45 points]. The total score is 128 points (83+0+45) representing a 38% change of 30-day morbidity.

mean POM rate of 2.8%, POM rates in the elderly are significantly higher ranging from 5.4% to 11.7% [10, 23-25].

Recent data support an alternative management with neoadjuvant chemotherapy followed by interval cytoreductive surgery in patients with extensive disease or diminished performance status and increased operative risk [26]. The decision to perform primary cytoreductive surgery should be based on a reproducible assessment of the ability to achieve maximal cytoreduction and the operative risk.

Predictive parameters for postoperative complications after primary cytoreduction for advanced stage EOC are age, performance status, co-morbidity, and extent of surgery [1, 27]. Risk-adjustment models can provide a more individual and accurate prediction of operative risk and corroborate the decision to withhold patients from extensive surgical procedures. Prediction models for operative risk can especially improve management in the enlarging subgroup of elderly patients by determining individual risk profiles [27]. Still many older women do not receive standard care and are treated more conservatively with less radical surgery, while outcome in elderly patients with comprehensive surgery is comparable to outcome in younger patients [28, 29].

In contrast to other available prediction models, the present authors' generated nomogram is based on preoperative parameters. This could facilitate prediction of 30-day morbidity in daily clinical practice and provide objective parameters to identify those patients who might benefit from an alternative treatment approach with neoadjuvant chemotherapy, followed by interval debulking surgery.

Uniform registration and definitions of 30-day morbidity are essential to determine the actual rate of complications and identification of risk factors for operative morbidity. The National Surgical Improvement Program (NSQIP) is a prospective risk-adjustment program generating periodically observed/expected ratios for 30-day morbidity and mortality after major surgical procedures. Due to identification of structural and procedural failures at the participating hospitals, morbidity and mortality rates have been decreased significantly [30].

The present authors suggest a prospective registration of all peri- and postoperative complications after major surgery. This registration should be based on NSQIP definitions.

The present study has several limitations. Due to the retrospective nature of data collection, the actual rate of complications could be underscored. Second, the optimal cytoreduction rate in this study was lower when compared to reports from specialized centres. This supports the general opinion that treatment of patients with an advanced stage EOC should be performed in high-volume hospitals with specialized surgeons [15]. However, since its insidious onset, heterogeneous presentation and clinical course, the vast majority of patients will be referred after an initial examination in a general hospital by a general gynecologist. An accurate preoperative assessment on resectability and operative risk is therefore essential to guarantee proper decision-making and management of these patients. As suggested by other authors, risk-adjustment models should be developed in a general population rather than in selected patients treated in specialized high-volume hospitals [1]. Third, 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 extra-abdominal disease. Finally, the present authors' nomogram was internally validated by bootstrapping. However, before applying the nomogram in daily clinical practise, the nomogram needs to be externally validated.

Conclusion

In conclusion, the authors developed a nomogram with preoperative parameters predicting 30-day morbidity after primary cytoreductive surgery for advanced stage EOC. This nomogram is valuable for predicting the risk of 30-day morbidity and mortality in the individual patient.

Acknowledgements

The authors would like to thank D.W. van der Spek and B.K. Gerestein-van Os for their help with data acquisition. They also thank all participating departments of gynecology and the registrars of the Rotterdam Cancer Registry for their cooperation in finding and interpreting the data.

References

[1] Aletti G.D., Santillan A., Eisenhauer E.L., Hu J., Aletti G., Podratz K.C., *et al.*: "A new frontier for quality of care in gynecologic oncology surgery: multi-institutional assessment of short-term outcomes for ovarian cancer using a risk-adjusted model". *Gynecol. Oncol.*, 2007, *107*, 99.

[2] Heintz A.P., Hacker N.F., Berek J.S., Rose T.P., Munoz A.K., Lagasse L.D.: "Cytoreductive surgery in ovarian carcinoma: feasibility and morbidity". *Obstet. Gynecol.*, 1986, *67*, 783.

[3] Eisenkop S.M., Spirtos N.M., Montag T.W., Nalick R.H., Wang H.J.: "The impact of subspecialty training on the management of advanced ovarian cancer". *Gynecol. Oncol.*, 1992, *47*, 203.

[4] Bristow R.E., Montz F.J., Lagasse L.D., Leuchter R.S., Karlan B.Y.: "Survival impact of surgical cytoreduction in stage IV epithelial ovarian cancer". *Gynecol. Oncol.*, 1999, *72*, 278.

[5] Michel G., De Iaco P., Castaigne D., el-Hassan M.J., Lobreglio R., Lhomme C., *et al.*: "Extensive cytoreductive surgery in advanced ovarian carcinoma". *Eur. J. Gynaecol. Oncol.*, 1997, *18*, 9.

[6] Chen S.S., Bochner R.: "Assessment of morbidity and mortality in primary cytoreductive surgery for advanced ovarian carcinoma". *Gynecol. Oncol.*, 1985, *20*, 190.

[7] Piver M.S., Baker T.: "The potential for optimal (less than or equal to 2 cm) cytoreductive surgery in advanced ovarian carcinoma at a tertiary medical center: a prospective study". *Gynecol. Oncol.*, 1986, *24*, 1.

[8] Venesmaa P., Ylikorkala O.: "Morbidity and mortality associated with primary and repeat operations for ovarian cancer". *Obstet. Gynecol.*, 1992, *79*, 168.

[9] Bristow R.E., Montz F.J.: "Complete surgical cytoreduction of advanced ovarian carcinoma using the argon beam coagulator". *Gynecol. Oncol.*, 2001, *83*, 39.
[10] Gerestein C.G., Damhuis R.A., Burger C.W., Kooi G.S.: "Postoperative mortality after primary cytoreductive surgery for advanced stage epithelial ovarian cancer: A systematic review". *Gynecol. Oncol.*, 2009, *114*, 523. doi: 10.1016/j.ygyno.2009.03.011. Epub 2009 Apr 2.
[11] Gerestein C.G., Nieuwenhuyzen-de Boer G.M., Eijkemans M.J., Kooi G.S., Burger C.W.: "Prediction of 30-day morbidity after primary cytoreductive surgery for advanced stage ovarian cancer". *Eur. J. Cancer*, 2010, *46*, 102.
[12] Charlson M.E., Pompei P., Ales K.L., MacKenzie C.R.: "A new method of classifying prognostic comorbidity in longitudinal studies: development and validation". *J. Chronic Dis.*, 1987, *40*, 373.
[13] Steyerberg E.W., Eijkemans M.J., Harrell F.E. Jr., Habbema J.D.: "Prognostic modelling with logistic regression analysis: a comparison of selection and estimation methods in small data sets". *Stat. Med.*, 2000, *19*, 1059.
[14] Bristow R.E., Tomacruz R.S., Armstrong D.K., Trimble E.L., Montz F.J.: "Survival effect of maximal cytoreductive surgery for advanced ovarian carcinoma during the platinum era: a meta-analysis". *J. Clin. Oncol.*, 2002, *20*, 1248.
[15] Shimizu Y., Kamoi S., Amada S., Hasumi K., Akiyama F., Silverberg S.G.: "Toward the development of a universal grading system for ovarian epithelial carcinoma. I. Prognostic significance of histopathologic features--problems involved in the architectural grading system". *Gynecol. Oncol.*, 1998, *70*, 2.
[16] "Changes in definitions of clinical staging for carcinoma of the cervix and ovary: International Federation of Gynecology and Obstetrics". *Am. J. Obstet. Gynecol.*, 1987, *156*, 263.
[17] Khuri S.F., Daley J., Henderson W., Hur K., Demakis J., Aust J.B., *et al.*: "The Department of Veterans Affairs' NSQIP: the first national, validated, outcome-based, risk-adjusted, and peer-controlled program for the measurement and enhancement of the quality of surgical care. National VA Surgical Quality Improvement Program". *Ann. Surg.*, 1998, *228*, 491.
[18] Waljee J.F., Windisch S., Finks J.F., Wong S.L., Birkmeyer J.D.: "Classifying cause of death after cancer surgery". *Surg. Innov.*, 2006, *13*, 274.
[19] van Buuren S., Boshuizen H.C., Knook D.L.: "Multiple imputation of missing blood pressure covariates in survival analysis". *Stat. Med.*, 1999, *18*, 681.
[20] Harrell F.E. Jr., Lee K.L., Mark D.B.: "Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors". *Stat. Med.*, 1996, *15*, 361.
[21] Van Houwelingen J.C., Le Cessie S.: "Predictive value of statistical models". *Stat. Med.*, 1990, *9*, 1303.
[22] Covens A.L.: "A critique of surgical cytoreduction in advanced ovarian cancer". *Gynecol. Oncol.*, 2000, *78*, 269.
[23] Alphs H.H., Zahurak M.L., Bristow R.E., Diaz-Montes T.P.: "Predictors of surgical outcome and survival among elderly women diagnosed with ovarian and primary peritoneal cancer". *Gynecol. Oncol.*, 2006, *103*, 1048.
[24] Diaz-Montes T.P., Zahurak M.L., Giuntoli R.L. 2nd., Gardner G.J., Gordon T.A., Armstrong D.K., *et al.*: "Surgical care of elderly women with ovarian cancer: a population-based perspective". *Gynecol. Oncol.*, 2005, *99*, 352.
[25] Cloven N.G., Manetta A., Berman M.L., Kohler M.F., DiSaia P.J.: "Management of ovarian cancer in patients older than 80 years of age". *Gynecol. Oncol.*, 1999, *73*, 137.
[26] Vergote I., Trope C.G., Amant F., Kristensen G.B., Ehlen T., Johnson N., *et al.*: "Neoadjuvant chemotherapy or primary surgery in stage IIIC or IV ovarian cancer". *N. Engl. J. Med.*, 2010, *363*, 943.
[27] Janda M., Youlden D.R., Baade P.D., Jackson D., Obermair A.: "Elderly patients with stage III or IV ovarian cancer: should they receive standard care?" *Int. J. Gynecol. Cancer*, 2008, *18*, 896.
[28] Goff B.A., Matthews B.J., Larson E.H., Andrilla C.H., Wynn M., Lishner D.M., *et al.*: "Predictors of comprehensive surgical treatment in patients with ovarian cancer". *Cancer*, 2007, *109*, 2031.
[29] Wimberger P., Lehmann N., Kimmig R., Burges A., Meier W., Hoppenau B., *et al.*: "Impact of age on outcome in patients with advanced ovarian cancer treated within a prospectively randomized phase III study of the Arbeitsgemeinschaft Gynaekologische Onkologie Ovarian Cancer Study Group (AGO-OVAR)". *Gynecol. Oncol.*, 2006, *100*, 300.
[30] Khuri S.F.: "The NSQIP: a new frontier in surgery". *Surgery*, 2005, *138*, 837.

Address reprint requests to:
G.M. NIEUWENHUYZEN-DE BOER, M.D.
Department of Obstetrics and Gynecology
Erasmus MC, University Medical Center Rotterdam
P.O.Box 2040
3000 CA Rotterdam (The Netherlands)
e-mail: g.nieuwenhuyzen-deboer@erasmusmc.nl