Value of Prediction Models in Determining Treatment Strategies in Patients with Advanced Stage Epithelial Ovarian Cancer

Kees Gerestein

Value of prediction models in determining treatment strategies in patients with advanced stage epithelial ovarian cancer

C.G. Gerestein

ISBN: 978-90-8559-933-3

Cover photo: coloured scanning electron micrograph (SEM) of an ovarian cancer cell, ANP Photo, Den Haag, The Netherlands.
Cover design: B.K. Gerestein-van Os.
Layout and printing: Optima Grafische Communicatie, Rotterdam.

The work described in this thesis was performed at the Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, Erasmus MC, Rotterdam, The Netherlands.

Printing of this thesis was financially supported by the Department of Obstetrics and Gynecology of the Erasmus MC, the Erasmus University Rotterdam, the Comprehensive Cancer Centre Rotterdam and BD Diagnostics.

Value of Prediction Models in Determining Treatment Strategies in Patients with Advanced Stage Epithelial Ovarian Cancer

Waarde van predictiemodellen bij het bepalen van behandelstrategieën bij patiënten met een gevorderd stadium epitheliaal ovarium carcinoom

Proefschrift

ter verkrijging van de graad van doctor aan de
Erasmus Universiteit Rotterdam
op gezag van de
rector magnificus

Prof.dr. H.G. Schmidt

en volgens besluit van het College voor Promoties

De openbare verdediging zal plaatsvinden op
vrijdag 5 maart 2010 om 13.30 uur.

door

Cornelis Gijsbertus Gerestein

geboren te Zeist

PROMOTIECOMMISSIE

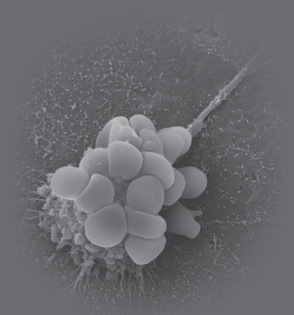
Promotor:	Prof.dr. C.W. Burger
Overige leden:	Prof.dr. R. de Wit Prof.dr. J.W.W. Coebergh Prof.dr. A.G.J. van der Zee
Co-promotor:	Dr. G.S. Kooi

TABLE OF CONTENTS

Chapter 1	General introduction.	7
Chapter 2	Prediction of suboptimal cytoreduction at primary cytoreductive surgery for advanced stage epithelial ovarian cancer.	17
	2.1 Prediction of residual disease after primary cytoreductive surgery for advanced stage ovarian cancer: accuracy of clinical judgment. *Int J Gynecol Cancer. 2009 Dec;19(9):1511-5.*	19
	2.2 Nomogram for suboptimal cytoreduction at primary surgery for advanced stage ovarian cancer. *Submitted.*	31
Chapter 3	Postoperative mortality after surgery for epithelial ovarian cancer.	43
	3.1 Postoperative mortality after primary cytoreductive surgery for advanced stage epithelial ovarian cancer: A systematic review. *Gynecol Oncol. 2009 Sep;114(3):523-7.*	45
	3.2 Causes of postoperative mortality after surgery for ovarian cancer. *Eur J Cancer. 2009 Nov;45(16):2799-803.*	57
Chapter 4	Prediction of 30-day morbidity after primary cytoreductive surgery for advanced stage ovarian cancer. *Eur J Cancer. 2010 Jan;46(1):102-9.*	69
Chapter 5:	The prediction of progression-free and overall survival in patients with an advanced stage of epithelial ovarian carcinoma. *BJOG 2009;116:372–380.*	83
Chapter 6:	General discussion.	99
Summary		107
Nederlandse samenvatting		113
List of co-authors		119
Publications		121
Dankwoord		123
Curriculum vitae		125

1

General introduction



1.1 EPIDEMIOLOGY

With approximately 200,000 new patients each year ovarian cancer accounts for 4% of all cancers in women worldwide. Ovarian cancer is the fourth most common cause of cancer-related death in women and has the worst prognosis of all gynecologic cancers.[1, 2] In the Netherlands each year 1100 new patients are diagnosed and approximately 900 women annually die due to this disease.[3]

1.2 HISTOPATHOLOGY

Eighty percent of the ovarian cancers are of epithelial origin. According to WHO guidelines, all epithelial ovarian tumours are subdivided in serous, mucinous, endometroid, clear cell, and undifferentiated adenocarcinoma.[4]
Differentiation is classified in grade 1 to 3, according to the Silverberg criteria.[5]

1.3 STAGING

Ovarian cancer is surgically staged according to the International Federation of Gynaecology and Obstetrics (FIGO) rules for classification. The staging classification is outlined in table 1 and figure 1. [6] At the time of diagnosis 70% of the patients will have advanced stage disease, defined as FIGO stage IIB-IV.[2]

1.4 TREATMENT

Treatment of patients with advanced stage epithelial ovarian cancer (EOC) is grounded on cytoreductive surgery and paclitaxel/platinum-based chemotherapy. Primary cytoreductive surgery aims to resect all macroscopic tumour or at least to lesions <1cm.[7, 8] Optimal cytoreduction is generally defined as residual disease ≤ 1cm. However, several recent studies have shown the prognostic importance of resection to no macroscopic residual tumor. [7-9]
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.[7, 10] Unfortunately only 20-40% of the patients with EOC actually benefits from this optimal treatment.[11]

Patients with residual disease >1cm 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 and consecutive chemotherapy.[8, 12-15]

Table 1. Carcinoma of the ovary: FIGO nomenclature for staging classification

Stage I Growth limited to the ovaries
Ia Growth limited to one ovary; no ascites present containing malignant cells. No tumor on the external surface; capsule intact
Ib Growth limited to both ovaries; no ascites present containing malignant cells. No tumor on the external surfaces; capsules intact
Ic a Tumor either Stage Ia or Ib, but with tumor on surface of one or both ovaries, or with capsule ruptured, or with ascites present containing malignant cells, or with positive peritoneal washings
Stage II Growth involving one or both ovaries with pelvic extension
IIa Extension and/or metastases to the uterus and/or tubes
IIb Extension to other pelvic tissues
IIc a Tumor either Stage IIa or IIb, but with tumor on surface of one or both ovaries, or with capsule(s) ruptured, or with ascites present containing malignant cells, or with positive peritoneal washings
Stage III Tumor involving one or both ovaries with histologically confirmed peritoneal implants outside the pelvis and/or positive retroperitoneal or inguinal nodes. Superficial liver metastases equals Stage III. Tumor is limited to the true pelvis, but with histologically proven malignant extension to small bowel or omentum
IIIa Tumor grossly limited to the true pelvis, with negative nodes, but with histologically confirmed microscopic seeding of abdominal peritoneal surfaces, or histologic proven extension to small bowel or mesentery
IIIb Tumor of one or both ovaries with histologically confirmed implants, peritoneal metastasis of abdominal peritoneal surfaces, none exceeding 2 cm in diameter; nodes are negative
IIIc Peritoneal metastasis beyond the pelvis >2 cm in diameter and/or positive retroperitoneal or inguinal nodes
Stage IV Growth involving one or both ovaries with distant metastases. If pleural effusion is present, there must be positive cytology to allot a case to Stage IV. Parenchymal liver metastasis equals Stage IV
a In order to evaluate the impact on prognosis of the different criteria for allotting cases to Stage Ic or IIc, it would be of value to know if rupture of the capsule was spontaneous, or caused by the surgeon; and if the source of malignant cells detected was peritoneal washings, or ascites.

Prediction of suboptimal cytoreduction

An accurate preoperative assessment of patients with advanced stage EOC whose disease cannot be optimally cytoreduced at primary surgery may facilitate more tailored treatment strategies.[16] Due to a poor detection of distant metastasis, prediction of suboptimal cytoreduction by physical examination and ultrasound is limited.[17] In order to increase the accuracy of the preoperative prediction, many authors have attempted to identify specific predictors for suboptimal cytoreduction. Presently available prediction models use clinical and radiographic characteristics. Firstly, the pre-operative CA125 level is associated with ability to predict suboptimal cytoreduction. Most studies define a cut-off level varying between 500 and 912 U/ml. The accuracy at the threshold level ranges between 56% and 78%.[18-23]

Secondly, several studies identified computed tomography (CT) scan parameters predictive for suboptimal cytoreduction.[16, 24-28] Accuracy ranges from 71% to 93%.[16, 25, 26] However accuracy drops with at least 20% when these models are extrapolated in other patient populations.[16, 29] These poor predictive performances of available predictors and prediction models could be explained by their identification in retrospective studies with mixed inclusion criteria and different treatment policies.

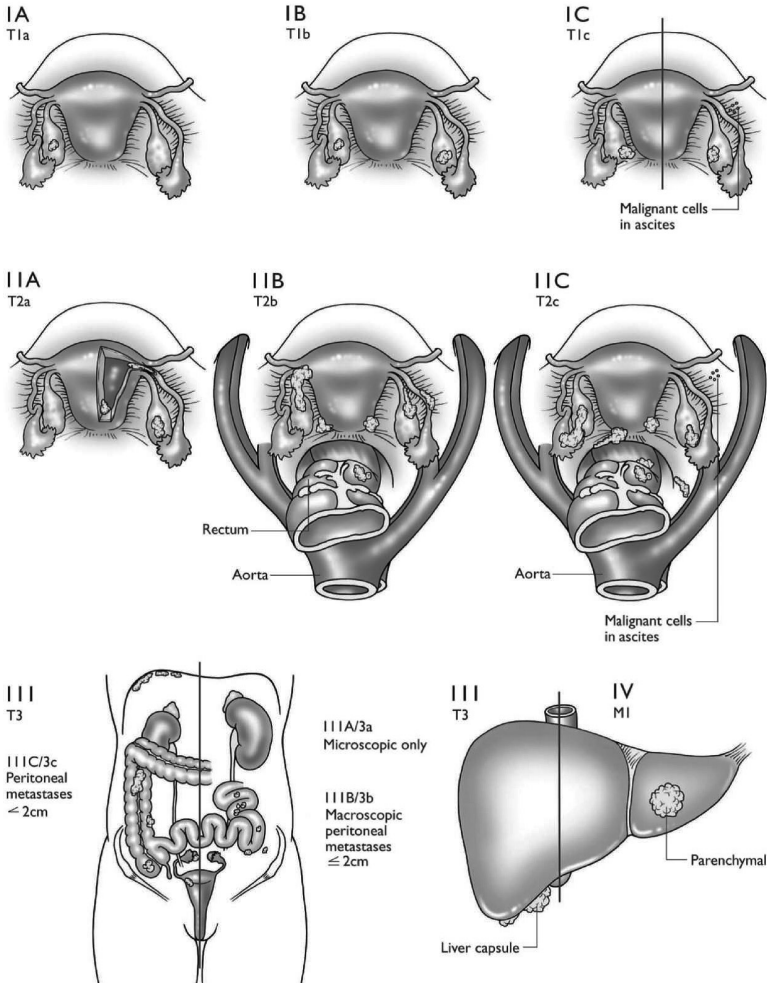


Figure 1. Carcinoma of the ovary. Staging ovarian cancer: primary tumor and metastases (FIGO and TNM). (Adapted from Heintz et al. (6))

Since CT and Magnetic resonance imaging (MRI) are equally accurate in detection of tumor locations and prediction of suboptimal cytoreduction, MRI generally has no additional value in the preoperative work-up of patients with suspected advanced stage EOC.[17, 30, 31]

Finally, laparoscopy is propagated to be highly accurate in addressing inoperable disease. Accuracy ranges from 67% to 96%.[32-34] Although possible development of port site metastases is thought to be without prognostic significance[35], laparoscopy is an invasive procedure and reports on its predictive performance describe single centre results and small study populations. Reports on inter-observer reproducibility are not available.

Postoperative morbidity and mortality

Extensive surgical procedures to achieve maximal cytoreduction are inevitably related to operative morbidity and mortality. Postoperative morbidity after primary cytoreductive surgery for advanced stage ovarian cancer is reported inconsistently, without standard definitions of postoperative morbidity. Unadjusted morbidity rates range from 11 to 67%.[36-46] Postoperative mortality (POM) is generally defined as death from any cause within 30 days of operation. Reports on 30-day mortality after primary cytoreductive surgery for ovarian cancer range from 1 to 6.2 per cent.[12, 37, 42, 44, 47] Most of these studies describe small series from single institutions and results may be deflated due to selection bias. Predictive parameters for postoperative complications after primary cytoreduction for advanced stage EOC are age, performance status, co-morbidity and extent of surgery. Alleti et al. developed a prediction model for morbidity and mortality after primary cytoreductive surgery for advanced stage ovarian cancer. Albumin, ASA and complexity of surgery were identified as predictors for 30-day morbidity. Predictors for 3-month mortality were age and ASA.[36]

1.5 PROGNOSIS

The average 5-year survival rate of women with EOC is 43%; however, up to 65% will eventually die from the disease.[48] Prognosis depends on FIGO stage and the ability to perform optimal cytoreductive surgery.[7, 13] Other prognostic factors are performance status, CA125 level, age at diagnosis, grade of tumour, histology, presence of ascites and albumin level. [49, 50]

1.6 AIM AND OUTLINE OF THE THESIS

This thesis aims to evaluate the value of prediction models in determining treatment strategies in patients with advanced stage epithelial ovarian cancer.
In **Chapter 2** the prediction of suboptimal cytoreduction at primary cytoreductive surgery for advanced stage EOC will be analysed. We investigate the accuracy and reproducibility of the offhand clinical assessment of irresectable disease and develop a predictive model based on CT scan and clinical parameters in a prospective multi-institutional observational study.

Chapter 3 focuses on peri- and postoperative complications in patients with cytoreductive surgery for advanced stage EOC. To obtain reference standards for postoperative mortality (POM), we perform a systematic review on published POM rates after primary cytoreductive surgery for advanced stage EOC. (**Chapter 3.1**)
To determine causes of 30-day mortality after surgery for EOC all postoperative deaths in the South Western part of the Netherlands over a 17-year period are analysed. (**Chapter 3.2**)

Prediction models for 30-day morbidity could facilitate prediction of surgical outcome in daily clinical practice and can provide objective parameters to identify those patients with an increased operative risk who might benefit from alternative treatment approaches. In **Chapter 4** we perform a retrospective analysis in a cohort of 293 patients on peri- and postoperative complications after primary cytoreductive surgery for EOC. Predictive parameters for 30-day morbidity are identified and a prediction model is generated. In the final part we aim to identify predictors for progression-free (PFS) and overall survival (OS) in patients with EOC who underwent primary cytoreductive surgery followed by first-line paclitaxel/platinum-based chemotherapy, with the identified parameters a predictive model for PFS and OS will be generated (**Chapter 5**)

The content of this thesis is discussed and recommendations for further research are suggested in **Chapter 6**.

REFERENCES

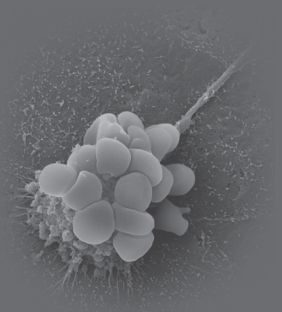
1. Globocan 2002 database http://www-dep.iarc.fr/ assessed april 20th 2009. In; .
2. Jemal A, Siegel R, Ward E, Hao Y, Xu J, Thun MJ. Cancer statistics, 2009. CA Cancer J Clin 2009;59(4):225-49.
3. Dutch Association of Comprehensive Cancer Centres. http://www.ikcnet.nl [accessed October 20, 2009]. In.
4. Scully RE. World Health Organization classification and nomenclature of ovarian cancer. Natl Cancer Inst Monogr 1975;42:5-7.
5. Shimizu Y, Kamoi S, Amada S, Hasumi K, Akiyama F, Silverberg SG. 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(1):2-12.
6. Heintz AP, Odicino F, Maisonneuve P, Quinn MA, Benedet JL, Creasman WT, et al. Carcinoma of the ovary. FIGO 6th Annual Report on the Results of Treatment in Gynecological Cancer. Int J Gynaecol Obstet 2006;95 Suppl 1:S161-92.
7. Bristow RE, Tomacruz RS, Armstrong DK, Trimble EL, Montz FJ. Survival effect of maximal cytoreductive surgery for advanced ovarian carcinoma during the platinum era: a meta-analysis. J Clin Oncol 2002;20(5):1248-59.
8. du Bois A, Reuss A, Pujade-Lauraine E, Harter P, Ray-Coquard I, Pfisterer J. Role of surgical outcome as prognostic factor in advanced epithelial ovarian cancer: A combined exploratory analysis of 3 prospectively randomized phase 3 multicenter trials: by the Arbeitsgemeinschaft Gynaekologische Onkologie Studiengruppe Ovarialkarzinom (AGO-OVAR) and the Groupe d'Investigateurs Nationaux Pour les Etudes des Cancers de l'Ovaire (GINECO). Cancer 2009;115(6):1234-44.
9. Crawford SC, Vasey PA, Paul J, Hay A, Davis JA, Kaye SB. Does aggressive surgery only benefit patients with less advanced ovarian cancer? Results from an international comparison within the SCOTROC-1 Trial. J Clin Oncol 2005;23(34):8802-11.
10. Vernooij F, Heintz P, Witteveen E, van der Graaf Y. The outcomes of ovarian cancer treatment are better when provided by gynecologic oncologists and in specialized hospitals: a systematic review. Gynecol Oncol 2007;105(3):801-12.
11. Carney ME, Lancaster JM, Ford C, Tsodikov A, Wiggins CL. A population-based study of patterns of care for ovarian cancer: who is seen by a gynecologic oncologist and who is not? Gynecol Oncol 2002;84(1):36-42.
12. Vergote I, De Wever I, Tjalma W, Van Gramberen M, Decloedt J, van Dam P. Neoadjuvant chemotherapy or primary debulking surgery in advanced ovarian carcinoma: a retrospective analysis of 285 patients. Gynecol Oncol 1998;71(3):431-6.
13. Hoskins WJ, McGuire WP, Brady MF, Homesley HD, Creasman WT, Berman M, et al. The effect of diameter of largest residual disease on survival after primary cytoreductive surgery in patients with suboptimal residual epithelial ovarian carcinoma. Am J Obstet Gynecol 1994;170(4):974-9; discussion 979-80.
14. Schwartz PE, Chambers JT, Makuch R. Neoadjuvant chemotherapy for advanced ovarian cancer. Gynecol Oncol 1994;53(1):33-7.
15. Vergote I, Trope C, Amant F, Kristensen GB, Sardi JE, Ehlen T, et al. EORTC-GCG/NCIC-CTG Randomised trial comparing primary debulking surgery with neoadjuvant chemotherapy in stage IIIC/IV ovarian, fallopian tube and peritoneal cancer. In: 12th Biennal Meeting International Gynecologic Cancer Society; 2008; Bangkok, Thailand; 2008.
16. Axtell AE, Lee MH, Bristow RE, Dowdy SC, Cliby WA, Raman S, et al. Multi-institutional reciprocal validation study of computed tomography predictors of suboptimal primary cytoreduction in patients with advanced ovarian cancer. J Clin Oncol 2007;25(4):384-9.
17. Buist MR, Golding RP, Burger CW, Vermorken JB, Kenemans P, Schutter EM, et al. Comparative evaluation of diagnostic methods in ovarian carcinoma with emphasis on CT and MRI. Gynecol Oncol 1994;52(2):191-8.
18. Obeidat B, Latimer J, Crawford R. Can optimal primary cytoreduction be predicted in advanced stage epithelial ovarian cancer? Role of preoperative serum CA-125 level. Gynecol Obstet Invest 2004;57(3):153-6.
19. Chi DS, Venkatraman ES, Masson V, Hoskins WJ. The ability of preoperative serum CA-125 to predict optimal primary tumor cytoreduction in stage III epithelial ovarian carcinoma. Gynecol Oncol 2000;77(2):227-31.

20. Brockbank EC, Ind TE, Barton DP, Shepherd JH, Gore ME, A'Hern R, et al. Preoperative predictors of suboptimal primary surgical cytoreduction in women with clinical evidence of advanced primary epithelial ovarian cancer. Int J Gynecol Cancer 2004;14(1):42-50.
21. Arits AH, Stoot JE, Botterweck AA, Roumen FJ, Voogd AC. Preoperative serum CA125 levels do not predict suboptimal cytoreductive surgery in epithelial ovarian cancer. Int J Gynecol Cancer 2008;18(4):621-8.
22. Gemer O, Lurian M, Gdalevich M, Kapustian V, Piura E, Schneider D, et al. A multicenter study of CA 125 level as a predictor of non-optimal primary cytoreduction of advanced epithelial ovarian cancer. Eur J Surg Oncol 2005;31(9):1006-10.
23. Vorgias G, Iavazzo C, Savvopoulos P, Myriokefalitaki E, Katsoulis M, Kalinoglou N, et al. Can the preoperative Ca-125 level predict optimal cytoreduction in patients with advanced ovarian carcinoma? A single institution cohort study. Gynecol Oncol 2009;112(1):11-5.
24. Everett EN, Heuser CC, Pastore LM, Anderson WA, Rice LW, Irvin WP, et al. Predictors of suboptimal surgical cytoreduction in women treated with initial cytoreductive surgery for advanced stage epithelial ovarian cancer. Am J Obstet Gynecol 2005;193(2):568-74; discussion 574-6.
25. Bristow RE, Duska LR, Lambrou NC, Fishman EK, O'Neill MJ, Trimble EL, et al. A model for predicting surgical outcome in patients with advanced ovarian carcinoma using computed tomography. Cancer 2000;89(7):1532-40.
26. Dowdy SC, Mullany SA, Brandt KR, Huppert BJ, Cliby WA. The utility of computed tomography scans in predicting suboptimal cytoreductive surgery in women with advanced ovarian carcinoma. Cancer 2004;101(2):346-52.
27. Risum S, Hogdall C, Loft A, Berthelsen AK, Hogdall E, Nedergaard L, et al. Prediction of suboptimal primary cytoreduction in primary ovarian cancer with combined positron emission tomography/computed tomography--a prospective study. Gynecol Oncol 2008;108(2):265-70.
28. Ferrandina G, Sallustio G, Fagotti A, Vizzielli G, Paglia A, Cucci E, et al. Role of CT scan-based and clinical evaluation in the preoperative prediction of optimal cytoreduction in advanced ovarian cancer: a prospective trial. Br J Cancer 2009;101(7):1066-73.
29. Gemer O, Gdalevich M, Ravid M, Piura B, Rabinovich A, Gasper T, et al. A multicenter validation of computerized tomography models as predictors of non- optimal primary cytoreduction of advanced epithelial ovarian cancer. Eur J Surg Oncol 2009.
30. Qayyum A, Coakley FV, Westphalen AC, Hricak H, Okuno WT, Powell B. Role of CT and MR imaging in predicting optimal cytoreduction of newly diagnosed primary epithelial ovarian cancer. Gynecol Oncol 2005;96(2):301-6.
31. Forstner R. Radiological staging of ovarian cancer: imaging findings and contribution of CT and MRI. Eur Radiol 2007;17(12):3223-35.
32. Fagotti A, Ferrandina G, Fanfani F, Garganese G, Vizzielli G, Carone V, et al. Prospective validation of a laparoscopic predictive model for optimal cytoreduction in advanced ovarian carcinoma. Am J Obstet Gynecol 2008;199(6):642 e1-6.
33. Brun JL, Rouzier R, Selle F, Houry S, Uzan S, Darai E. Neoadjuvant chemotherapy or primary surgery for stage III/IV ovarian cancer: contribution of diagnostic laparoscopy. BMC Cancer 2009;9:171.
34. Brun JL, Rouzier R, Uzan S, Darai E. External validation of a laparoscopic-based score to evaluate resectability of advanced ovarian cancers: clues for a simplified score. Gynecol Oncol 2008;110(3):354-9.
35. Vergote I, Marquette S, Amant F, Berteloot P, Neven P. Port-site metastases after open laparoscopy: a study in 173 patients with advanced ovarian carcinoma. Int J Gynecol Cancer 2005;15(5):776-9.
36. Aletti GD, Santillan A, Eisenhauer EL, Hu J, Aletti G, Podratz KC, 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(1):99-106.
37. Heintz AP, Hacker NF, Berek JS, Rose TP, Munoz AK, Lagasse LD. Cytoreductive surgery in ovarian carcinoma: feasibility and morbidity. Obstet Gynecol 1986;67(6):783-8.
38. Eisenkop SM, Spirtos NM, Montag TW, Nalick RH, Wang HJ. The impact of subspecialty training on the management of advanced ovarian cancer. Gynecol Oncol 1992;47(2):203-9.

39. Bristow RE, Montz FJ, Lagasse LD, Leuchter RS, Karlan BY. Survival impact of surgical cytoreduction in stage IV epithelial ovarian cancer. Gynecol Oncol 1999;72(3):278-87.
40. Suzuki M, Ohwara M, Sekiguchi I, Sato I. Radical cytoreductive surgery combined with platinums-carboplatin and cisplatin chemotherapy for advanced ovarian cancer. Int J Gynecol Cancer 1999;9(1):54-60.
41. Michel G, De Iaco P, Castaigne D, el-Hassan MJ, Lobreglio R, Lhomme C, et al. Extensive cytoreductive surgery in advanced ovarian carcinoma. Eur J Gynaecol Oncol 1997;18(1):9-15.
42. Chen SS, Bochner R. Assessment of morbidity and mortality in primary cytoreductive surgery for advanced ovarian carcinoma. Gynecol Oncol 1985;20(2):190-5.
43. Piver MS, 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):1-8.
44. Venesmaa P, Ylikorkala O. Morbidity and mortality associated with primary and repeat operations for ovarian cancer. Obstet Gynecol 1992;79(2):168-72.
45. Guidozzi F, Ball JH. Extensive primary cytoreductive surgery for advanced epithelial ovarian cancer. Gynecol Oncol 1994;53(3):326-30.
46. Bristow RE, Montz FJ. Complete surgical cytoreduction of advanced ovarian carcinoma using the argon beam coagulator. Gynecol Oncol 2001;83(1):39-48.
47. Hacker NF, Berek JS, Lagasse LD, Nieberg RK, Elashoff RM. Primary cytoreductive surgery for epithelial ovarian cancer. Obstet Gynecol 1983;61(4):413-20.
48. Gatta G, Capocaccia R, De Angelis R, Stiller C, Coebergh JW. Cancer survival in European adolescents and young adults. Eur J Cancer 2003;39(18):2600-10.
49. Clark TG, Stewart ME, Altman DG, Gabra H, Smyth JF. A prognostic model for ovarian cancer. Br J Cancer 2001;85(7):944-52.
50. Board RE, Bruijns CT, Pronk AE, Ryder WD, Wilkinson PM, Welch R, et al. Stage- and CA125-related survival in patients with epithelial ovarian cancer treated at a cancer center. Int J Gynecol Cancer 2006;16 Suppl 1:18-24.

2

Prediction of suboptimal cytoreduction at primary cytoreductive surgery for advanced stage epithelial ovarian cancer.

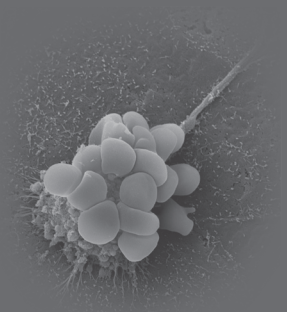


2.1

Prediction of residual disease after primary cytoreductive surgery for advanced stage ovarian cancer: accuracy of clinical judgment.

C.G. Gerestein
D.W. van der Spek
M.J. Eijkemans
J. Bakker
G.S. Kooi
C.W. Burger

Int J Gynecol Cancer. 2009 Dec;19(9):1511-5.



ABSTRACT

Objectives: Treatment of patients with an advanced stage epithelial ovarian cancer (EOC) is based on cytoreductive surgery and platinum-based chemotherapy. Amount of residual disease after primary cytoreductive surgery is an important prognostic factor. Objective of the present study was to evaluate the accuracy and reproducibility of preoperative clinical judgment of residual disease after primary cytoreductive surgery and to compare the predictive performance of the offhand assessment to the predictive performance of prediction models.

Materials and Methods: Fifteen observers (5 gynecologic oncologists, 5 gynecologists, and 5 senior residents) were offered preoperative data of twenty patients with advanced stage EOC who underwent primary cytoreductive surgery. The observers were asked to predict residual disease after cytoreductive surgery (≤1 or >1cm). Their estimation was compared to the performance of two prediction models.

Results: Overall, suboptimal cytoreduction was predicted with a sensitivity of 50% and a specificity of 56%. The intraclass correlation coefficient was 0.27.

Chi-square test showed no significant difference in prediction of suboptimal cytoreduction between the different subgroups or prediction models.

Conclusions: Clinical judgment of residual disease after primary cytoreductive surgery in patients with advanced stage EOC shows limited accuracy. Given the poor inter-observer reproducibility prediction models could attribute to uniform treatment decisions and improve counselling.

INTRODUCTION

Ovarian carcinoma represents 25% of all malignancies of the female genital tract and is the most common cause of death from gynecologic malignancies.[51]The vast majority of patients present with advanced stage disease.
Treatment in advanced-stage epithelial ovarian cancer (EOC) is based on primary cytoreductive surgery followed by platinum based chemotherapy. The amount of residual disease after primary cytoreductive surgery is an important predictor of prognosis.[7] Optimal cytoreduction is generally defined as residual disease ≤ 1cm, although some authors advocate to change this definition in no macroscopic residual tumor.[7]

Although optimal cytoreduction has been demonstrated to be a highly significant predictor of outcome, the benefit of suboptimal cytoreduction is less evident.[13]
Patients with a suboptimal cytoreduction may probably more profit from an alternative treatment approach with neoadjuvant chemotherapy and interval cytoreductive surgery. [12, 15]
An accurate preoperative assessment of patients with advanced stage EOC whose disease cannot be optimally cytoreduced at primary surgery may facilitate more tailored treatment strategies.[16] In order to increase the accuracy of the preoperative prediction, many authors have attempted to identify specific predictors for suboptimal cytoreduction. Available prediction models use clinical and radiographic characteristics. First the preoperative CA125 level is associated with ability to predict suboptimal cytoreduction. Most studies define a cut off value. Accuracy rates range from 50 to 78%. [18-21]
Computed tomographic (CT) scan predictors of suboptimal cytoreductive surgery are diaphragm disease, diffuse peritoneal thickening and large bowel mesentery implants. Six studies describe the predictive value of a preoperative CT scan. In these studies accuracy ranges from 71 to 93%. [16, 25, 26, 52] However, external validation of these CT prediction models showed that accuracy was not as good as it appeared to be at initial presentation.[16]
In view of these data, it is questionable whether the predictive performance of these models is superior to the offhand assessment that is made by clinicians when assessing a patient with suspected advanced stage ovarian cancer.

The objective of the present study was to evaluate the accuracy and reproducibility of the preoperative clinical judgment of suboptimal cytoreduction after primary cytoreductive surgery in patients with advanced stage EOC and to compare the predictive performance of the offhand assessment with the predictive performance of prediction models.

MATERIALS AND METHODS

Patients were recruited from a prospective registration study on treatment of ovarian cancer in the South Western part of the Netherlands. This region comprises 1 university hospital, 4 teaching hospitals and 11 non-teaching hospitals serving a population of 2, 4 million inhabitants. Patients with advanced stage EOC (FIGO >IIB) who underwent primary cytoreductive surgery were eligible for this study.

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

All patients were operated by a gynecologic oncologist with the intention of optimal cytoreduction. Cytoreductive surgery was performed using an abdominal midline incision and included total hysterectomy, bilateral salpingo-oophorectomy, and omentectomy. Other procedures such as bowel resection and lymph note removal were performed if warranted to achieve optimal cytoreduction, defined as residual disease 1cm or smaller.

Histologic finding was classified according to the WHO criteria (2002) and stage of disease was determined according to the Federation of Obstetricians and Gynaecologists (FIGO) guidelines.[53]

Between October 2005 and December 2008, 147 women with suspected advanced stage EOC were prospectively included. All patients had a Risk of Malignancy Index (RMI) greater than 200, based on CA125 level, ultrasound examinations and menopausal status.[54]

Eighteen patients were excluded because final histologic finding was different from EOC. Another 7 patients with early stage disease were excluded. Finally, 122 patients with advanced stage EOC were available for analysis. The characteristics of the study population are depicted in Table 1.

Twenty cases were randomly selected from this dataset and presented to fifteen observers (5 gynecologic oncologists, 5 gynecologists, and 5 senior residents).

A senior resident is in training to become a gynecologist. The residents participating in this trial already finished at least 4 years of the 6-year training program.

Each observer, blinded for surgical outcome, was asked to estimate the outcome of primary cytoreductive surgery for each patient. This prediction was categorized in residual disease ≤ 1 or > 1cm. The clinical judgment of surgical outcome was compared to the achieved result at primary cytoreductive surgery.

Case histories described a complete preoperative work-up.

Standard preoperative work-up of the cases consisted of the patient's history, physical examination (including vaginal examination) and transvaginal sonography.

Table 1. Characteristics of the complete dataset of patients with advanced stage EOC who underwent primary surgery between October 2005 and December 2008. For the present study twenty cases were randomly selected from this dataset. TH-BSO=Total hysterectomy and bilateral-salpingo-oophorectomy.

Characteristics of the Study Population	
Number of patients	122
Age (years)	
Median	61
Range	15-84
FIGO stage, *n* (%)	
IIB	6 (4.9)
IIC	1 (0.8)
IIIA	5 (4.1)
IIIB	10 (8.2)
IIIC	79(64.8)
IV	21(17.2)
Histologic grade, *n* (%)	
I	27 (22.1)
II	31 (25.4)
III	64 (52.5)
Histologic classification, *n* (%)	
Serous	87 (71.3)
Other	35(28.7)
Operative procedure, *n (%)*	
TH-BSO	98 (80.3)
Omentectomy	93 (76.2)
Pelvic lymphadenectomy	3 (2.5)
Para-aortic lymphadenectomy	3 (2.5)
Pelvic peritoneum stripping	6 (4.9)
Small bowel resection	5 (4.1)
Large bowel resection	10 (8.2)
Residual disease, n (%)	
No gross residual disease	34 (27.9)
≤ 1cm	59 (48.4)
> 1cm	63 (52.6)

Subsequently, a preoperative abdominal CT scan was performed within 4 weeks before primary cytoreductive surgery. A standard CT scanning protocol was used. With oral and intravenous contrast images with a 5mm collimation area were obtained.

The observers received a written description of transvaginal sonography and CT scan results, and could review the preoperative CT scan themselves

Blood samples for measurement of CA125, blood platelet count, hemoglobin, and albumin serum concentrations were withdrawn within one week prior to surgery. Cancer antigen 125 was assessed by enzyme immunoassay (Roche E170) using a sandwich method with chemo luminescence (Roche Diagnostics BV, Almere, the Netherlands). Serum levels of albumin were

assessed by a Hitachi 917 system (Roche GmbH, Mannheim, Germany). The blood platelet count and hemoglobin were assessed by a Sysmex XE 2100 system (Sysmex Corporation, Kobe, Japan).

Analysis

Sensitivity, specificity, PPV and NPV for prediction of suboptimal cytoreduction were calculated for all observers together, as well as for gynaecologic oncologists, general gynaecologists and senior residents. The Chi-square test was used to detect significant differences between the different subgroups.

Subsequently, the offhand assessment of suboptimal cytoreduction was compared to the predictive performance of two previously published prediction models.[19, 25]

These models were chosen because they were also restricted to patients with advanced stage EOC and showed a similar optimal cytoreduction rate.

The first prediction model describes prediction of suboptimal cytoreduction after primary cytoreductive surgery based on preoperative CA125 level. In 100 patients with stage III EOC and an 45 % optimal cytoreduction rate, a cut-off level of 500 U/ml predicted suboptimal cytoreduction with a sensitivity of 78% and specificity of 73%.[19, 55]

Next a predictive model constructed with 13 CT features and performance status was applied to our dataset. This model was developed in 41 patients with stage III/IV disease. Optimal cytoreduction was achieved in 20 patients (48.8%). Significant predictors were assigned a Predictive index value between 1 and 2.

A total predictive index score of ≥ 4 predicted residual disease more than 1cm with a sensitivity of 100% and a specificity of 85%.[25]

To assess inter-observer reproducibility intraclass correlation coefficients (ICC) were calculated.[56] The ICC expresses the degree to which the total variance can be attributed to the true variance: true differences between subjects. It not only assesses the strength of correlation between two measurements but also detects systemic errors.

ICC ranges from 0 to 1. Inter-observer reproducibility or strength of agreement is regarded as 'slight' if the ICC value is between 0 and 0.2, between 0.2 and 0.4 as 'fair', between 0.4 and 0.6 as 'moderate', between 0.6 and 0.8 as 'substantial' and between 1.0 as almost 'perfect'.[57]

The statistical accuracy of agreement depends both on the number of subjects assessed and the number of assessors. To limit the burden of individual assessors, we chose to have a rather high number of assessors per group (N=5) with a rather modest number of subjects to be assessed (N=20).

With this design the width of the 95% confidence Interval would be +/- 0.2 around the estimated value of the ICC.[58]

RESULTS

As previously stated all twenty patients selected for this study were diagnosed with advanced stage EOC; 1patient was diagnosed with FIGO stage IIC disease, 15 patients with FIGO stage III disease and 4 patients with FIGO stage IV disease.

Median age was 60 years (range 31-81 years). Fifteen patients (75%) had ovarian carcinoma of serous histology, 1 patient had a clear cell carcinoma, 1 had an endometrioid carcinoma, and in 3 patients histologic finding was classified as undifferentiated adenocarcinoma. Optimal cytoreduction was achieved in 9 patients (45%).

We received 300 completed questionnaires resulting in a 100% response rate.

Participants used the CT scan in 286 judgements (95%). Laboratory results provided additional value in 116 judgments (39%).

The predictive performance of the offhand assessment by the participating clinicians is listed in Table 2. Overall, suboptimal cytoreduction was predicted with a sensitivity of 50% and a specificity of 56%. Gynecologic oncologists showed a sensitivity of 45%, and a specificity of 62%, whereas sensitivity and specificity for general gynecologists was 62% and 49%, respectively. Residents predicted residual disease >1cm with a sensitivity of 44% and a specificity of 56%.

Table 2. Sensitivity, specificity, PPV and NPV for all observers, gynecological oncologists, general gynecologists and residents for prediction of suboptimal cytoreduction. In parentheses the predictive performance as described in the original cohort is shown.

Observer	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Overall (N=15)	50	56	58	48
Gynecological oncologists (N=5)	45	62	59	48
Gynecologists (N=5)	62	49	60	51
Residents (N=5)	44	56	55	45
CA125 (<500U/ml)[8]	73 (78)	44 (73)	62 (78)	57 (73)
CT scan[12]	55 (100)	44 (85)	55 (87)	44 (100)

CA125 level was higher than 500 in 13 patients. This implied a sensitivity of 73% and a specificity of 44% for prediction of suboptimal cytoreduction.

If residual disease was estimated with a prediction model based on CT predictors, residual disease >1cm was predicted with a sensitivity of 55% and a specificity of 44%.

Chi square test showed no significant difference between prediction by the different subgroups or prediction models.

The ICC for all participants was 0.27 (95% CI 0.15-0.47). For gynecologic oncologists the ICC was 0.23 (95% CI 0.058-0.480). General gynecologists showed an ICC of 0.28 (95% CI 0.097-0.528) and finally the ICC for residents was 0.18 (95% CI 0.021-0.428). The poor inter-observer reproducibility is illustrated in figure 1. For each observer the fraction of true positives (TPR = true positive rate) is plotted versus the fraction of false positives (FPR = false positive rate). Each point represents the ability to distinguish between an optimal and a suboptimal cytoreduction.

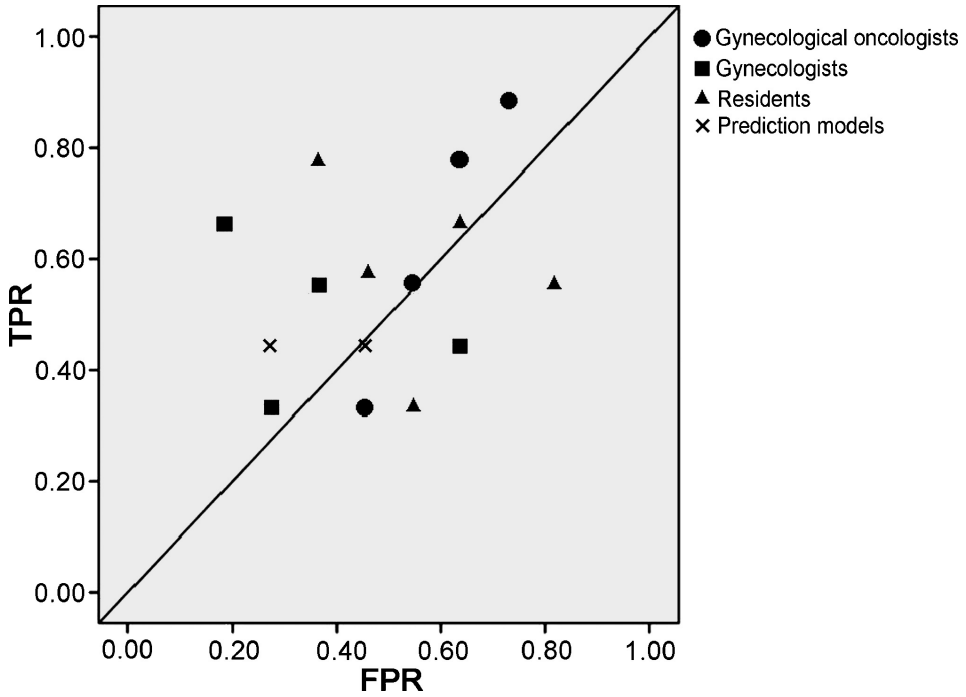


Figure 1. For each observer the fraction of true positives (TPR or sensitivity) is plotted versus the fraction of false positives (FPR or one minus specificity).

The closer the point is to the upper left corner (TPR 1, FPR 0, sensitivity 100% and specificity 100%), the higher the accuracy of the estimation.

DISCUSSION

This study demonstrates a limited predictive performance and a poor inter-observer reproducibility of the preoperative offhand assessment of suboptimal cytoreduction at primary cytoreductive surgery in patients with an advanced stage EOC.

Residual disease after primary cytoreductive surgery is an important prognostic parameter in patients with advanced stage EOC.[7, 13] This supports maximal efforts to reduce present tumor load to minimal residual disease at primary cytoreductive surgery. On the contrary, patients with suboptimal cytoreductive surgery will have limited survival benefit from this procedure. Although the actual value of an alternative treatment approach with neo-adjuvant chemotherapy followed by interval cytoreductive surgery is still under debate, these patients in particular are generally thought to be candidates for this strategy.

Prediction models identifying those patients with a high risk for suboptimal cytoreduction could help guiding treatment decisions. Yet, available predictors or prediction models are not sufficient enough to guarantee proper management.
Prediction models based on radiographic and clinical characteristics show accuracy rates ranging from 50 to 93%.[16, 19, 20, 25, 26] However accuracy drops when these models are extrapolated in other patient populations.[16] The poor predictive performance of available predictors and prediction models could be explained by their identification in retrospective studies with mixed inclusion criteria and different treatment policies.

Laparoscopy is propagated to be highly accurate in addressing inoperable disease. [34] Although possible development of port site metastases is thought to be without prognostic significance[35], laparoscopy is an invasive procedure and reports on its predictive performance describe single centre results and small study populations. Reports on inter-observer reproducibility are not available.

The observed poor inter-observer reproducibility of the offhand assessment of suboptimal cytoreduction is the main argument to use prediction models in the preoperative assessment of patients with suspected advanced stage EOC. This lack of concordance between gynaecologists is also seen in estimating pregnancy changes in sub fertile couples. [59]
Apparently the clinical estimation of the individual physician is often based on subjective personal parameters. Improving outcome in advance stage ovarian cancer demands uniform selection criteria that can identify patients who benefit from other treatment strategies.

There are several limitations of the current study. First, the lack of statistically significant differences in predictive performance could be explained by the small sample size used in our study. This design was suitable to determine reproducibility of the offhand assessment and limited the burden of the individual assessors. A large prospective multi-institutional study is necessary to determine the actual predictive performance of the offhand assessment. Second, according to currently used classification guidelines of advanced stage disease, patients with FIGO stage IIB and IIC disease were also included. Other studies restrict their analyses to patients with bulky disease, defined as FIGO stage IIIC (with extensive peritoneal disease) and IV disease, reflecting to a clear need for a revised sub classification of advanced stage disease.[60] Although 90% of our included patients were diagnosed with FIGO stage IIIC or IV it would have been more appropriate to include only those patients who will need substantial cytoreduction. Future studies should limit their inclusion to patients with FIGO stage IIIC (with extensive peritoneal disease) and IV.
Finally, although our observers had access to the objective preoperative parameters, such as laboratory results and CT-scan results, subjective parameters, most importantly physical examination, were only available on paper. Clinical examination can improve the predictive performance of the offhand clinical judgement in daily clinical practise.

An adequate preoperative assessment of operation risk and operability is essential to ensure optimal treatment for the individual patient. Predictive models should be able to identify patients with irresectable disease. Ovarian cancer is a heterogeneous disease entity therefore the perfect prediction model remains an illusion. However large prospective multicentre trials should be able to improve performance or identify more accurate predictors. In the future computerized patient files will facilitate easily application and updating of institutional or regional prediction models.

In conclusion, preoperative clinical judgment of suboptimal cytoreduction at primary cytoreductive surgery in patients with advanced stage EOC shows limited accuracy. Given the poor inter-observer reproducibility prediction models could attribute to uniform treatment decisions and improve counseling.

ACKNOWLEDGMENTS

The authors would like to thank the observers who judged the cases.

REFERENCES

1. Harries M, Gore M. Part I: chemotherapy for epithelial ovarian cancer-treatment at first diagnosis. Lancet Oncol 2002;3(9):529-36.
2. Bristow RE, Tomacruz RS, Armstrong DK, Trimble EL, Montz FJ. Survival effect of maximal cytoreductive surgery for advanced ovarian carcinoma during the platinum era: a meta-analysis. J Clin Oncol 2002;20(5):1248-59.
3. Hoskins WJ, McGuire WP, Brady MF, Homesley HD, Creasman WT, Berman M, et al. The effect of diameter of largest residual disease on survival after primary cytoreductive surgery in patients with suboptimal residual epithelial ovarian carcinoma. Am J Obstet Gynecol 1994;170(4):974-9; discussion 979-80.
4. Vergote I, De Wever I, Tjalma W, Van Gramberen M, Decloedt J, van Dam P. Neoadjuvant chemotherapy or primary debulking surgery in advanced ovarian carcinoma: a retrospective analysis of 285 patients. Gynecol Oncol 1998;71(3):431-6.
5. Vergote I, Trope C, Amant F, Kristensen GB, Sardi JE, Ehlen T, et al. EORTC-GCG/NCIC-CTG Randomised trial comparing primary debulking surgery with neoadjuvant chemotherapy in stage IIIC/IV ovarian, fallopian tube and peritoneal cancer. In: 12th Biennal Meeting International Gynecologic Cancer Society; 2008; Bangkok, Thailand; 2008.
6. Axtell AE, Lee MH, Bristow RE, Dowdy SC, Cliby WA, Raman S, et al. Multi-institutional reciprocal validation study of computed tomography predictors of suboptimal primary cytoreduction in patients with advanced ovarian cancer. J Clin Oncol 2007;25(4):384-9.
7. Obeidat B, Latimer J, Crawford R. Can optimal primary cytoreduction be predicted in advanced stage epithelial ovarian cancer? Role of preoperative serum CA-125 level. Gynecol Obstet Invest 2004;57(3):153-6.
8. Chi DS, Venkatraman ES, Masson V, Hoskins WJ. The ability of preoperative serum CA-125 to predict optimal primary tumor cytoreduction in stage III epithelial ovarian carcinoma. Gynecol Oncol 2000;77(2):227-31.
9. Brockbank EC, Ind TE, Barton DP, Shepherd JH, Gore ME, A'Hern R, et al. Preoperative predictors of suboptimal primary surgical cytoreduction in women with clinical evidence of advanced primary epithelial ovarian cancer. Int J Gynecol Cancer 2004;14(1):42-50.
10. Arits AH, Stoot JE, Botterweck AA, Roumen FJ, Voogd AC. Preoperative serum CA125 levels do not predict suboptimal cytoreductive surgery in epithelial ovarian cancer. Int J Gynecol Cancer 2008;18(4):621-8.
11. Nelson BE, Rosenfield AT, Schwartz PE. Preoperative abdominopelvic computed tomographic prediction of optimal cytoreduction in epithelial ovarian carcinoma. J Clin Oncol 1993;11(1):166-72.
12. Bristow RE, Duska LR, Lambrou NC, Fishman EK, O'Neill MJ, Trimble EL, et al. A model for predicting surgical outcome in patients with advanced ovarian carcinoma using computed tomography. Cancer 2000;89(7):1532-40.
13. Dowdy SC, Mullany SA, Brandt KR, Huppert BJ, Cliby WA. The utility of computed tomography scans in predicting suboptimal cytoreductive surgery in women with advanced ovarian carcinoma. Cancer 2004;101(2):346-52.
14. 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(1):263-4.
15. Tingulstad S, Hagen B, Skjeldestad FE, Halvorsen T, Nustad K, Onsrud M. The risk-of-malignancy index to evaluate potential ovarian cancers in local hospitals. Obstet Gynecol 1999;93(3):448-52.
16. Chi DS, Zivanovic O, Palayekar MJ, Eisenhauer EL, Abu-Rustum NR, Sonoda Y, et al. A contemporary analysis of the ability of preoperative serum CA-125 to predict primary cytoreductive outcome in patients with advanced ovarian, tubal and peritoneal carcinoma. Gynecol Oncol 2009;112(1):6-10.
17. Fleiss J. Statistical Methods for Rates and Proportions. New York: John Wiley; 1981.
18. Landis JR, Koch GG. The measurement of observer agreement for categorical data. Biometrics 1977;33(1):159-74.
19. Giraudeau B, Mary JY. Planning a reproducibility study: how many subjects and how many replicates per subject for an expected width of the 95 per cent confidence interval of the intraclass correlation coefficient. Stat Med 2001;20(21):3205-14.

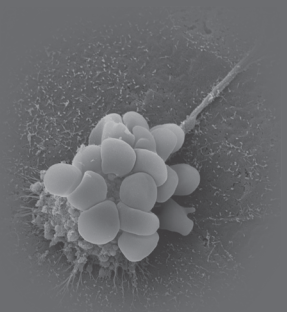
20. Brun JL, Rouzier R, Uzan S, Darai E. External validation of a laparoscopic-based score to evaluate resectability of advanced ovarian cancers: clues for a simplified score. Gynecol Oncol 2008;110(3):354-9.
21. Vergote I, Marquette S, Amant F, Berteloot P, Neven P. Port-site metastases after open laparoscopy: a study in 173 patients with advanced ovarian carcinoma. Int J Gynecol Cancer 2005;15(5):776-9.
22. van der Steeg JW, Steures P, Eijkemans MJ, Habbema JD, Bossuyt PM, Hompes PG, et al. Do clinical prediction models improve concordance of treatment decisions in reproductive medicine? Bjog 2006;113(7):825-31.
23. Petru E, Luck HJ, Stuart G, Gaffney D, Millan D, Vergote I. Gynecologic Cancer Intergroup (GCIG) proposals for changes of the current FIGO staging system. Eur J Obstet Gynecol Reprod Biol 2009;143(2):69-74.

2.2

Nomogram for suboptimal cytoreduction at primary surgery for advanced stage ovarian cancer.

C.G. Gerestein
M.J. Eijkemans
J. Bakker
O.E. Elgersma
M.E.L van der Burg
G.S. Kooi
C.W. Burger

submitted



ABSTRACT

Objectives: 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 >1cm, could guide treatment decisions and improve counselling. The objective of this study is to identify predictive computed tomography (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 is 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 fifteen patients with FIGO stage III/IV EOC entered the study protocol. Optimal cytoreduction was achieved in 52 (45%) patients. A suboptimal cytoreduction could be predicted by preoperative blood platelet count (P = 0.1990; 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 cuts (P = 0.0385; OR 2.294) with a for optimism corrected c-statistic of 0.67.

Conclusions: Suboptimal cytoreduction could be 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.

INTRODUCTION

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 Placlitaxel 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. [7, 61] Patients with residual disease >1cm 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 neo-adjuvant chemotherapy followed by interval cytoreduction.[8, 12-15]
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.[7, 10] It is suggested that outcome could be improved by referral of all patients with suspected EOC to high volume centres.
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 under treatment in 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.[11, 62]

Several studies identified computed tomography (CT) scan parameters predictive for suboptimal cytoreduction at primary cytoreduction for advanced stage EOC.[16, 24-27] Accuracy ranges between 71 and 93%.[16, 25, 26] Each study identifies a different set of CT scan predictors in relatively small single centre data sets with retrospective study designs, resulting in a disappointing predictive performance if applied to other patients cohorts. [16, 29] 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 easy to use in daily clinical practise.

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.[54]

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 neo-adjuvant chemotherapy was not the standard of care and only reserved for patients unable to withstand extensive surgical procedures due to a poor physical condition or with extensive extra-abdominal disease.
The study was approved by the Medical Ethical Committee of the Erasmus University Medical Center and was performed according to the standards outlined in the Declaration of Helsinki.

Pre-operative 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 made within 4 weeks prior to surgery. A standard CT scanning protocol was used. With oral and intravenous contrast images with a 5mm 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.[63]
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 cuts
and diaphragm disease. [16, 24-27]
DPT was defined as peritoneal thickening to ≥ 4mm involving at least two 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.[26]
Blood samples for measurement of CA125, blood platelet count, and albumin serum concentrations were drawn within four weeks prior to surgery. CA 125 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.

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 ≤1cm. Bowel resection, splenectomy, diaphragmatic stripping, partial liver resection and lymphadenectomy were performed if warranted to achieve an optimal cytoreduction, defined as residual disease ≤ 1cm.

Histo-pathological assessment

Histology was classified as serous, mucinous, endometroid, clear cell, and undifferentiated adenocarcinoma. Differentiation was classified in grade 1 to 3, according to the Silverberg criteria.[5] Subsequently, stage of the disease was determined according to FIGO guidelines.[53]

Study parameters and outcome measures

Parameters for analysis were the earlier described CT scan parameters, WHO performance status, CA125, albumin and blood platelet concentrations.
Primary outcome measure was suboptimal cytoreduction, defined as residual tumor >1cm.

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 pre-operative serum concentrations of log CA 125, 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 diffuse peritoneal thickening (DPT), large bowel mesentery implants (LBMI), ascites and diaphragm disease between the groups of patients with residual disease > 1cm to the group of patients with residual disease ≤ 1cm. $P<0.05$ was considered as statistically significant. We accounted for missing values by multiple imputation.[64] 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.[63] 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 patients with optimal cytoreduction, was expressed by means of the c-statistic.[65] 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.[65, 66] 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 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 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 excluded.

Finally, 115 patients with advanced stage EOC were eligible.

Median age was 62.4 years (range 15.9-83.6 years), with thirty-seven patients (32%) aged ≥ 70 years at time of surgery. Twenty-seven patients (23.5%) were cytoreduced to no macroscopic residual disease; cytoreduction to residual disease < 1cm was achieved in another twenty-five patients (21.7%).

Five patients were diagnosed with FIGO stage IIIA, 10 patients with FIGO stage IIIB, 79 patients with FIGO stage IIIC (extensive peritoneal disease) and 21 patients with stage IV disease. Further patients characteristics are depicted in Table 1.

Table 1. Patient characteristics of the study population.

Characteristics of the Study Population			
	Study Population	Residual disease ≤ 1cm	Residual disease > 1cm
Number of patients, *n* (%)	115	52 (45.2)	63 (54.8)
Age, *n* (%)			
< 50 years	15 (13.0)	6 (11.5)	9 (14.3)
50-59 years	31 (27.0)	18 (34.6)	14 (22.2)
60-69 years	32 (27.8)	17 (32.7)	15 (23.8)
≥ 70 years	37 (32.2)	11 (21.2)	26 (41.3)
WHO performance, *n* (%)			
WHO 0-I	106 (92.2)	51 (98.0)	55 (87.3)
WHO 2	5 (4.3)	0 (0)	5 (7.9)
WHO >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)

Initial predictive parameters for suboptimal cytoreduction

Median preoperative platelet count differed markedly between patients with residual disease ≤ 1cm and those with residual disease > 1cm; 341± 144.5 vs. 419.0 ± 177.7 *10^9/L (*P*=0.033), respectively. WHO performance status, preoperative serum CA125 level and albumin were comparable in both groups. (Table 2)

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

Table 2 Predictive parameters for suboptimal cytoreduction in patients with advanced stage of epithelial ovarian cancer. Differences, if any, between the group of patients with residual disease ≤ 1cm and those with residual disease >1cm are tested with Student-T and Chi square tests. Data is presented as median with standard deviation or in absolute numbers, when applicable. DPT=diffuse peritoneal thickening; LBMI=large bowel mesentery implants.

Predictors for suboptimal cytoreduction in Patients with Advanced Stage Epithelial Ovarian Cancer (FIGO III-IV)			
	Residual disease ≤ 1cm	Residual disease > 1cm	Significance
Number of patients	52	63	
WHO performance, *n* (%)			
WHO 0	26 (50.0)	25 (39.7)	0.140
WHO 1	25 (48.1)	30 (47.6)	
≥WHO 2	1 (1.9)	8 (12.7)	
Platelet count (*10^9/L)	341.0 ± 144.5	419.0 ± 177.7	**0.033**
Log CA 125 (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* (%)			
Diffuse peritoneal thickening	19 (36.5)	42 (66.7)	**0.001**
Large bowel mesentery implants	14 (26.9)	27 (42.9)	0.076
Ascites on two thirds of CT scan cuts	15 (28.8)	36 (57.1)	**0.002**
Diaphragm disease	9 (17.3)	23 (36.5)	**0.022**

Multivariate analysis of predictors for suboptimal cytoreduction

The results of the univariate analyses are depicted in Table 3. The variables with P<0.30 in the univariate analysis were assessed by multivariate Cox' regression, utilizing a backward elimination procedure. A suboptimal cytoreduction could be predicted by preoperative blood platelet count (*P*= 0.1990, OR 1.002), DPT (*P*=0.0074, OR 3.021) and presence of ascites (*P*= 0.0385, OR2.494) with a c-statistic of 0.74. In other words our model accurately discriminated patients with and without suboptimal cytoreduction in 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

Table 3. Univariate analysis of predictors of suboptimal cytoreduction. CT= computed tomography scan; DPT= diffuse peritoneal thickening; LBMI= large bowel mesentery implants; OR= odds ratio; NS=not significant; CI=confidence interval.

Univariate analysis of predictors of suboptimal cytoreduction		
Variable	Significance	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)**
Diaphragm Disease	0.3197	2.042 (0.500-8.330)

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.

DISCUSSION

In the current study we identified predictors for suboptimal cytoreduction at primary cytoreductive surgery for advanced stage EOC. Preoperative platelet count, diffuse peritoneal thickening (DPT) and presence of ascites on two thirds of the CT scan cuts were predictive for residual disease >1cm. 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 minimally tumor residu.[7, 8]
On the contrary, patients with suboptimal cytoreductive surgery will have limited survival benefit from this procedure. To determine the actual value of an alternative treatment approach with neo-adjuvant chemotherapy, the EORTC initiated a randomized trial to compare these two treatment approaches in patients with FIGO stage IIIC and IV EOC. The first results of these trial show no difference in progression-free and overall survival between both treatment strategies.[15] The most important prognostic factor was complete resection of all macroscopic tumor.

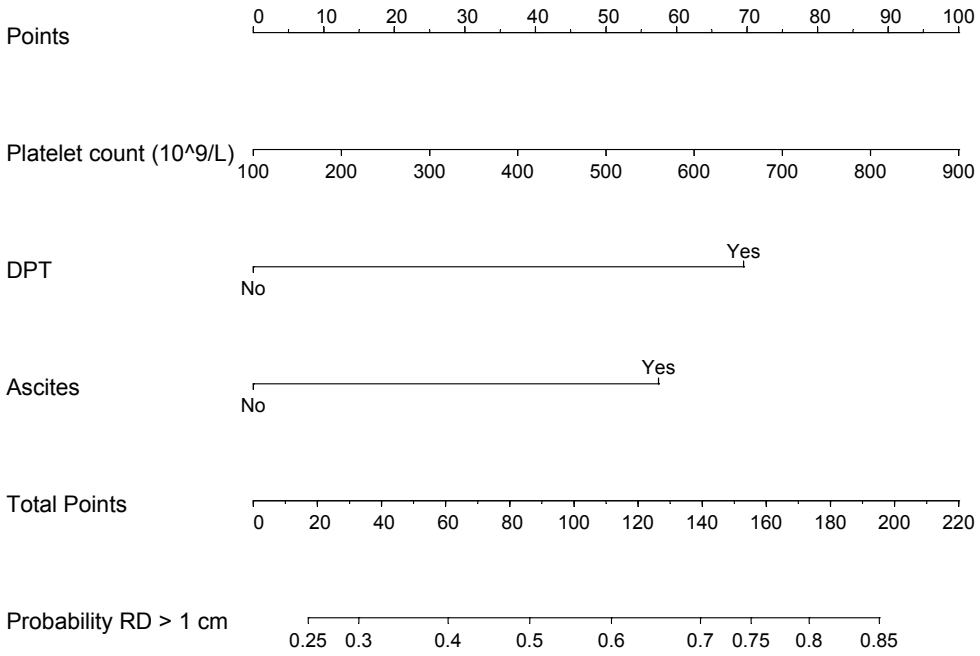


Figure 1. Nomogram for prediction of suboptimal cytoreduction.
For each level of predictive factors there is a number of points allocated at the point scale above. By adding the points of each parameter, the total points could be calculated. This number represents the probability of suboptimal cytoreduction.
RD=residual disease; DPT=diffuse peritoneal thickening.
For example in a patient with respectively a preoperative platelet count of 300 [25 points], DPT [70 points] and ascites on two thirds of the CT scan cuts [57 points] the total score is 152 points (25+70+57) representing a 74% change of suboptimal cytoreduction.

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.

Prediction models based on radiographic characteristics show accuracy rates ranging from 71 to 93%.[16, 25, 26, 30, 52, 67, 68] However accuracy drops when these models are extrapolated in other patient populations.[16, 29]

Our nomogram accurately predicted surgical outcome in 74% of the patients. This confirms the limited accuracy of currently available predictors. Nevertheless, we do believe prediction models could be of value in the management of these 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 in the individual patient. Future research should be directed into identifying more accurate predictors of surgical outcome.[69]

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.[16, 24-27] With this design we were able to generate a model with identical predictors as described by Dowdy et al.[26] 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 in other patient populations, these data support the predictive importance of those CT predictors in patients with an advanced stage EOC. In contrast to earlier described prediction models, we aimed to generate a simple model which is easy to use in daily clinical practise.[28] The annotation in a nomogram facilitates a convenient clinical utilization.

Nevertheless, our current study has several limitations that must me recognized and considered in interpreting these data. Firstly, the optimal cytoreduction rate is 45 %, although within range of other reports, relatively low, this could reflect a less aggressive philosophy. Unfortunately, our study population was to small to determine the impact of individual surgeon's skills and philosophy on surgical outcome.
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 to a clear need for a revised sub classification of advanced stage disease.[60]
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, diffuse peritoneal thickening (DPT) and presence of ascites on two thirds of the CT scan cuts were predictive for residual disease >1cm.
The generated nomogram can, after external validation, be used to estimate surgical outcome in each individual patient and be valuable for counselling and electing tailored treatment strategies.

Acknowledgments

The authors would like to thank D.W. van der Spek and G.M. Nieuwenhuyzen-de Boer for their help with data acquisition. We thank all participating departments of gynaecology for their cooperation and efforts to include patients in this study.

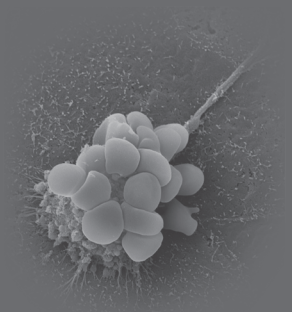
REFERENCES

1. Globocan 2002 database http://www-dep.iarc.fr/ assessed april 20th 2009. In; .
2. Bristow RE, Tomacruz RS, Armstrong DK, Trimble EL, Montz FJ. Survival effect of maximal cytoreductive surgery for advanced ovarian carcinoma during the platinum era: a meta-analysis. J Clin Oncol 2002;20(5):1248-59.
3. du Bois A, Reuss A, Pujade-Lauraine E, Harter P, Ray-Coquard I, Pfisterer J. Role of surgical outcome as prognostic factor in advanced epithelial ovarian cancer: A combined exploratory analysis of 3 prospectively randomized phase 3 multicenter trials: by the Arbeitsgemeinschaft Gynaekologische Onkologie Studiengruppe Ovarialkarzinom (AGO-OVAR) and the Groupe d'Investigateurs Nationaux Pour les Etudes des Cancers de l'Ovaire (GINECO). Cancer 2009.
4. Vergote I, De Wever I, Tjalma W, Van Gramberen M, Decloedt J, van Dam P. Neoadjuvant chemotherapy or primary debulking surgery in advanced ovarian carcinoma: a retrospective analysis of 285 patients. Gynecol Oncol 1998;71(3):431-6.
5. du Bois A, Reuss A, Pujade-Lauraine E, Harter P, Ray-Coquard I, Pfisterer J. Role of surgical outcome as prognostic factor in advanced epithelial ovarian cancer: A combined exploratory analysis of 3 prospectively randomized phase 3 multicenter trials: by the Arbeitsgemeinschaft Gynaekologische Onkologie Studiengruppe Ovarialkarzinom (AGO-OVAR) and the Groupe d'Investigateurs Nationaux Pour les Etudes des Cancers de l'Ovaire (GINECO). Cancer 2009;115(6):1234-44.
6. Hoskins WJ, McGuire WP, Brady MF, Homesley HD, Creasman WT, Berman M, et al. The effect of diameter of largest residual disease on survival after primary cytoreductive surgery in patients with suboptimal residual epithelial ovarian carcinoma. Am J Obstet Gynecol 1994;170(4):974-9; discussion 979-80.
7. Schwartz PE, Chambers JT, Makuch R. Neoadjuvant chemotherapy for advanced ovarian cancer. Gynecol Oncol 1994;53(1):33-7.
8. Vergote I, Trope C, Amant F, Kristensen GB, Sardi JE, Ehlen T, et al. EORTC-GCG/NCIC-CTG Randomised trial comparing primary debulking surgery with neoadjuvant chemotherapy in stage IIIC/IV ovarian, fallopian tube and peritoneal cancer. In: 12th Biennal Meeting International Gynecologic Cancer Society; 2008; Bangkok, Thailand; 2008.
9. Vernooij F, Heintz P, Witteveen E, van der Graaf Y. The outcomes of ovarian cancer treatment are better when provided by gynecologic oncologists and in specialized hospitals: a systematic review. Gynecol Oncol 2007;105(3):801-12.
10. Goff BA, Matthews BJ, Larson EH, Andrilla CH, Wynn M, Lishner DM, et al. Predictors of comprehensive surgical treatment in patients with ovarian cancer. Cancer 2007;109(10):2031-42.
11. Carney ME, Lancaster JM, Ford C, Tsodikov A, Wiggins CL. A population-based study of patterns of care for ovarian cancer: who is seen by a gynecologic oncologist and who is not? Gynecol Oncol 2002;84(1):36-42.
12. Everett EN, Heuser CC, Pastore LM, Anderson WA, Rice LW, Irvin WP, et al. Predictors of suboptimal surgical cytoreduction in women treated with initial cytoreductive surgery for advanced stage epithelial ovarian cancer. Am J Obstet Gynecol 2005;193(2):568-74; discussion 574-6.
13. Bristow RE, Duska LR, Lambrou NC, Fishman EK, O'Neill MJ, Trimble EL, et al. A model for predicting surgical outcome in patients with advanced ovarian carcinoma using computed tomography. Cancer 2000;89(7):1532-40.
14. Axtell AE, Lee MH, Bristow RE, Dowdy SC, Cliby WA, Raman S, et al. Multi-institutional reciprocal validation study of computed tomography predictors of suboptimal primary cytoreduction in patients with advanced ovarian cancer. J Clin Oncol 2007;25(4):384-9.
15. Dowdy SC, Mullany SA, Brandt KR, Huppert BJ, Cliby WA. The utility of computed tomography scans in predicting suboptimal cytoreductive surgery in women with advanced ovarian carcinoma. Cancer 2004;101(2):346-52.
16. Risum S, Hogdall C, Loft A, Berthelsen AK, Hogdall E, Nedergaard L, et al. Prediction of suboptimal primary cytoreduction in primary ovarian cancer with combined positron emission tomography/computed tomography--a prospective study. Gynecol Oncol 2008;108(2):265-70.

17. Gemer O, Gdalevich M, Ravid M, Piura B, Rabinovich A, Gasper T, et al. A multicenter validation of computerized tomography models as predictors of non- optimal primary cytoreduction of advanced epithelial ovarian cancer. Eur J Surg Oncol 2009.
18. Tingulstad S, Hagen B, Skjeldestad FE, Halvorsen T, Nustad K, Onsrud M. The risk-of-malignancy index to evaluate potential ovarian cancers in local hospitals. Obstet Gynecol 1999;93(3):448-52.
19. Steyerberg EW, Eijkemans MJ, Harrell FE, Jr., Habbema JD. Prognostic modelling with logistic regression analysis: a comparison of selection and estimation methods in small data sets. Stat Med 2000;19(8):1059-79.
20. Shimizu Y, Kamoi S, Amada S, Hasumi K, Akiyama F, Silverberg SG. 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(1):2-12.
21. 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(1):263-4.
22. van Buuren S, Boshuizen HC, Knook DL. Multiple imputation of missing blood pressure covariates in survival analysis. Stat Med 1999;18(6):681-94.
23. Harrell FE, Jr., Lee KL, Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. Stat Med 1996;15(4):361-87.
24. Van Houwelingen JC, Le Cessie S. Predictive value of statistical models. Stat Med 1990;9(11):1303-25.
25. Saygili U, Guclu S, Uslu T, Erten O, Demir N, Onvural A. Can serum CA-125 levels predict the optimal primary cytoreduction in patients with advanced ovarian carcinoma? Gynecol Oncol 2002;86(1):57-61.
26. Nelson BE, Rosenfield AT, Schwartz PE. Preoperative abdominopelvic computed tomographic prediction of optimal cytoreduction in epithelial ovarian carcinoma. J Clin Oncol 1993;11(1):166-72.
27. Meyer JI, Kennedy AW, Friedman R, Ayoub A, Zepp RC. Ovarian carcinoma: value of CT in predicting success of debulking surgery. AJR Am J Roentgenol 1995;165(4):875-8.
28. Qayyum A, Coakley FV, Westphalen AC, Hricak H, Okuno WT, Powell B. Role of CT and MR imaging in predicting optimal cytoreduction of newly diagnosed primary epithelial ovarian cancer. Gynecol Oncol 2005;96(2):301-6.
29. Salani R, Axtell A, Gerardi M, Holschneider C, Bristow RE. Limited utility of conventional criteria for predicting unresectable disease in patients with advanced stage epithelial ovarian cancer. Gynecol Oncol 2008;108(2):271-5.
30. Ferrandina G, Sallustio G, Fagotti A, Vizzielli G, Paglia A, Cucci E, et al. Role of CT scan-based and clinical evaluation in the preoperative prediction of optimal cytoreduction in advanced ovarian cancer: a prospective trial. Br J Cancer 2009;101(7):1066-73.
31. Petru E, Luck HJ, Stuart G, Gaffney D, Millan D, Vergote I. Gynecologic Cancer Intergroup (GCIG) proposals for changes of the current FIGO staging system. Eur J Obstet Gynecol Reprod Biol 2009;143(2):69-74.

3

Postoperative mortality after surgery for epithelial ovarian cancer.

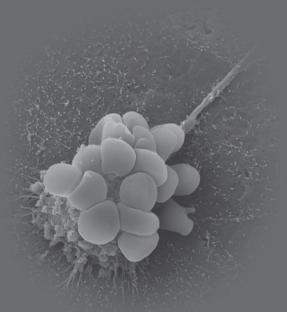


3.1

Postoperative mortality after primary cytoreductive surgery for advanced stage epithelial ovarian cancer.

C.G. Gerestein
R.A.M. Damhuis
C.W. Burger
G.S. Kooi

Gynecol Oncol. 2009 Sep;114(3):523-7.



ABSTRACT

Objectives: Accurate estimation of the risk of postoperative mortality (POM) is essential for the decision whether or not to perform cytoreductive surgery in a patient with advanced stage ovarian cancer. To ascertain modern reference figures, a systematic review of studies reporting POM after primary cytoreductive surgery for advanced stage epithelial ovarian cancer (EOC) was performed.

Materials and Methods: A Medline search was performed to retrieve papers on primary cytoreductive surgery for advanced stage EOC. Twenty-three papers met the inclusion criteria and were reviewed.

Results: According to population-based studies, POM after primary cytoreductive surgery for EOC is 3.7% on average. Single centre studies report an average rate of 2.5%. The overall mean POM is 2.8%. POM is more frequent for elderly women and after extensive procedures. Accurate information on age-specific and procedure-specific rates could not be obtained.

Conclusions: POM rates after surgery for EOC are satisfactorily low. There is a clear need for reliable reference figures for mortality after debulking surgery in the elderly.

INTRODUCTION

Epithelial ovarian cancer (EOC) continues to be the leading cause of death from gynecological cancer.[51] Cure rates are low because most patients are diagnosed with advanced disease. Treatment is based on cytoreductive surgery and platinum-based chemotherapy. Individual prognosis depends on FIGO (International Federation of Gynaecology and Obstetrics) stage [53] and the ability to perform optimal cytoreductive surgery.[7, 70, 71] To achieve a minimal residual tumour load, surgery may need to be quite extensive and can be accompanied by postoperative complications.

Postoperative morbidity and mortality depend upon the extent of surgery, age, performance status and comorbidity.[36, 72-74] Cytoreductive surgery clearly improves survival but may be withheld if the operative risk is deemed too high. The role of upfront cytoreductive surgery in patients with unresectable disease is under debate. Several studies suggest that neoadjuvant chemotherapy followed by interval surgery will lead to similar survival with less operative morbidity. [12, 14, 75]

POM is generally defined as death from any cause within 30 days of operation and has been suggested as a performance indicator for other types of cancer. For ovarian cancer, POM is considered to be low but may yet be useful as an objective parameter of surgical care. To obtain reference standards for POM, we performed a systematic review on published POM rates after primary cytoreductive surgery for advanced stage EOC.

MATERIALS AND METHODS

Search methods

We performed a Medline search of English-language articles published between January 1, 1981, and March 1, 2008. The keywords used were: "ovarian carcinoma", "ovarian cancer" ,"ovarian neoplasma" and "cytoreductive surgery", "surgical outcome", "30-day mortality", "in hospital mortality", "postoperative death", "postoperative mortality" and "postoperative complications". Additionally, the Cochrane Library and Embase were searched for any relevant reports.

Inclusion criteria

POM was defined as death from any cause within 30 days of operation and in-hospital mortality as death of a patient without being discharged after surgery. Manuscripts were included if POM or in-hospital mortality after primary cytoreductive surgery for advanced stage (FIGO stage III/IV) EOC, fallopian tube or peritoneal cancer was reported.

Studies reporting results from interval cytoreductive surgery, surgery for recurrent ovarian cancer and those reporting results of second-look laparotomy were excluded from analysis.

Data extraction

Two authors (C.G.G. and R.A.D.) reviewed the articles that fulfilled the inclusion criteria. From the selected articles we abstracted the following information: name of the first author, year of publication, type of patient cohort, type of surgery, number of patients, median patient age, FIGO stage, optimal cytoreduction rate, definition of optimal cytoreduction, number and percentage of patients who died in the postoperative period. If mentioned, cause of death information was also extracted. Cause of death was reclassified according to the methodology proposed by Waljee et al.[76] In this classification the complication that attributed most to the patient's death during a postoperative course has to be assigned and stratified in five main categories. (Table 4)

Data analysis

Included studies were divided in two main categories: studies reporting results of general primary cytoreductive surgery and studies reporting specific surgical procedures at primary surgery in patients with advanced stage EOC. Subsequently, study results were sorted and summarized in tables according to type of cohort reported (population-based, single centre, multi centre) and year of publication.

RESULTS

Description of studies

We identified 23 eligible reports on primary cytoreductive surgery for advanced stage EOC. Twenty reports described retrospectively collected data; three studies reported results of a prospective study.

Population-based studies

Three population-based case series on cytoreductive surgery for advanced stage EOC were found, with a mean POM rate of 3.7% (range 2.5 - 4.8%) (Table1).

Single centre studies

Twenty single centre reports, on primary cytoreductive surgery for advanced stage EOC, reported data on postoperative mortality. POM ranged from 0 to 6.7 % (mean 2.5%) (Table 2).

Table 1. Review of population-based studies describing postoperative mortality after primary cytoreductive surgery for advanced stage EOC. N= number of patients; POM=postoperative mortality; RD=residual disease; NA=not applicable.

Article	Publication year	Country	N	Median age (years)	FIGO stage	Optimal Cytoreduction		POM
						%	RD	N (%)
Soegaard (30)	2005	Denmark	83	NA	III-IV	79%	<1cm	4 **(4.8)**
Engelen (23)	2006	Netherlands	240	NA	III	52%	<2cm	6 **(2.5)**
Marx (31)	2007	Denmark	292	62	III	39%	<1cm	13 **(4.4)**

Table 2. Postoperative mortality after primary debulking surgery for advanced stage EOC reported from single institutions.

Article	Year of publication	N	Median age (years)	FIGO stage	Optimal cytoreduction %	RD	Definition POM	POM N (%)
1980-1990								
Hacker(32)	1983	47	58	III-IV	66	<1.5cm	30d	1 **(2.1)**
Chen(33)	1985	60	59	III-IV	100	<1.5cm	30d	1 **(1.7)**
Piver(34)	1986	50	62	III-IV	76	≤2cm	30d	0 **(0)**
Heintz(35)	1986	70	58	III-IV	46	≤1cm	H	2 **(2.9)**
1991-2000								
Eisenkop(36)	1992	263	61	IIIC-IV	54	≤1cm	28d	16 **(6.1)**
Venesmaa(37)	1992	264	NA	III-IV	NA		30d	4 **(1.5)**
Marchetti(19)	1993	70	63	III-IV	37	≤2cm	30d	1 **(1.4)**
Guidozzi(38)	1994	30	56	III-IV	76	≤2cm	30d	2 **(6.7)**
Michel(39)	1997	152	NA	IIIB-IV	91	≤2cm	30d	2 **(1.3)**
Liu(40)	1997	47	NA	IV	30	≤2cm	30d	1 **(2.1)**
Lichtenegger(41)	1998	117	NA	III-IV	57	≤2cm	30d	2 **(1.7)**
Vergote(12)	1998	112	56	III-IV	89	≤1.5cm	30d	7 **(6.2)**
Bristow(42)	1999	84	61	IV	30	≤1cm	30d	5 **(6)**
Suzuki(43)	1999	45	NA	III-IV	57	≤2cm	30d	0 **(0)**
2001-2008								
Bristow(44)	2001	45	62	IIIB-IV	84	≤1cm	30d	1 **(2.2)**
Eisenkop(45)	2003	408	63	IIIC	96	≤1cm	30d	10 **(2.5)**
Eltabbakh(46)	2004	72	60	III-IV	49	≤1cm	30d	1 **(1.4)**
Chi(47)	2004	140	60	IIIC-IV	63	≤1cm	30d	1 **(0.7)**
Aletti(48)	2006	244	64	IIIC-IV	NA		30d	3 **(1.2)**
Susini(15)	2007	47	NA	III-IV	45	<1cm	30d	0 **(0)**

N= number of patients; RD=residual disease; 30d= 30-day mortality; H= in-hospital mortality; NA=not applicable.

Reports on specific surgical procedures

Subsequently, 7 reports on specific surgical procedures at primary surgery in patients with advanced stage EOC were added (Table 3). Again, the majority described retrospective data (86%). POM rates after surgery for EOC including bowel surgery varied between 0 en 5.9 % (mean 2.7%). Most reports described small case series (median 66 patients, range 42-101). Two studies reporting results of operations involving splenectomy met the inclusion criteria, they described a POM rate of 8.8 and 17% (Table 3).

Cause of death

Cause of death was specified in 11 studies (48%). Most common causes of death were sepsis (20.8%) and pulmonary embolism (25.0%) (Table 4).

Table 3. Postoperative mortality after primary cytoreductive surgery for advanced stage EOC including bowel resection or splenectomy.

Article	Year of publication	Perspective	N	Median age (years)	FIGO stage	Optimal cytoreduction %	RD	Definition POM	POM N(%)
Bowel									
Scarabelli(49)	2000	Single	66	NA	IIIC-IV	100	≤2cm	30d	0 **(0)**
Gilette-Cloven(50)	2001	Multi-center	101	65	III-IV	30	<1cm	30d	6 **(5.9)**
Mourton(51)	2005	Single	70	59	IIIC-IV	79	≤1cm	30d	1 **(1.4)**
Estes(52)	2006	Single	48	66	III-IV	52	≤1cm	30d	2 **(4)**
Cai(53)	2007	Single	42	52	IIIC	67	≤1cm	30d	0 **(0)**
Splenectomy									
Sonnendecker(54)	1989	Single	6	56	III-IV	100	≤1cm	30d	1 **(17)**
Ayhan(55)	2004	Single	34	60	IIIC	NA		month	3 **(8.8)**

N= number of patients; 30d= 30-day mortality; month= postoperative mortality within one month after surgery; RD=residual disease; NA=not applicable.

Table 4. Tabulation of causes of death.

Cause of death	N (%)
Surgical site complications	***7 (29)***
Haemorrhage	1
Surgical site infection Sepsis	5
Bowel perforation	1
Pulmonary failure	***1 (4)***
Pneumonia	1
Prolonged ventilator assistance	
Unplanned intubation	
Cardiac complications	***3 (13)***
Myocardial infarction	3
Unexplained cardiac arrest	
Congestive heart failure	
Venous thrombo- embolism	***6 (25)***
Deep venous embolism	
Pulmonary embolus	6
Other	***7 (29)***
Bowel obstruction	1
Renal failure	1
Stroke	2
Progressive disease	3

DISCUSSION

Population-based reports on POM after primary cytoreductive surgery for advanced stage EOC vary with rates ranging from 2.5% to 4.8%, with a mean of 3.7%. Reports from single centres present slightly better results, with a mean POM of 2.5%. The overall POM is 2.8% on average. Published results may, however, be biased due to reporting and publication bias.

The low operative risk corroborates the current treatment strategy of primary cytoreductive surgery followed by platinum based chemotherapy in patients with advanced stage EOC. Thus far, retrospective studies on neoadjuvant chemotherapy and interval surgery have shown inconsistent results. Until prospective trials demonstrate a clear benefit on survival or operative morbidity, the latter approach should be reserved for patients with probable residual disease and for patients in a poor physical condition.

Risk factors for POM

The studies included describe cohorts with rather heterogeneous patient and treatment characteristics. Documentation of these characteristics was too inconsistent to assess risk factors for POM but death in the postoperative period is known to be more common in elderly patients and after extensive surgery.

Unfortunately, many reports on cytoreductive surgery in the elderly had to be excluded from our analysis,. Although cytoreductive surgery for EOC is feasible at higher age procedures will be associated with increased morbidity and mortality [72, 74, 77-80]. This can be attributed to diminished vital functions and the presence of co-morbidity [72, 74].

Postoperative mortality rates in patients aged 80 years and older range from 5,4% till 11,7% [72, 73, 81, 82]. We recently reviewed all postoperative deaths after surgery for EOC in the south-western part of the Netherlands between 1989 and 2005. In this analysis POM increased with age from 1,5% for the age group 20-69 to 6,6 % for the age group 70-79 and 9,8% for patients aged 80 years or older. These results corroborate an increased POM rate for the elderly. Exclusion criteria may, however, seriously confound comparisons and information on comorbidity and performance status is necessary to interpret results in elderly series. In this context the risk factor profile proposed by Janda et al. provides a more individual risk assessment which may guide optimal choice of treatment [74]. This risk profile is based on age, FIGO stage, co-morbidity status and type of hospital. Patients are assigned to one of three groups, respectively, low-, moderate- and high risk for dying within 12 months from diagnosis. POM for patients aged ≥ 80 years was 0%, 9% and 21% in the low-, moderate- and high-risk groups, respectively.

Surgery for EOC is very heterogeneous and may range from a simple ovariectomy to major debulking operations involving bowel surgery and removal of internal organs. Obviously, POM will be associated with the extent of procedures performed but few studies report results by type of operation. Unfortunately, none of the population-based studies featured data on this subject. Reports on extensive procedures during primary cytoreductive surgery definitely show higher postoperative morbidity rates but the relation with POM is less evident. No relevant difference in postoperative mortality was seen if surgery included bowel surgery but a splenectomy has a negative impact on the peri- and postoperative course.

Treatment in high-volume hospitals and by specialized surgeons improves prognosis of EOC patients [7, 10, 83] but reports focusing on hospital procedures volume and surgeon specialty thus far failed to show a statistically significant association with operative morbidity or mortality [73, 83-85]. No studies were found reporting a significant difference in POM rate related to hospital

procedures volume or surgeon specialty. Engelen et al. demonstrated a difference in POM after cytoreductive surgery by general gynecologists compared to gynecologic oncologists (3.4% versus 1.0%) but this was non-significant (p=0.41) [85]. In a Canadian population-based study, POM did not differ markedly by hospital volume, institution type, or surgeon volume [84]. Earle et al. found a 2.1% POM rate for patients treated by gynecologic oncologists, 2.1% for patients treated by general gynecologists and 4% for patients treated by general surgeons (p=0.01) [83]. Results for the advanced stages could not be extracted from this report.

Individual preoperative risk assessment is suggested as a method to reduce postoperative mortality. Such an assessment should not only estimate the risk of peri- and postoperative complications but also predict the probability of extensive residual disease. Alleti et al. recently developed a prediction model for morbidity and mortality after primary cytoreductive surgery for advanced stage ovarian cancer. Albumin, American Society of Anesthesiologists (ASA) score and complexity of surgery were identified as the main predictors for 30-day morbidity. Predictors for 3-month mortality were age and ASA score [36]. Given the absence of other treatment options with an intention for cure, it is unsure at what risk patients should be advised to refrain from surgical treatment. In high-risk patients surgery may be delayed to optimize the patient's physical condition, for example by improving the nutritional status or adequate treatment of co-morbidity [86, 87].

Unfortunately, the actual cause of death is only reported in a minority of the studies. Overall, cause of death appears to be more often related to general events than to surgical complications. Thrombosis and pulmonary embolism are frequently reported, underlining the importance of adequate antithrombotic therapy in surgery for ovarian cancer[88].

Systematic assessment of the peri- and postoperative course after major surgery is suggested to improve results. This is confirmed by reports on the National Surgical Quality Improvement Program (NSQIP) [89-91]. This program started in 1994 and assesses surgical quality by registration and analysis of peri- and postoperative complications after major surgery in the USA. With the use of these data, case-mix adjusted results can be generated for participating clinics, allowing these centres to compare their performance. Since the onset of this program, 30-day mortality rate after major surgery has decreased by 31% [91]. Periodically performed institutional evaluations of postoperative complications can improve surgical quality by identifying structure and process failures. To determine similar reference standards and case-mix models for ovarian cancer, a meta-analysis of individual data from multiple centers will be required. An international standard for data collection and reporting needs to established.

In conclusion, POM after primary cytoreductive surgery for advanced stage EOC is satisfactory low. For elderly patients with extensive disease, other treatment strategies may be considered. However, even in the elderly cytoreductive surgery can be performed at acceptable risk. POM

prediction models can be used to identify patients who may benefit from alternative treatment approaches. Assessment of prognostic factors needs to be facilitated by accurate and uniform registration during the pre-, peri- and postoperative period across a broad cohort of patients.

REFERENCES

1. Harries M, Gore M. Part I: chemotherapy for epithelial ovarian cancer-treatment at first diagnosis. Lancet Oncol. 2002 Sep;3(9):529-36.
2. Changes in definitions of clinical staging for carcinoma of the cervix and ovary: International Federation of Gynecology and Obstetrics. Am J Obstet Gynecol. 1987 Jan;156(1):263-4.
3. Teramukai S, Ochiai K, Tada H, Fukushima M. PIEPOC: a new prognostic index for advanced epithelial ovarian cancer--Japan Multinational Trial Organization OC01-01. J Clin Oncol. 2007 Aug 1;25(22):3302-6.
4. Winter WE, 3rd, Maxwell GL, Tian C, Sundborg MJ, Rose GS, Rose PG, et al. Tumor residual after surgical cytoreduction in prediction of clinical outcome in stage IV epithelial ovarian cancer: a Gynecologic Oncology Group Study. J Clin Oncol. 2008 Jan 1;26(1):83-9.
5. Bristow RE, Tomacruz RS, Armstrong DK, Trimble EL, Montz FJ. Survival effect of maximal cytoreductive surgery for advanced ovarian carcinoma during the platinum era: a meta-analysis. J Clin Oncol. 2002 Mar 1;20(5):1248-59.
6. Alphs HH, Zahurak ML, Bristow RE, Diaz-Montes TP. Predictors of surgical outcome and survival among elderly women diagnosed with ovarian and primary peritoneal cancer. Gynecol Oncol. 2006 Dec;103(3):1048-53.
7. Aletti GD, Santillan A, Eisenhauer EL, Hu J, Aletti G, Podratz KC, 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 Oct;107(1):99-106.
8. Diaz-Montes TP, Zahurak ML, Giuntoli RL, 2nd, Gardner GJ, Gordon TA, Armstrong DK, et al. Surgical care of elderly women with ovarian cancer: a population-based perspective. Gynecol Oncol. 2005 Nov;99(2):352-7.
9. Janda M, Youlden DR, Baade PD, Jackson D, Obermair A. Elderly patients with stage III or IV ovarian cancer: should they receive standard care? Int J Gynecol Cancer. 2008 Sep-Oct;18(5):896-907.
10. Schwartz PE, Chambers JT, Makuch R. Neoadjuvant chemotherapy for advanced ovarian cancer. Gynecol Oncol. 1994 Apr;53(1):33-7.
11. Jacob JH, Gershenson DM, Morris M, Copeland LJ, Burke TW, Wharton JT. Neoadjuvant chemotherapy and interval debulking for advanced epithelial ovarian cancer. Gynecol Oncol. 1991 Aug;42(2):146-50.
12. Vergote I, De Wever I, Tjalma W, Van Gramberen M, Decloedt J, van Dam P. Neoadjuvant chemotherapy or primary debulking surgery in advanced ovarian carcinoma: a retrospective analysis of 285 patients. Gynecol Oncol. 1998 Dec;71(3):431-6.
13. Waljee JF, Windisch S, Finks JF, Wong SL, Birkmeyer JD. Classifying cause of death after cancer surgery. Surg Innov. 2006 Dec;13(4):274-9.
14. Wright JD, Herzog TJ, Powell MA. Morbidity of cytoreductive surgery in the elderly. Am J Obstet Gynecol. 2004 May;190(5):1398-400.
15. Susini T, Amunni G, Busi E, Villanucci A, Carriero C, Taddei G, et al. Ovarian cancer in the elderly: feasibility of surgery and chemotherapy in 89 geriatric patients. Int J Gynecol Cancer. 2007 May-Jun;17(3):581-8.
16. Lawton FG, Hacker NF. Surgery for invasive gynecologic cancer in the elderly female population. Obstet Gynecol. 1990 Aug;76(2):287-9.
17. Bruchim I, Altaras M, Fishman A. Age contrasts in clinical characteristics and pattern of care in patients with epithelial ovarian cancer. Gynecol Oncol. 2002 Sep;86(3):274-8.
18. Cloven NG, Manetta A, Berman ML, Kohler MF, DiSaia PJ. Management of ovarian cancer in patients older than 80 years of Age. Gynecol Oncol. 1999 Apr;73(1):137-9.
19. Marchetti DL, Lele SB, Priore RL, McPhee ME, Hreshchyshyn MM. Treatment of advanced ovarian carcinoma in the elderly. Gynecol Oncol. 1993 Apr;49(1):86-91.
20. Vernooij F, Heintz P, Witteveen E, van der Graaf Y. The outcomes of ovarian cancer treatment are better when provided by gynecologic oncologists and in specialized hospitals: a systematic review. Gynecol Oncol. 2007 Jun;105(3):801-12.
21. Earle CC, Schrag D, Neville BA, Yabroff KR, Topor M, Fahey A, et al. Effect of surgeon specialty on processes of care and outcomes for ovarian cancer patients. J Natl Cancer Inst. 2006 Feb 1;98(3):172-80.

22. Elit L, Bondy SJ, Paszat L, Przybysz R, Levine M. Outcomes in surgery for ovarian cancer. Gynecol Oncol. 2002 Dec;87(3):260-7.
23. Engelen MJ, Kos HE, Willemse PH, Aalders JG, de Vries EG, Schaapveld M, et al. Surgery by consultant gynecologic oncologists improves survival in patients with ovarian carcinoma. Cancer. 2006 Feb 1;106(3):589-98.
24. Geisler JP, Linnemeier GC, Thomas AJ, Manahan KJ. Nutritional assessment using prealbumin as an objective criterion to determine whom should not undergo primary radical cytoreductive surgery for ovarian cancer. Gynecol Oncol. 2007 Jul;106(1):128-31.
25. Zaloga GP. Parenteral nutrition in adult inpatients with functioning gastrointestinal tracts: assessment of outcomes. Lancet. 2006 Apr 1;367(9516):1101-11.
26. Black D, Iasonos A, Ahmed H, Chi DS, Barakat RR, Abu-Rustum NR. Effect of perioperative venous thromboembolism on survival in ovarian, primary peritoneal, and fallopian tube cancer. Gynecol Oncol. 2007 Oct;107(1):66-70.
27. Khuri SF, Daley J, Henderson W, Barbour G, Lowry P, Irvin G, et al. The National Veterans Administration Surgical Risk Study: risk adjustment for the comparative assessment of the quality of surgical care. J Am Coll Surg. 1995 May;180(5):519-31.
28. Khuri SF, Daley J, Henderson W, Hur K, Demakis J, Aust JB, 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 Oct;228(4):491-507.
29. Khuri SF. The NSQIP: a new frontier in surgery. Surgery. 2005 Nov;138(5):837-43.
30. Soegaard Andersen E, Knudsen A, Svarrer T, Lund B, Nielsen K, Grove A, et al. The results of treatment of epithelial ovarian cancer after centralisation of primary surgery. Results from North Jutland, Denmark. Gynecol Oncol. 2005 Dec;99(3):552-6.
31. Marx C, Bendixen A, Hogdall C, Ottosen C, Kehlet H, Ottesen B. Organisation and quality of primary surgical intervention for ovarian cancer in Denmark. Acta Obstet Gynecol Scand. 2007;86(12):1496-502.
32. Hacker NF, Berek JS, Lagasse LD, Nieberg RK, Elashoff RM. Primary cytoreductive surgery for epithelial ovarian cancer. Obstet Gynecol. 1983 Apr;61(4):413-20.
33. Board RE, Bruijns CT, Pronk AE, Ryder WD, Wilkinson PM, Welch R, et al. Stage- and CA125-related survival in patients with epithelial ovarian cancer treated at a cancer center. Int J Gynecol Cancer. 2006 Jan-Feb;16 Suppl 1:18-24.
34. Piver MS, 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 May;24(1):1-8.
35. Heintz AP, Hacker NF, Berek JS, Rose TP, Munoz AK, Lagasse LD. Cytoreductive surgery in ovarian carcinoma: feasibility and morbidity. Obstet Gynecol. 1986 Jun;67(6):783-8.
36. Eisenkop SM, Spirtos NM, Montag TW, Nalick RH, Wang HJ. The impact of subspecialty training on the management of advanced ovarian cancer. Gynecol Oncol. 1992 Nov;47(2):203-9.
37. Venesmaa P, Ylikorkala O. Morbidity and mortality associated with primary and repeat operations for ovarian cancer. Obstet Gynecol. 1992 Feb;79(2):168-72.
38. Guidozzi F, Ball JH. Extensive primary cytoreductive surgery for advanced epithelial ovarian cancer. Gynecol Oncol. 1994 Jun;53(3):326-30.
39. Michel G, De Iaco P, Castaigne D, el-Hassan MJ, Lobreglio R, Lhomme C, et al. Extensive cytoreductive surgery in advanced ovarian carcinoma. Eur J Gynaecol Oncol. 1997;18(1):9-15.
40. Liu PC, Benjamin I, Morgan MA, King SA, Mikuta JJ, Rubin SC. Effect of surgical debulking on survival in stage IV ovarian cancer. Gynecol Oncol. 1997 Jan;64(1):4-8.
41. Lichtenegger W, Sehouli J, Buchmann E, Karajanev C, Weidemann H. Operative results after primary and secondary debulking-operations in advanced ovarian cancer (AOC). J Obstet Gynaecol Res. 1998 Dec;24(6):447-51.
42. Bristow RE, Montz FJ, Lagasse LD, Leuchter RS, Karlan BY. Survival impact of surgical cytoreduction in stage IV epithelial ovarian cancer. Gynecol Oncol. 1999 Mar;72(3):278-87.

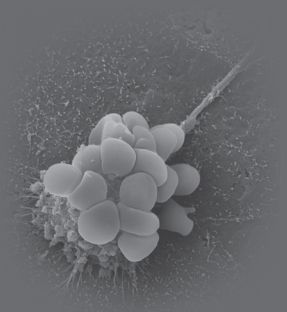
43. Suzuki M, Ohwara M, Sekiguchi I, Sato I. Radical cytoreductive surgery combined with platinums-carboplatin and cisplatin chemotherapy for advanced ovarian cancer. Int J Gynecol Cancer. 1999 Jan;9(1):54-60.
44. Bristow RE, Montz FJ. Complete surgical cytoreduction of advanced ovarian carcinoma using the argon beam coagulator. Gynecol Oncol. 2001 Oct;83(1):39-48.
45. Eisenkop SM, Spirtos NM, Friedman RL, Lin WC, Pisani AL, Perticucci S. Relative influences of tumor volume before surgery and the cytoreductive outcome on survival for patients with advanced ovarian cancer: a prospective study. Gynecol Oncol. 2003 Aug;90(2):390-6.
46. Eltabbakh GH, Mount SL, Beatty B, Simmons-Arnold L, Cooper K, Morgan A. Factors associated with cytoreducibility among women with ovarian carcinoma. Gynecol Oncol. 2004 Nov;95(2):377-83.
47. Chi DS, Franklin CC, Levine DA, Akselrod F, Sabbatini P, Jarnagin WR, et al. Improved optimal cytoreduction rates for stages IIIC and IV epithelial ovarian, fallopian tube, and primary peritoneal cancer: a change in surgical approach. Gynecol Oncol. 2004 Sep;94(3):650-4.
48. Aletti GD, Dowdy SC, Podratz KC, Cliby WA. Surgical treatment of diaphragm disease correlates with improved survival in optimally debulked advanced stage ovarian cancer. Gynecol Oncol. 2006 Feb;100(2):283-7.
49. Scarabelli C, Gallo A, Franceschi S, Campagnutta E, De G, Giorda G, et al. Primary cytoreductive surgery with rectosigmoid colon resection for patients with advanced epithelial ovarian carcinoma. Cancer. 2000 Jan 15;88(2):389-97.
50. Gillette-Cloven N, Burger RA, Monk BJ, McMeekin DS, Vasilev S, DiSaia PJ, et al. Bowel resection at the time of primary cytoreduction for epithelial ovarian cancer. J Am Coll Surg. 2001 Dec;193(6):626-32.
51. Mourton SM, Temple LK, Abu-Rustum NR, Gemignani ML, Sonoda Y, Bochner BH, et al. Morbidity of rectosigmoid resection and primary anastomosis in patients undergoing primary cytoreductive surgery for advanced epithelial ovarian cancer. Gynecol Oncol. 2005 Dec;99(3):608-14.
52. Estes JM, Leath CA, 3rd, Straughn JM, Jr., Rocconi RP, Kirby TO, Huh WK, et al. Bowel resection at the time of primary debulking for epithelial ovarian carcinoma: outcomes in patients treated with platinum and taxane-based chemotherapy. J Am Coll Surg. 2006 Oct;203(4):527-32.
53. Cai HB, Zhou YF, Chen HZ, Hou HY. The role of bowel surgery with cytoreduction for epithelial ovarian cancer. Clin Oncol (R Coll Radiol). 2007 Dec;19(10):757-62.
54. Sonnendecker EW, Guidozzi F, Margolius KA. Splenectomy during primary maximal cytoreductive surgery for epithelial ovarian cancer. Gynecol Oncol. 1989 Dec;35(3):301-6.
55. Ayhan A, Al RA, Baykal C, Demirtas E, Ayhan A, Yuce K. The influence of splenic metastases on survival in FIGO stage IIIC epithelial ovarian cancer. Int J Gynecol Cancer. 2004 Jan-Feb;14(1):51-6.

3.2

Causes of postoperative mortality after surgery for ovarian cancer.

C.G. Gerestein
R.A.M. Damhuis
M. de Vries
A. Reedijk
C.W. Burger
G. S. Kooi

Eur J Cancer. 2009 Nov;45(16):2799-803.



ABSTRACT

Objectives: Residual disease after cytoreductive surgery is an important prognostic factor in patients with advanced stage epithelial ovarian cancer (EOC). Aggressive surgical procedures necessary to achieve maximal cytoreduction are inevitably associated with postoperative morbidity and mortality.

The objective of the present study was to determine causes of postoperative mortality after surgery for epithelial ovarian cancer .

Materials and Methods: The Rotterdam Cancer Registry records all newly diagnosed cases of cancer in the south-western part of the Netherlands. All patients who died within 30 days after surgery for cancer of the ovary or fallopian tube over a 17-year period were identified and analysed by reviewing medical notes.

Results: Between 1989 and 2005, 2434 patients underwent cytoreductive surgery for EOC. Sixty-seven patients (3.1%) died within 30 days after surgery. Postoperative mortality increased with age from 1.5% (26/1765) for the age-group 20-69 to 6.6 % (32/486) for the age-group 70-79 and 9.8% (18/183) for patients aged 80 years or older. Pulmonary failure (18%) and surgical site infection (15%) were the most common causes of death. Only a quarter of deaths resulted from surgical site complications.

Conclusions: Our results suggest that causes of postoperative mortality after surgery for EOC are very heterogeneous. Given the impact of general complications, progress in preoperative risk assessment, preoperative preparation and postoperative care seem essential to reduce the occurrence of fatal complications.

INTRODUCTION

Treatment of patients with advanced stage epithelial ovarian cancer (EOC) is based on cytoreductive surgery and platinum based chemotherapy. Prognosis mainly depends on FIGO (International Federation of Gynaecology and Obstetrics) stage and the extent of residual disease after primary cytoreductive surgery.[7, 8, 92]
Aggressive surgical procedures, necessary to achieve maximal cytoreduction, are associated with peri- and postoperative morbidity and mortality.[36, 37, 42] Extent of surgery, age, comorbidity and performance status are important predictors for short-term postoperative outcomes.[36, 72]
Postoperative morbidity after primary cytoreductive surgery for advanced stage ovarian cancer is reported inconsistently, without standard definitions of postoperative morbidity. Unadjusted morbidity rates range between 11 and 67%.
Postoperative mortality (POM) is generally defined as death from any cause within 30 days of operation. POM rates after primary cytoreductive surgery for advanced stage EOC vary between 0 and 6.7%, with a mean POM rate of 2.8%.[93]

Little is known about the causes of postoperative mortality after surgery for EOC. Hospital series are generally too small whereas population-based studies lack clinical information. In an attempt to detect preventable complications, we decided to perform a retrospective chart review of all postoperative deaths in a region with 16 hospitals over a 17-year period.

MATERIALS AND METHODS

Information on all patients who died within 30 days after surgery for cancer of the ovary or fallopian tube was retrieved from the Rotterdam Cancer Registry. This registry started in 1982 and reached complete coverage of the south western part of the Netherlands in 1989. Newly diagnosed cases of cancer are reported to the registry by pathology laboratories and by the hospital administration for discharge records. The region comprises one university hospital, four teaching hospitals and eleven non-teaching hospitals serving a population of 2,4 million inhabitants.
The study was approved by the Medical Ethical Committee of the Erasmus University Medical Center and was performed according to the standards outlined in the Declaration of Helsinki.

From 1989 through 2005, 3257 patients were diagnosed with EOC and in 2434 patients (75%) some form of resectional surgery, excluding diagnostic biopsies, had been performed. 1217 (50%) of the patients were operated in a teaching hospital. For all patients who died within 30 days of surgery (n=76, 3.1%), information was sent to the hospitals to obtain access to the medical records for review by two clinicians (CG and MdV). General case notes, surgical reports and pathology reports were reviewed. When available, autopsy records (n=8) were also examined.

Preoperative patient characteristics included age, World Health Organization (WHO) performance status, ASA classification, preoperative CA125 level and comorbidity status. Comorbidity was scored and categorized using a modification of the Charlson comorbidity index (CCI).[94] Type of surgery, surgical procedures, type of surgeon, type of hospital, duration of surgery, estimated blood loss, and postoperative residual disease were registered. Optimal cytoreduction was defined as residual disease < 1 cm.[1,2] To assess the extent of surgical procedures, the surgical complexity score (SCS) described by Aletti and colleagues.[36] was adopted. Based on number and complexity of the surgical procedures performed patients are assigned to one of three groups: low-, intermediate and complex surgery. (Table 3)
Stage of disease was established as defined by the International Federation of Gynaecology and Obstetrics (FIGO).[53] Tumour type was described according to the WHO guidelines. Tumour differentiation was classified as well (grade I), moderately (grade II), or poorly differentiated (grade III).

All peri- and postoperative complications were registered and classified according to the definitions of the National Surgical Quality Improvement Program.[90] This instrument divides complications into two broad categories, surgical and medical.(Table 4) Cause of death was systematically described by applying the methodology proposed by Waljee and colleagues.[76] In this classification the complication that attributed most to the patient´s death during a postoperative course has to be assigned.

All patient data were entered in a computerized relational database (Microsoft Access 2000). Tabulations and statistical testing (chi-square) were performed using SPSS 14.0 for Windows (Chicago, IL).

RESULTS

During the study period the Rotterdam Cancer Registry recorded 76 patients (3.1%) who died within 30 days after surgery for ovarian cancer.
Fourteen patients had to be excluded because medical records were not available (n=9) or incomplete (n=5). In seven patients, final histological diagnosis was different from epithelial ovarian cancer, leaving a study population of fifty-five patients.

Patient characteristics are depicted in Table 1. The median age at operation was 75 years (range 42 to 97). Operative mortality increased with age from 1,5% (26/1765) for the age-group 20-69 to 6,6 % (32/486) for the age-group 70-79 and 9,8% (18/183) for patients aged 80 years or older.

The WHO performance status was 0 or 1 in 51 patients (93%) and only 7 patients (13%) were classified with ASA 3.

Table 1. Patient characteristics (N=55).

		N	%
Age (years)	20-69	18	33
	70-79	22	40
	> 79	15	27
WHO performance score	0	15	27
	1	36	66
	≥2	4	7
ASA	1	22	40
	2	26	47
	3	7	13
Comorbidity Index	0	21	38
	1	18	33
	2	9	16
	>2	6	11
	Unknown	1	2
FIGO stage	I	8	14
	II	2	4
	III	29	53
	IV	16	29
Residual tumor	≥ 1cm	37	67
	< 1cm	18	33
Differentiation grade	I	5	9
	II	18	33
	III	27	49
	Not specified	5	9
Morphology	Serous	22	40
	Mucinous	10	18
	Clear Cell	5	9
	Endometrioid	5	9
	Mixed mullerian	3	5
	Undifferentiated	10	18

Coronary artery disease (22%) and hypertension (16%) were the most frequent comorbid conditions (Table 2). Peripheral artery disease, diabetes, pulmonary disease and a prior malignant tumour were seen in 11% of patients. The CCI was >1 in 15 patients (27%). Mean CA125 level was 975 UI/ml (range 10-5977 UI/ml).

In 44 patients (80%) primary cytoreductive surgery was performed (Table 3). Two patients underwent interval debulking surgery, one patient was operated for staging purposes. Six patients needed emergency surgery (for bowel obstruction or perforation). In two patients ovarian cancer was accidentally diagnosed during surgery without previous suspicion (laparotomy for cervical neoplasia in one and hernia epigastrica repair in the other patient).

Residual disease was < 1cm in 18 patients (32 %). The vast majority of patients (85%) were diagnosed with advanced stage disease (FIGO stage III/IV).

Table 2. Prevalence of comorbid conditions according to the modified Charlson comorbidity index.

Comorbid condition	Index Points	Number of patients[a]	(%)
Coronary artery disease [b]	1	12	22
Congestive heart failure	1	2	4
Cerebrovascular disease	1	5	9
Peripheral vascular disease	1	6	11
Hypertension	1	9	16
Dementia	1	2	4
Diabetes (mild or moderate)	1	6	11
Pulmonary disease	1	6	11
Renal disease	1	2	4
Any prior malignant tumour	2	6	11
Hepatic disease	3	2	4

[a] One patient may have several comorbid conditions
[b] Including myocardial infarction, coronary artery bypass graft, percutaneous transluminal coronary angioplasty and angina pectoris

Table 3. Procedures performed in the analysed patients and their surgical complexity score. Based on number and complexity of the surgical procedures performed patients are assigned to one of three groups: low-,intermediate- and complex surgery. SCS=surgical complexity score.

Operative procedure	N	SCS
Hysterectomy	22	1
Salpingo-oophorectomy	49	1
Omentectomy	28	1
Lymphadenectomy (pelvic or para-aortic)	5	1
Small bowel resection	4	1
Large bowel resection	11	2
Colostomy	8	2

Complexity score groups
SCS ≤ 3: Low complex surgery
SCS 4-7: Intermediate complex surgery
SCS ≥ 8: High complex surgery

The operative procedure was classified as low complex surgery (SCS ≤ 3) in 47 patients (85%). Thirty-two patients (58%) were treated in a teaching hospital, including four patients operated on in the university hospital. Surgery was performed by a gynecologic oncologist in 16 (29%) patients. Mean operative time was 135 minutes (range 24-258 minutes), mean estimated blood loss was 841 ml (range 100 to 3500 ml).

Eighty-seven intra- and postoperative complications were recorded according to the NSQIP definitions. (Table 4) The main surgical complication was surgical site infection (36%). Pulmonary failure was the most frequent medical complication (33%). Seven patients required a reoperation, which was called for by postoperative bleeding in two patients, and by bowel perforation, gastric perforation, intraabdominal abscess, fascial disruption and peritonitis in the other five.

Table 4. Peri- and postoperative complications according to National Surgical Quality Improvement Program definitions.

Surgical complications (45)		**N**
Haemorrhage (8)	Intraoperative	3
	Postoperative	5
Bowel laceration (7)	Large bowel laceration	2
	Small bowel laceration	5
Bowel obstruction		6
Surgical site infection (16)	Sepsis	8
	Intraabdominal abcess	1
	Peritonitis	2
	Urinary tract infection	3
	Superficial wound infection	2
Wound dehiscence/fascial disruption		1
Reoperation		7
Medical complications (42)		N
Cardiac (11)	Myocardial infarction	1
	Atrial and ventricular arrhythmias	2
	Unexplained cardiac arrest	3
	Congestive heart failure	5
Venous thrombo-embolism (7)	Deep venous embolism	2
	Pulmonary embolus	5
Pulmonary failure (14)	Pneumonia	7
	Prolonged ventilator assistance	5
	Unplanned intubation	2
Renal failure		4
Gastrointestinal bleeding		4
Stroke		2
Other (liver failure)		1

The main causes of death were surgical site infection (n=8) and pulmonary failure (n=10) (Table 5, figure 1). Death occurred within a mean of 13 days (range 0 to 30 days) after surgery. Pulmonary failure was a more common cause of death if surgery was performed by gynaecologic oncologists or in a teaching hospital. Surgical site complications were the most common cause of death in patients operated on by a general gynaecologist, general surgeon or in non teaching hospitals. These differences were not statistically significant.

Table 5. Tabulation of causes of death.

Cause of death	N (%)
Surgical site complications	***13 (23.6)***
Haemorrhage	5
Surgical site infection	8
Pulmonary failure	***10 (18.2)***
Pneumonia	3
Prolonged ventilator assistance	5
Unplanned intubation	2
Cardiac complications	***7 (12.7)***
Myocardial infarction	1
Unexplained cardiac arrest	2
Congestive heart failure	4
Venous thrombo- embolism	***6 (10.9)***
Deep venous embolism	2
Pulmonary embolus	4
Other	***19 (34.5)***
Bowel obstruction	1
Gastrointestinal bleeding	3
Renal failure	1
Stroke	1
Liver failure	1
Treatment refusal	1
Progressive disease	7
Infection during chemotherapy	1
Unknown	3

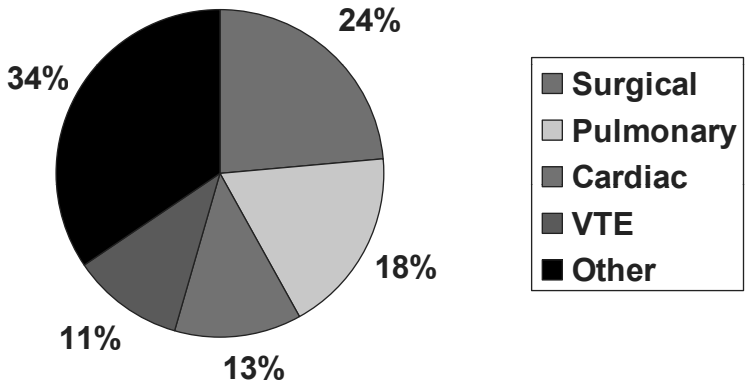


Figure 1. Pie chart with distribution of the identified causes of death. Surgical=surgical site complication; pulmonary=pulmonary failure; cardiac=cardiac complication; VTE=venous thrombo-embolism.

DISCUSSION

This study is one of the first reports that focuses on causes of death in patients who die in the postoperative phase after cytoreductive surgery for EOC. The main cause of death was pulmonary failure and only a quarter of deaths resulted from surgical site complications. Our results show that causes of death are very heterogeneous and the major importance of general

complications such as thrombo-embolism (11%), pulmonary failure (18%) and cardiac failure (13%) suggests that interventions will rather rely on improvement of general postoperative care than on changes in surgical management.

Cytoreductive surgery is the cornerstone of treatment for advanced stage EOC but coincides with a considerable risk of morbidity and mortality. The 3,1% POM rate in our study is comparable with other series[93], despite the high proportion of elderly patients. At higher age, the operative risk tends to increase, which is confirmed by the 7.5 % postoperative mortality in patients aged 70 years and older. Diaz-Montes and colleagues previously described a 2.3 times higher 30-day mortality rate for patients aged 80 years and older and suggested a higher frequency of emergency surgery.[73] In our series, of the 15 patients aged 80 years or older, 5 (33%) died after emergency surgery.

Residual disease after primary cytoreductive surgery is an import prognostic factor in advanced stage epithelial ovarian cancer[7, 8] and the ability to achieve optimal cytoreduction is related to surgeons specialty and type of hospital.[7, 10, 83, 85] One would expect a higher postoperative mortality after more extensive surgery and for audit purposes the SCS should be used to allow meaningful comparisons.[36]

Whether the causes of death were accurately determined, might be questioned. Due to the retrospective nature of this study and an autopsy rate of only 15%, we had to rely on standard case notes. Accurate prospective recording of comorbidity, extent of surgery and postoperative complications seems important to develop preventive measures. Alleti and colleagues recently developed a prediction model for morbidity and mortality after primary cytoreductive surgery for advanced stage ovarian cancer. Albumin, ASA and complexity of surgery were identified as predictors for 30-day morbidity. Predictors for 3-month mortality were age and ASA.[36] Our study corroborates the importance of comorbidity and performance status. Sixty-two percent of the patients was known with some comorbid condition and in 65% performance status was influenced at the time of cancer diagnosis. Prediction models may identify patients who can benefit from alternative treatment strategies such as neoadjuvant chemotherapy or optimize physical performance before surgery, for example by improving the nutritional status.

For several reasons, postoperative mortality appears to be a poor quality indicator for gynaecological surgery. First, it is a rare event, considering that an average hospital would encounter only one case every four years. Second, results depend on the extent of surgery performed and fatal complications tend to be non-surgery related.
It also remains remarkable that in our series most surgical procedures were low complex and that in two thirds of patients tumour removal was suboptimal. Several authors suggested that surgery for ovarian cancer should be centralized in specialized hospitals.[10, 95] Others suggest that results can be improved by a consultant gynecologic oncologist.[85]To reduce postoperative

mortality, the latter option will be less effective. To ensure optimal care all aspects, diagnostics, selection, surgery and postoperative care need to be of high standard.

In conclusion, clinical evaluation of adverse events remains an essential method to improve the quality of care. Nonetheless, postoperative complications will inevitably occur after surgery for ovarian cancer. To some extent, age and comorbidity can predict the postoperative risk but even in elderly patients cytoreductive surgery should be considered given the poor results of alternative options.

ACKNOWLEDGMENTS

We thank all participating departments of gynecology and the registrars of the Rotterdam Cancer Registry for their cooperation in finding and interpreting the data.

REFERENCES

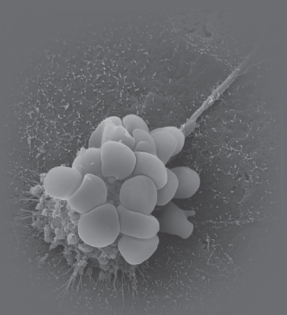
1. Bristow RE, Tomacruz RS, Armstrong DK, Trimble EL, Montz FJ. Survival effect of maximal cytoreductive surgery for advanced ovarian carcinoma during the platinum era: a meta-analysis. J Clin Oncol 2002;20(5):1248-59.
2. Tingulstad S, Skjeldestad FE, Halvorsen TB, Hagen B. Survival and prognostic factors in patients with ovarian cancer. Obstet Gynecol 2003;101(5 Pt 1):885-91.
3. du Bois A, Reuss A, Pujade-Lauraine E, Harter P, Ray-Coquard I, Pfisterer J. Role of surgical outcome as prognostic factor in advanced epithelial ovarian cancer: A combined exploratory analysis of 3 prospectively randomized phase 3 multicenter trials: by the Arbeitsgemeinschaft Gynaekologische Onkologie Studiengruppe Ovarialkarzinom (AGO-OVAR) and the Groupe d'Investigateurs Nationaux Pour les Etudes des Cancers de l'Ovaire (GINECO). Cancer 2009;115(6):1234-44.
4. Chen SS, Bochner R. Assessment of morbidity and mortality in primary cytoreductive surgery for advanced ovarian carcinoma. Gynecol Oncol 1985;20(2):190-5.
5. Heintz AP, Hacker NF, Berek JS, Rose TP, Munoz AK, Lagasse LD. Cytoreductive surgery in ovarian carcinoma: feasibility and morbidity. Obstet Gynecol 1986;67(6):783-8.
6. Aletti GD, Santillan A, Eisenhauer EL, Hu J, Aletti G, Podratz KC, 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(1):99-106.
7. Alphs HH, Zahurak ML, Bristow RE, Diaz-Montes TP. Predictors of surgical outcome and survival among elderly women diagnosed with ovarian and primary peritoneal cancer. Gynecol Oncol 2006;103(3):1048-53.
8. Gerestein CG, Damhuis RA, Burger CW, Kooi GS. Postoperative mortality after primary cytoreductive surgery for advanced stage epithelial ovarian cancer: A systematic review. Gynecol Oncol 2009.
9. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987;40(5):373-83.
10. 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(1):263-4.
11. Khuri SF, Daley J, Henderson W, Hur K, Demakis J, Aust JB, 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(4):491-507.
12. Waljee JF, Windisch S, Finks JF, Wong SL, Birkmeyer JD. Classifying cause of death after cancer surgery. Surg Innov 2006;13(4):274-9.
13. Diaz-Montes TP, Zahurak ML, Giuntoli RL, 2nd, Gardner GJ, Gordon TA, Armstrong DK, et al. Surgical care of elderly women with ovarian cancer: a population-based perspective. Gynecol Oncol 2005;99(2):352-7.
14. Vernooij F, Heintz P, Witteveen E, van der Graaf Y. The outcomes of ovarian cancer treatment are better when provided by gynecologic oncologists and in specialized hospitals: a systematic review. Gynecol Oncol 2007;105(3):801-12.
15. Engelen MJ, Kos HE, Willemse PH, Aalders JG, de Vries EG, Schaapveld M, et al. Surgery by consultant gynecologic oncologists improves survival in patients with ovarian carcinoma. Cancer 2006;106(3):589-98.
16. Earle CC, Schrag D, Neville BA, Yabroff KR, Topor M, Fahey A, et al. Effect of surgeon specialty on processes of care and outcomes for ovarian cancer patients. J Natl Cancer Inst 2006;98(3):172-80.
17. 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(2):300-7.

4

Prediction of 30-day morbidity after primary cytoreductive surgery for advanced stage ovarian cancer.

C.G. Gerestein
G.M. Nieuwenhuyzen-de Boer
M.J. Eijkemans
G.S. Kooi
C.W. Burger

Eur J Cancer. 2010 Jan;46(1):102-9.



ABSTRACT

Objectives: Treatment in advanced stage epithelial ovarian cancer (EOC) is based on primary cytoreductive surgery followed by platinum-based chemotherapy. Successful cytoreduction to minimally residual tumour burden is the most important determinant of prognosis. However, extensive surgical procedures to achieve maximal debulking are inevitably associated with postoperative morbidity and mortality. The objective of this study is to determine predictors of 30-day morbidity after primary cytoreductive surgery for advanced stage EOC.

Materials and Methods: All patients in the South Western part of the Netherlands who underwent primary cytoreductive surgery for advanced stage EOC between January 2004 and December 2007 were identified from the Rotterdam Cancer Registry database. All peri- and postoperative complications within 30 days after surgery were registered and classified according to the definitions of the National Surgical Quality Improvement Program (NSQIP).
To investigate independent predictors of 30-day morbidity, a Cox' proportional hazard model with backward stepwise elimination was utilized. The identified predictors were entered into a nomogram.

Results: Two hundred ninety-three patients entered the study protocol. Optimal cytoreduction was achieved in 136 (46%) patients. 30-day morbidity was seen in 99 (34%) patients. Postoperative morbidity could be predicted by age (P = 0.007; OR 1.034), WHO performance status (P= 0.046; OR 1.757), extent of surgery (P= 0.1308; OR=2.101), and operative time (P = 0.017; OR 1.007) with a for optimism corrected c-statistic of 0.68.

Conclusions: 30-day morbidity could be predicted by age, WHO performance status, operative time and extent of surgery. The generated nomogram could be valuable for predicting operative risk in the individual patient.

INTRODUCTION

Currently, treatment in advanced stage epithelial ovarian cancer (EOC) is based on primary cytoreductive surgery followed by platinum-based chemotherapy.
Successful cytoreduction to minimally residual tumor burden is the most important determinant of prognosis.[7, 61, 71, 96] However, extensive surgical procedures to achieve maximal debulking are inevitably associated with postoperative morbidity and mortality. Reported 30-day morbidity after primary cytoreductive surgery for advanced stage EOC ranges from 11 to 67 %.[36-43, 45, 46, 85, 97] Postoperative mortality (POM) rates vary between 0 and 6.7%, with a mean POM rate of 2.8%.[93]
Predictive parameters for postoperative complications after primary cytoreduction for advanced stage EOC are age, performance status, co-morbidity and extent of surgery. Risk-adjustment models for postoperative morbidity and mortality after major surgical procedures, developed for inter- and intra-institutional audits, have shown to improve surgical outcome.[91] We currently know of only one study on risk-adjustment for surgical outcome in EOC patients.[36] Prediction models for 30-day morbidity could facilitate prediction of surgical outcome in daily clinical practice and can provide objective parameters to identify those patients who might benefit from alternative treatment approaches.

The objective of this study was to identify predictive parameters for 30-day morbidity after primary cytoreductive surgery for advanced stage EOC and to develop a nomogram to predict 30-day morbidity.

MATERIALS AND METHODS

Selection of patients and study design

From January, 2004 to December, 2007 all patients with primary surgery for EOC were retrieved from the Rotterdam Cancer Registry database.
The Rotterdam Cancer Registry covers the South Western part of the Netherlands, this region comprises one university hospital, four teaching hospitals and eleven non-teaching hospitals serving a population of 2,4 million inhabitants. All newly diagnosed cases of cancer are reported to the Registry by pathology laboratories and by the hospital administration for discharge records. Patients with advanced stage EOC, defined as International Federation of Gynecology and Obstetrics (FIGO) stage III/IV, who underwent primary cytoreductive surgery were eligible for this study. For all patients information was sent to the hospitals to obtain access to the medical records for review by two clinicians (CG and GMN). General case notes, surgical reports and pathology reports were reviewed.
The study was approved by the Medical Ethical Committee of the Erasmus University Medical Center and was performed according to the standards outlined in the Declaration of Helsinki.

Pre-operative assessments

Standard preoperative work-up of the patients consisted of patients' history, physical examination and transvaginal sonography. CT-scans were electively made at the discretion of the attending physician. Blood samples for measurement of CA125, blood platelet count, and haemoglobin concentrations were withdrawn within one week prior to surgery. CA125 was assessed by enzyme immunoassay (Roche E170) using a sandwich method with chemo luminescence (Roche Diagnostics BV, Almere, the Netherlands). The blood platelet count and haemoglobin were assessed by a Sysmex XE 2100 system (Sysmex Corporation, Kobe, Japan).

Treatment regimen

Primary cytoreductive surgery was performed using an abdominal midline incision and included total hysterectomy, bilateral salpingo-oophorectomy, and omentectomy and resection of all visible and palpable bulky tumour. The aim of this procedure was to resect all macroscopic tumour or at least to lesions < 1cm.[7, 61] Bowel resection, pancreas resection, splenectomy, diaphragmatic stripping, partial liver resection and lymphadenectomy were performed if warranted to achieve an optimal cytoreduction, defined as residual disease <1cm.

Histo-pathological assessment

Histology was classified as serous, mucinous, endometroid, clear cell, and undifferentiated adenocarcinoma. Differentiation was classified in grade 1 to 3, according to the Silverberg criteria.[5] Subsequently, stage of the disease was determined according to FIGO guidelines.[53]

Study parameters and outcome measures

Preoperative parameters for analysis were patients' age, clinical condition according to the WHO performance scale, comorbidity status, presence of ascites prior to surgery, CA125-, blood platelet- and haemoglobin concentrations. Ascites was defined as the presence of pelvic fluid on ultrasound, CT-scan and/or at laparotomy. Comorbidity was scored and categorized using a modification of the Charlson comorbidity index (CCI) (Table 1).[94]

Postoperative parameters for analysis were residual disease, type of surgeon, extent of surgical procedures, operative time, histology, histological differentiation and FIGO stage. To assess the extent of surgical procedures, the surgical complexity score (SCS) described by Aletti and colleagues was adopted.[36] Based on number and complexity of the surgical procedures performed patients are assigned to one of three groups: low-, intermediate and complex surgery. (Table 2). All peri- and postoperative complications were registered and classified according to the definitions of the National Surgical Quality Improvement Program (NSQIP).[76, 90, 98] Postoperative mortality (POM) was defined as death from any cause within 30 days of operation. Cause of death was systematically described by applying the methodology proposed by Waljee and colleagues. In this classification the complication that attributed most to the patient's death during a postoperative course has to be assigned.[76] (Table 7)

Table 1. The Modified Charlson Comorbidity Index.[21]

Comorbid condition	Index Points
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. Surgical complexity score and complexity score groups developed by Alleti and colleagues. SCS=Surgical complexity score;TH-BSO=Total hysterectomy and bilateral-salpingo-oophorectomy.[13]

Operative procedure	SCS
TH-BSO	1
Omentectomy	1
Pelvic lymphadenectomy	1
Para-aortic lymphadenectomy	1
Pelvic peritoneum stripping	1
Abdominal peritoneum stripping	1
Small bowel resection	1
Large bowel resection	2
Liver resection	2
Splenectomy	2
Diaphragm stripping	2
Recto-sigmoidectomy T-T anastomosis	3

Complexity score groups
SCS ≤ 3: Low complex surgery
SCS 4-7: Intermediate complex surgery
SCS ≥ 8: High complex surgery

Postoperative morbidity included the following selection of adverse events seen within 30 days after surgery: POM, bleeding requiring>4 U of transfused blood, sepsis, pneumonia, venous thrombo-embolism (pulmonary embolus or deep venous thrombosis), any type of complication requiring re-operation, any bowel injury (leak, fistula, anastomotic leakage), prolonged ileus (>6 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, 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 patients' age, operative time and preoperative serum concentrations of log CA125, blood platelet, and haemoglobin between the group of patients with 30-day morbidity and those patients with an uncomplicated postoperative course. Chi square tests were used to compare the preoperative presence of ascites, WHO performance status, CCI, FIGO stage, residual disease, extent of surgical procedures performed, type of surgeon, histological differentiation and histology between the groups of patients with 30-day morbidity to the group of patients with an uncomplicated postoperative course. 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. In order to prevent overestimation and to achieve a better model performance parameters with $P < 0.15$ were entered into our prognostic model.[63] We accounted for missing values by multiple imputation.[64]

The discriminative ability of the prognostic model, or the ability to distinguish patients with the poor outcome from patients with a favourable outcome, was expressed by means of the c-statistic.[65] 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.[65, 66] 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 generated with the identified predictive parameters.

RESULTS

Recruitment and demographic characteristics of the patients

Between January 2004 and December 2007, 494 patients underwent primary surgery for EOC. One hundred eighty-eight patients with early stage EOC and 13 patients with emergency surgery were excluded. Finally, 293 patients with advanced stage EOC who underwent primary cytoreductive surgery entered the study protocol.

Median age was 64 years (range 15.0-90.5 years), with ninety-one patients (31%) aged ≥ 70 years at time of surgery. 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%) patients with stage IV disease. Sixty-seven patients (22.9%) were cytoreduced to no gross residual disease; optimal cytoreduction (residual disease < 1cm) was achieved in another sixty-nine patients (23.5%).

30-day morbidity was seen in 99 patients (34%). POM was 4.8% (N=14). Cause of death is listed in Table 3. Further patients characteristics are depicted in Table 4-6.

Table 3. Tabulation of causes of death. CCI=Charlson comorbidity index; SCS=surgery complexity score; VTE= VTE=venous thromboembolism.

	Age (years)	WHO	CCI	FIGO	Residual Tumor	SCC	Cause of death
1	43	1	1	IIIC	>1cm	1	Sepsis
2	81	0	0	IV	>1cm	1	Haemorraghe
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	Haemorraghe
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

Table 4. Preoperative characteristics of study population. 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.

Preoperative Characteristics of the Study Population of Patients with Advanced Stage Ovarian Cancer (FIGO III-IV)				
	Study Population	**No complications**	**30-day morbidity**	***p*-value**
Number of patients (n)	293	194(66%)	99 (34%)	
Preoperative parameters				
Age, n (%)				
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 (73.5)	9 (26.5)	
50-59 years	80 (27.3)	60 (75.0)	20 (25.0)	
60-69 years	88 (30.0)	57 (64.8)	31 (35.2)	
≥ 70 years	91 (31.0)	52 (57.1)	39 (42.9)	
WHO performance, n (%)				**0.043**
WHO 0	161 (54.9)	118 (73.3)	43 (26.7)	
WHO I	117 (39.9)	68 (58.1)	49 (41.9)	
≥WHO II	15 (5.1)	8 (53.3)	7 (46.7)	
CCI, n (%)				0.981
0	129 (44.0)	89 (69.0)	40 (31.0)	
1	84 (28.7)	55 (65.5)	29(34.5)	
≥2	80 (27.3)	50 (62.5)	30(37.5)	
Presence of ascites, n (%)	174 (59.3)	109 (62.6)	65 (37.4)	0.665
Preoperative serum parameters				
Haemoglobin (mmol/L)±SD	7.9±0.99	8.0±0.98	7.6±0.99	0.051
Platelet count (*109/L)±SD	381±140	380±142	388±137	0.221
Log CA125 (kU/L)±SD	2.80±3.90	2.67±3.98	2.98±3.40	0.459

Table 5. Perioperative characteristics of study population. 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. Min=minutes, SCS=Surgical complexity score

Perioperative Characteristics of the Study Population of Patients with Advanced Stage Ovarian Cancer (FIGO III-IV)				
	Study Population	**No complications**	**30-day morbidity**	***p*-value**
Type of surgeon, n (%)				0.217
Gynaecologic oncologist	109(37.2)	77(70.6)	32(29.4)	
General gynaecologist	184(62.8)	117(63.5)	67(36.4)	
Operative time				**<0.0001**
Mean (range)	152 min. (40-384)	124 min. (40-327)	189 min. (40-384)	
SCS, n (%)				**<0.0001**
1	259 (88.4)	182 (70.3)	77 (29.7)	
2	32 (10.9)	12 (37.5)	20 (62.5)	
3	2 (0.7)	0 (0)	2 (100)	

Table 6. Postoperative characteristics of study population. 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.

Postoperative Characteristics of the Study Population of Patients with Advanced Stage Ovarian Cancer (FIGO III-IV)				
	Study Population	**No complications**	**30-day morbidity**	***p*-value**
Number of patients (n)				
Postoperative parameters				
FIGO, n (%)				0.228
III	245 (83.6)	162 (66.1)	83 (33.9)	
IV	48 (16.4)	32 (66.7)	16 (33.3)	
Differentiation, n (%)				0.051
1	17 (5.8)	8(47.1)	9 (52.9)	
2	96 (32.8)	55 (57.3)	41 (42.7)	
3	139 (47.4)	97 (69.8)	42 (30.2)	
unknown	41 (14.0)	34(82.9)	7 (17.1)	
Residual disease, n (%)				0.991
No macroscopic disease	67 (22.9)	45 (67.2)	22 (32.8)	
<1cm	69 (23.5)	45 (65.2)	24 (34.8)	
>1cm	157 (53.6)	104 (66.2)	53(33.8)	
Histology, n(%)				0.162
Serous	209(71.3)	142 (67.9)	67 (32.1)	
endometrioid	22(7.5)	14 (63.6)	8 (36.4)	
mucinous	17 (5.8)	7 (41.2)	10 (58.8)	
Clear cell	10(3.4)	7 (70.0)	3 (30.0)	
Undifferentiated adenocarcinoma	26 (8.9)	20 (76.9)	6 (23.1)	

Initial predictive parameters for 30-day morbidity

Median age was higher in the group of patients with 30-day morbidity when compared to the group of patients without complications, 66.7±12.2 vs. 62.5±11.3 years with *P*=0.012. WHO performance status was significantly better in the group of patients with an uncomplicated postoperative course (*P*=0.043). Co-morbidity status, preoperative haemoglobine, serum CA125 level, platelet count, and presence of ascites were comparable in both groups. (Table 4)
Mean operative time differed markedly between those patients with 30-day major morbidity and those without complications, 189± 93 vs. 124± 61 minutes with *P*<0.0001. SCS was >1 in 22 (22.2%) patients with 30-day morbidity vs. 12 (6.2%) patients without complications with *P*<0.0001. (Table 5)
Optimal cytoreduction rate, type of surgeon, histology, histological differentiation and FIGO stage were similar in both groups. (Table 6)

Uni- and multivariate analysis of predictors for 30-day major morbidity

The results of the univariate analyses are depicted in table 7. The variables with P<0.50 in the univariate analysis were assessed by multivariate Cox' regression, utilizing a backward elimination procedure. Postoperative morbidity could be predicted by age (*P* = 0.007; OR 1.034), WHO performance status (*P*= 0.046; OR 1.757), extent of surgery (*P*= 0.1308; OR=2.101), and operative time (*P* = 0.017; OR 1.007) with a c-statistic of 0.73. In other words our model accurately discriminated

Table 7. Univariate analysis of the potential predictors of 30-day morbidity. 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; SCS=surgery complexity score.

Univariate analysis of predictors of 30-day morbidity		
Variable	**Significance**	**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		
Haemoglobin	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)
Postoperative parameters		
Residual tumour < 1cm	0.991	0.997 (0.614 - 1.620)
Histological differentiation	0.080	1.304 (0.770 - 2.210)
Histology	0.324	0.662 (0.241 - 1.820)
FIGO stage	0.942	0.976 (0.506 - 1.880)
Type of surgeon	0.218	1.378 (0.827 - 2.290)
SCS	<0.0001	4.333 (2.042 - 9.190)
Operative time	0.002	1.008 (1.003 - 1.010)

patients with and without 30-day morbidity in 73% 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 0.68 (Table 5). A shrinkage factor of 0.79 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 0.79 smaller. The generated nomogram, consisting of age, WHO performance status, extent of surgery, and operative time, for the probability of 30-day morbidity is depicted in figure 1.

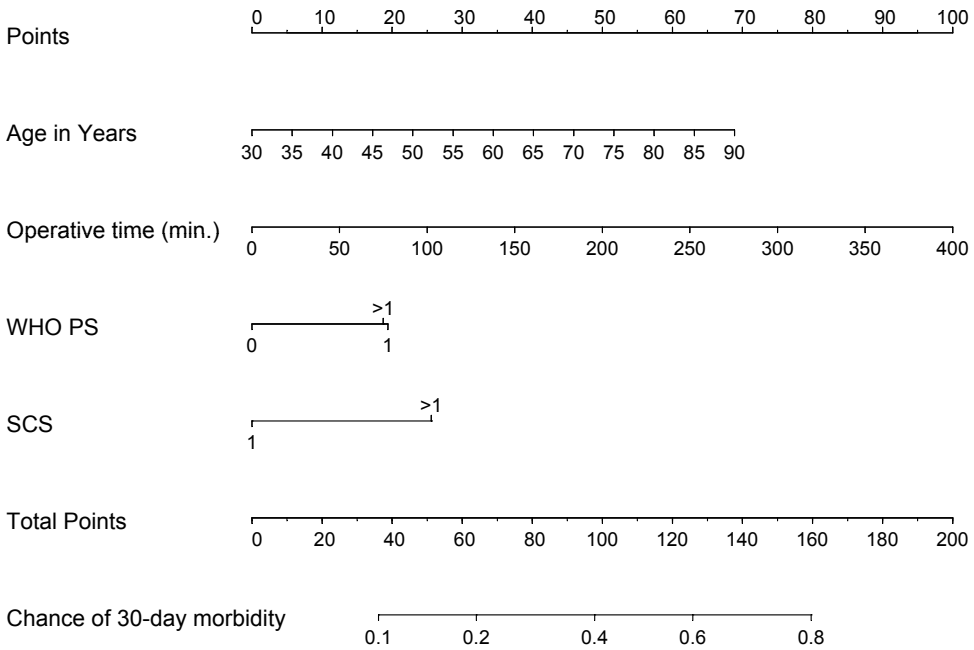


Figure 1. Nomogram for prediction of 30-day morbidity.
For each level of predictive factors there is a number of points allocated at the point scale above. By adding the points of each parameter, the total points could be calculated. This number represents the probability of 30-day morbidity.
For example in a 80-year-old patient [57 points] with respectively a WHO 0 performance status [0 points], SCS of 1 [0 points] and operative time of 150 minutes [37 points] the total score is 94 points (57+37+0+0) representing a 38% change of 30-day morbidity.

DISCUSSION

In the above study we identified predictors for postoperative morbidity and mortality after primary cytoreductive surgery for advanced stage EOC. Age, WHO performance status, operative time and extent of surgery were predictive for 30-day morbidity. With these parameters a nomogram was generated to predict operative risk in the individual patient.

The ability to perform cytoreduction to minimal residual disease determines disease free interval and survival in patients with advanced stage EOC.[7, 61] Aggressive surgical procedure including upper abdominal procedures increases optimal cytoreduction rates, resulting in improved overall survival.[99, 100] However extensive surgical procedures are inevitably related to operative morbidity and mortality.
Postoperative morbidity after primary cytoreductive surgery for advanced stage ovarian cancer is reported inconsistently, without standard definitions of postoperative morbidity. Unadjusted morbidity rates range between 11 and 67%.[36-46] In our study one out of three patients experienced a major complication.
Although overall POM is low with a mean POM rate of 2.8%, POM rates in the elderly are significantly higher ranging from 5.4% till 11.7%.[72, 73, 81, 93]
To provide accurate reference figures an international standard for data collection and reporting of 30-day morbidity needs to be established. In our opinion these standard could be derived from the National Surgical Quality Improvement Program (NSQIP) methodology.[90, 98] This risk-adjustment program started in 1994, and generates periodically observed/expected ratios for 30-day morbidity and mortality after major surgical procedures. With these data inter- and intra-institutional audits are performed to identify structural and procedural failures at the participating hospitals. Ten year after its introduction the overall morbidity- and mortality rates after major surgery decreased significantly.

Predictive parameters for postoperative complications after primary cytoreduction for advanced stage EOC are age, performance status, co-morbidity and extent of surgery. Aletti and colleagues developed a risk-adjustment model for primary surgery in advanced stage EOC. Independent predictors of 30-day morbidity were serum albumin level, performance status (ASA) and surgical complexity. [91] In our study those parameters were also predictive for morbidity. Unfortunately, albumin level was not available in most patients and for this reason not included in our analysis. Our generated nomogram facilitates prediction of 30-day morbidity in daily clinical practice and provides objective parameters to identify those patients who might benefit from an alternative treatment approach with neoadjuvant chemotherapy followed by interval debulking surgery. The actual value of this approach is still under debate, but several studies show comparable survival outcomes with less operative morbidity at least in a subgroup of patients. [12, 14, 15, 101]

The importance of individual risk assessment is even more important in the elderly.
Cytoreductive surgery for EOC at higher age is associated with increased morbidity and mortality. Exclusion criteria may, however, seriously confound comparisons and information on co-morbidity and performance status is necessary to interpret results in elderly series. In our opinion maximal cytoreduction is feasible in the majority of patients at higher age. Prediction models for operative risk can improve management in this enlarging subgroup of patients by determining individual risk profiles.[74]

Our 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 our 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.[7] 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 a selection of patients treated in specialized high volume hospitals.[36]

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 30-day morbidity after primary cytoreductive surgery for advanced stage EOC.

This nomogram is valuable for predicting operative risk in the individual patient.

ACKNOWLEDGMENTS

The authors would like to thank D.W. van der Spek and B.K. Gerestein-van Os for their help with data acquisition. We 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. Bristow RE, Tomacruz RS, Armstrong DK, Trimble EL, Montz FJ. Survival effect of maximal cytoreductive surgery for advanced ovarian carcinoma during the platinum era: a meta-analysis. J Clin Oncol 2002;20(5):1248-59.
2. du Bois A, Reuss A, Pujade-Lauraine E, Harter P, Ray-Coquard I, Pfisterer J. Role of surgical outcome as prognostic factor in advanced epithelial ovarian cancer: A combined exploratory analysis of 3 prospectively randomized phase 3 multicenter trials: by the Arbeitsgemeinschaft Gynaekologische Onkologie Studiengruppe Ovarialkarzinom (AGO-OVAR) and the Groupe d'Investigateurs Nationaux Pour les Etudes des Cancers de l'Ovaire (GINECO). Cancer 2009.
3. Allen DG, Heintz AP, Touw FW. A meta-analysis of residual disease and survival in stage III and IV carcinoma of the ovary. Eur J Gynaecol Oncol 1995;16(5):349-56.
4. Winter WE, 3rd, Maxwell GL, Tian C, Sundborg MJ, Rose GS, Rose PG, et al. Tumor residual after surgical cytoreduction in prediction of clinical outcome in stage IV epithelial ovarian cancer: a Gynecologic Oncology Group Study. J Clin Oncol 2008;26(1):83-9.
5. Chen SS, Bochner R. Assessment of morbidity and mortality in primary cytoreductive surgery for advanced ovarian carcinoma. Gynecol Oncol 1985;20(2):190-5.
6. Suzuki M, Ohwara M, Sekiguchi I, Sato I. Radical cytoreductive surgery combined with platinums-carboplatin and cisplatin chemotherapy for advanced ovarian cancer. Int J Gynecol Cancer 1999;9(1):54-60.
7. Heintz AP, Hacker NF, Berek JS, Rose TP, Munoz AK, Lagasse LD. Cytoreductive surgery in ovarian carcinoma: feasibility and morbidity. Obstet Gynecol 1986;67(6):783-8.
8. Eisenkop SM, Spirtos NM, Montag TW, Nalick RH, Wang HJ. The impact of subspecialty training on the management of advanced ovarian cancer. Gynecol Oncol 1992;47(2):203-9.
9. Eisenkop SM, Spirtos NM, Friedman RL, Lin WC, Pisani AL, Perticucci S. Relative influences of tumor volume before surgery and the cytoreductive outcome on survival for patients with advanced ovarian cancer: a prospective study. Gynecol Oncol 2003;90(2):390-6.
10. Bristow RE, Montz FJ, Lagasse LD, Leuchter RS, Karlan BY. Survival impact of surgical cytoreduction in stage IV epithelial ovarian cancer. Gynecol Oncol 1999;72(3):278-87.
11. Engelen MJ, Kos HE, Willemse PH, Aalders JG, de Vries EG, Schaapveld M, et al. Surgery by consultant gynecologic oncologists improves survival in patients with ovarian carcinoma. Cancer 2006;106(3):589-98.
12. Bristow RE, Montz FJ. Complete surgical cytoreduction of advanced ovarian carcinoma using the argon beam coagulator. Gynecol Oncol 2001;83(1):39-48.
13. Aletti GD, Santillan A, Eisenhauer EL, Hu J, Aletti G, Podratz KC, 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(1):99-106.
14. Piver MS, 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):1-8.
15. Guidozzi F, Ball JH. Extensive primary cytoreductive surgery for advanced epithelial ovarian cancer. Gynecol Oncol 1994;53(3):326-30.
16. Michel G, De Iaco P, Castaigne D, el-Hassan MJ, Lobreglio R, Lhomme C, et al. Extensive cytoreductive surgery in advanced ovarian carcinoma. Eur J Gynaecol Oncol 1997;18(1):9-15.
17. Gerestein CG, Damhuis RA, Burger CW, Kooi GS. Postoperative mortality after primary cytoreductive surgery for advanced stage epithelial ovarian cancer: A systematic review. Gynecol Oncol 2009.
18. Khuri SF. The NSQIP: a new frontier in surgery. Surgery 2005;138(5):837-43.
19. Shimizu Y, Kamoi S, Amada S, Hasumi K, Akiyama F, Silverberg SG. 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(1):2-12.
20. 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(1):263-4.
21. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987;40(5):373-83.

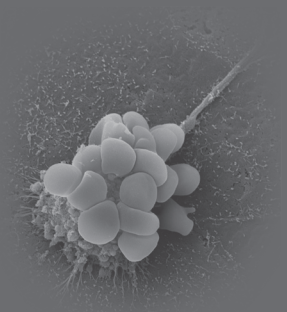
22. Khuri SF, Daley J, Henderson W, Hur K, Demakis J, Aust JB, et al. The Department of Veterans Affairs' NSQIP: the first national, validated, outcome-based, risk-adjusted, and peer-controlled program for the measurement and enhancement of the quality of surgical care. National VA Surgical Quality Improvement Program. Ann Surg 1998;228(4):491-507.
23. Waljee JF, Windisch S, Finks JF, Wong SL, Birkmeyer JD. Classifying cause of death after cancer surgery. Surg Innov 2006;13(4):274-9.
24. Daley J, Khuri SF, Henderson W, Hur K, Gibbs JO, Barbour G, et al. Risk adjustment of the postoperative morbidity rate for the comparative assessment of the quality of surgical care: results of the National Veterans Affairs Surgical Risk Study. J Am Coll Surg 1997;185(4):328-40.
25. Steyerberg EW, Eijkemans MJ, Harrell FE, Jr., Habbema JD. Prognostic modelling with logistic regression analysis: a comparison of selection and estimation methods in small data sets. Stat Med 2000;19(8):1059-79.
26. van Buuren S, Boshuizen HC, Knook DL. Multiple imputation of missing blood pressure covariates in survival analysis. Stat Med 1999;18(6):681-94.
27. Harrell FE, Jr., Lee KL, Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. Stat Med 1996;15(4):361-87.
28. Van Houwelingen JC, Le Cessie S. Predictive value of statistical models. Stat Med 1990;9(11):1303-25.
29. Chi DS, Franklin CC, Levine DA, Akselrod F, Sabbatini P, Jarnagin WR, et al. Improved optimal cytoreduction rates for stages IIIC and IV epithelial ovarian, fallopian tube, and primary peritoneal cancer: a change in surgical approach. Gynecol Oncol 2004;94(3):650-4.
30. Eisenhauer EL, Abu-Rustum NR, Sonoda Y, Levine DA, Poynor EA, Aghajanian C, et al. The addition of extensive upper abdominal surgery to achieve optimal cytoreduction improves survival in patients with stages IIIC-IV epithelial ovarian cancer. Gynecol Oncol 2006;103(3):1083-90.
31. Venesmaa P, Ylikorkala O. Morbidity and mortality associated with primary and repeat operations for ovarian cancer. Obstet Gynecol 1992;79(2):168-72.
32. Alphs HH, Zahurak ML, Bristow RE, Diaz-Montes TP. Predictors of surgical outcome and survival among elderly women diagnosed with ovarian and primary peritoneal cancer. Gynecol Oncol 2006;103(3):1048-53.
33. Diaz-Montes TP, Zahurak ML, Giuntoli RL, 2nd, Gardner GJ, Gordon TA, Armstrong DK, et al. Surgical care of elderly women with ovarian cancer: a population-based perspective. Gynecol Oncol 2005;99(2):352-7.
34. Cloven NG, Manetta A, Berman ML, Kohler MF, DiSaia PJ. Management of ovarian cancer in patients older than 80 years of Age. Gynecol Oncol 1999;73(1):137-9.
35. Vergote I, De Wever I, Tjalma W, Van Gramberen M, Decloedt J, van Dam P. Neoadjuvant chemotherapy or primary debulking surgery in advanced ovarian carcinoma: a retrospective analysis of 285 patients. Gynecol Oncol 1998;71(3):431-6.
36. Vergote I, Trope C, Amant F, Kristensen GB, Sardi JE, Ehlen T, et al. EORTC-GCG/NCIC-CTG Randomised trial comparing primary debulking surgery with neoadjuvant chemotherapy in stage IIIC/IV ovarian, fallopian tube and peritoneal cancer. In: 12th Biennal Meeting International Gynecologic Cancer Society; 2008; Bangkok, Thailand; 2008.
37. Schwartz PE, Chambers JT, Makuch R. Neoadjuvant chemotherapy for advanced ovarian cancer. Gynecol Oncol 1994;53(1):33-7.
38. Huober J, Meyer A, Wagner U, Wallwiener D. The role of neoadjuvant chemotherapy and interval laparotomy in advanced ovarian cancer. J Cancer Res Clin Oncol 2002;128(3):153-60.
39. Janda M, Youlden DR, Baade PD, Jackson D, Obermair A. Elderly patients with stage III or IV ovarian cancer: should they receive standard care? Int J Gynecol Cancer 2008;18(5):896-907.

5

The prediction of progression-free and overall survival in patients with an advanced stage of epithelial ovarian carcinoma.

C.G. Gerestein
M.J. Eijkemans
R.H.M. Dykgraaf
D. de Jong
G.S. Kooi
A. Baalbergen
M.E.L van der Burg
C.W. Burger
A.C. Ansink

BJOG 2009;116:372–380.



ABSTRACT

Objectives: Prognosis in ovarian cancer patients mainly depends on FIGO stage and the ability to perform optimal cytoreductive surgery. Since ovarian cancer has a heterogeneous presentation and clinical course, predicting progression-free (PFS) and overall survival (OS) in the individual patient is difficult. The objective of this study is to determine predictors of PFS and OS in patients with advanced stage epithelial ovarian cancer (EOC) after primary cytoreductive surgery and first-line platinum-based chemotherapy.

Materials and Methods: All patients who underwent primary cytoreductive surgery for advanced stage EOC followed by first-line platinum-based chemotherapy at three regional clinics between January 1998 and October 2004 were identified from the Ovarian Cancer Database. To investigate independent predictors of PFS and OS, a Cox' proportional hazard model was utilized. Nomograms were generated with the identified predictive parameters.

Results: A total of 118 patients entered the study protocol. Median PFS and OS were 15 and 44 months, respectively. Preoperative platelet count (P=0.007), and residual disease <1 cm (P=0.004) predicted PFS with a for optimism corrected c-statistic of 0.63. Predictive parameters for OS were preoperative haemoglobin serum concentration (P=0.012), preoperative platelet counts (P=0.031) and residual disease <1 cm (P=0.028) with a for optimism corrected c-statistic of 0.67.

Conclusions: PFS could be predicted by postoperative residual disease and pre-operative platelet counts whereas residual disease, preoperative platelet counts and preoperative haemoglobin serum concentration were predictive for OS. The proposed nomograms needs to be externally validated.

INTRODUCTION

With approximately 1,500 new cases and 1,100 deaths annually, ovarian cancer is the leading cause of death from gynecological malignancies in the Netherlands.[1] Worldwide, approximately 192,000 women are annually diagnosed with ovarian cancer.[2] The majority (>80 %) of these malignant ovarian tumours are epithelial carcinomas.[3] 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.[4] The average five-year survival rate of women with epithelial ovarian cancer is 43%, however up to 65% will eventually die from the disease.[5] Due to the insidious onset of the disease, the majority of cases are not detected before the disease progressed to an advanced stage.[6]

The standard of care treatment for advanced ovarian cancer, defined by the International Federation of Gynecology and Obstetrics (FIGO) as stage IIB-IV[7], consists of upfront cytoreductive surgery, followed by platinum-based intravenous chemotherapy.[8,9]

Achieving resection of all macroscopic disease to lesions <1 cm, and preferably complete resection of all macroscopic disease, by upfront cytoreductive surgery offers the best prognosis for patients with advanced ovarian cancer in terms of survival.[10,11] Median survival increases with 5.5% for every 10% gain in optimal surgical cytoreduction rate.[10]

However, residual disease is not the only predictor for survival. Other predictive parameters include age, performance status, race, tumour grade, histology, FIGO stage, pre-operative CA125 serum concentration, pre-operative haemoglobin, pre-operative platelet count, the presence or absence of ascites, and various molecular markers.[12-15]

To provide better information to the patient and to select the most optimal treatment for the individual patient, prediction models for outcome are extremely valuable. Alternatively, these models may serve as instruments to assess the efficacy of treatment. Nomograms have been developed as predictive tools for outcomes in malignancies such as prostate cancer, sarcoma, and gastric carcinoma.[16-18] A limited number of nomograms for survival in ovarian cancer have been proposed previously.[19,20] These nomograms consist of respectively nine and six parameters and, as a consequence, are inconvenient to use in daily routine practice. Hence, a simple nomogram for survival in ovarian cancer is desired.

The objective of this study was to develop a nomogram to predict the probability of a 5-year PFS and OS after primary cytoreductive surgery followed by paclitaxel/ platinum-based chemotherapy for advanced stage epithelial ovarian cancer that relies on less clinical parameters in comparison to the previous reported nomograms.

MATERIALS AND METHODS

Selection of patients and study design

All patients with ovarian cancer who underwent primary cytoreductive surgery followed by platinum-based chemotherapy at three regional clinics between January 1998 and October 2004 were identified from the Ovarian Cancer Database. Patients with advanced ovarian cancer, defined as FIGO stage IIB-IV were eligible for the study. Patients with respectively non-epithelial ovarian carcinoma, a history of prior cancer and those receiving neoadjuvant chemotherapy were excluded. The studied population is a subset of patients described previously.[21]
The study was approved by the Medical Ethical Committee and was performed according to the standards outlined in the Declaration of Helsinki.

Pre-operative assessments

Standard preoperative work-up of the patients consisted of patient history, physical examination and transvaginal sonography (TVS). CT-scans were electively made at the discretion of the attending physician. Blood samples for measurement of CA 125, blood platelet count, haemoglobin, albumin and lactate dehydrogenase (LDH) serum concentrations were withdrawn within one week prior to surgery. CA 125 was assessed by enzyme immunoassay (Roche E170) using a sandwich method with chemoluminescence (Roche Diagnostics BV, Almere, the Netherlands). The inter- and intra-assay coefficient of variance were 2.8 and 0.2%, respectively. Serum levels of LDH and albumin were assessed by a Hitachi 917 system (Roche GmbH, Mannheim, Germany). The blood platelet count and haemoglobin were assessed by a Sysmex XE 2100 system (Sysmex Corporation, Kobe, Japan).

Treatment regimen

Upfront cytoreductive surgery was performed by abdominal midline incision. This procedure was characterized by total hysterectomy, bilateral salpingo-oophorectomy (BSO), sampling of any intraperitoneal fluid, omentectomy and resection of all visible and palpable bulky tumor. Bowel resection, pancreas resection, splenectomy, diaphragmatic stripping, partial liver resection and lymphadenectomy were performed if warranted to achieve an optimal cytoreduction. The aim of this procedure was to resect all macroscopic tumour or at least to lesions < 1 cm.[10] Surgery was performed by gynecological oncologists or gynecologists with specific oncological expertise.
Following surgical debulking, patients received 6 to 9 cycles paclitaxel (175 mg/m^2) carboplatin (AUC 6), paclitaxel (175 mg/m^2) cisplatin (75 mg/m^2) or induction therapy with weekly paclitaxel (90 mg/m^2) carboplatin (AUC 6) aiming to achieve a sustained remission of the disease. Patients with residual disease >1cm after primary cytoreductive surgery underwent interval debulking surgery after induction chemotherapy.

Follow-up assessments

Subsequent to the initial treatment, patients were followed up at regular intervals by a gynecological oncologist and medical oncologist. Standard follow-up examination consisted of general physical and gynecological examination, transvaginal ultrasound and/or CT-scans, and serum CA 125 levels. Response and progression were defined according to the RECIST criteria and GCIG modifications.[22,23] Patients with recurrent disease received three-weekly or weekly cycles with paclitaxel/platinum and secondary cytoreductive surgery if warranted. Follow-up data were available until June 2006.

Histo-pathological assessment

Tissue obtained by surgical staging, upfront debulking, and interval debulking was histologically classified as serous, mucinous, endometroid, clear cell, and undifferentiated adenocarcinoma. Differentiation was classified in grade 1 to 3, according to the Silverberg criteria.[24] Subsequently, stage of the disease was determined according to FIGO guidelines.[7]

Study parameters and outcome measures

Preoperative parameters for analysis were patients' age, clinical condition according to the WHO performance scale, presence of ascites prior to surgery, and CA 125, blood platelet, haemoglobin, albumin and LDH serum concentrations. Ascites was defined as the presence of any pelvic fluid on ultrasound, CT-scan and/or at laparotomy.

Postoperative parameters for analysis were residual tumour, histology, histological differentiation and FIGO stage. The primary outcome measure was OS and the secondary outcome measures were response and PFS. Operation date was considered the starting point of patient PFS and OS. End points in PFS were disease progression, death, or last follow-up date. End points in patient OS were death , or last follow-up date.

Statistical Analysis

Data analysis, utilizing the software package SPSS 14.0 (SPSS, Chicago, IL, USA) and Graphpad Prism 5.01 (Graphpad Software, San Diego, CA, USA), was performed on all patients fulfilling in- and exclusion criteria of the study. The Student-t test was utilized to compare patients' age and pre-operative serum concentrations of log CA 125, blood platelet, haemoglobin, albumin and LDH between the group of patients with progressive disease or who died and the group of patients without a recurrence or who were alive at last date of follow-up, respectively. Chi square tests were used to compare the preoperative presence of ascites, FIGO stage, presence of postoperative residual disease, response, histological differentiation and histology between the groups of patients with progressive disease or who died of their disease to the group of patients without a recurrence or who were alive at last date of follow-up, respectively. The Kaplan-Meier method was applied for calculating PFS and OS. Based on the univariate analysis, initial predictive parameters for PFS and OS with $P < 0.30$ were selected to be assessed by multivariate Cox' regression analysis with backward stepwise elimination. The selected parameters

were entered into a prognostic model. We accounted for missing values by multiple imputation.[25]

The discriminative ability of the prognostic model, or the ability to distinguish patients with the poor outcome from patients with a favorable outcome, was expressed by means of the c-statistic.[26] 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.[26,27] 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.

Nomograms were generated with the identified predictive parameters. $P<0.05$ was considered as statistically significant.

RESULTS

Recruitment and demographic characteristics of the patients

Of the previously reported dataset, consisting of 179 patients with the clinical suspicion of advanced ovarian cancer,[21] 143 patients were surgically staged as FIGO stage IIB-IV. In 25 patients surgery was not followed by chemotherapy. This was because of death within 30 days after surgery (n=12), poor physical condition (n=5) and patient refusal (n=8). The 118 patients who received intravenous platinum-based chemotherapy following upfront surgical cytoreduction were analyzed for this study.

The median age of the patients at time of surgery was 62 (range 28-85) years. Median follow-up of patients alive at time of analysis was 40 (range 16-94) months. Further details are listed in Table 1.

Treatment modalities

An optimal cytoreduction, defined as < 1 cm residual tumour, was established in 57 patients of the 118 patients (48.3%). Patients received median 6 (range 1-12) cycles paclitaxel carboplatin or cisplatin in a weekly and/or 3-weekly regimen. Further details are depicted in Figure 1.

Treatment outcome

A complete clinical response was achieved in 86 patients (73%). In 14 patients a partial response was established and three patients had stable disease. In 15 patients (12.7 %) progressive disease was observed during first-line chemotherapy. Multivariate logistic regression revealed postoperative residual tumor < 1cm as the single prognostic parameter for achieving a complete clinical response to therapy ($P<0.001$).

Table 1. Patient characteristics of the study population.

	Study Population	Progressive Disease	Dead of Disease
Number of patients (n)	118	88	63
Age (n,%)			
< 50 years	22 (18.6%)	17 (19.3%)	13 (20.6%)
50-59 years	30 (25.4%)	22 (25.0%)	12 (19.0%)
60-69 years	43 (36.4%)	33 (37.5%)	23 (36.5%)
≥ 70 years	23 (19.5%)	16 (18.2%)	15 (23.8%)
WHO performance (n.%)			
WHO 0	46 (39.0%)	36 (40.9%)	20 (31.7%)
WHO I	49 (41.5%)	33 (37.5%)	24 (38.1%)
WHO II	4 (3.4%)	4 (4.5%)	4 (6.3%)
Unknown	19 (16.1%)	15 (17.0%)	15 (23.8%)
FIGO stage (n,%)			
II	10 (8.5%)	5 (5.7%)	2 (3.2%)
III	89 (75.4%)	65 (73.9%)	46 (73.0%)
IV	19 (16.1%)	18 (20.5%)	15 (23.8%)
Histologic grade (n,%)			
I	6 (5.1%)	2 (2.3%)	1 (1.6%)
II	34 (28.8%)	26 (29.5%)	18 (28.6%)
III	78 (66.1%)	60 (68.2%)	44 (69.8%)
Histological classification (n,%)			
Serous	90 (76.3%)	67 (76.1%)	46 (73.0%)
Mucinous	11 (9.3%)	8 (9.1%)	8 (12.7%)
Undifferentiated	8 (6.8%)	8 (9.1%)	5 (7.9%)
Miscellaneous	9 (7.6%)	5 (5.7%)	4 (6.3%)

Recurrent disease was observed in 73 patients (62%). The median PFS was 15.4 months (95% CI 12.3-18.4 months) with a 5-year PFS probability of 20.5% (95% CI 12.3-28.7%). A total of 63 patients (53%) died during follow-up. Sixty-two patients died of ovarian cancer and one patient died of acute myeloid leukaemia. The median OS was 44.1 months (95% CI 36.6-51.5 months) with a 5-year OS probability of 32% (CI 26-37%). The overall survival curve is depicted in Figure 2.

Initial predictive parameters for survival

The median preoperative serum blood platelet counts were higher in the groups of patients with progressive disease and of those who died of their disease when compared to the group of patients without recurrence and those alive at last follow-up date, 332 ± 124 and 334 ± 127 vs. 251 ± 122 and 267 ± 115*10^9/L with $P = 0.005$ and < 0.0001, respectively (Figure 3). The haemoglobin concentrations were lower in patients who died of their disease in comparison to those in patients who survived, 7.75 ± 0.90 vs. 8.02 ± 0.67 mmol/L, $P = 0.033$ (Figure 3). Differences in serum haemoglobin concentration between patients with progressive disease and

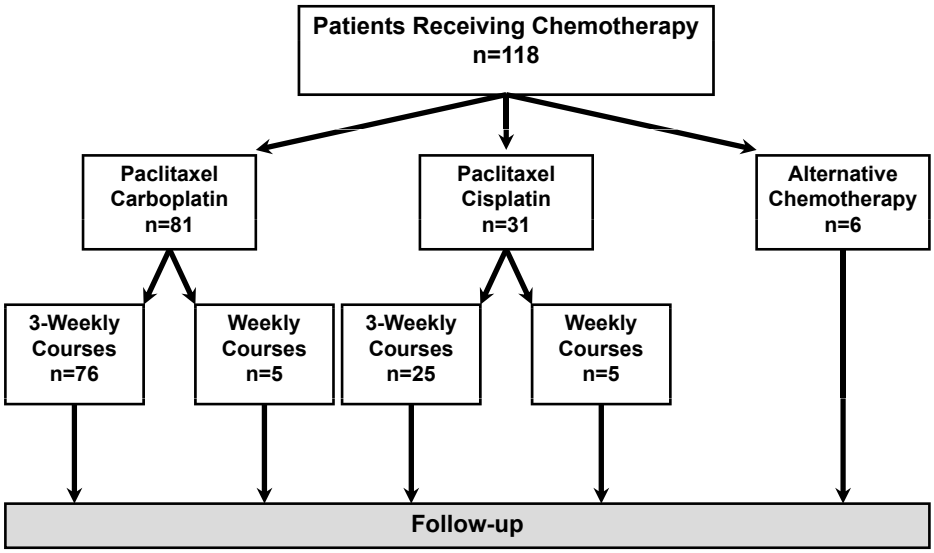


Figure 1. Flow chart of all 118 patients receiving intravenous chemotherapy following upfront surgical cytoreduction. Patients received courses of concomitant paclitaxel (175 mg/m2) carboplatin (AUC 6) or paclitaxel (175 mg/m2) cisplatin (75 mg/m2) every week or three-weekly. A total of six patients received an alternative chemotherapeutic regimen.

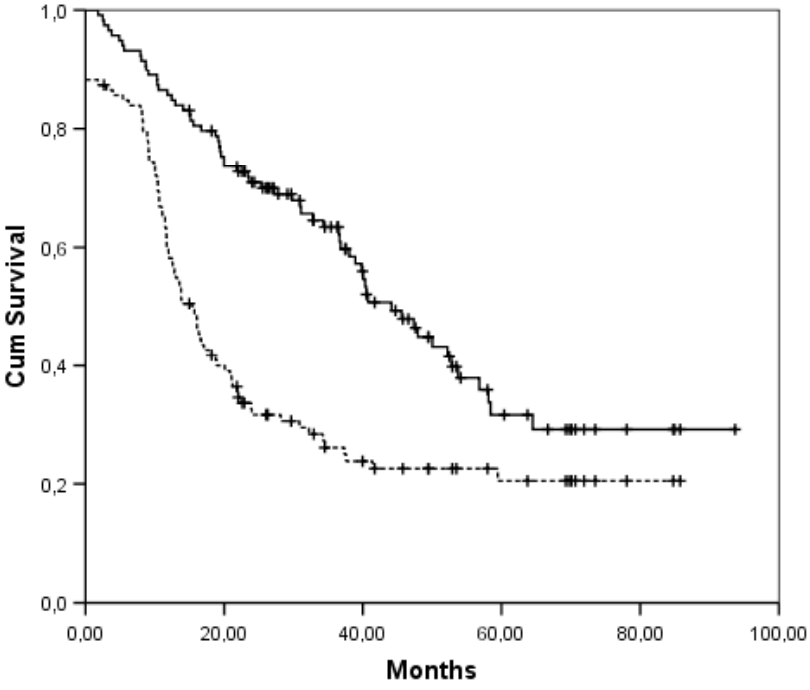


Figure2. Kaplan-Meier survival curve of patients with advanced ovarian cancer (n = 118) undergoing upfront surgical cytoreduction followed by courses of intravenous chemotherapy. The black line represents the overall survival (OS) and the dotted black line represents the progression-free survival (PFS).

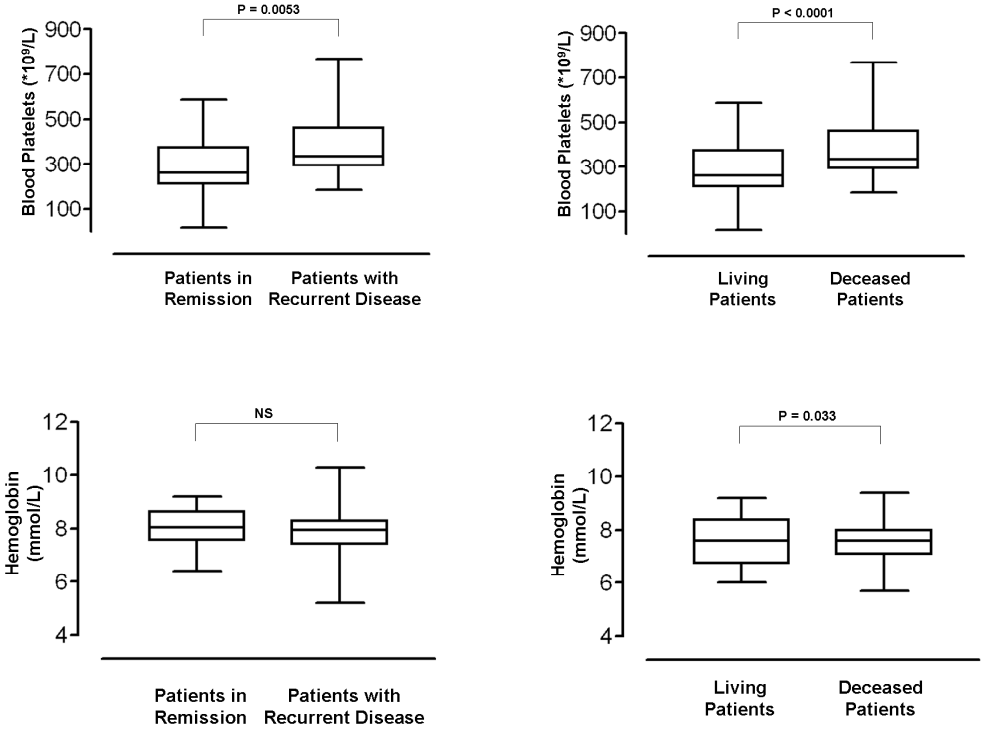


Figure 3. Box and whisker plots of pre-operative blood platelet counts(top) and haemoglobin (bottom) serum concentrations in patients with an advanced stage of epithelial ovarian cancer. Top panels: The left plot represents blood platelet counts in patients with recurrent disease compared to the counts in patients in remission. The right plot represents the blood platelet counts in patients who died of their disease compared those of patients alive with or without disease. Bottom panels: The left plot represents serum haemoglobin concentrations in patients with recurrent disease compared to the concentrations in patients in remission. The right plot represents the serum haemoglobin concentrations in patients who died of their disease compared those of patients alive with or without disease.

patients in remission were not significant. Preoperative performance status, serum albumin, LDH, logarithmically transformed CA 125 level and presence of ascites were comparable in all groups (Table 2 and 3).

Postoperative residual tumour > 1cm was more frequently observed in the progressive disease and death of disease groups of patients when compared to the remission and survivor groups, 52 and 43 vs. 9 and 18; $P < 0.006$ and <0.0001 (Table 2 and 3).

Histology, histological differentiation and FIGO stage were similar in all groups (data not shown).

Multivariate analysis of predictors for survival

The variables showing a statistical difference between the group of patients with progressive disease and those in remission in the univariate analysis were assessed by multivariate Cox' regression, utilizing a backward elimination procedure. PFS could be predicted by preoperative blood platelet counts (P=0.007) and postoperative residual tumour < 1 cm (P=0.004) were able to predict PFS with a for optimism corrected c-statistic of 0.63 (Table 4). The shrinkage

Table 2. Predictive parameters for progression-free survival in patients with advanced stage of epithelial ovarian cancer. Differences, if any, between the group of patients with progressive disease and those with no evidence of disease are tested with Student-T and Chi square tests, when applicable. Data are presented as median and range between brackets or in absolute numbers with standard deviation, when applicable.

	Recurrent Disease	No evidence of disease	Significance
Number of patients (n)	88	30	
Preoperative parameters			
Age (years)	62 (28-85)	61 (30-83)	0.958
Presence of ascites (n)	63 (71.6%)	20 (66.7%)	0.610
Preoperative serum parameters			
Haemoglobin (mmol/L)	7.83 ± 0.85	8.03 ± 0.68	0.125
Platelet count (*10^9/L)	332.0 ± 124.4	251 ± 122.8	0.005
Log CA 125 (kU/L)	2.71 ± 3.36	2.53 ± 3.55	0.053
Albumin (g/L)	34 ± 8.02	34.5 ± 10.59	0.964
LDH (E/l)	408.5 ± 247.0	375 ± 527.48	0.558
Postoperative parameters			
FIGO stage (n)			0.082
II	5	5	
III	65	24	
IV	18	1	
Residual tumour (n)			0.006
< 1 cm	36 (40.9%)	21 (70%)	
≥ 1 cm	52 (59.1%)	9 (30%)	

Table 3. Predictive parameters for overall survival in patients with an advanced stage of epithelial ovarian cancer. Differences, if any, between the group of patients who died and those with alive with or without disease are tested with Mann-Whitney U and Chi square tests, when applicable. Data are presented as median (range) or in absolute numbers with standard deviation, when applicable.

	Dead of Disease	Alive with or without Disease	Significance
Number of patients (n)	63	55	
Preoperative parameters			
Age (years)	64.0 (28-85)	59.7 (30-83)	0.395
Presence of ascites, n(%)	45 (71)	38 (69)	0.782
Preoperative serum parameters			
Haemoglobin (mmol/L)	7.75 ± 0.90	8.02 ± 0.67	0.033
Platelet count (*10^9/L)	334 ± 127	267 ± 115	<0.0001
Log CA 125 (kU/L)	2.68 ± 3.19	3.25 ± 3.72	0.405
Albumin (g/L)	32 ± 7.77	36.5 ± 9.67	0.252
LDH (E/l)	408 ± 273.7	395 ± 396	0.653
Postoperative parameters			
FIGO stage (n)			0.061
II	2	8	
III	46	43	
IV	15	4	
Residual tumour, n(%)			<0.0001
< 1 cm	20 (32)	37 (67)	
≥ 1 cm	43 (68)	18 (33)	

Table 4. Multivariate Cox' regression analysis with backward stepwise elimination. With the potential predictive parameters for progression-free and overall survival in patients with an advanced stage of epithelial ovarian cancer. Optimism corrected c-statistics were 0.63 and 0.67, respectively. HR= hazard ratio; NS=not significant; CI=confidence interval.

Variable	Progression-free survival		Overall survival	
	Significance	**HR (95% CI)**	**Significance**	**HR (95%CI)**
Preoperative parameters				
Age (years)	NS		NS	
WHO performance status	NS		NS	
Presence of ascites	NS		NS	
Preoperative serum parameters				
Haemoglobin	NS		0.012	0.70 (0.52-0.92)
Platelet count	0.007	1.002 (1.001-1.003)	0.031	1.002 (1.000-1.004)
Log CA 125	NS		NS	
Albumin	NS		NS	
LDH	NS		NS	
Postoperative parameters				
Residual tumour < 1cm	0.004	0.50 (0.31-0.80)	0.028	0.50 (0.27-0.93)
Histological differentiation	NS		NS	
Histology	NS		NS	
FIGO stage	NS		NS	

factor of 0.27 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 0.27 smaller. The generated nomogram, consisting of blood platelet counts and residual tumour, for the probability of 5-year PFS is depicted in Figure 4.

The initial predictive parameters for OS were assessed by a similar method of multivariate analysis. OS could be predicted by preoperative blood platelet counts ($P = 0.031$), preoperative haemoglobin serum concentrations ($P = 0.012$) and postoperative residual tumour < 1 cm ($P = 0.028$) were able to predict OS with a for optimism corrected c-statistic of 0.67 (Table 4). The resulting nomogram for OS, consisting of blood platelet counts, haemoglobin and residual tumour, is depicted in Figure 5.

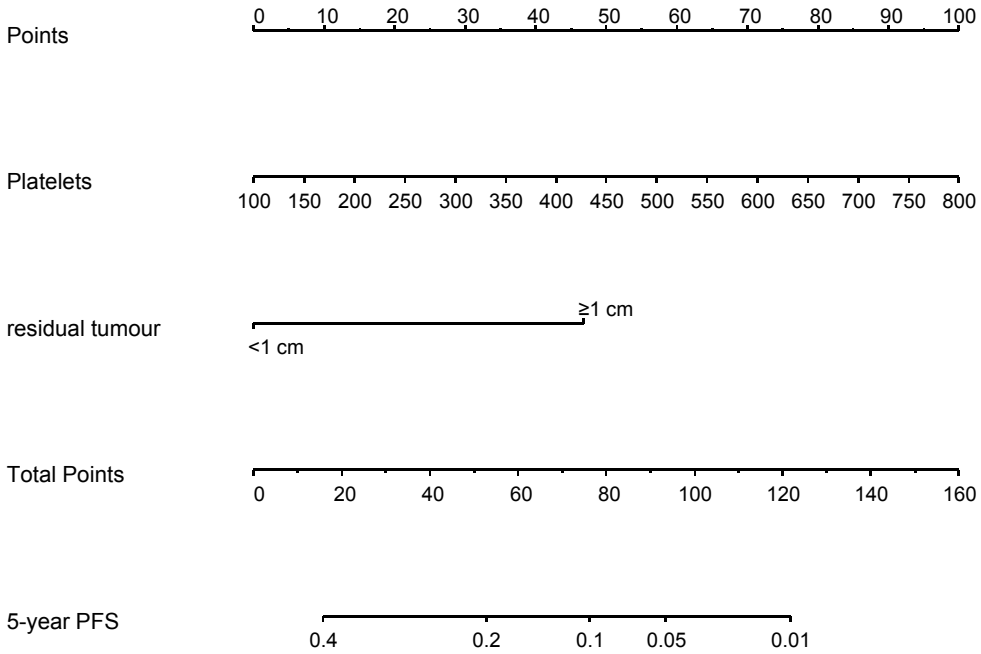


Figure 4. Nomogram for prediction of 5-year progression-free survival (PFS).
For each level of prognostic factors there is a number of points allocated at the point scale above. By adding the points of each parameter, the total points could be calculated. This number represents the probability of 5-year progression-free survival (PFS). For example: patient A; Platelets; 375 [40 points]; Residual tumour < 1cm [0 points]; total score 40+0= 40 points; probability of 5-year progression-free survival: 27%.

DISCUSSION

Data of the presented study showed that survival for the individual patient with advanced epithelial ovarian cancer was predictable by their preoperative blood platelet counts and haemoglobin serum concentrations in addition to postoperative residual tumour.

Following upfront cytoreductive surgery and subsequent paclitaxel carboplatin cycles, the specific estimate for the survival outcomes in each individual patient with advanced epithelial ovarian cancer is inaccurate when these estimates are based on FIGO data.[6] These data represent overall survival stratified for FIGO stage and postoperative residual tumour. As a result, counselling of the patients following treatment often results in inaccurate estimations of prognosis.

Although postoperative residual tumor is a strong predictor for prognosis[10,11], we demonstrated that it was not the only predictive parameter for survival in advanced epithelial ovarian cancer. Several other parameters have been suggested to be predictive for survival in advanced ovarian cancer including age[13], performance status[29], tumor histology[30], histological grade[31], presence of ascites[14,32], and preoperative blood platelets[33,34], hemoglobin[32], albumin[29,35], LDH[36], and CA125[35,36,37] serum concentrations. Most of these studies focused on

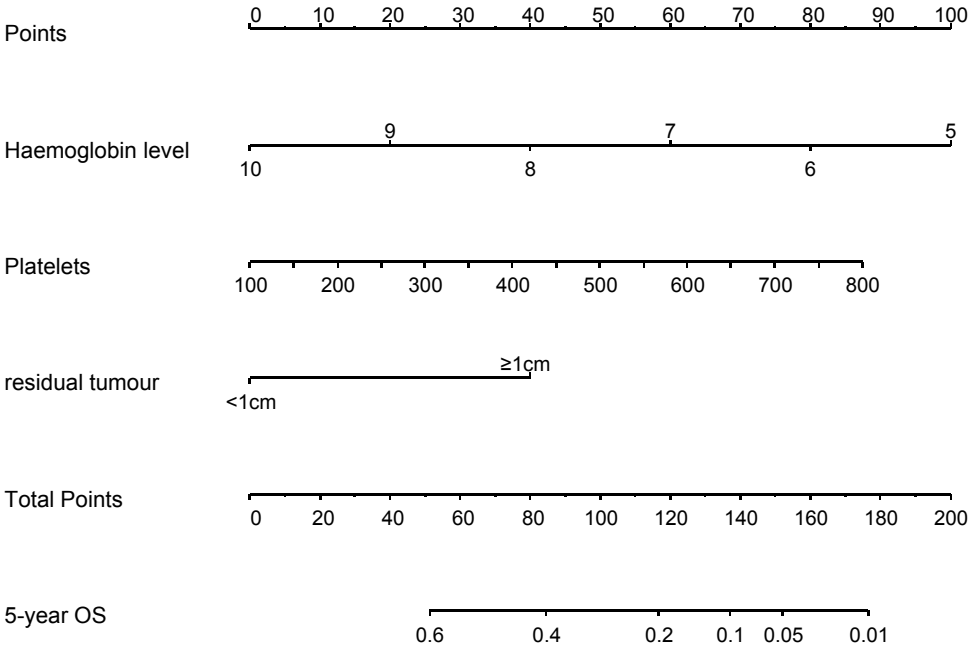


Figure 5. Nomogram for prediction of 5-year overall survival (OS).
For each level of prognostic factors there is a number of points allocated at the point scale above. By adding the points of each parameter, the total points could be calculated. This number represents the probability of 5-year overall survival (OS). For example in a patients with respectively haemoglobin = 9 [20 points], platelets = 375 [40 points], and residual tumour < 1cm [0 points] the total score is 60 points (20+40+0) representing a 55% probability of 5-year survival.

identification of prognostic parameters. Multivariate analysis of these predictors attempts to exclude interrelated factors and by combining the remaining predictors outcome in advanced ovarian cancer may be predicted.

When analyzed in these terms, this study was able to generate a nomogram for predicting both the PFS and OS in advanced ovarian cancer. While prediction of PFS may be of value for determining trial eligibility criteria and designing alternative therapeutic strategies, in addition prediction of OS is particularly valuable for counselling the patients in addition to the previously mentioned arguments. Alternative nomograms for the prediction of overall survival have been proposed previously.[19,20] These nomograms consisted of six to nine predictive parameters. However, the contribution of tumour histology and histological grade in predicting survival was limited to 20 of the 240 points in the nomogram proposed by Chi et al. The goal of this study was to design a simple nomogram that is suitable for utilization in daily routine practice. In our opinion, a nomogram of three parameters is better suited for this purpose. Moreover, the c-statistic of our nomogram was similar to the nomogram proposed by Chi et al. Analyses aiming to predict survival in advanced ovarian cancer should include clinical, histopathological, and (peri)operative parameters. However, a recently proposed prognostic index, without including preoperative serum parameters[38], could be externally validated.[39] Although

in the univariate analysis more parameters showed to be predictive, solely post operative residual tumour and preoperative blood platelet and/or hemoglobin serum concentrations were predictive in the final model indicating that the other parameters may be interrelated to the predictive parameters in the final model. Indeed, a previous report demonstrated that preoperative albumin and CA125 serum concentrations are strongly related to postoperative residual tumour.[21] Other parameters may have been omitted for similar reasons.

The proposed nomograms were internally validated by bootstrapping. However, the external validation of the nomograms is still lacking, thus the nomograms are not yet suitable for application in daily routine practice. In addition, external validation of the models in a large population of patients with advanced ovarian cancer may overcome the limitation that the model may solely be applicable in this relatively small population of patients with advanced ovarian cancer.

In conclusion, we developed and internally validated a 2-variable nomogram for predicting PFS and a 3-variable nomogram for predicting OS in patients undergoing upfront surgical cytoreduction followed by paclitaxel platinum-based chemotherapy for advanced stage epithelial ovarian cancer. The nomogram for predicting PFS maybe valuable for academic purposes while the nomogram for predicting OS is extremely valuable for counseling patients, follow-up logistics, determine trial eligibility criteria, and electing tailored treatment strategies. The individual OS of patients could be predicted accurately with a c-statistic of 0.67. Prior to applying the nomogram in daily routine practice, the nomogram needs to be externally validated.

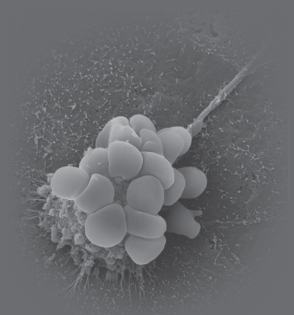
REFERENCES

1. Dutch Association of Comprehensive Cancer Centres. Guidelines for oncological and palliative care in the Netherlands. Available from URL: http://www.oncoline.nl [accessed January 7, 2008].
2. Parkin DM, Bray F, Ferlay J, Pisani P: Estimating the world cancer burden: Globocan 2000. *Int J Cancer*. 2001;94:153-6.
3. DiSaia PJ, Creasman WT: Epithelial ovarian cancer. In: DiSaia and Creasman, editors. *Clinical gynecologic oncology*. 6th ed. St. Louis: Mosby, Inc., 2002: 289-343.
4. Harries M, Gore M: Part I: Chemotherapy for epithelial ovarian cancer-treatment at first diagnosis. *Lancet Oncol*. 2002;3:529-36.
5. Gatta G, Lasota MB, Verdecchia A: Survival of European women with gynaecological tumours, during the period 1978-1989. *Eur J Cancer.* 1998;34:2218-25.
6. Petterson F: Annual report on the results of treatment in gynecological cancer, FIGO, 1994. Vol 22. Stockholm, Sweden: International Federation of Gynecology and Obstetrics, 1994:83-102.
7. FIGO 1987: Changes in definitions of clinical staging for carcinoma of the cervix and ovary. *Am J Obstet Gynecol.* 1987;156:263-4.
8. Hoskins WJ, Bundy BN, Thigpen JT, Omura GA: The influence of cytoreductive surgery on recurrence-free interval and survival in small-volume stage III epithelial ovarian cancer: a Gynecologic Oncology Group study. *Gynecol Oncol.* 1992;47:159-66.
9. Aure JC, Hoeg K, Kolstad P: Clinical and histologic studies of ovarian carcinoma. Long-term follow-up of 990 cases. *Obstet Gynecol.* 1971;37:1-9.
10. Bristow RE, Tomacruz RS, Armstrong DK, et al.: Survival effect of maximal cytoreductive surgery for advanced ovarian carcinoma during the platinum era: a meta-analysis. *J Clin Oncol.* 2002;20:1248-59.
11. Hoskins WJ, McGuire WP, Brady MF, et al.: The effect of diameter of largest residual disease on survival after primary cytoreductive surgery in patients with suboptimal residual epithelial ovarian carcinoma. *Am J Obstet Gynecol*. 1994;170:974-9.
12. Omura GA, Brady MF, Homesly HD, et al.: Long-term follow-up and prognostic factor analysis in advanced ovarian carcinoma: the Gynecologic Oncology Group experience. *J Clin Oncol*.1991;9:1138-50.
13. Thigpen T, Omura GA, Creasman WT, et al.: Age as a prognostic factor in ovarian carcinoma. The Gynecologic Oncology Group experience. *Cancer.* 1993;71:606-14.
14. Chi DS, Liao JB, Leon LF, et al.: Identification of prognostic factors in advanced epithelial ovarian carcinoma. *Gynecol Oncol.* 2001;82:532-7.
15. Zhang L, Cornejo-Garcia JR, Katsaros D, et al.: Intratumoral T cells, recurrence, and survival in epithelial ovarian cancer. *N Engl J Med*. 2003;348:203-13.
16. Kattan MW, Zelefsky MJ, Kupelian PA, et al.: Pretreatment nomogram for predicting outcome of three-dimensional conformal radiotherapy in prostate cancer. *J Clin Oncol*. 2000;18:3352-9.
17. Kattan MW, Leung DH, Brennan MF: Postoperative nomogram for 12-year sarcoma-specific death. *J Clin Oncol.* 2002;20:791–6.
18. Kattan MW, Karpeh MS, Mazumdar M, Brennan MF: Postoperative nomogram for disease-specific survival after an RO resection for gastric carcinoma. *J Clin Oncol.* 2003;21:3647-50.
19. Clark TG, Sterwart ME, Altman DG, et al.: A prognostic model for ovarian cancer. *Br J Cancer*. 2001;85:944-52.
20. Chi DS, Palayekar MJ, Sonoda Y, Abu-Rustum NR, Awtrey CS, Huh J, et al.: Nomogram for survival after primary surgery for bulky stage IIIC ovarian carcinoma. *Gynecol Oncol*. 2008;108:191-4.
21. de Jong D, Eijkemans MJ, Lie Fong S, Gerestein CG, Kooi GS, Baalbergen A, et al.: Preoperative predictors for residual tumor after surgery in patients with ovarian carcinoma. *Oncology*. 2008;72:293-301.
22. Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, et al.: New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst*. 2000;92:205-16.
23. Therasse P, Eisenhauer EA, Verweij J: RECIST revisited: a review of validation studies on tumour assessment. *Eur J Cancer.* 2006;42:1031-9.

24. ShimizuY, Kamoi S, Amada S, et al.: 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;70:2-12.
25. van Buuren S, Boshuizen HC, Knook DL: Multiple imputation of missing blood pressure covariates in survival analysis. *Stat Med*.1999;18:681-94.
26. Harrell Jr FE, Lee KL, Mark DB: Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. *Stat Med.* 1996;15:361-87.
27. Van Houwelingen JC, Le Cessie S: Predictive value of statistical models. *Stat Med*.1990;9:1303-25.
28. Hosmer DW, Lemeshow S. *Applied logistic regression*. 2nd ed. New York: Wiley & Sons, Inc., 2000.
29. Warwick J, Kehoe S, Earl H, et al.: Long-term follow-up of patients with advanced ovarian cancer treated in randomised clinical trials. *Br J Cancer.* 1995;72:1513-7.
30. Makar AP, Baekelandt M, Tropé CG, Kristensen GB: The prognostic significance of residual disease, FIGO substage, tumor histology, and grade in patients with FIGO stage III ovarian cancer. *Gynecol Oncol.* 1995;56:175-80.
31. van Houwelingen JC, ten Bokkel Huinink WW, van der Burg ME, et al.: Predictability of the survival of patients with advanced ovarian cancer. *J Clin Oncol.* 1989;7:769-73.
32. Zeimet AG, Marth C, Müller-Holzner E, et al.: Significance of thrombocytosis in patients with epithelial ovarian cancer. *Am J Obstet Gynecol*.1994;170:549-54.
33. Chalas E, Welshinger M, Engellener W, et al.: The clinical significance of thrombocytosis in women presenting with a pelvic mass. *Am J Obstet Gynecol*. 1992;166:974-7.
34. Li AJ, Madden AC, Cass I, et al.: The prognostic significance of thrombocytosis in epithelial ovarian carcinoma. *Gynecol Oncol*. 2004;92:211-4.
35. Parker D, Bradley C, Bogle SM, et al.: Serum albumin and CA125 are powerful predictors of survival in epithelial ovarian cancer. *Br J Obstet Gynaecol.* 1994;101:888-93.
36. Schneider D, Halperin R, Halperin D, et al.: Prediction of the survival of patients with advanced ovarian cancer according to a risk model based on a scoring system. *Eur J Gynaecol Oncol*.1998;19:547-52.
37. Geisler JP, Miller GA, Lee TH, et al.: Relationship of preoperative serum CA-125 to survival in epithelial ovarian carcinoma. *J Reprod Med.* 1996;41:140-2.
38. Teramukai S, Ochiai K, Tada H, et al.: PIEPOC: a new prognostic index for advanced epithelial ovarian cancer-Japan Multinational Trial Organization OC01-01. *J Clin Oncol.* 2007;25:3302-6.
39. Clark TG, Stewart M, Rye T, et al.: Validation of a new prognostic index for advanced epithelial ovarian cancer: results from its application to a UK-based cohort. *J Clin Oncol.* 2007;25:5669-70.

6

General discussion.



This thesis aims to evaluate the value of prediction models in determining treatment strategies in patients with advanced stage epithelial ovarian cancer (EOC).
In this final chapter the content of this thesis is discussed and recommendations for further research are suggested.

6.1 Prediction of suboptimal cytoreduction

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 optimal cytoreduction, with the best outcome in patients with no macroscopic tumor residuals after cytoreductive surgery. [1, 2] On the other hand patients with residual disease >1cm after primary cytoreduction will not have a substantial survival advantage from this procedure.[3, 4] These patients will probably benefit from an alternative approach with neo-adjuvant chemotherapy followed by interval cytoreductive surgery.[5] To determine the actual value of neo-adjuvant chemotherapy, the European Organisation for Research and Treatment of Cancer (EORTC) initiated a randomized trial to compare these two treatment approaches in patients with FIGO stage IIIC and IV EOC. The first results of these trial show no difference in overall survival between both treatment strategies and less operative morbidity in the neo-adjuvant chemotherapy arm.[6]
Together with the advantage of avoidance of aggressive surgery in women with chemoresistant disease, these data support an alternative management in patients with high chances on suboptimal cytoreduction or with an increased operative risk.
The preoperative assessment of expected stage of disease and expected residual disease after cytoreduction becomes even more important to facilitate a more tailored treatment. Furthermore, an adequate assessment could improve counselling patients to their chances of extensive surgical procedures and in the decision whether or not to refer the patient to an expert centre.
In clinical practise this preoperative assessment is most often based on a subjective assessment based on clinical features and experience. Our study on the accuracy and reproducibility of this offhand assessment of residual disease showed the limitations of this assessment. (**Chapter 2.1**) This study was designed to evaluate the inter-observer reproducibility and lacked the statistical power to determine the actual predictive performance of the offhand assessment. However, the observed poor reproducibility of the offhand assessment offers opportunities for prediction models to improve management of patients with advanced stage EOC.
Unfortunately, currently available predictors are not accurate enough to guarantee proper management. Our study, described in chapter 2.2, is the second large multicentre prospective study on CT predictors of suboptimal cytoreduction. Preoperative platelet count, diffuse peritoneal thickening and presence of ascites on at least two thirds of CT scan cuts were identified and used to generate a nomogram. Our model accurately discriminates patients with and without suboptimal cytoreduction in 74 % of the time. Nevertheless, our current study has several limitations that must be recognized and considered in interpreting these data.

Firstly, selection of predictors in relatively small data sets incorporates a risk of overfitting or overestimation of regression coefficients. To prevent overfitting the number of possible predictive parameters should be in reasonable balance with the number of events. In general the number of events per parameter should be at least ten. In our studies we adopted the methodology as described by Steyerberg et al. They suggest to select a limited set of important earlier described predictors and improve performance by shrinkage of the regression coefficients.[7]
Secondly, we were not able to account for the impact of surgeon's skills and philosophy on surgical outcome. This parameter is one of the key determinants of optimal surgical resection, but essentially impossible to control or study. The impact of surgeon capacities 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.
Thirdly, we include all patients with stage III-IV EOC, whilst the only patients who will need substantial cytoreduction are those with bulky disease. Future studies on prediction of suboptimal cytoreduction should limit their inclusion to stage IIIC (with bulky disease) and stage IV EOC. A new sub classification of stage IIIC disease seems obligatory, since current FIGO guidelines classifies both patients with positive retroperitoneal or inguinal nodes and patients with extensive upper-abdominal disease as stage IIIC disease. Obviously those two patient groups are not comparable with respect to chances on optimal cytoreduction and prognosis.
The same argument can be made with respect to inclusion of all histologic types. Given the prognostic differences between different histologic types, future trials should also stratify for histologic type. Since serous histology is by far the most common histologic type in advanced stage EOC, focussing on patients with serous histology seems defendable in future trials. The other histologic types should be investigated in other trials.
Finally, external validation is mandatory before our nomogram can be used in clinical practise.

In conclusion, due to the heterogeneity of ovarian cancer a perfect prediction model remains an illusion. However large prospective multicentre trials with well defined inclusion criteria should be able to improve performance or identify more accurate predictors. In the future computerized patient files will facilitate easily application and updating of institutional or regional prediction models. These models should incorporate the impact of surgeon's skills and philosophy.
Although accuracy of available models is limited, prediction models on suboptimal cytoreduction could provide a uniform basis for decision-making on feasibility of optimal cytoreduction in a multidisciplinary setting.

6.2 Prediction of 30-day morbidity

According to unadjusted morbidity rates approximately one out of three patients will experience a serious complication after primary cytoreductive surgery for EOC.

Age, performance status and co morbidity status are patient related risk factors for peri- and postoperative complications.[8, 9]

Our systematic review on postoperative mortality (POM) after cytoreductive surgery for EOC revealed a mean POM rate of 2.8%, POM rates in the elderly are significantly higher ranging from 5.4% till 11.7%.[10-13]. (**Chapter 3.1)**
The low operative risk corroborates the current treatment strategy of primary cytoreductive surgery followed by paclitaxel/platinum-based chemotherapy in patients with advanced stage EOC. For elderly patients with extensive disease and a diminished performance status, other treatment strategies may be considered.

POM is more often related to general complications rather than surgical complications, this demands improvement of preoperative risk-assessment, preoperative preparation and post-operative care. **(Chapter 3.2)**
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.[14]
We suggest a prospective registration of all peri- and postoperative complications after major surgery. This registration should be based on NSQIP definitions.
Treatment of patients with EOC should be limited to hospitals with high quality peri and postoperative care.

Risk-adjustment models can provide a more individual and accurate prediction of operative risk and corroborate the decision to withheld 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. Our proposed nomogram (**chapter 4)** is to our knowledge the second prediction model on 30-day morbidity after primary cytoreductive surgery for EOC. Age, WHO performance status, operative time and extent of surgery were predictive for 30-day morbidity. Further studies are warranted to validate currently available models and to identify preoperative predictors of 30-day morbidity.

6.3 Prediction of overall survival

Finally prediction of prognosis is an important issue in this heterogeneous patient population. In our study on prediction of progression-free and overall survival we confirmed the importance of other prognostic factors than FIGO stage alone**. (Chapter 5)** Platelet count and residual disease were indentified as most important predictors.

Our series again confirm the importance of residual disease after cytoreduction in patients with advanced stage EOC. This advocates aggressive surgical procedures to achieve minimal tumor residuals. Highest rates of optimal and complete cytoreduction are achieved in high volume hospitals and when surgery is performed by gynecologic oncologists. Referral of all patients with suspected advanced stage EOC to specialized hospitals is suggested to improve prognosis. [15, 16]

In contrast to other studies on prediction of prognosis with difficult prediction models, the annotation in a nomogram in our study facilitates an easy clinical use.[17-19]

6.4 Conclusion

Ovarian cancer is a heterogeneous disease. This demands an individualization of treatment. In this thesis we describe the benefits and limitations of prediction models in managing patients with advanced stage EOC. Prediction models can be valuable in determining treatment strategies by providing a more uniform basis for treatment decisions, counselling, and selection of patients for clinical trials.

Patients with suspected advanced stage EOC should be treated in high volume hospitals by experienced teams with the availability of optimal peri- and postoperative care. The decision to perform primary cytoreductive surgery should be based on a reproducible assessment of resectability and operative risk. To provide accurate reference figures an international standard for data collection and reporting of 30-day morbidity needs to be established.

The proposed prediction models in this thesis may support an objective estimation of surgical outcome and prognosis. However, before application in clinical practice external validation is warranted.

Large prospective multi-centre trials are necessary to determine the true value of prediction models based on biochemical-, radiological-, clinical- and laparoscopic parameters. Future models on prediction of suboptimal cytoreduction should concentrate on patients with serous stage IIIC (bulky disease) and IV EOC and incorporate the impact of surgeon's skills and philosophy.

Generated prediction models should be simple and easy to use in daily clinical practise by annotation in a nomogram or by development of a computer program. [20] Furthermore, future trials should be directed to identify more accurate predictors and to develop new techniques which can improve predictive performance.[21]

REFERENCES

1. Covens AL. A critique of surgical cytoreduction in advanced ovarian cancer. Gynecol Oncol 2000;78(3 Pt 1):269-74.
2. Markman M. Concept of optimal surgical cytoreduction in advanced ovarian cancer: a brief critique and a call for action. J Clin Oncol 2007;25(27):4168-70.
3. Hoskins WJ, McGuire WP, Brady MF, Homesley HD, Creasman WT, Berman M, et al. The effect of diameter of largest residual disease on survival after primary cytoreductive surgery in patients with suboptimal residual epithelial ovarian carcinoma. Am J Obstet Gynecol 1994;170(4):974-9; discussion 979-80.
4. Bristow RE, Eisenhauer EL, Santillan A, Chi DS. Delaying the primary surgical effort for advanced ovarian cancer: a systematic review of neoadjuvant chemotherapy and interval cytoreduction. Gynecol Oncol 2007;104(2):480-90.
5. Vergote I, De Wever I, Tjalma W, Van Gramberen M, Decloedt J, van Dam P. Neoadjuvant chemotherapy or primary debulking surgery in advanced ovarian carcinoma: a retrospective analysis of 285 patients. Gynecol Oncol 1998;71(3):431-6.
6. Vergote I, Trope C, Amant F, Kristensen GB, Sardi JE, Ehlen T, et al. EORTC-GCG/NCIC-CTG Randomised trial comparing primary debulking surgery with neoadjuvant chemotherapy in stage IIIC/IV ovarian, fallopian tube and peritoneal cancer. In: 12th Biennal Meeting International Gynecologic Cancer Society; 2008; Bangkok, Thailand; 2008.
7. Steyerberg EW, Eijkemans MJ, Harrell FE, Jr., Habbema JD. Prognostic modelling with logistic regression analysis: a comparison of selection and estimation methods in small data sets. Stat Med 2000;19(8):1059-79.
8. Aletti GD, Santillan A, Eisenhauer EL, Hu J, Aletti G, Podratz KC, 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(1):99-106.
9. Janda M, Youlden DR, Baade PD, Jackson D, Obermair A. Elderly patients with stage III or IV ovarian cancer: should they receive standard care? Int J Gynecol Cancer 2008;18(5):896-907.
10. Alphs HH, Zahurak ML, Bristow RE, Diaz-Montes TP. Predictors of surgical outcome and survival among elderly women diagnosed with ovarian and primary peritoneal cancer. Gynecol Oncol 2006;103(3):1048-53.
11. Diaz-Montes TP, Zahurak ML, Giuntoli RL, 2nd, Gardner GJ, Gordon TA, Armstrong DK, et al. Surgical care of elderly women with ovarian cancer: a population-based perspective. Gynecol Oncol 2005;99(2):352-7.
12. Cloven NG, Manetta A, Berman ML, Kohler MF, DiSaia PJ. Management of ovarian cancer in patients older than 80 years of Age. Gynecol Oncol 1999;73(1):137-9.
13. Gerestein CG, Damhuis RA, Burger CW, Kooi GS. Postoperative mortality after primary cytoreductive surgery for advanced stage epithelial ovarian cancer: A systematic review. Gynecol Oncol 2009.
14. Khuri SF. The NSQIP: a new frontier in surgery. Surgery 2005;138(5):837-43.
15. Vernooij F, Heintz P, Witteveen E, van der Graaf Y. The outcomes of ovarian cancer treatment are better when provided by gynecologic oncologists and in specialized hospitals: a systematic review. Gynecol Oncol 2007;105(3):801-12.
16. Engelen MJ, Kos HE, Willemse PH, Aalders JG, de Vries EG, Schaapveld M, et al. Surgery by consultant gynecologic oncologists improves survival in patients with ovarian carcinoma. Cancer 2006;106(3):589-98.
17. Clark TG, Stewart M, Rye T, Smyth JF, Gourley C. Validation of a new prognostic index for advanced epithelial ovarian cancer: results from its application to a UK-based cohort. J Clin Oncol 2007;25(35):5669-70; author reply 5670-1.
18. Clark TG, Stewart ME, Altman DG, Gabra H, Smyth JF. A prognostic model for ovarian cancer. Br J Cancer 2001;85(7):944-52.
19. Teramukai S, Ochiai K, Tada H, Fukushima M. PIEPOC: a new prognostic index for advanced epithelial ovarian cancer--Japan Multinational Trial Organization OC01-01. J Clin Oncol 2007;25(22):3302-6.
20. Ravdin PM, Siminoff LA, Davis GJ, Mercer MB, Hewlett J, Gerson N, et al. Computer program to assist in making decisions about adjuvant therapy for women with early breast cancer. J Clin Oncol 2001;19(4):980-91.
21. Helleman J, Jansen MP, Span PN, van Staveren IL, Massuger LF, Meijer-van Gelder ME, et al. Molecular profiling of platinum resistant ovarian cancer. Int J Cancer 2006;118(8):1963-71.

SUMMARY

This thesis aims to evaluate the value of prediction models in determining treatment strategies in patients with advanced stage epithelial ovarian cancer (EOC).
The background of treatment and treatment decisions in these heterogeneous patient population is described in the first chapter. **Chapter 2** investigates the accuracy of an offhand clinical assessment of irresectable disease and proposes a predictive model of suboptimal cytoreduction based on computed tomography (CT) scan and clinical parameters. **Chapter 3** evaluates the incidence and causes of postoperative mortality after cytoreductive surgery for EOC. **Chapter 4** aims to identify predictive parameters and generate a predictive model of 30-day morbidity. **Chapter 5** concerns development of a predictive model of prognosis in patients with advanced stage EOC. Finally, **chapter 6** discusses the content of this thesis and recommendations for further research are suggested.

Chapter 1.

General introduction

Ovarian cancer is the fourth most common cause of cancer-related death in women and has the worst prognosis of all gynecologic cancers. Prognosis mainly depends on the International Federation of Gynaecology and Obstetrics (FIGO) stage and the ability to achieve maximal cytoreduction with minimal or no macroscopic residual disease.
In the Netherlands each year 1100 new patients are diagnosed and approximately 900 women annually die due to this disease. The vast majority of patients presents with an advanced stage of disease, defined as FIGO stage IIB-IV. Treatment in advanced stage EOC is based on primary cytoreductive surgery followed by paclitaxel/platinum-based chemotherapy. Optimal cytoreduction is generally defined as residual disease ≤ 1cm. However, several recent studies have shown the prognostic importance of resection to no macroscopic residual tumor. Patients with residual disease >1cm 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 neo-adjuvant chemotherapy followed by interval cytoreduction and consecutive chemotherapy. An accurate preoperative assessment of patients with advanced stage EOC whose disease cannot be optimally cytoreduced at primary surgery may facilitate more tailored treatment strategies. In order to increase the accuracy of the preoperative prediction, many authors have attempted to identify specific predictors for suboptimal cytoreduction. Unfortunately, presently available predictors and prediction models are not accurate enough to achieve widespread applicability. The poor predictive performances can be explained by identification of predictors in retrospective studies with mixed inclusion criteria and different treatment policies.
Aggressive surgical procedures necessary to achieve maximal cytoreduction are inevitably associated with postoperative morbidity and mortality.

Postoperative morbidity is reported inconsistently, without standard definitions of postoperative morbidity. Unadjusted morbidity rates range from 11 to 67%. Reports on 30-day mortality after primary cytoreductive surgery for ovarian cancer range from 1 to 6.2 per cent. Predictive parameters for postoperative complications after primary cytoreduction for advanced stage EOC are age, performance status, co-morbidity and extent of surgery.

Chapter 2

Prediction of suboptimal cytoreduction at primary cytoreductive surgery for advanced stage epithelial ovarian cancer.

Chapter 2.1

Prediction of residual disease after primary cytoreductive surgery for advanced stage ovarian cancer: accuracy of clinical judgment

An accurate preoperative assessment of patients with advanced stage EOC whose disease cannot be optimally cytoreduced at primary surgery may facilitate more tailored treatment strategies. In daily clinical practice prediction of irresectable disease is often based on an off-hand clinical estimation. With this chapter we aim to evaluate the accuracy and reproducibility of this judgment. Fifteen observers (5 gynecologic oncologists, 5 gynecologists, and 5 senior residents) are offered preoperative data of twenty patients with advanced stage EOC who underwent primary cytoreductive surgery. The observers are asked to predict residual disease after cytoreductive surgery (≤1 or >1cm). Their estimation is compared to the performance of two prediction models. Overall, suboptimal cytoreduction is predicted with a sensitivity of 50% and a specificity of 56%. The intraclass correlation coefficient is 0.27.

Chi-square test shows no significant difference in prediction of suboptimal cytoreduction between the different subgroups or prediction models.

In conclusion clinical judgment of residual disease after primary cytoreductive surgery in patients with advanced stage EOC shows limited accuracy. Given the poor inter-observer reproducibility prediction models can attribute to uniform treatment decisions and improve counselling.

Chapter 2.2

Nomogram for suboptimal cytoreduction at primary surgery for advanced stage ovarian cancer

In order to determine the actual value of CT scan and clinical predictors we have 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 aim to identify CT

scan and clinical predictors and to generate a nomogram for suboptimal cytoreduction easy to use in daily clinical practise.
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 enter the study protocol.
To investigate independent predictors of suboptimal cytoreduction, a Cox' proportional hazard model with backward stepwise elimination is utilized.
One hundred fifteen patients with FIGO stage III/IV EOC enter the study protocol. Optimal cytoreduction is achieved in 52 (45%) patients. A suboptimal cytoreduction can be predicted by preoperative blood platelet count (P = 0.1990; 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 cuts (P = 0.0385; OR 2.294) with a for optimism corrected c-statistic of 0.67. The generated nomogram can, after external validation, be used to estimate surgical outcome and to identify those patients who may benefit from alternative treatment approaches.

Chapter 3.

Postoperative mortality after surgery for epithelial ovarian cancer.

Chapter 3.1

Postoperative mortality after primary cytoreductive surgery for advanced stage epithelial ovarian cancer: A systematic review

Accurate estimation of the risk of postoperative mortality (POM) is essential for the decision whether or not to perform cytoreductive surgery in a patient with advanced stage ovarian cancer. To ascertain modern reference figures, a systematic review of studies reporting POM after primary cytoreductive surgery for advanced stage epithelial ovarian cancer (EOC) is performed. A Medline search is performed to retrieve papers on primary cytoreductive surgery for advanced stage EOC. Twenty-three papers met the inclusion criteria and are reviewed. According to population-based studies, POM after primary cytoreductive surgery for EOC is 3.7% on average. Single centre studies report an average rate of 2.5%. The overall mean POM is 2.8%. POM is more frequent for elderly women and after extensive procedures. Accurate information on age-specific and procedure-specific rates can not be obtained.
In conclusion POM rates after surgery for EOC are satisfactorily low. There is a clear need for reliable reference figures for mortality after debulking surgery in the elderly.

Chapter 3.2

Causes of postoperative mortality after surgery for ovarian cancer

To determine causes of postoperative mortality after surgery for EOC all postoperative deaths in the South Western part of the Netherlands over a 17-year period are identified and are analysed by reviewing medical notes.

Between 1989 and 2005, 2434 patients undergo cytoreductive surgery for EOC. Sixty-seven patients (3.1%) die within 30 days after surgery. Postoperative mortality increases with age from 1.5% (26/1765) for the age-group 20-69 to 6.6 % (32/486) for the age-group 70-79 and 9.8% (18/183) for patients aged 80 years or older. Pulmonary failure (18%) and surgical site infection (15%) are the most common causes of death. Only a quarter of deaths result from surgical site complications.

Our results suggest that causes of postoperative mortality after surgery for EOC are very heterogeneous. Given the impact of general complications, progress in preoperative risk assessment, preoperative preparation and postoperative care seem essential to reduce the occurrence of fatal complications.

Chapter 4.

Prediction of 30-day morbidity after primary cytoreductive surgery for advanced stage ovarian cancer.

The objective of this chapter is to determine predictors of 30-day morbidity after primary cytoreductive surgery for advanced stage EOC. All patients in the South Western part of the Netherlands who underwent primary cytoreductive surgery for advanced stage EOC between January 2004 and December 2007 are identified from the Rotterdam Cancer Registry database. All peri- and postoperative complications within 30 days after surgery are registered and are classified according to the definitions of the National Surgical Quality Improvement Program (NSQIP).

To investigate independent predictors of 30-day morbidity, a Cox' proportional hazard model with backward stepwise elimination is utilized. The identified predictors are entered into a nomogram. Two hundred ninety-three patients enter the study protocol. Optimal cytoreduction is achieved in 136 (46%) patients. 30-day morbidity is seen in 99 (34%) patients. Postoperative morbidity is predicted by age ($P = 0.007$; OR 1.034), WHO performance status ($P = 0.046$; OR 1.757), extent of surgery ($P = 0.1308$; OR=2.101), and operative time ($P = 0.017$; OR 1.007) with a for optimism corrected c-statistic of 0.68. The generated nomogram can, after external validation, be used to estimate surgical outcome and to identify those patients who may benefit from alternative treatment approaches.

Chapter 5.

The prediction of progression-free and overall survival in patients with an advanced stage of epithelial ovarian carcinoma.

Since ovarian cancer has a heterogeneous presentation and clinical course, predicting progression-free (PFS) and overall survival (OS) in the individual patient is difficult. The objective of this chapter is to determine predictors of PFS and OS in patients with advanced stage epithelial ovarian cancer (EOC) after primary cytoreductive surgery and first-line paclitaxel/platinum-based chemotherapy.

All patients who underwent primary cytoreductive surgery for advanced stage EOC followed by first-line platinum-based chemotherapy at three regional clinics between January 1998 and October 2004 are identified from the Ovarian Cancer Database. To investigate independent predictors of PFS and OS, a Cox' proportional hazard model is utilized. Nomograms are generated with the identified predictive parameters.

Hundred-eighteen patients enter the study protocol. Optimal cytoreduction is achieved in 57 (48%) patients. Eighty-eight patients (74%) develop progressive disease. Sixty-three patients (53%) die. Median PFS and OS are 15 and 44 months, respectively.

Preoperative platelet count (P=0.007), and residual disease <1 cm (P=0.004) predict PFS with a for optimism corrected c-statistic of 0.63. Predictive parameters for OS are preoperative hemoglobin serum concentration (P=0.012), preoperative platelet counts (P=0.031) and residual disease <1cm (P=0.028) with a for optimism corrected c-statistic of 0.67.

In conclusion PFS is predicted by postoperative residual disease and pre-operative platelet counts whereas residual disease, preoperative platelet counts and preoperative hemoglobin serum concentration are predictive for OS. The proposed nomograms needs to be externally validated.

Chapter 6.

General discussion

Ovarian cancer is a heterogeneous disease. This demands an individualization of treatment. In this thesis we describe the benefits and limitations of prediction models in managing patients with advanced stage EOC. Prediction models can be valuable in determining treatment strategies by providing a more uniform basis for treatment decisions, counselling, and selection of patients for clinical trials.

Patients with suspected advanced stage EOC should be treated in high volume hospitals by experienced teams with the availability of optimal peri- and postoperative care. The decision to perform primary cytoreductive surgery should be based on a reproducible assessment of resectability and operative risk. To provide accurate reference figures an international standard for data collection and reporting of 30-day morbidity needs to be established.

The proposed prediction models in this thesis may support an objective estimation of surgical outcome and prognosis. However, before application in clinical practice external validation is warranted.

Large prospective multi-centre trials are necessary to determine the true value of prediction models based on biochemical-, radiological-, clinical- and laparoscopic parameters. Future models on prediction of suboptimal cytoreduction should concentrate on patients with serous stage IIIC (bulky disease) and IV EOC and incorporate the impact of surgeon's skills and philosophy.

Generated prediction models should be simple and easy to use in daily clinical practise by annotation in a nomogram or by development of a computer program. Furthermore, future trials should be directed to identify more accurate predictors and to develop new techniques which can improve predictive performance.

NEDERLANDSE SAMENVATTING

Het doel van dit proefschrift is het evalueren van de waarde van predictiemodellen bij het bepalen van behandelstrategieën bij patiënten met een gevorderd stadium epitheliaal ovariumcarcinoom (EOC).

Hoofdstuk 1 beschrijft de achtergrond van behandeling en van behandelkeuzes in deze heterogene patiëntenpopulatie. Het tweede hoofdstuk onderzoekt de waarde van de klinische blik in het voorspellen van het operatieresultaat bij gevorderd stadium EOC. Daarnaast wordt een predictiemodel voor suboptimale cytoreductie gebaseerd op computertomografie (CT-) scan- en klinische parameters ontwikkeld. **Hoofdstuk 3** evalueert de incidentie en de oorzaken van postoperatieve sterfte na cytoreductieve chirurgie voor EOC. **Hoofdstuk 4** heeft als doel factoren te vinden die het optreden van morbiditeit binnen 30 dagen na primaire cytoreductieve chirurgie voor gevorderd stadium EOC kunnen voorspellen. Met de gevonden factoren wordt een predictiemodel gegenereerd. **Hoofdstuk 5** beoogt ontwikkeling van een predictiemodel voor prognose in patiënten met een gevorderd stadium EOC. Tot slot, wordt in **hoofdstuk 6** de inhoud van dit proefschrift bediscussieerd en worden aanbevelingen gedaan voor nieuwe onderzoeken in de toekomst.

HOOFDSTUK 1.

Algemene introductie

Ovariumcarcinoom is de vierde oorzaak van kankergerelateerde sterfte bij vrouwen en heeft de slechtste prognose van alle gynaecologische maligniteiten. De prognose wordt voornamelijk bepaald door het stadium van de ziekte en de mogelijkheid tot het bereiken van maximale cytoreductie met achterlaten van een minimale hoeveelheid tumor.

In Nederland worden per jaar 1100 nieuwe patiënten met ovariumcarcinoom gediagnosticeerd en ongeveer 900 vrouwen sterven jaarlijks ten gevolge van deze ziekte. De meeste patiënten presenteren zich met een gevorderd stadium, dit wordt gedefinieerd als FIGO (International Federation of Gynaecology and Obstetrics) stadium IIB-IV. De behandeling van gevorderd stadium ovariumcarcinoom bestaat uit primaire cytoreductieve chirurgie gevolgd door placlitaxel/platinum bevattende chemotherapie. Patiënten met een suboptimale cytoreductie, gedefinieerd als tumorrest > 1cm, hebben over het algemeen weinig overlevingswinst van deze uitgebreide procedure en zijn wellicht beter af met een alternatieve behandeling middels neo-adjuvante chemotherapie gevolgd door uitgestelde cytoreductieve chirurgie. Een adequate preoperatieve beoordeling van patiënten met niet optimaal te reseceren ziekte kan zorgen voor een individualisatie van behandelstrategieën. Veel onderzoekers hebben geprobeerd specifieke parameters voor suboptimale cytoreductie te vinden waarmee de preoperatieve inschatting verbeterd kan worden. Helaas zijn de huidige voorspellende factoren en predictiemodellen niet accuraat genoeg om te kunnen worden toegepast in de praktijk. De

tegenvallende resultaten kunnen worden verklaard door het feit dat de predictoren geïdentificeerd zijn in retrospectieve studies met wisselende inclusiecriteria en behandelprotocollen.

Uitgebreide chirurgische procedures die nodig zijn om maximale cytoreductie te bereiken zijn onherroepelijk geassocieerd met postoperatieve morbiditeit en mortaliteit. Postoperatieve morbiditeit wordt inconsequent en zonder gebruik van vaste definities geregistreerd. Het optreden van morbiditeit varieert tussen de 11 en 67%. Gerapporteerde postoperatieve mortaliteit varieert tussen de 1 en 6.2%. Risicofactoren voor het optreden van postoperatieve complicaties zijn een toegenomen leeftijd, slechte performance status, aanwezigheid van comorbiditeit en uitgebreidere chirurgie.

HOOFDSTUK 2.

Predictie van suboptimale cytoreductie bij primaire cytoreductieve chirurgie voor gevorderd stadium epitheliaal ovariumcarcinoom.

Hoofdstuk 2.1

Waarde van de klinische blik in het voorspellen van het operatieresultaat bij gevorderd stadium ovariumcarcinoom.

In de praktijk wordt de beslissing om af te zien van een primaire debulking gebaseerd op een afweging van de verwachte voor- en nadelen van een dergelijke uitgebreide ingreep. Bij deze 'klinische blik' spelen patiënt gerelateerde factoren (bv. aanwezige comorbiditeit en leeftijd) en tumor gerelateerde factoren (bv. aanwezigheid van afstand metastasen) een belangrijke rol. Er is tot op heden geen onderzoek gedaan naar de accuratesse van deze 'klinische blik'. Doel van dit hoofdstuk is het bepalen van de accuratesse en reproduceerbaarheid van inschatting van het operatieresultaat o.b.v. de 'klinische blik'.

Vijftien onderzoekers (5 gynaecoloog-oncologen, 5 gynaecologen, 5 arts-assistenten in opleiding tot gynaecoloog) worden twintig casus met een gevorderd stadium (FIGO III-IV) ovariumcarcinoom voorgelegd. Het betreft patiënten bij wie een primaire debulking is verricht. Onderzoekers zijn niet op de hoogte van het resultaat van deze operatie. De onderzoekers wordt gevraagd of zij denken dat optimale cytoreductieve chirurgie (afzonderlijke tumorrest < 1 cm) heeft plaatsgevonden. Om dit te kunnen beoordelen kunnen zij gebruik maken van de volgende parameters: anamnese, lichamelijk onderzoek, laboratoriumwaarden (o.a. CA125), echogegevens en CT-abdomen.

De inschatting van de onderzoekers wordt vergeleken met een inschatting op basis van 2 predictiemodellen.

Het operatieresultaat wordt in 53% van de patiënten juist voorspeld. Gynaecoloog-oncologen voorspellen het operatieresultaat met een accuraatheid van 53%. Voor gynaecologen is dit 56% en voor de arts-assistenten in opleiding 49%.
Accuraatheid van de voorspelling is, wanneer gebruik gemaakt wordt van predictiemodellen gebaseerd op CA125 of CT-scan parameters, respectievelijk 60% en 50%. Het verschil in accuraatheid tussen de verschillende onderzoeksgroepen en predictiemodellen is niet statistisch significant.
De intra-class-correlatiecoëfficiënt voor alle onderzoekers is 0.27. Voor de gynaecoloog-oncologen 0.23, gynaecologen 0.28 en voor de arts-assistenten in opleiding 0.18.
Concluderend kan gesteld worden dat de 'klinische blik' een beperkte accuratesse heeft ten aanzien van het voorspellen van het operatieresultaat bij patiënten met een gevorderd stadium EOC. Mede gezien de lage intra-class-correlatiecoëfficiënt, lijkt er toch een rol weggelegd voor het gebruik van predictiemodellen.

Hoofdstuk 2.2

Nomogram voor voorspellen van suboptimale cytoreductie bij primaire cytoreductieve chirurgie voor gevorderd stadium ovariumcarcinoom.

Ten einde de werkelijke waarde van CT-scan- en klinische predictoren te bepalen zal een prospectieve multicentrum cohortstudie worden uitgevoerd met als doel identificatie van CT-scan- en klinische predictoren en ontwikkelen van een nomogram voor suboptimale cytoreductie bij primaire cytoreductieve chirurgie voor gevorderd stadium EOC.
Tussen oktober 2005 en december 2008 worden alle patiënten, in zes deelnemende ziekenhuizen in Zuidwest Nederland, met het vermoeden op een gevorderd stadium EOC bij wie primaire cytoreductieve chirurgie wordt uitgevoerd, geïncludeerd. Om onafhankelijke voorspellers voor suboptimale cytoreductie te achterhalen wordt gebruikt gemaakt van logistische regressie. Honderdvijftien patiënten met FIGO stadium III/IV EOC worden geïncludeerd. Optimale cytoreductie wordt bereikt in 52 (45%) patiënten.
Suboptimale cytoreductie kan worden voorspeld o.b.v. het preoperatieve thombocytenaantal ($P = 0.1990$; OR 1.002), diffuse peritoneale verdikking (DPT) ($P= 0.0074$; OR 3.021) en aanwezigheid van ascites op tenminste tweederde van de CT-scan beelden($P = 0.0385$; OR 2.294) met een voor optimisme gecorrigeerde c-statistic van 0.67. Het ontwikkelde nomogram kan, na externe validatie, worden gebruikt om het operatieresultaat te voorspellen en patiënten te identificeren die beter af zijn met een alternatieve behandelstrategie.

HOOFDSTUK 3.

Postoperatieve mortaliteit na chirurgie voor epitheliaal ovariumcarcinoom

Hoofdstuk 3.1

Postoperatieve mortaliteit na primaire cytoreductieve chirurgie voor gevorderd stadium epitheliaal ovariumcarcinoom: Een systematische review.

Accurate inschatting van het risico op postoperatieve mortaliteit (POM) is essentieel voor de beslissing om al dan niet cytoreductieve chirurgie uit te voeren in een patiënte met gevorderd stadium EOC. Ten einde referentiecijfers te verkrijgen wordt een systematische review naar POM na cytoreductieve chirurgie voor gevorderd stadium EOC uitgevoerd. Een Medline zoekactie wordt verricht om artikelen te vinden waarin geschreven wordt over POM. Drieëntwintig artikelen voldoen aan de gestelde inclusiecriteria en worden meegenomen in de analyse. Volgens populatie gebaseerde studies is POM gemiddeld 3.7%. De gemiddelde POM in studies waarin resultaten uit één ziekenhuis worden beschreven is 2.5%. De gemiddelde POM is 2.8% wanneer de resultaten uit alle artikelen worden samengenomen. POM komt vaker voor bij oudere patiënten en na uitgebreide procedures. Accurate informatie m.b.t. leeftijdspecifieke en procedurespecifieke aantallen kan niet worden verkregen. Concluderend blijkt POM na primaire cytoreductieve chirurgie voor gevorderd stadium EOC laag. Daarnaast is er een grote behoefte aan betrouwbare referentiecijfers voor postoperatieve sterfte bij ouderen.

Hoofdstuk 3.2

Oorzaken van postoperatieve mortaliteit na chirurgie voor ovariumcarcinoom.

Om oorzaken te vinden van postoperatieve sterfte na chirurgie voor EOC worden alle postoperatieve sterftegevallen in Zuidwest Nederland gedurende een periode van 17 jaar achterhaald en geanalyseerd.

Tussen 1989 en 2005, is bij 2434 patiënten cytoreductieve chirurgie voor EOC verricht. Zevenenzestig patiënten (3.1%) stierven binnen 30 dagen na de operatie. Postoperatieve mortaliteit neemt toe met oplopende leeftijd van 1.5% (26/1765) in de patiënten van 20 tot 69 jaar tot 6.6 % (32/486) in patiënten van 70-79 jaar en 9.8% (18/183) in patiënten van 80 jaar of ouder. Pulmonaal falen (18%) en infectie gerelateerd aan de uitgevoerde chirurgie (15%) zijn de meest voorkomende oorzaken van overlijden. Slechts een kwart van de sterfte wordt veroorzaakt door complicaties tijdens de operatie.

Onze resultaten suggereren dat de oorzaken van POM na chirurgie voor EOC zeer heterogeen zijn. Gezien de impact van algemene, niet direct aan chirurgie gerelateerde complicaties, zijn preoperatieve risico-inschatting, preoperatieve voorbereiding en postoperatieve zorg essentieel om de incidentie van fatale complicaties verder terug te dringen.

HOOFDSTUK 4.

Voorspellen van 30-dagen morbiditeit na primaire cytoreductieve chirurgie voor gevorderd stadium ovarium carcinoom.

Het doel van dit hoofdstuk is predictoren te vinden voor 30-dagen morbiditeit na primaire cytoreductieve chirurgie voor gevorderd stadium EOC.

Alle patiënten in Zuidwest Nederland bij wie primaire cytoreductieve chirurgie wordt verricht tussen januari 2004 en december 2007 worden geïdentificeerd uit de gegevens van het Integrale Kanker centrum Rotterdam (IKR). De peri- en postoperatieve complicaties binnen 30-dagen na de operatie worden geregistreerd en geclassificeerd volgend de definities van het National Surgical Quality Improvement Program (NSQIP).

Om onafhankelijke voorspellers voor 30-dagen morbiditeit te achterhalen wordt gebruikt gemaakt van logistische regressie. Met de gevonden predictoren wordt een nomogram ontwikkeld. Tweehonderd drieënnegentig patiënten worden geïncludeerd Optimal cytoreductie wordt bereikt bij 136 (46%) patiënten. 30-dagen morbiditeit wordt gezien in negenennegentig (34%) patiënten. Postoperatieve morbiditeit kan worden voorspeld door leeftijd ($P = 0.007$; OR 1.034), WHO performance status ($P= 0.046$; OR 1.757), uitgebreidheid van chirurgie ($P= 0.1308$; OR=2.101), en duur van de ingreep ($P = 0.017$; OR 1.007) met een voor optimisme gecorrigeerde c-statistic van 0.68. Het ontwikkelde nomogram kan, na externe validatie, worden gebruikt om uitkomst van chirurgie te voorspellen en om patiënten te identificeren die gebaat zijn bij alternatieve behandelstrategieën.

HOOFDSTUK 5.

Het voorspellen van progressievrije en totale overleving van patiënten met een gevorderd stadium epitheliaal ovariumcarcinoom.

Omdat ovariumcarcinoom gekenmerkt wordt door een heterogene presentatie en heterogeen klinisch beloop is het voorspellen van progressievrije (PFS)- en totale overleving (OS) in de individuele patiënt moeilijk. Het doel van dit hoofdstuk is predictoren te vinden voor PFS en OS in patiënten met een gevorderd stadium EOC die behandeld zijn met primaire cytoreductieve chirurgie en eerstelijns op paclitaxel/platinum gebaseerde chemotherapie.

Alle patiënten in drie regionale centra die behandeld zijn met primaire cytoreductieve chirurgie en eerstelijns op paclitaxel/platinum gebaseerde chemotherapie tussen januari 1998 en oktober 2004 worden geïdentificeerd uit de ovariumcarcinoom databank. Het Cox regressiemodel wordt gebruikt om onafhankelijke voorspellers voor PFS en OS te vinden. Met de gevonden parameters worden nomogrammen ontwikkeld. Honderdachttien patiënten worden geïncludeerd. Optimale cytoreductie wordt bereikt in 57 (48%) patiënten. Achtentachtig patiënten (74%) ontwikkelen progressieve ziekte. Drieënzestig patiënten (53%) zijn overleden tijdens de studieperiode. Mediane PFS en OS zijn 15 en 44 maanden, respectievelijk.

Het preoperatieve aantal thrombocyten (*P*=0.007) en resttumor <1 cm (*P*=0.004) voorspellen PFS met een voor optimisme gecorrigeerde c-statistic van 0.63. Predictieve factoren voor OS zijn preoperatieve hemoglobine (*P*=0.012), het preoperatieve aantal thrombocyten (*P*=0.031) en resttumor <1cm (*P*=0.028) met een voor optimisme gecorrigeerde c-statistic van 0.67.
Concluderend kan gesteld worden dat PFS wordt voorspeld door de aanwezigheid van resttumor na operatie en het preoperatieve aantal thrombocyten. Hemoglobine, het aantal thrombocyten en resttumor na de ingreep zijn voorspellend voor OS. De ontwikkelde nomogrammen moeten voor klinische toepassing worden gevalideerd.

HOOFDSTUK 6.

Algemene discussie

Ovariumcarcinoom is een heterogeen ziektebeeld. Dit vereist een geïndividualiseerde behandeling. In dit proefschrift worden de voordelen en beperkingen van het gebruik van predictiemodellen bij patiënten met een gevorderd stadium EOC beschreven. Predictiemodellen kunnen waardevol zijn bij het bepalen van behandelstrategieën door een meer uniforme basis te bieden voor behandelbeslissingen, voorlichting en selectie van patiënten voor klinische studies.
De behandeling van patiënten met het vermoeden op een gevorderd stadium EOC moet plaatsvinden door ervaren teams in gespecialiseerde ziekenhuizen waar optimale peri- en postoperatieve zorg gegarandeerd kan worden. De beslissing om primaire cytoreductieve chirurgie uit te voeren moet worden genomen op basis van een reproduceerbare inschatting van operabiliteit en operatie risico. Om goede referentiecijfers te krijgen is een internationale standaard voor gegevens verzameling en rapportage van 30-dagen morbiditeit noodzakelijk.
De door ons in dit proefschrift beschreven predictiemodellen kunnen een objectieve inschatting van het operatieresultaat en de prognose geven. Voordat de modellen toegepast kunnen worden in de kliniek moeten zij echter eerst worden gevalideerd in andere patiënten populaties.
Grote prospectieve multicentrum studies zijn nodig om de exacte waarde van predictiemodellen gebaseerd op biochemische, radiologische, klinische en laparoscopische parameters te kunnen bepalen. Toekomstige predictiemodellen voor suboptimale cytoreductie moeten zich concentreren op patiënten met een FIGO stadium IIIC (met uitgebreide ziekte) en IV sereus EOC en zij moeten de invloed van chirurgische vaardigheden en filosofie incorporeren. De te ontwikkelen predcitiemodellen moeten gemakkelijk te gebruiken zijn in de praktijk door bijvoorbeeld gebruik te maken van een nomogram of door integratie in een computerprogramma. Tot slot moeten toekomstige studies zich richten op het vinden van meer accurate predictoren en het ontwikkelen van nieuwe technieken die de accuraatheid van de voorspelling kunnen verbeteren.

LIST OF CO-AUTHORS AND THEIR AFFILIATIONS

A.C. Ansink	Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, Erasmus MC, Rotterdam, The Netherlands, currently Comprehensive Cancer Centre, Rotterdam, The Netherlands
A. Baalbergen	Department of Obstetrics and Gynecology, Reinier De Graaf Hospital, Delft, The Netherlands
J. Bakker	Department of Radiology, Albert Schweitzer Hospital, Dordrecht, The Netherlands
M.E.L van der Burg	Department of Medical Oncology, Erasmus MC, Rotterdam, The Netherlands
C.W. Burger	Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, Erasmus MC, Rotterdam, The Netherlands
R. A. M. Damhuis	Comprehensive Cancer Centre, Rotterdam, The Netherlands
R.H.M. Dykgraaf	Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, Erasmus MC, Rotterdam, The Netherlands
M.J. Eijkemans	Department of Public Health, Erasmus MC, Rotterdam, The Netherlands, currently Department of Public Health, UMC Utrecht, Utrecht, The Netherlands
O.E. Elgersma	Department of Radiology, Albert Schweitzer Hospital, Dordrecht, The Netherlands
D. de Jong	Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, Erasmus MC, Rotterdam, The Netherlands
G.S. Kooi	Department of Obstetrics and Gynecology, Albert Schweitzer Hospital, Dordrecht, The Netherlands
G.M. Nieuwenhuyzen-de Boer	Department of Obstetrics and Gynecology, Albert Schweitzer Hospital, Dordrecht, The Netherlands
A. Reedijk	Comprehensive Cancer Centre, Rotterdam, The Netherlands
D.W. van der Spek	Division of Gynecologic Oncology, Department ofObstetrics and Gynecology, Erasmus MC, Rotterdam, The Netherlands
M. de Vries	Department of Obstetrics and Gynecology, Albert Schweitzer Hospital, Dordrecht, The Netherlands

PUBLICATIONS

Right Ventricular Outflow Tract Reconstruction With an Allograft Conduit. **CG Gerestein**, JJ Takkenberg, FB Oei, AH Cromme-Dijkhuis, SE Spitaels, LA van Herwerden, EW Steyerberg, AJ Bogers. The Annals of Thoracic Surgery 2001; 71:911-8.

Transcatheter pulmonary valve perforation and balloon dilatation in neonates with pulmonary atresia and intact ventricular septum. **C.G. Gerestein**, R.M.F. Berger, M. Dalinghaus, A.J.J.C. Bogers, M. Witsenburg, Netherland Heart Journal, volume 11, number 11, nov 2003, 447-452.

Het epitheliaal ovariumcarcinoom. **C.G. Gerestein**, G.S. Kooi. Oncologica, number 3, 2005;124-127.

Preoperative predictors for suboptimal debulking in patients with advanced stage ovarian carcinoma. S. Lie Fong, M.J. Eijkemans, D. de Jong, **C.G. Gerestein**, G.S. Kooi, A. Baalbergen, M.E. van der Burg, C.W. Burger, A.C. Ansink. Oncology 2007;72:293-301.

The prediction of progression-free and overall survival in patients with an advanced stage of epithelial ovarian carcinoma.
C.G. Gerestein, M.J. Eijkemans, D. de Jong, M.E.L. van der Burg, R.H.M. Dykgraaf, G.S. Kooi, A. Baalbergen, C.W. Burger, A.C. Ansink. BJOG 2009;116:372–380.

Causes of postoperative mortality after surgery for ovarian cancer.
C.G. Gerestein, R.A. Damhuis, M. de Vries, A. Reedijk, C.W. Burger, G.S. Kooi
Eur J Cancer. 2009 Nov;45(16):2799-803.

Postoperative mortality after primary cytoreductive surgery for advanced stage epithelial ovarian cancer: A systematic review.
C.G. Gerestein, R. A. M. Damhuis; C. W. Burger; G. S. Kooi
Gynecol Oncol. 2009 Sep;114(3):523-7.

Prediction of residual disease after primary cytoreductive surgery for advanced stage ovarian cancer: accuracy of clinical judgment.
C.G. Gerestein, D.W. van der Spek, M.J. Eijkemans, J. Bakker, C.W. Burger, G.S. Kooi. Int J Gynecol Cancer. 2009 Dec;19(9):1511-5.

Prediction of 30-day morbidity after primary cytoreductive surgery for advanced stage ovarian cancer.
C.G. Gerestein, G. M. Nieuwenhuyzen, M.J. Eijkemans, C.W. Burger and G.S. Kooi.
Eur J Cancer. 2010 Jan;46(1):102-9.

Nomogram for suboptimal cytoreduction at primary surgery for advanced stage ovarian cancer.
C.G. Gerestein, M.J. Eijkemans, J. Bakker, O.E. Elgersma, G.S. Kooi and C.W. Burger.
Submitted

DANKWOORD

Dit dankwoord vormt het sluitstuk van mijn proefschrift. Na vier jaar komt er een einde aan een drukke periode. Het begon als een idee samen met Sjarlot en met hulp van velen is het uitgegroeid tot het boekje dat voor u ligt.

In de eerste plaats gaat mijn dank uit naar mijn promotor en co-promotor.
Geachte prof. Burger, beste Curt, toen ik mijn plan voor een promotieonderzoek met je kwam bespreken heb je me afgeraden om dit tijdens de opleiding te doen. Eigenwijs als ik ben heb ik dat toen voor kennisgeving aangenomen en ben toch begonnen. Achteraf moet ik je toch gelijk geven. Hoewel het doen van onderzoek verdieping heeft gegeven van mijn opleiding, is het zeker ook ten koste gegaan van andere aspecten van de opleiding en is het voor het thuisfront, zoals je voorspelde, niet altijd even makkelijk geweest. Bedankt dat je me altijd hebt gesteund en ondersteund, het wordt enorm gewaardeerd.
Beste Sjarlot, vanaf het allereerste moment was er een klik, we zaten meteen op één lijn en dat is eigenlijk altijd zo gebleven. Dat maakt(e) de samenwerking erg prettig, je hebt aan één woord genoeg. Door jouw ruimdenkendheid, steun en inzet heb ik voldoende tijd en ruimte gehad om dit onderzoek tot een goed einde te brengen.

Ik wil de leden van de kleine en grote commissie bedanken voor de kritische beoordeling van het manuscript en voor de bereidwilligheid vandaag oppositie te voeren.

Beste Rene, ik besef nu pas, nu je niet meer in het Erasmus werkt, wat een voorrecht ik heb gehad om zomaar bij je binnen te kunnen lopen en samen analyses te kunnen doen. Met je expertise op het gebied van predictiemodellen behoor je tot een select groepje en het is een voorrecht geweest om met je samen te mogen werken.

Beste Lena, vanaf het eerste moment heb je me voorgehouden vooral te blijven focussen. Als er weer een nieuw project in me opkwam of zich op een andere manier een project aandiende moest ik hier steeds opnieuw aan denken. Naast mijn dank voor je hulp bij het opstarten van deze studie wil ik je vooral ook hiervoor bedanken.

Beste Anca, tijdens mijn werkzaamheden in de Daniel heb ik , onder jouw bezielende leiding, efficiënt werken geleerd. Bedankt voor alle support.
Beste Diederick, na een wat stroef begin hebben we een vruchtbare samenwerkingsvorm gevonden. Ik hoop dat we die in de toekomst nog verder kunnen uitbreiden.
Beste Maria, natuurlijk mag jij hier niet ontbreken. Bedankt voor je adviezen en hulp bij de diverse studies.
Beste Ronald, ook jij bent vanaf het begin betrokken. Bedankt voor je kritische blik en hulp bij het achterhalen en uitwerken van de data.

Beste Janet en Otto, bedankt voor het monnikenwerk dat jullie voor me verricht hebben.

De medewerkers van het Integraal Kanker Centrum Rotterdam (IKR) en in het bijzonder Sandra en Marjolijn wil ik bedanken voor hun hulp en ondersteuning.

Alle contactpersonen van de deelnemende ziekenhuizen in de regio wil ik danken voor hun hulp bij de inclusie van patiënten en het verkrijgen van de benodigde data.
Hiervoor wil ik ook Marjolijn, Gatske en Ineke bedanken, zonder jullie hulp was het nooit gelukt.

Uiteraard ben ik veel dank verschuldigd aan de diverse (oncologie-) verpleegkundigen (in het bijzonder Anja, Marion en Tineke) en secretariaten (in het bijzonder Anita) van de participerende ziekenhuizen.

Al mijn (ex-) collega's wil ik danken voor hun zichtbare en onzichtbare steun.
Hans ik ben blij dat je vandaag naast me wilt staan. We begonnen nagenoeg gelijktijdig met de opleiding en vormden voor elkaar een klankbord voor alle dagelijkse beslommeringen. Ik heb dit altijd erg gewaardeerd.
Beste Bas, onze 'wekelijkse' hardlooprondjes werkten altijd erg stimulerend en zorgden voor de broodnodige relativering. Bedankt dat je vandaag mijn paranimph wilt zijn.

Lieve Mirthe, Noortje en Karlijn, ik weet niet wat ik zou moeten zonder jullie. Ik ben blij dat het nu af is en dat ik nu weer wat meer tijd voor jullie krijg.
Tot slot liefste Berney, jij hebt zonder twijfel het meest te lijden gehad onder dit project. Desondanks heb je me altijd volledig gesteund. Bedankt voor je geduld en flexibiliteit. Ik beloof dat ik nu weer meer ´quality time´ zal gaan vrijmaken en hoop nog lang samen te kunnen genieten.

CURRICULUM VITAE

C.G. Gerestein was born March 7, 1976 in Zeist, The Netherlands.
He attended secondary school at the Christelijk Lyceum in Zeist, the Netherlands.
He started Medical School at the Catholic University of Leuven, Belgium, in 1994 and continued Medical School at the Erasmus University in Rotterdam, The Netherlands, in 1995, including a six-week traineeship at the department of Gynecology and Obstetrics at Paarl Hospital in Paarl, South-Africa.
After obtaining his Medical Degree in September 2001 he worked as a resident at the department of Obstetrics and Gynecology at the Reinier the Graaf Gasthuis in Delft, The Netherlands. In June 2003 he started his training in Obstetrics and Gynecology at the Albert Schweitzer Hospital (dr. G.S. Kooi) in Dordrecht and the Erasmus Medical Center (prof.dr. C.W. Burger) in Rotterdam, The Netherlands. After finishing his residency in June 2009, he is currently working as a gynecologist at the department of gynecologic oncology at the Erasmus Medical Center in Rotterdam, the Netherlands.
He is married to Berney. They have three daughters, Mirthe, Noortje and Karlijn.