Thieme

The Impact of Upper Abdominal Surgery Regarding the Outcome of Patients with Advanced Ovarian Cancer

Auswirkung der Oberbauchchirurgie auf die Prognose von Patientinnen mit fortgeschrittenem Ovarialkarzinom

Authors
Maximilian Pietschmann[1‡], Anna Jaeger[1‡], Susanne Reuter[1], Barbara Schmalfeldt[1]

Affiliations
1 Department of Gynecology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

Keywords
cancer registry, ovarian cancer, ovary

Schlüsselwörter
Krebsregister, Ovarmalignom, Ovar

received 23.2.2024
accepted after revision 17.5.2024
published online 4.7.2024

Bibliography
Geburtsh Frauenheilk 2024; 84: 866–875
DOI 10.1055/a-2331-0900
ISSN 0016-5751

Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany

Correspondence
Dr. med. Maximilian Pietschmann
Department of Gynecology
University Medical Center Hamburg-Eppendorf
Martinistraße 52
20246 Hamburg, Germany
maxpie@hotmail.de
m.pietschmann@uke.de

ABSTRACT

Objective
Residual tumor after cytoreductive surgery is the most important prognostic parameter for the outcome of patients with advanced ovarian cancer (5-year survival rate FIGO III 39 %, FIGO IV 20 %). As more than half of the patients suffer from upper abdominal tumor burden, surgery in this area is inevitable in order to achieve adequate cytoreduction. Our analysis focuses on the impact of upper abdominal interventions (UAI) regarding residual tumor and prognosis (OS, PFS).

Methods
A total of n = 261 patients with advanced primary ovarian cancer stage FIGO III and IV and radical cytoreductive surgery at the Gynecologic Cancer Center Hamburg-Eppendorf between 2014 and 2019 were analyzed in a retrospective study design and divided into two groups: one with UAI (n = 160) and one without UAI (n = 101).

Results
Patients with UAI showed significantly more often a residual tumor of less than 1 cm (R1) than patients without UAI and had a significantly longer OS (59 vs. 45 months [p = 0.041]). Deperitonealization of the diaphragm was the most common (144/160) and prognostically most relevant procedure for UAI. Especially the subgroup with FIGO IIIC stage seemed to benefit most from UAI. However, in multivariate analysis residual tumor burden was the strongest prognostic parameter for survival, followed by FIGO stage and UAI. Mortality was low within in the UAI group (0.6 %).

Conclusion
UAI is an essential part of cytoreductive surgery in advanced ovarian cancer patients with tumor spread into the upper abdomen as it significantly prolongs survival. The procedure appears to be safe with low mortality. Achieving R1 rather than R2 due to radical surgery combined with UAI should be

‡ These authors contributed equally.

preferred compared to the early termination of the operation, as this has a significant impact on the prognosis of the patients.

ZUSAMMENFASSUNG

Zielsetzung
Der Resektionsstatus nach zytoreduktiver Chirurgie ist der wichtigste prognostische Parameter für die Prognose von Patientinnen mit fortgeschrittenem Ovarialkarzinom (5-Jahres-Überlebensrate: FIGO III 39 %, FIGO IV 20 %). Da mehr als die Hälfte der Patientinnen an einem Tumorbefall im Oberbauch leiden, ist ein chirurgischer Eingriff in diesem Bereich unausweichlich, um eine adäquate Zytoreduktion zu erzielen. Unsere Analyse untersucht den Einfluss von chirurgischen Eingriffen am Oberbauch (OB) auf den Resektionsstatus und die Prognose.

Methoden
Es handelt sich um eine retrospektive Studie von Patientinnen mit fortgeschrittenem primären Ovarialkarzinom im FIGO-Stadium III und IV. Insgesamt wurden n = 261 Patientinnen zwischen 2014 und 2019 im Universitätsklinikum Hamburg-Eppendorf einer radikalen zytoreduktiven Chirurgie unterzogen. Für die retrospektive Analyse wurden die Patientinnen in 2 Gruppen unterteilt: Die erste Gruppe erhielt einen OB-EIngriff (n = 160), und die zweite Gruppe wurde ohne OB-Eingriff operiert (n = 101).

Ergebnisse
Patientinnen mit OB-Eingriff hatten signifikant häufiger einen Tumorrest unter 1 cm (R1) als Patientinnen, die keine OB-Intervention erhalten hatten. Das Gesamtüberleben von Patientinnen nach einem OB-Eingriff war zudem signifikant länger (59 vs. 45 Monate [p = 0,041]). Die Deperitonealisierung des Diaphragmas war der häufigste (144/160) und prognostisch relevanteste OB-Eingriff. Die Untergruppe mit FIGO-Stadium IIIC schien am meisten von der OB-Chirurgie zu profitieren. Eine multivariate Analyse zeigte aber, dass die verbleibende Tumorlast der wichtigste prognostischer Parameter für das Gesamtüberleben war, gefolgt von FIGO-Stadium und einem OB-Eingriff. Die Mortalität in der OB-Interventionsgruppe war niedrig (0,6 %).

Schlussfolgerung
Die Durchführung eines Eingriffs am Oberbauch ist ein wesentlicher Bestandteil der zytoreduktiven Chirurgie bei Patientinnen mit fortgeschrittenem Ovarialkarzinom und Tumorausbreitung im Oberbauch und verlängert das Überleben signifikant. Der OB-Eingriff gilt als sicher und hat eine niedrige Mortalität. Das Ziel sollte eher eine R1- als eine R2-Resektion sein. Damit ist bei Tumorbefall die Oberbauchchirurgie im Rahmen des Tumordebulking im Gegensatz zu einer frühzeitigen Beendigung des chirurgischen Eingriffs zu bevorzugen, da der zu erreichende R1-Status einen signifikanten Einfluss auf die Prognose der Patientinnen hat.

Introduction

In Germany, approximately 7300 women are diagnosed with ovarian cancer per year. The 5-year-survival across all FIGO stages is 42 % [1, 2] due to late diagnosis in advanced stages (72–76 %) and high recurrence rates [3, 4].

In addition to FIGO stage and age, several clinical and histopathological factors are known to be associated with prognosis, most important residual tumor following cytoreductive surgery result, grading, histological subtype, performance status and effectiveness of systemic therapy [5, 6, 7].

Cytoreductive surgery followed by platinum-based chemotherapy is considered the standard treatment of advanced epithelial ovarian cancer (AEOC) [6, 8]. Several studies have demonstrated that complete resection (R0) remains the most important aim of surgery in view of the significant association with prolonged overall survival (OS) of the patients [4, 5, 6, 8]. In addition, Eisenkop et al. showed in a prospective study that cytoreduction with no macroscopically visible tumor had a more significant impact on survival than the amount and dissemination of tumor in the peritoneal cavity prior to surgery [9].

In patients with AEOC, it is well known that upper abdomen tumor spread represents a major obstacle (76 %) in order to obtain optimal resection [10, 11]. In particular, the frequent involvement of the diaphragmatic peritoneum (up to 40–70 %) appears to be the most challenging part within the surgical treatment [12, 13]. Recent studies have shown that surgery of the affected diaphragm increases the number of optimally debulked patients and improves 5-year-survival around 38 % [13]. In addition, splenectomy [14], resection of the transverse colon [15], pancreas [16, 17] and liver structures [11] have been described as relevant stepstones to achieve optimal cytoreduction [18]. However, the available previous data mainly focused on individual upper abdomen interventions (UAI) rather than systematically evaluating possible UAI. A retrospective study showed that resection of the diaphragmatic peritoneum affected by the tumor improved survival when R0 resection was feasible.

In view of the continuous certification of gynecological cancer centers and the performance of surgery by experienced gynecological oncologists as well as improved perioperative management by interdisciplinary approach, radical UAI continuously became a more feasible aspect within the debulking process [8, 19]. Nevertheless, patients should be carefully selected prior to surgery, as multivisceral resections potentially increase the risk of perioperative complications (20–42 %) [12, 17, 20, 21]. A Medline analysis showed that 30-day-mortality after debulking surgery

ranged from 0–6.7%, with a higher risk in older women and extensive surgery [22].

In this analysis, the effect of UAI was examined with regard to prognosis and rate of tumor resection in primary and neoadjuvant cytoreduction of AEOC patients.

Methods

Patients

A retrospective monocentric follow-up study was performed with all patients diagnosed with primary AEOC who underwent surgery at the Department of Gynaecology at the University Medical Center Hamburg-Eppendorf, between January 2014 and December 2019. Patients who underwent primary surgery as well as interval debulking were included.

Written informed consent was obtained from patients prior to enrollment (Ethics Committee Hamburg, 190520004). Patient data were collected from the Hamburg Cancer Registry and clinicopathological factors were assessed (Soarian Clinicals, version 4.3.200). Anonymized data integration was performed using a password-protected Excel database (Microsoft Excel Mac, version 16.37).

Staging was defined according to the International Federation of Obstetricians and Gynaecologists (FIGO) staging system [23]. Inclusion criteria were clinically (FIGO III/IV) or pathologically (pT3a–T4) defined malignant epithelial ovarian cancer.

UAI was defined as surgery of the gallbladder, liver, spleen, stomach, pancreas, omentum minus, transverse colon or diaphragm. No macroscopic tumor at completion of surgery was described as R0, residual tumor ≤ 1 cm as R1 and residual tumor > 1 cm as R2 [6]. Postoperative mortality was defined as death occurring within 30 days after surgery.

Statistical analysis

To investigate prognostic factors, statistical analysis was performed using Statistical Package for Social Sciences (IBM Corporation SPSS Statistics, version 27.0.0.0). Perioperative factors were summarized using standard descriptive statistics.

Pearson's chi-square test was used to compare categorical data. Time-to-event data were estimated using the Kaplan-Meier method and the log-rank test.

Cox proportional hazards models were used to identify prognostic factors for survival by estimating hazard ratios with 95% confidence intervals. Multivariate testing was conducted by Cox regression analysis.

In accordance with the journal's guidelines, we will provide our data for independent analysis by a selected team by the Editorial Team for the purposes of additional data analysis or for the reproducibility of this study in other centers if such is requested.

Results

Main study characteristics

In total, 335 patients diagnosed with AEOC were documented between 2014 and 2019. 49 patients have been excluded due to other tumor entities or different tumor origin. 26 patients never underwent surgery due to comorbidities, personal preferences and death.

Consequently, the study population included 261 patients who were divided into two groups according to UAI. The main characteristics are summarized in ▶ **Table 1**. UAI were connected to more surgical effort: Higher perioperative hemoglobin loss was observed in the group; the rates of intraoperative blood transfusions were higher as well. Additionally mean duration of surgery was longer in the UAI group.

Patients with FIGO stage IIIA and IIIB were more frequently present in the non-UAI group and FIGO stage IIIC patients tend to show significantly more often to be treated with UAI.

Regarding tumor grading, low-grade carcinomas have been detected more often in non-UAI patients. In addition, the most common histological subtype, high-grade serous carcinoma (83%), has been found significantly more often in the UAI group. Patients with nodal involvement were more frequently observed in the UAI group. Significantly more patients with ascites volume > 500 mL at time of diagnosis had UAI compared to patients without documented ascites.

Operative characteristics

▶ **Table 2** shows the surgical data and postoperative treatment. 220 patients received primary surgery and 38 patients were treated with neoadjuvant therapy. Patients were equally divided between both groups.

Overall, complete macroscopic tumor resection was achieved in 144 patients (55%, stage III 61%, stage IV 40%), in 60 patients (23%) R1 resection was obtained and in 54 patients R2 resection (21%). Remarkably, significant differences between the groups regarding the R1 and R2 results have been detected. The R0 rate was comparable in UAI and non-UAI, whereas R1 status was more frequently achieved in the UAI group (29% vs. 14%; $p < 0.005$). In contrast, R2 status was more often documented in the non-UAI cohort (32% vs. 14%; $p < 0.001$). The improved cytoreduction rate (59% vs. 40%) in patients with UAI was confirmed in a subgroup analysis of stage IIIC patients.

During initial hospital stay, no significant postoperative complications were documented between both groups. In total, postoperative mortality occurred in 3 patients: The causes were one mesenteric ischemia in the UAI cohort, one mechanical ileus with aspiration and one postoperative sepsis in the non-UAI group.

Basic surgical procedures such as hysterectomy (98%) and bilateral adnexectomy (100%) were performed more often (39%) in the UAI cohort whereas more specific procedures like pelvical deperitonealization (96%) and bowel resections (81%) have been carried out more often in the UAI group.

In total, 254 patients received chemotherapy. Combination chemotherapy with carboplatin and paclitaxel was applied more often in the UAI group (97%), whereas carboplatin monotherapy was administered more frequently in the non-UAI group (13%). In total (n = 223), a median of 5.8 cycles of standard chemotherapy consisting of carboplatin and paclitaxel) after primary diagnosis was administered (range 0–18). No significant difference regarding the cycles of applied chemotherapy was observed between the two cohorts. In 85% (123/145), six cycles of the standard com-

▶**Table 1** Patient (n = 261) clinical (age, surgical effort, duration of hospital stay, perioperative blood values and ascites volume) and pathological characteristics (FIGO stage, grading, type of histology, nodal state) in comparison of the two subgroups with non-UAI (n = 101) and UAI (n = 160). Statistical analysis was performed with Pearson's chi-square test and P value less than 0.05 was considered statistically significant.

Characteristics	total (n = 261)	non-UAI (n = 101)	UAI (n = 160)	P value
	total (100 %)	101/261 (39 %)	160/261 (61 %)	
Median age in years (*range*)	60 (26–91)	63 (26–91)	59 (30–90)	
Mean duration of surgery (min)	302 (34–513)	245 (34–422)	337 (71–513)	
Mean duration of hospital stay (days)	15 (6–100)	15 (7–52)	15 (6–100)	
Hemoglobin preoperative (g/dL)	12.2 (8–16)	12.2 (9–16)	12.2 (8–16)	
Hemoglobin loss (g/dL)	2.9 (− 4.4–7.7)	2.7 (− 1.5–6.7)	3.1 (− 4.4–7.7)	
Blood transfusion	0.48 (0–12)	0.15 (0–4)	0.69 (0–12)	
Platelets preoperative (bn./L)	365.1 (108–929)	342.8 (108–929)	378.4 (109–875)	
Albumin preoperative (g/dL)	33.3 (16–42)	33.2 (16–41)	33.4 (18–42)	
CA 12–5 preoperative (U/mL)	1371 (5–18600)	1152 (5–18600)	1500 (7–12068)	
FIGO stage				
III	196/261 (75 %)	75/101 (74 %)	116/160 (73 %)	
▪ IIIA	16/196 (8 %)	14/101 (14 %)	2/160 (1 %)	< 0.001
▪ IIIB	25/196 (13 %)	15/101 (15 %)	10/160 (6 %)	0.02
▪ IIIC	150/196 (77 %)	46/101 (46 %)	104/160 (65 %)	0.002
▪ III – unclassified	6/196 (1 %)			
IV	64/261 (25 %)	20/101 (20 %)	44/160 (27 %)	
▪ IVA	24/64 (37.5 %)	7/101 (7 %)	17/160 (11 %)	0.31
▪ IVB	24/64 (37.5 %)	9/101 (9 %)	15/160 (9 %)	0.89
▪ IV – unclassified	16/64 (25 %)	4/101 (4 %)	12/160 (7 %)	
Grading				
Low-grade	18/261 (7 %)	11/101 (11 %)	7/160 (4 %)	0.043
Medium-grade	4/261 (1 %)	1/101 (1 %)	3/160 (2 %)	0.571
High-grade	234/261 (90 %)	85/101 (85 %)	149/160 (93 %)	0.021
Unknown	5/261 (2 %)			
Histology				
Low-grade serous	18/261 (7 %)	11/101 (11 %)	7/160 (4 %)	0.043
High-grade serous	216/261 (82 %)	75/101 (75 %)	141/160 (88 %)	0.004
Endometrioid	5/261 (2 %)	3/101 (3 %)	2/160 (2 %)	0.323
Mucinous	6/261 (2 %)	3/101 (3 %)	3/160 (2 %)	0.565
Unclassified	16/261 (6 %)			
Nodal state				
Negative	40/261 (15 %)	13/101 (13 %)	27/160 (17 %)	0.38
Positive	140/261 (54 %)	43/101 (43 %)	97/160 (61 %)	0.004
Unknown	81/261 (31 %)			
Initial ascites volume				
< 500 mL	56/261 (21 %)	23/101 (23 %)	33/160 (21 %)	0.618
> 500 mL	154/261 (59 %)	47/101 (47 %)	107/160 (67 %)	0.001
No	33/261 (13 %)	18/101 (18 %)	15/160 (9 %)	0.046
Unknown	18/261 (7 %)			

▶**Table 2** Patient (n = 261) operative characteristics (therapy scheme, residual disease after surgery, mortality after 30 days, single surgical procedures and perioperative complications during initial hospital stay) and postoperative treatment (chemotherapy and VEGF-inhibitor therapy) in comparison of the two subgroups with non-UAI (n = 101) and UAI (n = 160). Statistical analysis was performed with Pearson's chi-square test and P value less than 0.05 was considered statistically significant.

Characteristics	Total (n = 261)	Non-UAI (n = 101)	UAI (n = 160)	P value
	total (100 %)	101/261 (39 %)	160/261 (61 %)	
Therapy scheme				
Primary surgery	220/261 (84 %)	84/101 (84 %)	136/160 (85 %)	0.88
Interval surgery	30/261 (12 %)	11/101 (11 %)	19/160 (12 %)	0.8
Re-staging	8/261 (3 %)	4/101 (4 %)	4/160 (2 %)	0.5
Unknown	3/261 (1 %)			
Residual disease				
R0	144/261 (55 %)	53/101 (53 %)	91/160 (57 %)	0.49
R1	60/261 (23 %)	14/101 (14 %)	46/160 (29 %)	0.005
R2	54/261 (21 %)	32/101 (32 %)	22/160 (14 %)	< 0.001
Unknown	3/261 (1 %)			
30-d-mortality	3/261 (1 %)	2/101 (2 %)	1/160 (1 %)	0.32
Surgical procedures				
Hysterectomy	181/205 (88 %)	57/78 (73 %)	124/127 (98 %)	< 0.001
Bilateral adnectomy	232/243 (95 %)	82/93 (88 %)	150/150 (100 %)	
Omentum majus	247/261 (95 %)	87/101 (86 %)	160/160 (100 %)	
Systematic LNE	90/261 (34 %)	27/101 (27 %)	63/160 (39 %)	0.04
Deperitonealization				
Pelvis	219/261 (84 %)	65/101 (65 %)	154/160 (96 %)	< 0.001
Colon gutter bilateral	146/254 (57 %)	22/98 (22 %)	124/156 (79 %)	< 0.001
Diaphragm	144/261 (55 %)	0/101 (0 %)	144/160 (90 %)	< 0.001
Bowel resection	181/260 (70 %)	52/101 (51 %)	129/159 (81 %)	< 0.001
Rectosigmoid	119/260 (45 %)	36/101 (36 %)	83/159 (52 %)	0.009
Colon	28/260 (11 %)	0/101 (0 %)	28/159 (18 %)	< 0.001
Transverse colon	27/260 (10 %)	0/101 (0 %)	27/159 (17 %)	< 0.001
Ileocecal	12/260 (5 %)	5/101 (5 %)	7/159 (4 %)	0.83
Ileum	9/260 (3 %)	3/101 (3 %)	6/159 (4 %)	0.73
Perioperative complications				
Revision	14/261 (5 %)	5/101 (5 %)	9/160 (6 %)	0.89
Thrombosis/embolism	10/261 (4 %)	3/101 (3 %)	7/160 (4 %)	0.66
Ileus	8/261 (3 %)	4/101 (4 %)	4/160 (2 %)	0.45
Pleural effusion	10/261 (4 %)	2/101 (2 %)	8/160 (5 %)	0.25
Systemic infection	6/261 (2 %)	3/101 (3 %)	3/160 (2 %)	0.52
Unknown	15/261 (6 %)			
Chemotherapy				
None	5/261 (2 %)	4/101 (4 %)	1/160 (1 %)	0.06
Carboplatin mono	16/261 (6 %)	13/101 (13 %)	3/160 (2 %)	< 0.001
Carboplatin + paclitaxel	236/261(90 %)	83/101 (82 %)	153/160 (97 %)	< 0.001
Carboplatin + doxorubicin	2/261 (1 %)	1/101 (1 %)	1/160 (1 %)	0.7
Unknown	2/261 (1 %)	0/101 (0 %)	2/160 (1 %)	

▶Table 2 continued

Characteristics	Total (n = 261)	Non-UAI (n = 101)	UAI (n = 160)	P value
	total (100 %)	101/261 (39 %)	160/261 (61 %)	
Bevacizumab				
Yes	171/261 (66 %)	58/101 (59 %)	113/160 (72 %)	0.03
No	73/261 (28 %)	38/101 (39 %)	35/160 (22 %)	0.006
Unknown	17/261 (7 %)	5/101 (5 %)	12/160 (7 %)	

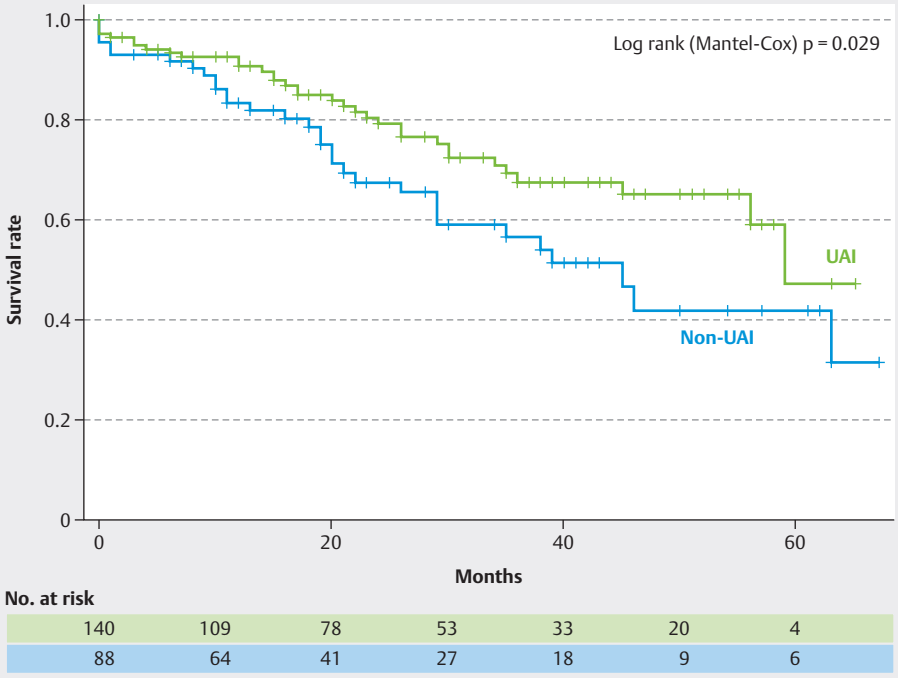
bination were given in the UAI group compared to 90 % in the non-UAI group (70/79). Regarding VEGF-inhibitor therapy, the UAI group was more likely to receive bevacizumab (72 %).

Survival analysis and surgical interventions

The median follow-up was 19 months. Median PFS was 26 months for patients with R0 status, 17 months for those with R1 status and 15 months with R2 status ($p < 0.001$). The risk of death or progression was reduced by 63 % in patients with complete resection. Median OS was calculated to be > 65 months in patients with R0 status, 63 months in those with R1 status and 21 months ($p < 0.001$) with R2 status. Achieving complete macroscopic tumor resection resulted in a reduced risk of death by 75 % ($p < 0.001$). Other factors associated with worse survival were stage IV and high-grade serous entities.

Survival according to the presence or absence of UAI is shown in ▶ **Fig. 1**. This graph highlights a significantly longer OS in the UAI group (59 vs. 45 months, $p = 0.029$). UAI was significantly associated with 40 % death reduction ($p = 0.04$). The analysis of stage IIIC patients showed a stronger risk reduction of 61 % ($p = 0.008$). A subgroup analysis of high-grade serous tumor biology demonstrated similar impact on survival with 48 % risk reduction ($p = 0.01$).

Upper abdominal metastases were treated in 160 patients as shown in ▶ **Table 3**. In the total cohort, diaphragm stripping was the most common procedure in the total cohort. Diaphragm surgery (n = 147) was mostly carried out by stripping the diaphragm (n = 144), in three cases a resection was executed (▶ **Table 3**). No other operative techniques removing diaphragmatic lesions were carried out during study period. Patients with that intervention had a significantly longer median OS than those without (59 vs.



▶ **Fig. 1** Kaplan-Meier survival curve of *overall survival* (OS) over 60 months of AEOC patients stratified by UAI (n = 140) vs. non-UAI (n = 88) with total numbers at risk. Statistical analysis was performed with the log-rank test and P value less than 0.05 was considered statistically significant.

▶**Table 3** Individual upper abdominal surgical interventions in comparison with total study population (n = 261) and predictors of median OS (with standard deviation, hazard ratio and P value) and R0 rate (no tumor residuals and P value). Statistical analysis was performed with Cox proportional hazard models and P value less than 0.05 was considered statistically significant. N = No; Y = Yes.

UAI charact,	(n = 261)	R0 rate	P value	median OS	SD	P value	HR	P value
Deperitonealization of diaphragm	N 45% (117)	50.40%	< 0.001	45	6.007	0.023	0.576	0.026
	Y 55% (144)	60.10%		59	–			
Diaphragm resection	N 99% (258)	55.30%	0.301	59	8.227	0.933	0.991	0.993
	Y 1% (3)	100%		–	–			
Liver	N 92% (240)	54%	0.321	59	8.664	0.551	0.759	0.554
	Y 8% (21)	71%		56	–			
Spleen	N 96% (250)	55.90%	0.444	63	–	0.067	2.484	0.079
	Y 4% (11)	55%		29	15.969			
Galllbladder	N 96% (250)	55.50%	0.614	59	8.251	0.157	1.907	0.167
	Y 4% (11)	63.60%		30	13.525			
Pancreas	N 98% (257)	55.90%	0.969	59	8.17	0.74	1.392	0.743
	Y 2% (4)	50.00%		29	–			
Stomach	N 97% (252)	56.60%	0.38	59	8.189	0.821	1.176	0.822
	Y 3% (9)	33.30%		–	–			
Transverse colon	N 90% (234)	58.20%	0.012	63	5.272	0.078	1.815	0.085
	Y 10% (27)	34.60%		30	6.508			
Omentum minus	N 86% (225)	58.10%	0.001	63	5.261	0.133	1.64	0.14
	Y 14% (36)	41.70%		29	2.084			

▶**Table 4** Multivariate analysis of variables (UAI, state of resection, age at primary diagnosis and FIGO stage) impacting OS during observation period. Statistical analysis was performed with Cox regression analysis and P value less than 0.05 was considered statistically significant.

Characteristic	HR	CI (95%)	P value
UAI vs. non-UAI	0.721	0.44–1.18	0.19
R0 vs. non-R0	0.306	0.18–0.53	< 0.001
Age of primary diagnosis	1.02	0.99–1.04	0.13
FIGO III vs. IV	0.532	0.32–0.87	0.01

45 months) and 60% R0 rate. In comparison, the numbers of other procedures were low: No OS differences could be observed in single interventions such as liver or gallbladder resections.

In a multivariate analysis including residual tumor, UAI, stage, age, only residuals were associated with a statistically significantly lower HR for OS (▶ **Table 4**). R0 status was associated with a significant risk reduction for death and had a more important impact on OS than UAI, stage III versus IV and age at diagnosis.

Discussion

Summary of main results

Maximal cytoreductive surgery remains the key factor within the treatment of AEOC. Our study confirms better survival with less tumor residuals and a 75% risk reduction of death by achieving R0 status. The performance of UAI improved the resection status and the OS outcome.

In terms of preoperative characteristics, our study demonstrated that UAI was more frequently performed in IIIC stage and in patients with ascites > 500 mL as a surrogate for tumor spread in the upper abdomen. Especially the FIGO stage IIIC and the high-grade serous subgroup seemed to profit from this procedure. The

most common UAI in our study was diaphragmatic peritoneal resection, which mainly led to the improved results of UAI.

In multivariate analysis, only resection-state and stage III, but not UAI, were associated with a significant reduction for OS. In general, the procedure appears to be safe with low mortality.

Results in the context of published literature

The observed rate of complete macroscopic tumor resection (R0) of 55% in this monocentric study is in line with data from the German national quality assurance program (QS-OVAR), where 53% R0 rate was reported for 2016 [24]. In the international phase-III-trial PAOLA complete macroscopic tumor resection was observed in 59–62% [7]. However, it is noteworthy that in trials, it is more likely to select patients with fewer comorbidities who are more suitable for radical surgery than in real-world populations [7, 25, 26]. In the current study, cytoreductive surgery included high rate of pelvic peritoneal stripping (84%), bowel resection (70%) and of UAI in general (61%) including diaphragmatic stripping (55%), partial hepatectomy (8%), splenectomy (11%) and distal pancreatectomy (2%). These numbers are significantly higher compared to a population-based US-American study of AEOC patients (2000–2013) identified from the SEER-Database [27]. Herein, the overall rate of bowel resection was low with 34%, as well as the rate of UAI, which increased from 5% in 2000 to 13% in 2013. Our surgical data are comparable with data from the LION study which included only AEOC patients with R0 status between 2008–2012 [28]. In this study, pelvic peritonectomy was performed in 85%, gastrointestinal resection in 52%, distal pancreatectomy in 2% and partial hepatectomy in 8%. Solely the rate of splenectomy was higher (19%) in comparison to our study. Also previous studies confirmed higher frequencies of radical surgery with advanced stage and higher incidence of ascites [29].

The performance of UAI was significantly associated with better resection rates and longer OS of AEOC patients as observed in previous studies [9, 18]. Interestingly, the large IIIC subgroup seemed to benefit from UAI as the HR was even lower. One of the main prognostic factors is the residual tumor: Chi et al. proved a significantly higher R0 rate after implementation of UAI as a surgical strategy in AEOC from 11% to 27% [30]. In the present study, R0 and R1 rates were higher in patients with UAI than in those without. Notably, a significantly higher R2 rate was observed in the non-UAI group. in conclusion, these data confirm that higher rates of tumor resection can possibly be achieved with UAI. However, the interpretation of the data is limited due to the fact that UAI is not always feasible based on simultaneously existing comorbidities.

Resection-state has been shown to be the strongest prognostic parameter for survival in AEOC patients [6, 8]. This is very much comparable to meta-analysis data [6] evaluating the impact of resection on survival in three AGO trials with 99.1 months (R0 status), 36.2 months (R1 status) and 29.6 months (R2 status). The HR for OS associated with R0 resection versus residual tumor was 68%.

As shown in previous studies, patients benefit in terms of OS when UAI is performed and R0 status or at least R1 status is achieved [13, 18]. Eisenhower et al. [18] showed that ovarian cancer patients with upper abdominal tumor spread and R0 resection had a similar OS compared to patients without upper abdomen involvement and R0 status.

Metastasis to the diaphragm peritoneum has been reported between 40–78% [12, 13] and resection rate in this study was 55%. Previous data demonstrated a higher 5-year OS benefit (38%) by resection of the affected diaphragm [13]. In line with these results, we demonstrated a significant improvement in OS by diaphragm stripping and a HR reduction of 42%. Other UAI such as liver resection, pancreatectomy and splenectomy have been shown to be an essential factor in order to achieve R0 resection [14, 18, 28, 30] – however in our study the amount for each procedure was too small to show a relevant impact on survival.

Nevertheless, the impact of postoperative complications after UAI should be considered carefully [12, 17, 20, 21, 31]. In a recent US-American population-based study, UAI was associated with an increased likelihood of cardiac (6%) and respiratory complications (16%) [27] that cannot be confirmed with our data. Kuhn et al. [32] also reported a higher morbidity and mortality in the UAI group, especially for distal pancreatectomy and splenectomy. In population-based studies mortality rates ranged from 2.5–3.7% [22]. In the present study, 30-day-mortality was low with 0.6% in the UAI group. In comparison, the LION trial had a mortality rate of 0.9–3% [28]. Therefore, the mortality rate seems acceptable, especially in view of the reported increased OS [20]. Furthermore, based on the increasing implementation of prehabilitation protocols increased perioperative outcome is more likely to be achieved [29, 33]: initially these programs have been introduced in order to improve the patients physical fitness and increase the perioperative outcomes [33], which may enhance the possibility of UAI if necessary.

Strengths and weaknesses

To date, only few studies of UAI in AEOC are based on a large study population from a gynecological cancer center – as a consequence, the evidence for the benefit of UAI is limited. Most of the comparative trials of UAI were performed several years ago. Since then, especially perioperative management has constantly changed putting an increased focus on prehabilitation and intraoperative hemodynamic monitoring resulting in less perioperative morbidity. Furthermore, many studies failed to define an optimal surgical outcome such as R0 resection which should be the considered as treatment standard nowadays [5, 10]. In addition, some studies compared surgical and prognostic results of different observation periods [18, 30]. Additionally, this study subdivides UAI into each single surgical procedure. As this study did not exclude patients with comorbidities the comparability with other studies [6] and prognostic data is limited, however, a more realistic description of clinical practice is provided.

The limitation of this retrospective monocentric analysis may be a possible selection bias in order to study the highly complex oncological disease. The heterogeneous distribution of the tumor and the improvement of medical treatment [7, 34] are relevant aspects reducing the validity. In addition, in contrast to other studies, no data could be collected on the initial tumor spread in the upper abdomen [29]. Furthermore, multivariate analysis did

not show a significant effect of UAI and improved survival in AEOC patients: Non-UAI patients had a significantly lower rate of general surgical procedures and systemic therapy (▶ **Table 2**), even though the same highly skilled surgeons performed the operations in both groups. The only possible conclusion is that the non-UAI group had more comorbidities that prevented more intensive surgery and systemic therapy. Therefore, no significant effect was shown in the multivariate analysis. Only a randomized study design could demonstrate the effect of UAI on outcome.

Implication for practice and future research

In conclusion, our results underline the importance of radical surgical intervention as an essential therapeutic cornerstone in the treatment of AEOC. Complete cytoreduction remains the most important aim in order to provide successful surgical treatment – including UAI when necessary [5, 6, 8]. In our study, we demonstrated that patients significantly benefit in terms of OS if R0 status or even R1 status is achieved with UAI. Specialized centers with highly experienced gynecological oncologists are essential to ensure an optimal surgical outcome based on increased perioperative management and standardization of surgical techniques in a multidisciplinary approach [33]. Large multicentric studies are necessary to examine correlation between the patients' health condition, preoperative tumor burden and UAI with every single surgical intervention in regard to resection state and prognosis.

Conclusion

UAI in AEOC patients prolonged the OS and improved resection rates significantly. This procedure is more likely to happen with stage IIIC patients, high-grade serous histology and presence of ascites. Especially diaphragmatic surgery appears to be a cornerstone in upper abdomen interventions. In multivariate analysis no effect of UAI on OS could be observed. As mortality appears to be low UAI can be carried out when adequate.

INFO BOX

What is already known on this topic: As advanced ovarian cancer indicates a poor survival it is crucial to evaluate prognostic factors. Complete resection is the main goal of the surgery and a broad analysis of individual surgical components is rare in literature.

What this study adds: Upper abdominal interventions should be performed if feasible as mortality is low and survival prognosis can be improved.

How this study might affect research, practice or policy: Surgery remains a key player in the prognosis of advanced ovarian cancer and should be correlated with modern medical treatment of the disease.

Conflict of Interest

Dr. med. Anna Jaeger: honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events: MSD, GSK, Roche Diagnostics, Astra Zeneca, Molecular Health, Clovis Oncology, Gedeon Pharma, ITF Pharma.
Dr. Reuter: Participation on a Data Safety Monitoring Board or Advisory Board: Scientific advisory services MSD.
Prof. Schmalfeldt: Consulting fees: GSK, AstraZeneca, Roche, MSD, Eisai, MedConcept, Daiichi Sankyo, ClinSol; Support for attending meetings and/or travel: Daiichi Sankyo, GSK, Roche, AstraZeneca; Participation on a Data Safety Monitoring Board or Advisory Board: GSK, AstraZeneca, Roche, MSD, Eisai, Daiichi Sankyo; Leadership or fiduciary role: Deutsche Gesellschaft für Gynäkologie und Geburtshilfe e.V. (DGGG), FIGO, Wehrmedizinischer Beirat, Fakultätsrat UKE, Arzneimittelkommission UKE.

References

[1] Robert-Koch-Institut. Krebs in Deutschland Eierstöcke 3.21 Eierstöcke: Robert-Koch-Institut und die Gesellschaft der epidemiologischen Krebsregister in Deutschland 10. Ausgabe. 2015. Accessed February 01, 2023 at: https://www.krebsdaten.de/Krebs/DE/Content/Publikationen/Krebs_in_Deutschland/krebs_in_deutschland_node.html

[2] Jemal A, Bray F, Center MM et al. Global cancer statistics. CA Cancer J Clin 2011; 61: 69–90. DOI: 10.3322/caac.20107

[3] Bankhead CR, Kehoe ST, Austoker J. Symptoms associated with diagnosis of ovarian cancer: a systematic review. BJOG 2005; 112: 857–865. DOI: 10.1111/j.1471-0528.2005.00572.x

[4] Burges A, Schmalfeldt B. Ovarian cancer: diagnosis and treatment. Dtsch Arztebl Int 2011; 108: 635–641. DOI: 10.3238/arztebl.2011.0635

[5] Chang SJ, Hodeib M, Chang J et al. Survival impact of complete cytoreduction to no gross residual disease for advanced-stage ovarian cancer: a meta-analysis. Gynecol Oncol 2013; 130: 493–498. DOI: 10.1016/j.ygyno.2013.05.040

[6] du Bois A, Reuss A, Pujade-Lauraine E et al. 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: 1234–1244. DOI: 10.1002/cncr.24149

[7] Ray-Coquard I, Pautier P, Pignata S et al. Olaparib plus Bevacizumab as First-Line Maintenance in Ovarian Cancer. N Engl J Med 2019; 381: 2416–2428. DOI: 10.1056/NEJMoa1911361

[8] 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: 1248–1259. DOI: 10.1200/JCO.2002.20.5.1248

[9] Eisenkop SM, Spirtos NM, Friedman RL et al. 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: 390–396. DOI: 10.1016/s0090-8258(03)00278-6

[10] Eisenkop SM, Spirtos NM. What are the current surgical objectives, strategies, and technical capabilities of gynecologic oncologists treating advanced epithelial ovarian cancer? Gynecol Oncol 2001; 82: 489–497. DOI: 10.1006/gyno.2001.6312

[11] Zivanovic O, Eisenhauer EL, Zhou Q et al. The impact of bulky upper abdominal disease cephalad to the greater omentum on surgical outcome for stage IIIC epithelial ovarian, fallopian tube, and primary peritoneal cancer. Gynecol Oncol 2008; 108: 287–292. DOI: 10.1016/j.ygyno.2007.10.001

[12] Cliby W, Dowdy S, Feitoza SS et al. Diaphragm resection for ovarian cancer: technique and short-term complications. Gynecol Oncol 2004; 94: 655–660. DOI: 10.1016/j.ygyno.2004.04.032

[13] Aletti GD, Dowdy SC, Podratz KC et al. Surgical treatment of diaphragm disease correlates with improved survival in optimally debulked advanced stage ovarian cancer. Gynecol Oncol 2006; 100: 283–287. DOI: 10.1016/j.ygyno.2005.08.027

[14] Eisenkop SM, Spirtos NM, Lin W-CM. Splenectomy in the context of primary cytoreductive operations for advanced epithelial ovarian cancer. Gynecol Oncol 2006; 100: 344–348. DOI: 10.1016/j.ygyno.2005.08.036

[15] Bristow RE, Peiretti M, Zanagnolo V et al. Transverse colectomy in ovarian cancer surgical cytoreduction: operative technique and clinical outcome. Gynecol Oncol 2008; 109: 364–369. DOI: 10.1016/j.ygyno.2008.02.020

[16] Bacalbasa N, Balescu I, Dima S et al. Pancreatic Resection as Part of Cytoreductive Surgery in Advanced-stage and Recurrent Epithelial Ovarian Cancer–A Single-center Experience. Anticancer Res 2015; 35: 4125–4129

[17] Kehoe SM, Eisenhauer EL, Abu-Rustum NR et al. Incidence and management of pancreatic leaks after splenectomy with distal pancreatectomy performed during primary cytoreductive surgery for advanced ovarian, peritoneal and fallopian tube cancer. Gynecol Oncol 2009; 112: 496–500. DOI: 10.1016/j.ygyno.2008.10.011

[18] Eisenhauer EL, Abu-Rustum NR, Sonoda Y 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: 1083–1090. DOI: 10.1016/j.ygyno.2006.06.028

[19] Reuter S, Schmalfeldt B, Haas SA et al. Impact of Introducing a PACU24 Concept on the Perioperative Outcome of Patients with Advanced Ovarian Cancer Treated with Cytoreductive Surgery. Geburtshilfe Frauenheilkd 2023; 83: 1022–1030. DOI: 10.1055/a-2055-9349

[20] Benedetti Panici P, Di Donato V, Fischetti M et al. Predictors of postoperative morbidity after cytoreduction for advanced ovarian cancer: Analysis and management of complications in upper abdominal surgery. Gynecol Oncol 2015; 137: 406–411. DOI: 10.1016/j.ygyno.2015.03.043

[21] Fanfani F, Fagotti A, Gallotta V et al. Upper abdominal surgery in advanced and recurrent ovarian cancer: role of diaphragmatic surgery. Gynecol Oncol 2010; 116: 497–501. DOI: 10.1016/j.ygyno.2009.11.023

[22] Gerestein CG, Damhuis RA, Burger CW et al. Postoperative mortality after primary cytoreductive surgery for advanced stage epithelial ovarian cancer: a systematic review. Gynecol Oncol 2009; 114: 523–527. DOI: 10.1016/j.ygyno.2009.03.011

[23] Berek JS, Kehoe ST, Kumar L et al. Cancer of the ovary, fallopian tube, and peritoneum. Int J Gynaecol Obstet 2018; 143 (Suppl 2): 59–78. DOI: 10.1002/ijgo.13878

[24] Hilpert F, du Bois A, Pfisterer J et al. Steigerung der Therapiequalität des Ovarialkarzinoms in Deutschland – Ergebnisse der eigenverantwortlichen QS Ovar. Geburtshilfe Frauenheilkd 2020; 80: P389

[25] Kehoe S, Hook J, Nankivell M et al. Primary chemotherapy versus primary surgery for newly diagnosed advanced ovarian cancer (CHORUS): an open-label, randomised, controlled, non-inferiority trial. Lancet 2015; 386: 249–257. DOI: 10.1016/S0140-6736(14)62223-6

[26] Moore K, Colombo N, Scambia G et al. Maintenance Olaparib in Patients with Newly Diagnosed Advanced Ovarian Cancer. N Engl J Med 2018; 379: 2495–2505. DOI: 10.1056/NEJMoa1810858

[27] Dottino JA, He W, Sun CC et al. National trends in bowel and upper abdominal procedures in ovarian cancer surgery. Int J Gynecol Cancer 2020; 30: 1195–1202. DOI: 10.1136/ijgc-2020-001243

[28] Harter P, Sehouli J, Lorusso D et al. A Randomized Trial of Lymphadenectomy in Patients with Advanced Ovarian Neoplasms. N Engl J Med 2019; 380: 822–832. DOI: 10.1056/NEJMoa1808424

[29] Horowitz NS, Miller A, Rungruang B et al. Does aggressive surgery improve outcomes? Interaction between preoperative disease burden and complex surgery in patients with advanced-stage ovarian cancer: an analysis of GOG 182. J Clin Oncol 2015; 33: 937–943. DOI: 10.1200/JCO.2014.56.3106

[30] Chi DS, Eisenhauer EL, Zivanovic O et al. Improved progression-free and overall survival in advanced ovarian cancer as a result of a change in surgical paradigm. Gynecol Oncol 2009; 114: 26–31. DOI: 10.1016/j.ygyno.2009.03.018

[31] Dowdy SC, Loewen RT, Aletti G et al. Assessment of outcomes and morbidity following diaphragmatic peritonectomy for women with ovarian carcinoma. Gynecol Oncol 2008; 109: 303–307. DOI: 10.1016/j.ygyno.2008.02.012

[32] Kuhn W, Florack G, Roder J et al. The influence of upper abdominal surgery on perioperative morbidity and mortality in patients with advanced ovarian cancer FIGO III and FIGO IV. Int J Gynecol Cancer 1998; 8: 56–63

[33] Nelson G, Altman AD, Nick A et al. Guidelines for postoperative care in gynecologic/oncology surgery: Enhanced Recovery After Surgery (ERAS®) Society recommendations – Part II. Gynecol Oncol 2016; 140: 323–332. DOI: 10.1016/j.ygyno.2015.12.019

[34] Aletti GD, Dowdy SC, Gostout BS et al. Aggressive surgical effort and improved survival in advanced-stage ovarian cancer. Obstet Gynecol 2006; 107: 77–85. DOI: 10.1097/01.AOG.0000192407.04428.bb