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Risk Factors for Severe Complications in Ovarian Cancer Surgery

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Abstract. *Backround: Due to extensive surgical intervention for macroscopic complete cytoreduction in epithelial ovarian cancer (EOC) patients, severe complications in the postoperative course are possible. Patients and Methods: A total of 345 EOC patients who underwent cytoreductive surgery were retrospectively evaluated regarding risk factors for an unfavorable postoperative course. Possible pre-, intra- and postoperative risk factors were statistically analyzed performing multivariate ordinal logistic regression. Results: A total of 345 EOC patients underwent cytoreductive surgery. There were no complications in 114 patients, mild complications in 114 patients and severe complications in 117 patients. The risk factor evaluation identified age (p=0.049), smoking (p=0.032) and duration of surgery (p<0.0001) as significant factors for severe postoperative morbidity. Conclusion: In EOC patients age, smoking and the duration of surgery have significant impact on the postoperative course. Only the duration of surgery can be positively influenced by a well-trained EOC team.*

In epithelial ovarian cancer (EOC) the prognostic impact of macroscopic complete cytoreduction has been shown unequivocally. Often, complex surgery will be needed harbouring the risk of severe postoperative complications (1). These postoperative complications may delay adjuvant therapy and therefore have a negative impact on survival (2). Using the Memorial Sloan Kettering Cancer Center secondary surgical event score we classified all postoperative complications within the first 60 days after surgery from grade 1 to 5. The aim of this study was the identification of possible risk factors for an unfavorable postoperative course (3).

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Patients and Methods

This retrospective study was conducted in accordance with the standards of the local ethics committe of the medical faculty of the Rheinische Friedrich Wilhelms University, Bonn, Germany (Nr: 314/20). All 345 patients who underwent cytoreductive surgery for EOC between 2004 and 2016 were included in this study and data were collected and analyzed. Postoperative complications were assessed by the Memorial Sloan Kettering Cancer Center secondary surgical event score (3). Histologies and surgical reports were used for a retrospective determination of the peritoneal cancer index (4). For statistical analysis, patients were divided into two groups; those with no or mild complications (secondary surgical events grade 1 and 2) and those with severe complications (secondary surgical events grade 3 to 5).

Possible risk factors for severe secondary surgical events were analyzed by multivariate ordinal logistic regression. The quality review was performed by Pearson and Deviance tests. Further data were analyzed by binary ordinal logistic regression. Differences were defined to be significant when $p \leq 0.05$. All statistical analyses were performed using Minitab Version 18.

Results

A total of 345 patients underwent cytoreductive surgery for EOC. Patient variables analyzed in the multivariate analysis are listed in Table I. Table II shows all secondary surgical events in detail while Table III shows all graded secondary surgical events and the number of patients affected. 7 patients died in the postoperative course within the first 60 days after surgery. 1 patient suffered a heart attack, 1 patient with a known aortic stenosis experienced postoperative

Table I. *Patient characteristics, surgical details and histology.*

Variable	Result
Mean age	60 years (16-85)
American Society of Anaesthesiologists (ASA) risk classification	Evaluated in 345 patients
1	47
2	203
3	94
4	1
Body mass index	Evaluated in 338 patients
<19	11 patients
19-24	162 patients
25-30	108 patients
30.1-40	44 patients
>40	13 patients
Comorbidities	
History of thrombembolic events (heart attac, thrombosis, embolism)	47 patients
Diabetes mellitus	27 patients
Smokers	48 patients
FIGO-Stages	345 patients
IA/IB	48 patients
IIA-IIB	21 patients
IIIA	4 patients
IIIB	16 patients
IIIc	216 patients
IV	40 patients
First diagnosis of EOC	301 patients
Recurrent EOC	44 patients
Neoadjuvant chemotherapy and secondary cytoreduction	137 patients
Primary debulking surgery	208 patients
Median peritoneal cancer index	10 (range=0-32)
Completeness of cytoreduction	227 patients
Incomplete cytoreduction	113 patients
No Information on completeness	5 patients
Median operating time	372 min (135-695)
Median number of erythrocyte concentrates	4.8 (range=0-38)
Median time in intensive care unit	1 day (range=0-43 days)
Median duration of postoperative mechanical ventilation	5.8 h (range=0-576 h)
Histology	
Serous	309 patients
Mucinous	14 patients
Endometroid	17 patients
Clear cell	4 patients
Seromucinous	1 patient
Lymph node dissection	281 patients
No Lymph node dissection	64 patients

Table II. *Postoperative complications (secondary surgical events) in the first 60 days after surgery.*

Specified secondary surgical events	Patients [number]	Percentage [%]
Anastomotic leackage	24	6.95
Abscess around the anastomosis	10	2.89
Peritonitis more than localized	17	4.92
Burst abdomen	12	3.48
Ileus	1	0.29
Paralytic Ileus	46	13.33
Stenosis of the anastomosis	1	0.29
Clostidium difficile infection	5	1.45
Hartmann stump insufficiency	1	0.29
Ureter lesion	1	0.29
Enterocutane fistula	2	0.58
Enterovesical fistula	1	0.29
Rectovaginal fistula	6	1.74
Billary fistula	1	0.29
Pancreatic fistula	6	1.74
Pancreatitis	2	0.58
Deep venous thrombosis	27	7.82
Lung embolia	10	2.89
Non-ST-segment elevation myocardial infarction	9	2.61
ST-segment elevation myocardial infarction	2	0.58
Tachyarrythmia absoluta	8	2.32
Artrial fibrillation	4	1.16
Atrioventricular -Bloc	1	0.29
Asystoly with successful reanimation	2	0.58
Stroke	1	0.29
Pleural effusion	80	23.19
Pneumonia	19	5.51
Secondary haemorrhage	10	2.89
Wound infection	75	21.74
Lymphocele	42	12.17
Pyelonephritis	2	0.58
Urinary tract infection	28	8.12
Urinary stasis	15	4.35
Kidney infarction	4	1.16
Renal insufficiency, partly transient	7	2.03
Port infection	3	0.87
Central venous catheter infection	2	0.58
Transfusion reaction	2	0.58
Hepatitis C due to fresh frozen plasma	1	0.29
Haematothorax	1	0.29
Sepsis	11	3.19
Postoperative delirium	8	2.32
Transient postoperative nerval irritation	28	8.12

cardiac decompensation while 2 patients died of septic pneumonia in the late postoperative course. 3 patients experienced a septic shock, 2 due to an anastomotic leckage and 1 due to an abscess followed by an enterocutaneous fistula. The most common secondary surgical events were pleural effusion, wound infection, and paralytic ileus.

The multivariate ordinal logistic regression analysis of 344 patient data (the data of 1 patient was missing for the duration of surgery) identified smoking (p=0.032) as the strongest preoperative factor for the development of severe complications. The age of the patients (p=0.049) and the duration of surgery (p<0.001) were the two other risk factors significantly associated with severe complications. Table IV shows the results

Table III. *Postoperative complications graded according to the MSKCC secondary surgical event score.*

Secondary surgical events	Patients [number]	Percentage [%]
None	114	33.04
G1	42	12.17
G2	72	20.87
G3	69	20.00
G4	41	11.88
G5	7	2.02

Table IV. *Multivariate analysis of potential risk factors (age, preoperative anemia, ASA, BMI, history of thrombembolic events, diabetes, elevated creatinin levles, neoadjuvant chemotherapy, smoking, recurrent disease, primary disease, number of transfused erythrocytes, complete or incomplete resection, duration of postoperative mechanical ventilation, duration of intensive care).*

Factor	Coefficient	Odds ratio	*p*-Value
Age	–0.020	0.98	0.049
Smoking	0.683	1.98	0.032
Duration of surgery	–0.004	1.00	<0.001

of the mulitvariate analysis. By performing binary logistic regression with 340 patient data (data on the completeness of cytoreduction was missing in 5 surgery reports), we found a significant decrease in complete cytoreduction with increasing age of patients (p=0.010). The risk of leaving surgery with a residual disease increased 1.29-fold every ten years with increasing patient age. The age of the patients was not related to a prolonged hospital stay (p=0.244).

The body mass index, available in 338 patients, was no predictor for residual disease (p=0.820; OR=1.03) or the duration of surgery (p=0.383). The duration of surgery had no impact on postoperative thrombembolic events (p=0.197) or the number of erythrocyte concentrates received (p=0.770). The risk of thrombembolic events was reduced in the group of patients with a history of thrombembolic events (OR=0.715).

The available data on the peritoneal cancer index in 330 patients demonstrated no significant correlation with a preoperative anemia or the duration of the postoperative intensive care. However, a peritoneal cancer index of more than 15 correlated with a higher incidence of a postoperative pancreatic fistula (OR=0.083). The peritoneal cancer index had significant impact on the duration of surgery (p<0.001) and the completeness of cytoreduction (p<0.001; OR=0.800). The significant correlation between the peritoneal cancer index and Ca125 (p=0.034) was negligible in the metric set (Figure 1).

The risk of a preoperative anemia was 1.57-fold higher in the group of patients with neoadjuvant chemotherapy than in the group of patients without neoadjuvant chemotherapy.

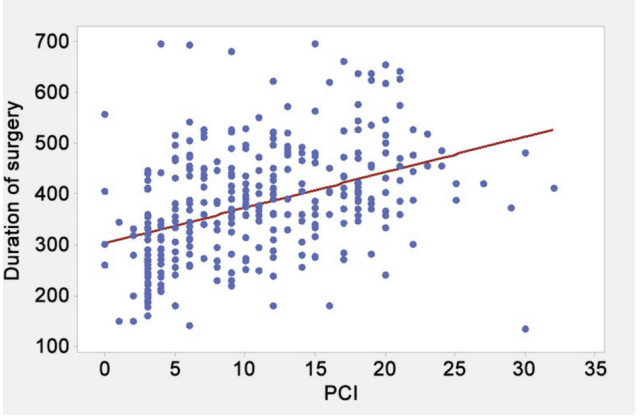

Figure 1. *Duration of surgery and PCI.*

Discussion

Optimal cytoreduction in EOC patients aims to increase overall survival but harbours the risk of increased morbidity and a prolonged recovery which in turn decreases survival (5). The preoperative prediction of postoperative complications would be ideal to define high-risk patients. Despite intensive efforts in the preoperative work up, this remains difficult. In the present study, smoking was identified as the strongest predictor for severe complications. The age of the patients and the duration of surgery were two other significant predictors of severe complications. Smoking in general shows an increased overall morbidity with wound complications, infections, pulmonary and neurological complications (6). The analysis of the database of the National Surgical Quality Improvement Program (NASQIP) identified smoking, elevated preoperative creatinine levels (above 1.5 mg/dl) and insulin-dependent and non-insulin-dependent diabetes as significant risk factors for a re-operation. Reoperation shortly after initial surgery increases morbidity and mortality (7-10). We did not find a correlation between diabetes and morbidity or an elevated creatinin and morbidity. But creatinin levels were elevated in only 3 patients. In line with the above, the evaluation of more than 500,000 patients data from the American College of Surgeons in NSQIP identified smoking as a significant promoter of pneumonia, cardiac arrest, myocardial infarction, stroke, sepsis, septic shock, organ space infection and increased postoperative mortality (10).

An age above 75 years has been determined as a risk factor for higher postoperative morbidity and mortality. In general surgery in the elderly is feasible but the risk for increased severe morbidity and increased mortality is almost 40%. In addition, adjuvant chemotherapy may be delayed or not administered at all. Even when complete cytoreduction is dispensed due to the age of the patient, incomplete surgery also bears the risk of increased perioperative morbidity. Especially in patients over 80 years of age, FIGO stage IV, low albumin levels, and higher risk classification according to the American Society of Anaesthesiologists (ASA), morbidity and mortality increases rapidly (11). Data analysis of the NSQIP demonstrated a linear progression of morbidity and an exponential progression of mortality with increasing age. The increase in morbidity and mortality was seen despite the absence of further risk factors at the age of 70 and over. Predictive factors for morbidity and mortality in the elderly patients were urgent surgery, unintentional weight loss, preoperative anemia, and blood transfusions. Preoperative anemia and blood transfusions had no significant impact on severe morbidity in our cohort. Furthermore, an age over 80 years was associated with the highest risk for wound infections without any correlation to other risk factors (12). The frailty of aging itself without additional specific comorbidities is not usually noticeable in the normal state. But the stress of surgery requires reserve capacities which may not be available in older patients. Therefore, age may sometimes be the only assessable risk factor in this patient cohort (13).

In addition to the experience of the surgeon, the complexity of the surgical intervention significantly determines the duration of the surgery and the postoperative morbidity, especially in the older patients (12). An increase in surgery duration of only 30 minutes in patients with EOC results in 17% more cardiovascular events, 7% more respiratory events, and 15% more wound infections (12). Surgery duration of more than 10 hours and an ASA risk classification of 3 or more were the only significant factors for grade 3 and 4 secondary surgical events in patients with pseudomyxoma peritonei (14). The Tennesse Surgical Quality Collaborative showed that the risk for secondary surgical events increases significantly after 2.1 hours of surgery. A significant risk of deep infections at the surgical site begins only after 42 minutes of surgery. Each additional hour of surgery time supports the development of a postoperative sepsis (15). Even in laparoscopic procedures, the duration of surgery represents a significant risk factor for postoperative complications (16). Well trained surgeons minimize the duration of surgery which results in a reduction in mortality of 69% (17).

The ASA risk classification was irrelevant in our study for severe secondary surgical events. This could be due to the previous policy of the clinic to administer neoadjuvant chemotherapy whenever aszites more than 500 cc was present. Therefore, severely and critically affected EOC patients may already have been excluded. Other studies have indeed shown that a higher ASA risk classification correlates with the grade of secondary surgical events. Especially in older patients, the ASA risk classification is significantly associated with severe secondary surgical events (11, 12, 14, 18). In a retrospective study even a 72% correct identification of high-risk patients was suggested based on the combination of ASA risk classification, low albumin levels, aszites, bleeding disorders, urgency of surgery, higher extended procedure score, and age of the patients (18).

Obesity is a known risk factor for decreased overall survival in patients with EOC (19). In some studies, morbid obesity, indicated by a body mass index of more than 39.9, has been associated with severe secondary surgical events (20). Other studies show that obese patients are only at risk for impaired wound healing (21). In our study the body mass index had no significant influence on the postoperative course, incomplete cytoreduction, or a prolonged duration of surgery. Nevertheless, it should be noted that morbid obesity with a body mass index of more than 39.9 was present in only 13 patients.

The strength of our study lies in its homogenous data set, since only those EOC patients who were actually assigned to cytoreductive surgery with the intention of complete resection were included in our analysis. However, due to the retrospective nature of the study, a possible bias in patient selection cannot be excluded.

Conclusion

In EOC patients the risk factors of age, smoking and the duration of surgery have a significant impact on the postoperative morbidity and mortality. Only the duration of surgery may be positively influenced by a well-trained EOC team. Therefore, detailed preoperative assessment of the expected surgical complexity in EOC patients is essential. The expertise of the EOC surgeon should be appropriate for the level of complexity of EOC surgery in order to reduce postoperative morbidity and mortality due to shorter duration of surgery.

Conflicts of Interest

The Authors declare no conflicts of interest.

Authors' Contributions

Conception and design: E.K. Egger, A. Mustea; Data analysis and interpretation: E.K. Egger, M. Condic, M.D. Keyver-Paik; Investigation: E.K. Egger, N. Kohls, D. Könsgen, S. Klaschik, T. Hilbert; Writing–original draft preparation: E.K. Egger, D. Exner; Writing–review and editing: T. Vilz, M.B. Stope; Supervision: A. Mustea.

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