Surgery at Primary *Versus* Relapsed Epithelial Ovarian Cancer: A Study on Aspects of Anaesthesiological Management

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Abstract. *Background: Primary cytoreductive surgery (CS) for epithelial ovarian cancer (EOC) is well-established. CS at relapse remains controversial, with an unclear morbidity profile. Patients and Methods: We analyzed 121 patients with EOC who underwent CS. Two groups were identified by timing of surgery due to primary disease and due to recurrent disease. Results: CS for primary versus recurrent EOC led to no differences in haemodynamic management, such as transfusion rates, application of vasopressors, ICU and hospital length of stay, or mortality. The risk for postoperative ileus was higher in patients with relapsed versus primary EOC. This might be attributed to patients being operated due to preoperative ileus and a higher small bowel resection rate at CS for relapse. Conclusion: CS for EOC relapse does not seem to be more challenging in terms of perioperative management compared to that at initial diagnosis. The major surgical morbidity profile was comparable apart from a higher risk for postoperative ileus at relapse.*

Epithelial ovarian cancer (EOC) has the highest mortality among gynaecological malignancies (1). The cornerstone of treatment consists of maximal-effort cytoreductive surgery combined with adjuvant cytotoxic and targeted-therapy. The quality of surgery plays a major role in its management, with the rate of postoperative residual tumor being the most important prognostic marker in settling of the primary disease (2). Despite innovative efforts over the past decades in both surgical and systemic treatment, the majority of patients will still experience relapse and succumb to their disease (3, 4). Optimal treatment at relapse is more challenging since the benefits from any intervention have to be carefully counterbalanced with the associated risks in, by definition, a palliative patient collective. Since the impact of cytoreductive surgery at EOC relapse has never been prospectively validated, many clinicians decide against it, in order to avoid a presumed higher morbidity in heavily pre-treated patients (5). Retrospective analysis clearly indicates, however, that even at relapse, patients benefit from total macroscopic tumor clearance and present two- to three-fold better overall outcomes compared to patients in whom this cannot not be achieved. The morbidity and mortality profile for these patients remains not well-defined and the perioperative management is also presumed to be more challenging, since the patients have more chronic tumor burden and are pre-treated with toxic agents that might influence anaesthesiological and surgical management.

The aim of this study was to compare, to our knowledge for the first time, the perioperative outcome and aspects of anaesthesiological management at surgery due to initial diagnosis of EOC *versus* recurrent disease, and to define the variations of the overall profile for these surgeries.

Patients and Methods

This was a systematic analysis of a prospectively maintained database evaluating the intraoperative tumor dissemination pattern in women undergoing laparotomy for cytoreductive surgery due to primary or relapse of EOC at the Department of Gynaecology at the Virchow Campus Clinic, Charité Medical University, between January 2005 and December 2008. Ethical approval was received from the Ethical Committee (Charité Medical University, Berlin, Germany: no.

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EA1/176/11). The characteristics for including patients in this study was the presence of follow-up data for more than six months after surgery and matching datasets from the Department of Gynaecology, the Department of Anaesthesiology and Intensive Care Medicine, and the hospital administration dataset at the Virchow Campus Clinic, Charité Medical University, between January 2005 and December 2008. All the relevant anaesthesiological management data, such as general data, physical status according to the American Society of Anesthesiologists (ASA), comorbidities, anaesthesiological techniques, perioperative vital parameters, perioperatively administered medications, fluids and transfusions, and all postoperative outcome variables for each patient were extracted from the database of the Department of Anaesthesiology and Intensive Care Medicine, Virchow Campus Clinic, Charité University Hospital.

Postoperative outcomes including the length of hospital stay and stay in the Department of Intensive Care Medicine, need for postoperative ventilator therapy and insurance-reimbursed hospital costs were extracted from a hospital dataset, provided by the hospital to healthcare insurance agencies for the description of accumulated costs. It is based on a payment system of diagnosis-related case groups (DRG) according to the law of hospital compensation by the insurances §7 no.1.

Out of 580 patients operated on due to EOC during that time period, we included 121 patients with matching datasets of tumor characteristics, complete anaesthesiological and hospital administration data.

The clinical pathway for patients undergoing surgery for EOC. Anaesthesiologically, the patients were treated within a clinical pathway defined by standard operating procedures (SOP) always accessible from the intranet of the Charité University Hospital, Berlin, Germany. Patients were given oral midazolame (3.75 to 7.5 mg) before surgery. Non-invasive monitoring was applied (electrocardiogram, non-invasive blood pressure and oxygen saturation) and antibiotics (1.5 g cefuroxime and 0.5 g metronidazole) were administered. An epidural catheter was usually placed (Th8/Th10) and equipped with an 8-10 ml bolus and a continuous basal rate of 6 ml/h of 0.2% ropivacaine and 1.0 μg/ml sufentanil. After induction of anaesthesia with 2-3 mg/kg BW of propofol or 3-5 mg/kg BW thiopental, and analgesia with 1-2 μg/kg BW fentanyl, the maintenance of anaesthesia was carried-out with total intravenous anaesthesia with 6-10 mg/kg BW/h of propofol or balanced anaesthesia with desflurane or sevoflurane depending on the risk score for postoperative nausea and vomiting and the preoperative cardiac status. Additionally, remifentanil at 0.05-0.3 μg/kg BW/min was given during surgery according to clinical necessity. Neuromuscular blocking was performed with 0.6 mg/kg BW of rocuronium or cisatracurium. Intraoperative neuromuscular blocking was assessed with acceleromyography and relaxants were given accordingly. Frequent blood gas analyses were performed and respiratory settings adapted accordingly if necessary. If considered necessary, an arterial line and a central venous line were placed for continuous measurement of blood pressure and central venous pressure. The patient was covered by a forced-air body warming system. For administration of anaesthetic drugs and replacement of perioperative fluid demands, a balanced crystalloid infusion was administered. To replace blood and intravascular volume demands during surgery, colloid solutions (Voluven®/Volulyte®) were administered. After exceeding the administration of 30-50 ml/kg BW of colloid infusion, transfusion of fresh-frozen plasma (FFP) were performed according to the clinical estimation of the surgeon and anaesthesiologist. Transfusion of red packed cells (RPC) was given on clinical judgement based on the measurements of haemoglobin in arterial blood. During the course of surgery and if necessary after surgery, an interdisciplinary board considered the surgical and anaesthesiological course of the operation to decide if observation or treatment of the patient in the Department of Intensive Care Medicine was indicated. According to its decision, the patient was transferred to the Intensive Care Unit (ICU) or the post-anaesthesia care unit or the surgical ward.

All operations were performed at the Charité-University of Medicine, Berlin, which is a European competence centre for ovarian cancer and a referral centre for ovarian cancer and advanced intensive care cases in Germany. All operations were conducted by one of four expert gynaecological oncological surgeons. Operative cytoreduction primarily aimed at a maximal tumor resection with no visible macroscopical residual tumor. Standard procedures in the primary setting included midline laparotomy, peritoneal cytology, hysterectomy, bilateral salpingo-oophorectomy, infragastric omentectomy and systematic pelvic and para-aortic lymph node dissection if a complete tumor resection was obtained. In cases of advanced tumor disease in the primary setting, additional procedures, such as deperitonealisation of the pelvis, abdominal wall or diaphragm; bowel resection; splenectomy; partial resection of other affected organs (*e.g.* urinary bladder, liver, and pancreas) were performed in order to achieve maximal cytoreduction. Standard procedures in the setting at relapse of EOC included midline laparotomy and maximal cytoreduction using multi-visceral strategies mentioned above. Postoperative complications were scaled according to the Clavien classification and considered major if the complication was grade II or higher (6).

Management for patients with primary cancer was conducted as upfront cytoreductive surgery with adjuvant chemotherapy. Neoadjuvant chemotherapy with three cycles of carboplatinum and paclitaxel followed by cytoreductive surgery and another three cycles of adjuvant chemotherapy, which is evolving to standard-of-care in some countries, was applied only for patients with severe cardiovascular or other comorbidities that were unable to tolerate radical upfront surgery.

The indication for surgery in the primary setting was curative in 78.3% of the patients. In the recurrent setting, the majority of patients (85.3%) were operated on with the goal of maximal cytoreduction. In these patients, preoperative evaluation due to DESKTOP OVAR (Descriptive Evaluation of preoperative Selection KriTeria for OPerability in recurrent OVARian cancer) criteria was performed and DESKTOP-positive patients were submitted to surgery, while DESKTOP-negative patients were treated with systemic chemotherapy (4, 7). In the remaining 24.7% of patients that were operated on in the recurrent setting, without the aim of maximal cytoreduction, preoperative ileus was the most common indication for surgery, for 12.0% of the patients. In these patients, no evaluation of DESKTOP criteria was performed.

Intraoperative mapping of ovarian cancer (IMO). The IMO is a detailed surgical and histopathological documentation system developed at the Department of Gynaecology at the Virchow Campus Clinic, Charité-University Medicine, Berlin, in order to obtain a better and more objective description of the spread of ovarian tumor within the abdominal cavity and to define the histopathological features of the malignancy more precisely (8). Within the Tumor Bank Ovarian Cancer project (www.toc.network.de), tumor tissue,

Table I. *General patient and baseline characteristics. Data are median (25%; 75% quartiles) or as number (n) of patients (%).*

Characteristic	Primary ovarian cancer (n=46)	Relapse ovarian cancer (n=75)	*p*-Value
Age (years)	57 (47; 63)	56 (48; 65)	0.541#
Body mass index (kg/m²)	25.5 (21.7; 28.2)	24.1 (22.5; 28.2)	0.866#
Present arterial hypertension, n (%)	13 (28.3)	13 (17.3)	0.176$
Numbers of comorbidites	0 (0; 1)	0 (0; 1)	0.124#
ASA score, n (%)			0.007§
I	9 (19.6)	3 (4.0)	
II	30 (65.2)	50 (66.7)	
III	7 (15.2)	22 (29.3)	
Duration of surgery (min)	230 (147; 300)	239 (183; 301)	0.559$
Peridural Anesthesia, n (%)	26 (56.5)	54 (72.0)	0.113$
Arterial Line, n (%)	35 (76.1)	67 (89.3)	0.038$
Central Venous Line, n (%)	33 (71.7)	65 (86.7)	0.032$
Narcotic to anaesthetize the patient at start of surgery, n (%)			0.291§
Thiopental	20 (43.5)	34 (45.3)	
Etomidate	9 (19.6)	6 (8.0)	
Propofol	13 (28.3)	26 (34.7)	
Narcotic drug used to maintain anesthesia, n (%)			<0.001§
Propofol	11 (23.9)	23 (30.7)	
Isoflurane	30 (65.2)	26 (34.7)	
Desflurane	1 (2.2)	17 (22.7)	
Induction with succinylcholine, n (%)	4 (8.7)	14 (18.7)	0.186$
Relaxans (mg/kg body weight/dose 2ED95)	1.40 (0.95; 1.98)	1.51 (1.17; 2.26)	0.117#
Fentanyl (μg/kg body weight)	4.34 (0.36; 6.81)	4.69 (0.56; 6.70)	0.901#
Fentanyl administration (%)	30 (65.2)	49 (65.3)	1.000$
Highest Remifentanil (μg/kg/min)	0 (0; 0.15)	0 (0; 0.20)	0.445#
Remifentanil administration (%)	13 (28.3)	27 (36.0)	0.411$
Lowest intraoperative body temperature (˚C)	35.3 (35.0; 35.8)	35.5 (35.1; 36.0)	0.163#
Last intraoperative body temperature (˚C)	35.7 (35.4; 36.0)	35.8 (35.5; 36.5)	0.065#

ASA: American Society of Anesthesiology. 2ED95: two times the 95% effective dose. *p*-Values were calculated for patients with primary ovarian cancer *versus* relapse of ovarian cancer using the exact #Wilcoxon-Mann-Whitney test, exact §Mantel-Haenszel test (ordered categories) or $exact Chi-square test as appropriate.

ascites, serum and blood were collected from each patient with malignant tumor. Each patient's informed consent was given prior to surgery, sample collection and documentation.

Statistical analysis. Because of the limited sample size and non-normal distribution of the observations, data are expressed as median (25% and 75% quartiles), or frequencies (%). For the same reason, differences between the groups in terms of interesting clinical parameters were univariately tested by using the non-parametric exact Mann-Whitney tests for independent groups, or exact Wilcoxon tests for pairwise comparisons within the intervention groups. Frequencies were (univariately) tested by the exact Mantel-Haenszel test (ordered categories) or the exact Chi-square test.

After global testing, post-hoc analyses were carried out to detect specific differences between groups at fixed times (Mann-Whitney tests), or within groups with respect to interesting pairs of time points (Wilcoxon tests). A two-tailed *p*-value of less than 0.05 was considered statistically significant. All tests should be considered as exploratory in data analysis. Therefore, no adjustments for multiple testing have been made. After univariate analysis of differences between patients with surgery for primary or relapse EOC, robust regression analysis with the amount of total administered intravenous fluids and transfusions as the response variable were conducted in order to confirm the results and to investigate the impact of further influencing factors.

All numerical calculations were performed with IBM© SPSS© Statistics, Version 21, 2010 (SPSS, Inc., Chicago, IL, USA, Copyright 1989, 2012 SPSS Inc. licensed for Charité-Universitätsmedizin Berlin) and the R project for Statistical Computing, Version 3.0.2 (R Development Core Team (2008). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. ISBN 3-900051-07-0, URL http://www.R-project.org).

Results

One hundred and twenty-one patients undergoing surgery for primary or relapse of EOC had sufficient documentation of data and were enrolled in the analysis. Forty-six patients underwent surgery for primary EOC and 75 underwent cytoreductive surgery at relapse. No significant differences were found between the two groups regarding general characteristics such as age, body-mass index and median number of comorbidities. The ASA physical classification differed between the groups, favouring the primary surgery

Table II. *Tumor characteristics and surgical procedures. Data are median (25%; 75% quartiles) or as number (n) of patients (%).*

Characteristic	Primary ovarian cancer (n=46)	Relapse ovarian cancer (n=75)	*p*-Value
Previous surgery due to ovarian cancer, n (%)			
None	46 (100)	-	-
One prior surgery	-	58 (77.3)	-
Two prior surgery	-	13 (17.3)	-
More than two prior surgeries	-	4 (5.3)	-
Curative goal of the procedure (*vs*. palliative), n (%)	36 (78.3)	-	-
Cytoreductive goal of the procedure (*vs*. palliative), n (%)	-	64 (85.3)	-
Surgery performed due to preoperative ileus, n (%)	0 (0)	9 (12.0)	0.013[$]
Ascites present at time of surgery, n (%)			0.539[§]
No ascites	19 (41.3)	37 (49.3)	
<500 ml	16 (34.8)	26 (34.7)	
>500 ml	10 (21.7)	11 (14.7)	
Reason for hospital admission, n (%)			0.911[§]
Confinement by practitioner	32 (69.6)	55 (73.3)	
Transfer from another hospital	4 (8.7)	2 (2.7)	
Emergency admission	10 (21.7)	17 (22.7)	
Intraoperative abdominal fields involved according to IMO (8), n (%)			<0.001[§]
0	4 (8.9)	0 (0)	
1	15 (33.3)	9 (12.5)	
2	7 (15.6)	7 (9.7)	
3	8 (17.8)	13 (18.1)	
4	4 (8.9)	8 (11.1)	
5	0 (0)	7 (9.7)	
6	1 (2.2)	5 (6.9)	
7	0 (0)	5 (6.9)	
8	3 (6.7)	6 (8.3)	
9	3 (6.7)	12 (16.7)	
Tumour dissemination pattern, n (%)			
Level 1, pelvic	42 (93.3)	65 (87.8)	0.532[$]
Level 2, extrapelvic	23 (51.1)	62 (83.8)	<0.001[$]
Level 3, extrapelvic	16 (35.6)	43 (58.1)	0.023[$]
Operative procedures performed, n (%)			
Large bowel resection, n (%)	16 (34.8)	34 (45.3)	0.342[$]
Type of large bowel resection, n (%)			0.453[§]
None	30 (66.7)	46 (62.2)	
Sigmoidal resection	5 (11.1)	9 (12.2)	
Partial colonic resection	4 (8.9)	7 (9.5)	
Anterior rectal resection	6 (13.3)	6 (8.1)	
Subtotal colonic resection	0 (0)	6 (8.1)	
Large bowel anastomosis, n (%)			0.411[§]
No anastomosis	32 (69.6)	47 (62.7)	
1 Anastomosis	13 (28.3)	24 (32.0)	
2 Anastomosis	1 (2.2)	4 (5.3)	
Small bowel resection, n (%)	9 (19.6)	29 (38.7)	0.043[$]
Type of small bowel resection, n (%)			0.023[§]
No resection	37 (80.4)	45 (61.6)	
Partial resection	9 (19.6)	24 (32.9)	
Ileocecal resection	0 (0)	4 (5.5)	
Small intestine anastomosis, n (%)			0.065[§]
No anastomosis	38 (82.6)	48 (64.0)	
1 Anastomosis	5 (10.9)	18 (24.0)	
2 Anastomosis	3 (6.5)	9 (12.0)	
Peritonectomy, n (%)	25 (54.3)	50 (66.7)	0.184[$]
Appendectomy, n (%)	27 (58.7)	8 (10.7)	<0.001[$]
Partial liver resection, n (%)	1 (2.2)	3 (4.0)	1.000[$]
Liver capsule resection, n (%)	5 (10.9)	11 (14.7)	0.783[$]

Table II. *Continued*

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Characteristic	Primary ovarian cancer (n=46)	Relapse ovarian cancer (n=75)	*p*-Value
Distal pancreatic resection, n (%)	0 (0)	3 (4.0)	0.287[$]
Splenectomy, n (%)	1 (2.2)	9 (12.0)	0.087[$]
Partial diaphragmatic resection, n (%)	6 (13.0)	4 (5.4)	0.180[$]
Partial gastric resection, n (%)	1 (2.2)	3 (4.0)	1.000[$]
Colostomy, n (%)	2 (4.3)	8 (10.7)	0.315[$]
Jejunostomy, n (%)	0 (0)	2 (2.7)	0.525[$]
Ileostomy, n (%)	0 (0)	4 (5.3)	0.296[$]
Any stoma sited, n (%)	2 (4.3)	11 (14.7)	0.128[$]
Postoperative tumor residuals			<0.001[§]
None	36 (78.3)	37 (49.3)	
<0.5 cm	2 (4.3)	12 (16.0)	
<1 cm	4 (8.7)	6 (8.0)	
≤2 cm	3 (6.5)	7 (9.3)	
>2 cm	1 (2.2)	13 (17.3)	
FIGO stage at primary diagnosis, n (%)			0.456[§]
I 6 (13.0)	6 (8.2)		
II 4 (8.7)	3 (4.1)		
III30 (65.2)	55 (75.3)		
IV	4 (8.7)	8 (11.0)	
Serous papillary histology, n (%)	36 (81.8)	56 (84.8)	0.778[$]
Preoperative CA125 (IU/l)	191 (74; 1186)	204 (89; 858)	0.981[#]
CA125 before chemotherapy (IU/l)	93 (29.5; 133)	80 (40; 127)	0.941[#]

p-Values were calculated for patients with primary ovarian cancer *versus* relapse of ovarian cancer using the exact [#]Wilcoxon-Mann-Whitney test, exact [§]Mantel-Haenszel test (ordered categories) or [$]exact Chi-square test as appropriate.

group with a higher percentage of ASA I (19.6% *vs*. 4.0%) and penalizing the relapse surgery group with more patients of ASA III (29.3% *vs*. 15.2%). Detailed data are shown in Table I.

Surgical procedures and tumor dissemination patterns according to IMO are presented in Table II. Similarly, the level of lymph node invasion is more extensive, showing a greater spread of tumor on surgery for relapsed EOC (58.1% *vs*. 35.6% extrapelvic lymph node invasion; level 3). Total macroscopic tumor clearance was achieved significantly more frequently at surgery for primary *versus* relapsed EOC (78.3% *vs*. 49.3%, $p<0.001$). Bowel resections were also performed more frequently at relapse *versus* primary surgery, with small bowel procedures being more common amongst them (38.7% in relapse surgery *vs*. 19.6% in primary surgery, *p*-value=0.043). The frequency of large bowel resections was not significantly different between the two patient collectives (45.3% *vs*. 34.8%, $p=0.34$). No differences were seen in preoperative cancer antigen 125 (CA125) levels. There were also no significant differences in the rate of multivisceral resections performed and the amount of preoperative ascites between the two groups.

Data regarding the anaesthesiological management are outlined in Table I. Perioperative management was slightly different in that placement of an arterial line and central vein catheters was more frequent for surgery at relapse. Arterial lines were implemented in 76.1% *vs*. 90.5% ($p=0.038$) and central lines in 71.7% *vs*. 87.8% ($p=0.032$), respectively. Pain management with epidural catheters was similar in both groups (56.5% *vs*. 72%; $p=0.113$). No differences between the groups was seen in choice and amount of narcotic and analgesic drugs, nor in intraoperative body temperature.

Table III provides an overview of intraoperative haemodynamic data. There was no difference in the amount of crystalloid and colloid infusions administered, or in the amount of erythrocyte transfusions given throughout surgery (Figure 1A and B). Episodes of derailed systolic arterial pressure values and derailed heart rate were distributed equally throughout the two groups. The administration of noradrenaline and other vasopressors was similar in both groups. A higher median number of FFP units was found in patients undergoing relapse surgery [2 (0, 4) units *vs*. 0 (0, 2) units FFP, $p=0.065$) but the difference was only a trend. Laboratory values showed no difference between the two groups.

Postoperative outcome variables are shown in Table IV. The number of patients transferred to the ICU after surgery was similar for both types of surgery (71.7% after primary surgery *vs*. 75.7% after surgery at relapsed EOC). In both groups, the median length of postoperative and overall ICU

Table III. *Infusion, transfusion and circulatory characteristics. Data are median (25%; 75% quartiles) or as number (n) of patients (%).*

Characteristic	Primary ovarian cancer (n=46)	Relapse ovarian cancer (n=75)	*p*-Value
Crystalloid administration (ml/kg BW)	58.1 (45.5; 75.9)	58.0 (41.1; 70.4)	0.634#
Colloid administration (ml/kg BW)	16.3 (9.0; 24.3)	19.2 (15.9; 25.0)	0.132#
Erythrocyte transfusion (units)	0 (0; 2)	0 (0; 2)	0.482#
Fresh frozen plasma (units)	0 (0; 2)	2 (0; 4)	0.065#
Intraoperative transfusion, n (%)			0.084§
None	29 (63.0)	31 (41.3)	
1 to 9 units	13 (28.3)	37 (49.3)	
>10 units	4 (8.7)	7 (9.3)	
Vasopressor administration during induction, n (%)	26 (56.5)	38 (50.7)	0.577$
Highest NA adminstration			0.497§
None	26 (56.5)	36 (48.0)	
Low dose (0> or <0.2 μg/kg/min)	16 (34.8)	34 (45.3)	
High dose (0.2> or <0.5 μg/kg/min)	4 (8.7)	3 (4.0)	
Very high dose (>0.5 μg/kg/min)	0 (0)	2 (2.7)	
Episodes of systolic arterial pressure <100 mmHg	8.5 (2.0; 20.3)	8 (3.0; 18.0)	0.918#
<90 mmHg	2 (0; 5.7)	1 (0; 5)	0.690#
<80 mmHg	0 (0; 0)	0 (0; 0)	0.576#
Episodes of heart rate >90/min	0 (0; 4.3)	0 (0; 8)	0.590#
>100/min	0 (0; 0.5)	0 (0; 0)	0.914#
>120/min	0 (0; 0)	0 (0; 0)	0.404#
Lowest intraoperative pH value	7.38 (7.32; 7.41)	7.37 (7.34; 7.40)	0.912#
Lowest intraoperative base excess (mM)	-1.5 (-5.3; 0.5)	-1.2 (-3.1; 1.7)	0.119#
Lowest intraoperative haemoglobin (g/dl)	9.5 (8.9; 10.9)	9.6 (8.9; 10.8)	0.903#
Lowest intraoperative potassium (mM/L)	3.2 (3.2; 3.8)	3.3 (3.1; 3.6)	0.968#
Highest intraoperative glucose (mg/dL)	106 (87; 129)	107 (89; 138)	0.614#
Highest intraoperative lactate (mg/dL)	7.0 (6.0; 8.6)	7.2 (6.0; 10.0)	0.348#

NA: Noradrenaline. *p*-Values were calculated for patients with primary ovarian cancer *versus* relapse of ovarian cancer using the exact #Wilcoxon-Mann-Whitney test, exact §Mantel-Haenszel test (ordered categories) or $exact Chi-square test as appropriate.

stay was one day. The length of hospital stay was a median of 16 (13.8, 21.3) days for patients after primary surgery and 17 (14.8, 23.8) days after relapse surgery (p=0.192). In patients undergoing relapse surgery as well as in patients operated due to primary EOC, the presence of ascites had a substantial impact on the length of hospital stay (Figure 1C and D).

There was no difference in minor or major postoperative complications between the two groups. There was a significantly higher incidence of postoperative ileus in patients with relapsed *versus* primary EOC: 21.6% *vs.* 4.3% (p=0.009). The number of patients requiring a colostomy or ileostomy also differed between the groups, but the difference did not reach a statistical significance (4.3% in the primary *versus* 14.7% in the recurrent setting; p=0.128) (Table II).

Regression analysis revealed that of the pre- and intraoperative factors, the presence of more than 500 ml ascites, the duration of surgery (in minutes) as well as the lowest intraoperative body temperature (in degrees Celsius), but not primary *vs.* relapse surgery, were associated with increased intraoperative demand for infusions and transfusions (Table V).

Discussion

The data of our analysis suggest that surgery at relapse of EOC does not seem to be more challenging in terms of perioperative anaesthesiological management than primary surgery. Similar results were recently shown by Woelber *et al.* (9).

The role of surgery for recurrent EOC remains controversial in many countries because of the underlying palliative situation and concerns for peri- and postoperative risks and possible impairment of the quality of life, which might weigh against a survival benefit reported in numerous retrospective analyses (10, 11). There is a reservation that in a palliative setting, heavily pre-treated patients might represent a much higher anaesthetic challenge with higher complication rates, necessity for ICU support, and volume management. In our present analysis, we clearly show that this is not the case at a centre with maximal infrastructure specialized in this type of ultraradical surgery. Surgical and anaesthesiological/ICU excellence and specialization are, however, important in order to guarantee overall quality. Numerous retrospective data and current prospective approaches clearly indicate that total macroscopic tumor clearance influences survival even in the palliative setting of

Table IV. *Postoperative outcome variables. Data are median (25%; 75% quartiles) or as number (n) of patients (%).*

Variable	Primary ovarian cancer (n=46)	Relapse ovarian cancer (n=75)	*p*-Value
Length of hospital stay (days)	16.0 (13.8; 21.3)	17.0 (14.8; 23.8)	0.192[#]
Treated postoperatively in ICU, n (%)	33 (71.7)	56 (74.7)	0.671[$]
Length of postoperative ICU stay (days)	1.0 (0; 2.0)	1.0 (0; 2.0)	0.760[#]
Re-admission to ICU, n (%)	3 (6.5)	6 (8.0)	1.000[$]
Overall Length of ICU Stay (days)	1.0 (0; 2.3)	1.0 (0; 2.0)	0.742[#]
Case-based lump sum of to the (€)[A] diagnosis-related case group (DRG)	10,213 (7,455; 12,792)	11,239 (8,077; 12,442)	0.926[#]
Amount of insurance compensation (€)	12,690 (9,458; 14,689)	11,616 (8996; 13,180)	0.310[#]
Exceeded maximum length of stay, related to the DRG[B]			
Number of patients (%)	9 (19.6)	9 (12.0)	0.298[$]
Reimbursement costs (€)	241 (228; 294)	270 (211; 280)	0.779[$]
Reimbursed time (days)	9.0 (3.5; 28.0)	13 (4.0; 23.5)	0.666[$]
Postoperative minor complications, n (%)			
Infection	7 (15.2)	10 (13.3)	0.792[$]
Urinary tract infection	7 (15.2)	12 (16.0)	1.000[$]
Pleural effusion	6 (13.0)	16 (21.6)	0.333[$]
Ascites postoperative	1 (2.2)	4 (5.4)	0.648[$]
Circulatory complication	17 (37.0)	19 (25.7)	0.222[$]
Anemia	27 (58.7)	53 (71.6)	0.166[$]
Coagulopathy/Thrombocytopenia	1 (2.2)	3 (4.1)	1.000[$]
Need for insulin administration	18 (39.1)	30 (40.5)	1.000[$]
Hypokalemia	24 (52.2)	44 (59.5)	0.454[$]
Patients with minor complications, n (%)	35 (76.1)	62 (83.8)	0.344[$]
Sum of minor complications per patients	2.0 (0.8; 3.0)	2.0 (1.0; 3.3)	0.332[#]
Postoperative major complications, n (%)			
Sepsis	3 (6.5)	4 (5.3)	1.000[$]
Respiratory failure	5 (10.9)	15 (20.3)	0.308[$]
Embolic event	3 (6.5)	4 (5.4)	1.000[$]
Circulatory shock	2 (4.3)	4 (5.4)	1.000[$]
Bleeding complication	2 (4.3)	3 (4.0)	1.000[$]
Postoperative ileus (all patients)	2 (4.3)	16 (21.3)	0.016[$]
Postoperative ileus (only patients without preoperative ileus)	2 (4.3)	11 (14.7)	0.128[$]
Intestinal perforation	3 (6.5)	3 (4.0)	0.673[$]
Anastomotic leakage	1 (2.2)	2 (2.7)	1.000[$]
Relaparotomy performed	5 (10.9)	6 (8.0)	0.746[$]
Patients with major complications, n (%)	11 (23.9)	28 (37.8)	0.160[$]
Sum of major complications per patients	0 (0; 0.3)	0 (0; 1.0)	0.152[#]
Discharge from hospital, n (%)			0.480[§]
Home	45 (97.8)	69 (93.2)	
Nursing home	0 (0)	1 (1.4)	
Transfer to another hospital	0 (0)	1 (1.4)	
Intrahospital mortality	1 (2.2)	3 (4.1)	

p-Values were calculated for patients with primary ovarian cancer *versus* relapse of ovarian cancer using the exact [#]Wilcoxon-Mann-Whitney test, exact [§]Mantel-Haenszel test (ordered categories) or [$]exact Chi-square test as appropriate. ADiagnosis-related case group according to the law of hospital compensation by the insurances [§]7 no.1. BMaximum length of hospital stay, defined by InEK GmbH (a partnership that includes the German Society of Hospitals, together with key insurance organizations).

the disease (4, 10-12). Therefore, indication for surgery at relapse should be carefully discussed with the patient and only performed in selected patients, where macroscopically tumor-free resection seems possible.

The present study clearly indicates that postoperative complications such as respiratory, circulatory or septic events, haemorrhage or coagulation disorders and electrolyte disturbances are found at an equal incidence in primary as

well as relapse surgery. The only exception seems to be the number of cases of postoperative ileus, which patients at relapse experience significantly more frequently. It is known that postoperative ileus continues to be the most common complication of abdominal surgery (13). This may be attributed to the higher incidence of adhesions in patients who have had extensive cytoreductive surgeries in the past (14). Data in the current literature state that the implementation of epidural catheters into perioperative pain management might not only prevent pain memory and chronic pain, but also reduces the risk for postoperative ileus and might even have an influence on the recurrence rate of cancer after surgery (15, 16). Compromising other advantageous features of epidural catheters, such as reduction of narcotics, faster mobilization of patients after surgery and myocardial protection, from our data, thoracic epidural catheters should be encouraged for perioperative management in patients undergoing cytoreductive surgery for EOC relapse (17, 18).

Another interesting fact was the number of bowel resections requiring stoma. This is a highly sensitive topic for the patient, and is always one of the focus points in counselling prior to surgery for primary and relapsed EOC alike. Our analysis showed a tendency but no significant difference in the rate of stoma application between the two groups. Even though it might be possible to restore continuity in a fraction of these stomas, this information is essential for the decision making of the patient when relapse surgery is discussed and should be brought to their attention by the clinician. Despite the fact that an interesting finding of our study was that surgery at relapse did not result in a significantly higher rate of stomas, it needs to be said that the vast majority of patients in our analysis were operated on with the goal of maximal cytoreduction and were selected preoperatively due to DESKTOP criteria (4, 7). This statement will most likely not translate to the group of patients that were operated on because of preoperative ileus. Even though in our analysis this group was too small to draw any safe conclusions (12.0%), the rate of stoma application would most certainly be higher in this sub-group when compared to those undergoing surgery for primary disease.

Total macroscopic tumor clearance in this study was achieved in half the patients undergoing surgery at relapse (49.3%). The study by Woelber and colleagues (9) showed comparable results, and in the current literature numbers are similar (19, 20). In the patient cohort of Woelber *et al.* analogous results were found regarding postoperative ileus. Nevertheless, the hospital stay in their study was longer by three days in the group of relapsed *versus* primary-ovarian cancer group (9). Another finding differing in these, otherwise similar, trials is the number of transfusions given during surgery. A slightly, non-significantly higher number of FFP units was given to patients undergoing surgery at relapse in our study, whereas there was no disparity in transfusion of erythrocyte transfusions. In Woelber *et al.*'s cohort, transfusion of blood products in general was reduced in secondary compared to primary surgery. Different surgical techniques, different therapy and prevention plans or transfusion strategies may explain this difference. However, the similar number of transfusions or even their reduction in those two surgical approaches testify to the possibility of accomplishming surgery even in the recurrent and therefore palliative setting.

In the present study, intraoperative haemodynamic parameters, fluid management and administration of noradrenaline were evaluated. No difference was found in our analysis, implying that the attempt at extensive surgery at relapse is not more of a challenge for a patient than is primary surgery. Taking into consideration patient ASA classification, which was higher in patients for relapse surgery probably due to progressive cancer (since comorbidities were distributed equally), this is an additional factor supporting the possibility of performing relapse surgery. No doubt, anaesthesiological management during surgery has to be highly vigilant and monitoring of

Table V. *Association of preoperative and intraoperative characteristics with the of total amount of intravenous fluids and transfusions administered by robust regression. Data are median (25%; 75% quartiles) or as number (n) of patients (%).*

Characteristic	Regression coefficient	95% Confidence interval	*p*-Value
Ascites <500 ml *vs.* none	−585	−1403-234	0.159
Ascites >500 ml *vs.* none	1177	116-2238	0.030
Primary surgery *vs.* relapse surgery	−57.9	−882-766	0.889
Age (per year increase)	−2.10	−37.6-33.4	0.907
ASA physical status 2 *vs.* ASA status 1	−143	−1413-1128	0.824
ASA physical status 3 *vs.* ASA status 1	−69.0	−1636-1498	0.930
Arterial hypertension, yes *vs.* no	694	−224-1612	0.137
IMO fields tumor involved (number)	93.0	−56.1-242	0.218
Preoperative CA-125 level (U ml^{-1})	−0.005	−0.113-0.103	0.926
Peridural catheter, implemented *vs.* not	493	−289-1275	0.213
Lowest intraoperative temperature (˚C)	−829	−1460-−197	0.011
Duration of surgery (min)	14.0	10.1-17.8	<0.001

ASA: American Society of Anesthesiology; IMO: intraoperative mapping of ovarian cancer (8).

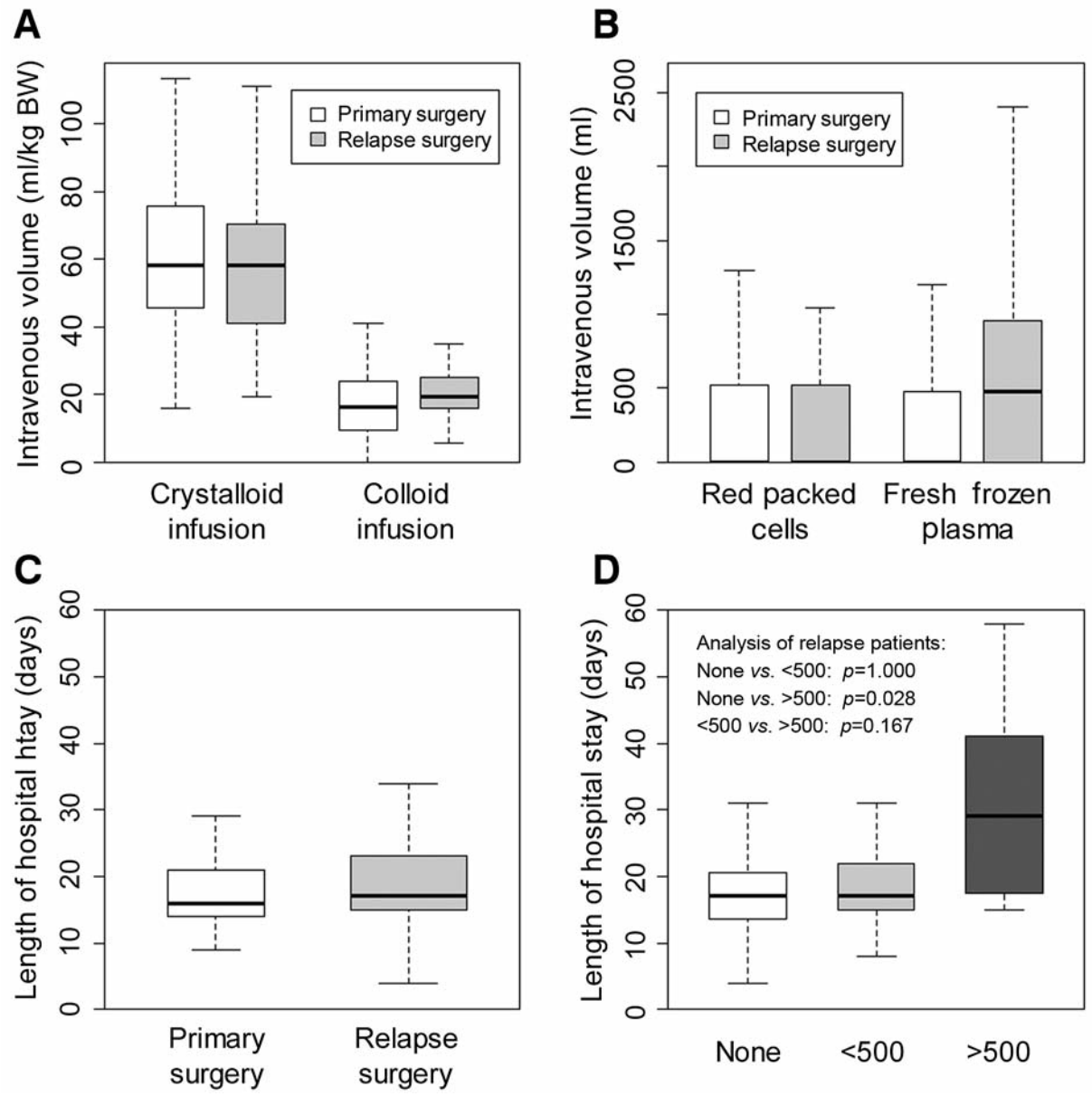

Figure 1. *Intravenous administration of crystalloid and colloid solutions (A), amount of red packed cells and fresh frozen plasma administered during surgery (B), length of hospital stay (C) for patients undergoing surgery for primary vs. relapsed ovarian cancer surgery, and the length of hospital stay for patients undergoing cytoreductive surgery due to relapse of ovarian cancer demonstrating the influence of ascites (D). Data are shown as the median [line], (25%; 75% [box]) quartiles and the maximum and minimum [whiskers] (excluding outliers more or less than 1.5-times of quartiles). p-Values were calculated using the Kuskal-Wallis test between patients with relapse of ovarian cancer without or with less than 500 ml or more than 500 ml ascites prior to surgery.*

haemodynamic parameters should be consistently good (21). This and the difficulty to predict the length and possible complications during secondary cytoreductive surgery might have been taken into consideration by the attending anaesthesiologists when more frequently choosing to implement arterial and central venous lines.

We recently reported that the presence of ascites is a risk factor for prolonged length of stay in ICU or the hospital, and patients with ascites had a higher demand for transfusions intraoperatively and were more frequently haemodynamically unstable (22). Our data show that the presence of ascites is still predictive in the recurrence setting for a

longer hospital stay in patients with more than 500 ml of ascites. The regression analysis of preoperative and intraoperative factors predisposing to a high intraoperative demand for infusions and transfusions predisposing to a higher complication rate (23) shows that primary *vs*. relapse surgery is not a relevant factor in contrast to previously published factors such as ascites (22) and the duration of surgery, as well as low intraoperative temperature (24, 25).

In conclusion, our analysis indicates that surgery at relapse is not more challenging than primary surgery for EOC from an anaesthetic and overall perioperative management point of view at a reference centre specialized in the surgical management of advanced EOC. The reservations and occasional attitude to nihilism in patients with relapse of EOC due to a presumed higher surgical, anaesthesiological and medical morbidity cannot be justified when in the hands of a specialized and multidisciplinary team. Our data provide a basis for further interventional studies focusing on the interdisciplinary optimization of the intra- and postoperative management of this special patient collective.

Conflicts of Interest

Support was provided from Institutional and Departmental sources. All Authors declare, that they have no conflicts of interest.

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