European Journal of Surgical Oncology xxx (xxxx) xxx

Contents lists available at ScienceDirect

European Journal of Surgical Oncology

journal homepage: www.ejso.com

Maximal surgical effort increases the risk of postoperative complications in the treatment of advanced ovarian cancer

Kati Kuusela [a], Niina Norppa [b], Annika Auranen [b, c], Sami Saarelainen [b, *]

[a] Tampere University, FI-33014, Tampere, Finland
[b] Tampere University Hospital, Department of Obstetrics and Gynecology, PO BOX 2000, FI-33521, Tampere, Finland
[c] Tays Cancer Centre, PO BOX 2000, FI-33521, Tampere, Finland

ARTICLE INFO

Article history:
Received 10 March 2022
Received in revised form
30 May 2022
Accepted 6 June 2022
Available online xxx

Keywords:
Advanced ovarian cancer
Ultra-radical surgery
Postoperative complications

ABSTRACT

Introduction: Surgery is the cornerstone of the treatment for advanced ovarian cancer. Reaching complete cytoreduction resulting in no gross residual disease often requires complex surgery. The aim of this study was to assess the impact of increased surgical radicality on the risk of complications in the treatment of advanced ovarian cancer.

Materials and methods: All consecutive patients with advanced ovarian cancer (FIGO Stage IIIB-IVB) who had undergone primary or interval debulking surgery during a six-year study period were identified. In the midst of the study period, a surgical practice change towards maximal surgical effort occurred. Two groups were formed for the analysis: cohort A, that consisted of patients operated before the surgical paradigm shift and cohort B, that consisted of patients operated under the period of increased surgical radicality.

Results: 252 patients were included in the analysis. Complete resection (R0) was achieved in 21.3% of surgeries in cohort A and in 51.2% in cohort B. The total postoperative complication rate was 76.2%. Most of the complications (86.5%) were minor (Clavien-Dindo I-IIIA). The patients in cohort B were at increased risk for complications, OR 2.94 (95%CI 1.58–5.47; $p = 0.001$). As for the approach to cytoreduction (primary vs. interval debulking), there was no statistically significant association with the occurrence of postoperative complications ($p = 0.659$).

Conclusion: In the present study more extensive surgeries led to better surgical results but increased postoperative morbidity. Postoperative complication rates were similar in both primary and interval debulking surgeries.

1. Introduction

Over 310, 000 women were diagnosed with ovarian cancer in 2020, making it the eighth most common cancer among women worldwide [1]. Ovarian cancer is diagnosed in advanced stage in 75% of cases [2]. Advanced disease presents a poor prognosis as the five-year relative survival rate in Europe is on average 38% [3]. Surgery is the cornerstone of the treatment, and the aim is to achieve maximal cytoreduction as the amount of residual disease is one of the main prognostic factors [4–6].

Recently, the need for more aggressive cytoreduction has resulted in the concept of maximal effort surgery that, in addition to the traditional ovarian cancer surgery, may comprise multiple bowel resections, extensive peritonectomy, diaphragm resection and multiple organ resections including splenectomy, cholecystectomy, pancreatectomy and liver resection. This is often referred to as ultra-radical surgery. There is some evidence that more extensive procedures and thus a better surgical outcome may result in a better progression-free and overall survival [7–13]. However, according to a recent study, ultra-radical surgery does not improve overall survival in surgically treated patients [14]. Thus, results from the previous studies are contradictory.

The extent of surgery and large bowel resections have been associated with postoperative complications, for example infections and hemorrhage. Hence, ultra-radical surgery poses a greater risk of complications and may be unsuitable for some patients [15,16]. As adjuvant chemotherapy is of paramount importance in the treatment of ovarian cancer, the increased

* Corresponding author. Department of Obstetrics and Gynecology, Tampere University Hospital, P.O. Box 2000, FI-33521, Tampere, Finland.
E-mail address: sami.saarelainen@pshp.fi (S. Saarelainen).

https://doi.org/10.1016/j.ejso.2022.06.007

complication rate may interfere with successful treatment.

In Tampere University Hospital, the surgical standard in the treatment of advanced ovarian cancer changed in March 2016, as maximal effort surgery was implemented into routine practice. The aim of this study was to assess the impact of the introduction of ultra-radical surgery in the risk of complications in the surgical treatment for advanced ovarian cancer.

2. Materials and Methods

We collected the data for this retrospective cohort study from the patient record system of Tampere University Hospital over the period from 2013 to 2019. Inclusion criteria were as follows: all consecutive patients with advanced ovarian cancer (FIGO 2014 Stage IIIB-IVB) who had undergone primary or interval debulking surgery were included [17]. The patients with a localized cancer (FIGO 2014 Stage IA-IIIA) and/or treated with a laparoscopic operation were excluded from the study. In addition, surgical operations for cancer recurrence were ruled out. All operations were performed by surgeons specialized in gynecologic oncologic surgery.

Two groups were formed for the analysis: cohort A, that consisted of patients operated before the surgical paradigm shift (2013–2016) and cohort B, that consisted of patients operated under the period of ultra-radical surgery (2016–2019). Differences between outcomes of primary surgery and interval surgery were analyzed. We also compared patients operated with maximal surgical effort to patients that were operated with conventional surgery (including laparotomies that remained as explorative).

Collected data consisted of patient, tumor, and surgery characteristics. The surgical outcome was classified based on the size of the residual disease (R0 = complete cytoreduction, no visible tumor left, R1 = 1 cm or less of residual disease and R2 = more than 1 cm of residual disease). The postoperative period was assessed by collecting data on complications and chemotherapy. Complications that occurred under a period of 30 days after the surgery were noted and graded according to the Clavien-Dindo Classification [18]. If a patient had more than one postoperative complication, only the most severe one was considered. In 10 cases, complete postoperative follow-up data (30 days) was unavailable.

Categorical variables were observed by calculating frequencies and compared by forming fourfold tables and using either the chi-square test or the Fisher's exact test. The Kolmogorov − Smirnov test was used to evaluate normal distribution of continuous variables. Comparison of the groups was performed using Kruskal-Wallis test and Mann − Whitney U- test. In addition, bivariate and multivariate analyses were performed by using logistic regression. P-value less than 0.05 was considered significant. The data was analyzed using statistical software SPSS Statistics 26 (IBM, Armonk, NY). Approval for the study was acquired from the hospital administration. Approval of the committee on research ethics was not required for a registry-based study.

3. Results

Total of 252 patients were included in the analysis, 127 patients in cohort A and 125 patients in cohort B (Table 1). The median age of the patients in cohort A and B was 67.0 and 68.0 years, respectively (p = 0.632). The median BMI in cohort A and B was 25.1 kg/m^2 and 25.0 kg/m^2 (p = 0.234) respectively. In 9 cases, BMI was missing. The most common FIGO stage was IIIC in both groups (66.9% and 48.8% in cohort A and B, respectively). Most of the tumors were high grade serous carcinomas (85.7%).

Surgery characteristics are presented in Table 2. The majority of the operations were primary debulking surgeries (n = 162, 64.3%). In all patients, the median estimated blood loss was 600 ml. The median estimated blood loss was less in cohort A than in cohort B (350 vs. 975 ml, respectively, p < 0.001). In 17 cases, the record of blood loss was unavailable. In addition, the median operative time was shorter in cohort A (162 vs. 340 min, p < 0.001). A standard thromboembolism prophylaxis (low-molecular-weight heparin started before surgery and continued for four weeks) and antimicrobial prophylaxis (cefuroxime and metronidazole administered before skin incision) protocols were routinely followed during the observed study period. More emphasis was placed on preoperative

Table 1
Patient and tumor characteristics.

	Total (n = 252)		Cohort A (n = 127)		Cohort B (n = 125)	
Age (y)						
Median (Range)	67.5 (24–89)		67.0 (24–87)		68.0 (31–89)	
BMI* (kg/m^2)						
Median (Range)	25.1 (15.1 −51.2)		25.1 (15.1 −38.7)		25.0 (17.2 −51.2)	
FIGO stage**	n	%	n	%	n	%
IIIB	21	8.3	6	4.7	15	12.0
IIIC	146	57.9	85	66.9	61	48.8
IVA	22	8.7	13	10.2	9	7.2
IVB	63	25.0	23	18.1	40	32.0
Histology	n	%	n	%	n	%
High grade serous	216	85.7	104	81.9	112	91.2
Low grade serous	13	5.2	4	3.1	9	7.2
Mucinous	5	2.0	4	3.1	1	0.8
Endometrioid	6	2.4	5	3.9	1	0.8
Clear cell	3	1.2	3	2.4	0	0
Other***	9	3.6	7	5.5	2	1.6

* Body mass index.
** International Federation of Gynecology and Obstetrics.
*** Carcinosarcoma, malignant germ cell tumor, small cell carcinoma, neuroendocrine carcinoma, squamous cell carcinoma of ovary.

Table 2
Surgery characteristics.

	Total (n = 252)		Cohort A (n = 127)		Cohort B (n = 125)		P-value
Approach to cytoreduction	n	%	n	%	n	%	0.081*
Primary	162	64.3	75	59.1	87	69.6	
Interval	90	35.7	52	40.9	38	30.4	
Type of surgery							<0,001*
Conventional debulking	196	77.8	127	100.0	69	55.2	
Ultra-radical	56	22.2	0	0	56	44.8	
Estimated blood loss (ml)							<0.001**
Median (Range)	600 (20 −4350)		350 (50 −3000)		975 (20 −4350)		
Duration of surgery (min)							<0.001**
Median (Range)	222 (59 −734)		162 (59 −393)		340 (83 −734)		
Surgical outcome***	n	%	n	%	n	%	<0.001*
R0	91	36.1	27	21.3	64	51.2	
R1	70	27.8	29	22.8	41	32.8	
R2	91	36.1	71	55.9	20	16.0	
Complications	n	%	n	%	N	%	
Total	192	76.2	85	66.9	107	85.6	0.001*
Clavien-Dindo grade							
I	41	21.4	23	27.1	18	16.8	
II	84	43.8	47	55.3	37	34.6	
IIIA	41	21.4	7	8.2	34	31.8	
IIIB	16	8.3	7	8.2	9	8.4	
IVA	7	3.6	0	0	7	6.5	
V	3	1.6	1	1.2	2	1.9	
Severity							0.136*
Minor (I-IIIA)	166	86.5	77	90.6	89	83.2	
Major (IIIB–V)	26	13.5	8	9.4	18	16.8	

* Chi-Square test.
** Mann-Whitney *U* Test.
*** R0; complete resection, R1; residual disease 1 cm or less, R2; residual disease over 1 cm.

optimization (nutrition, alcohol consumption and smoking cessation, carbohydrate loading) after the surgical paradigm shift. However, a routinely followed protocol was not yet established.

R0 was achieved in 21.3% of surgeries in cohort A and in 51.2% in cohort B. Logistic regression was performed to compare the optimal outcomes (R0) between the two groups. The chance of R0 was greater in the cohort B, OR 3.89 (95% CI 2.24–6.74; $p < 0.001$). In addition, the possible association between the approach to cytoreduction (primary vs. interval debulking) and the achievement of complete cytoreduction was examined, but no statistically significant correlation was observed ($p = 0.494$). As a result of more aggressive surgery, R0 was achieved more often in operations defined as ultraradical ($p < 0.001$).

The total postoperative complication rate was 76.2%. The majority of the complications (86.5%) were minor (Clavien-Dindo I-IIIA), such as mild infections, that needed antimicrobial treatment and did not have a clinically significant effect on patients' recovery. Although Clavien-Dindo IIIA is commonly classified as a major complication, it was considered a minor complication in this study. A large proportion of IIIA complications consisted of drainage of pleural effusion, that rarely has any effect on patient's recovery. One pleural drainage was performed in cohort A and 22 in cohort B. In cohort A, a reoperation was necessitated for seven patients, including three with a wound dehiscence, two with postoperative bleeding, one with an anastomotic leakage and one with a bowel volvulus. In cohort B, a reoperation was required for 13 patients, out of which six had an anastomotic leakage, four had postoperative bleeding, three had a wound dehiscence and one had a pericardial effusion that required a sternotomy. It should be noted that due to the classification system, only the highest complication class was recorded.

In cohort A, 90.6% of complications were minor, and they were also dominant in cohort B (83.2%). The complication rate was higher in cohort B compared to cohort A (85.6% vs. 66.9%, respectively, $p = 0.001$) following that the patients in cohort B were at increased risk for complications, OR 2.94 (95%CI 1.58–5.47; $p = 0.001$). On the other hand, we found no statistically significant association between the cohort groups and the severity of postoperative complications ($p = 0.136$). The lack of statistical significance is probably due to a small number of patients in the major complication groups.

Differences regarding postoperative complications between solely ultra-radical and conventional radical surgeries were also studied. The patients who underwent surgery with maximal surgical effort (ultra-radical) were at higher risk of developing postoperative complications than patients treated with conventional surgery, OR 23.69 (95%CI 3.20–175.21; $p = 0.002$). However, the rate of major complications did not significantly differ between these two subgroups, 18.2% vs. 11.7%, respectively ($p = 0.234$).

As for the timing of cytoreduction, there was no statistically significant association with the occurrence of postoperative complications ($p = 0.659$). The complication rate was 75.3% and 77.8% in primary and interval surgery groups, respectively. The rate of major complications was also comparable in these subgroups ($p = 0.188$).

The median blood loss of patients with postoperative complications and patients without complications was 700 ml (range 20–4350) and 350 ml (range 100–2300), respectively ($p < 0.001$). The median operative time was also greater for patients with complications (249 min (range 59–734) vs. 164 min (range 65–500), $p < 0.001$). The median age of patients with complications and patients without complications was 68.0 (range 24–89) and 66.0 (range 42–81) ($p = 0.051$). The median BMI was the same in both groups: 25.1 kg/m^2 (range 15.1–51.2) of patients with complications and 25.1 kg/m (range 16.9–42.8) of patients without complications ($p = 0.971$).

The association between surgical procedures (Fig. 1) and postoperative complications was also analyzed. Large bowel resection (colon resection, isolated rectosigmoid resection or pelvic en-bloc resection), bowel anastomosis, total peritonectomy and laparoscopic port scar resection seemed to increase the risk of postoperative complications. 85 patients (91.4%), who underwent large bowel resection, developed complications after surgery. In fact, large bowel resection was associated with an approximately five-fold increased risk of complications in general, OR 5.16 (95%CI 2.33–11.46; $p < 0.001$). Yet, there was no statistically significant association between large bowel resection and the severity of the complications ($p = 0,057$). In connection to large bowel resection, bowel anastomosis seemed to increase the risk of postoperative complications, as the complication rate was 92.8% ($n = 64$), OR 5.50 (95%CI 2.10–14.41; $p = 0.001$) in patients with a bowel anastomosis. The risk of major complications was also increased, OR 2.71 (95%CI 1.17–6.27; $p = 0.020$). In cohort A, 5.9% of bowel anastomoses resulted in anastomotic leakage whereas in cohort B the rate of this potentially fatal complication was higher, 11.5%.

In addition, nearly all patients (98.2%, $n = 56$) who had a total peritonectomy performed, developed some postoperative complication. The procedure was found to increase the risk of complications, OR 24.29 (95%CI 3.29–179.66; $p = 0.002$) but did not have association with the severity of complications ($p = 0.262$). Furthermore, there seems to be an association between laparoscopic port scar resection and postoperative complications, OR 6.47 (95%CI 1.51–27.74; $p = 0.012$). As for the severity of complications, no statistically significant finding occurred ($p = 0.792$).

A multivariate analysis was performed to assess the surgical procedures associated with the occurrence of postoperative complications. The model included bowel resection, bowel anastomosis, total peritonectomy and port-site metastasis resection. Three subgroups were formed for bowel resection: no resection (reference group), one resection and two or more resections. Using the backward conditional method, it was discovered that total peritonectomy still increased the risk of postoperative complications, OR 13.86 (95% CI 1.80–106.83; $p = 0.012$). In addition, the patients who underwent one bowel resection were at increased risk for complications, OR 3.59 (95% CI 1.51–8.56; $p = 0.004$). If more resections were made, the increase in risk was not anymore statistically significant, OR 4.29 (95% CI 0.51–35.85; $p = 0.179$).

Chemotherapy was given for 235 patients (93.3%). 17 patients did not receive chemotherapy. The complication rate was 74.9% ($n = 176$) and 94.1% ($n = 16$) in the chemotherapy group and non-chemotherapy group, respectively. The difference in complication rates was not statistically significant ($p = 0.082$). Of the patients not receiving chemotherapy, two were chosen to receive hormonal therapy instead, two had other medical conditions that prevented further treatment, three had repeated relaparotomies and intra-abdominal abscesses and ten did not recover adequately to receive chemotherapy. The median length of time from surgery until the initiation of chemotherapy in cohort A and B was 35.0 (range 18–57) and 36.0 days (range 15–71) ($p = 0.005$), respectively. The median interval from surgery to chemotherapy for patients with postoperative complications was 35.0 days (range 20–71) and for patients without complications 35.0 days (range 15–64), $p = 0.423$. The median interval for patients with mild complications and patients with severe complications was 35.0 (range 20–64) and 42.5 (range 27–71), respectively. When the last three above-mentioned groups were compared (Kruskal-Wallis-test), statistically significant differences occurred both between no complication and severe complication ($p = 0.001$) and mild complication and severe complication groups ($p < 0.001$). Initiation of chemotherapy occurred within four weeks in 26 patients (cumulative percent 17.1), within five weeks in 122 patients

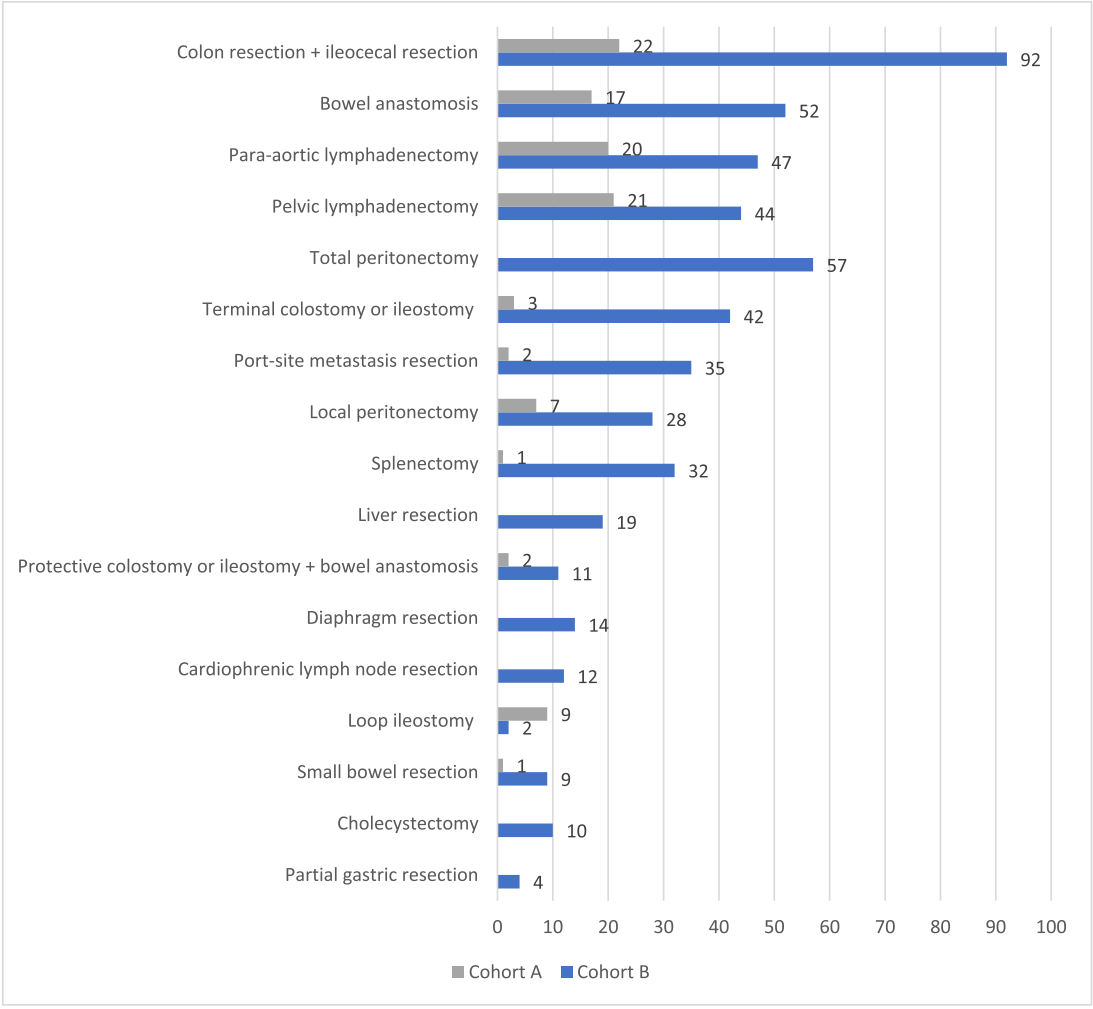

Fig. 1. Surgical interventions. Hysterectomy, bilateral salpingo-oophorectomy, omentectomy and appendicectomy are not included in the figure.

(cumulative percent 55.2) and within six weeks in 195 patients (cumulative percent 84.1). The cumulative percentages of patients were similar in both primary and interval surgery groups (17.3% vs. 16.7%, 54.3% vs. 56.7% and 84.6% vs. 83.3%, respectively, $p = 0.161$).

4. Discussion

This retrospective cohort study demonstrates the consequences of increased radicality in advanced ovarian cancer surgeries. We focused our research on surgical outcomes, postoperative complications, and the differences between primary and interval debulking surgeries. As regards to surgery characteristics, the estimated blood loss and operative time were both greater in operations with a maximal surgical effort. In fact, the median estimated blood loss was nearly three times greater and the median operative time over twice as long in cohort B as in cohort A. Hence, clearly the increased radicality comes with some negative surgery related effects.

As regards the tumor stages, they differed between the cohort groups ($p = 0.004$). Especially stage IVB was more common in cohort B than in cohort A (32.0% vs 18.1%). Due to the increase in surgical radicality in cohort B, parenchymal resections and diaphragm resections were performed more often. As a result, there are more stage IVB patients. Likewise, there is a decrease in stage IVA patients. In other words, as the surgical complexity increased, the patients who would have previously been stage IVA became stage IVB.

As expected, surgical outcome was better in more extensive surgeries. The rate of complete cytoreduction (R0) was 21.3% and 51.2% in cohort A and B, respectively. This finding favors ultra-radical procedures, as previous studies have demonstrated that residual disease is one of the main prognostic factors of disease survival [4–6,19–22]. The need for maximal surgical effort to achieve satisfying results has been previously evaluated. Turnbull et al. report that approximately half of the patients with metastatic ovarian, fallopian tube or primary peritoneal cancer needed upper abdominal procedures when optimal (less than 1 cm) or complete cytoreduction (no macroscopic disease) was attempted [23]. On the other hand, the attempt to achieve maximal cytoreduction might not always be beneficial. Winter et al. conducted a retrospective study that focused on the prognostic factors of stage IV epithelial ovarian cancer patients. They reported that progression-free and overall survival were same among patients with 0.1–1 cm or 1.1–5 cm of residual disease. Prognosis was best for the patients without macroscopic residual disease and worst for the patients with residual disease over 5 cm. They concluded that primary cytoreduction might not be beneficial if preoperatively the gross amount of disease is less than 5 cm, and it is probable that complete cytoreduction will not be achieved [24].

During the study period, the indication to perform a routine pelvic and para-aortic lymphadenectomy changed in 2017 due to the results of LION study that demonstrated that

lymphadenectomy did not have an effect on survival in the surgery of advanced ovarian cancer. This has an effect on the number of lymphadecnetomies performed [25].

The total complication rate in this study was 76.2%, which is rather high compared with the results by Rafii et al. [15]. They performed a multi-center study on postoperative morbidity and mortality after optimal cytoreductive surgery for advanced ovarian cancer. The study included 180 women, of which 61 presented with complications (33%). This difference in complication rates is most likely due to the Clavien-Dindo classification system that was strictly followed in the present study, especially as regards to classes I and II. Chi et al. examined morbidity after extensive upper abdominal procedures and reported a major complication (grade 3–5) rate of 22% and mortality of 1.4% [26]. In the present study, the rate of major complications in surgically more complex cohort B was 16.8% and 30-day mortality 1.9%. Rafii et al. report an even lower rate of major complications (grade 3–5), 11% (n = 21) [15]. It should be noted that the classification of complications may vary slightly between studies. In the present study the Clavien-Dindo grade IIIA was considered as a minor complication as it rarely has any effect on postoperative recovery.

In this study, more extensive surgeries led to higher postoperative complication rates. Complications interfered with the following treatment as major complications delayed the start of the chemotherapy. As in the study by Raspagliesi et al. [10], we found no statistically significant association between ultra-radical procedures and major (IIIB–V) postoperative morbidity. This is in contrast with some previously published studies, in which major morbidity did increase as surgical complexity increased [15,16].

In a retrospective review by Phillips et al. especially multiple bowel resections are emphasized as risk factors for postoperative morbidity [27]. Similarly, large bowel resection and bowel anastomosis were associated with increased risk of complications in our study as well. Total peritonectomy, performed only in ultra-radical surgeries, was also a risk factor for postoperative morbidity. In addition, laparoscopic port scar resection was associated with increased risk of complications. That is probably due to multiple other procedures that were performed simultaneously. Hysterectomy, salpingo-oophorectomy, omentectomy, appendicectomy, small bowel resection, pelvic lymphadenectomy, para-aortic lymphadenectomy, cardiophrenic lymphadenectomy, liver resection, partial gastric resection, cholecystectomy or local peritonectomy were not associated with postoperative complications in this study. Hence, not all procedures performed in these ultra-radical surgeries increase postoperative morbidity. As Phillips et al. mention, it is probably the growing number of procedures that increase the risk of major complications more than one specific high-risk procedure [27]. In addition, operative time and blood loss seem to increase the risk of complications, even though both are related to surgical complexity. Smoking is a generally known factor that affects postoperative recovery but in the present study patient's smoking status could not be reliably recovered from the patient record system and thus was not assessed.

We examined differences between primary surgery followed by chemotherapy and neoadjuvant chemotherapy followed by interval debulking surgery. The median interval from surgery to chemotherapy (35.0 and 36.0 days in cohort A and B, respectively) was longer in our study than is generally recommended (within 4 weeks after surgery). This is due to former institutional protocol, and it has been given more attention since then. Traditionally, primary debulking surgery has had a major role in the treatment protocol of ovarian cancer. However, it has been reported that regarding treatment efficacy, neo-adjuvant chemotherapy is not inferior to primary surgery [28,29]. Fewer postoperative complications have been seen as one of the benefits of interval debulking surgery [30]. Interestingly, in our study cohort, primary and interval surgeries did not differ in postoperative complication rates. This can be a result of our strict assessment of carcinomatosis in the interval debulking surgeries. According to our protocol any peritoneal scarring or sign of carcinomatosis that has responded to chemotherapy is considered as active disease and needs to be resected. Our approach is based on a previous study showing that visualisation of active carcinomatosis is very difficult in interval debulking surgery [31]. Therefore, the extent of our interval surgeries is often similar to the extent of our primary debulking surgeries. Our results suggest that perhaps the benefits of primary and interval surgeries do not differ as much as it has been considered before. More prospective studies are needed in the future to assess this issue.

Limitations of this study are the relatively small population size and the retrospective single-center study design, which may cause selection bias. The strengths of this study are the thorough examination of all postoperative complications and setting in a tertiary care hospital.

The present study demonstrates that more complex surgeries tend to increase postoperative morbidity. However, a clear benefit of more extensive surgeries are better surgical results.

CRediT authorship contribution statement

Kati Kuusela: Investigation, Formal analysis, Writing – original draft, Writing – review & editing, Visualization. **Niina Norppa:** Investigation, Writing – original draft, Writing – review & editing. **Annika Auranen:** Methodology, Writing – review & editing, Funding acquisition, Supervision. **Sami Saarelainen:** Conceptualization, Methodology, Writing – review & editing, Supervision, Project administration.

Declaration of competing interest

None

Acknowledgements

This study was supported by State Research Funding of Tampere University Hospital (9X002).

References

[1] Globocan [Internet], Available from, https://gco.iarc.fr/today/online-analysis-table?v=2020&mode=cancer&mode_population=continents&population=900&populations=900&key=asr&sex=2&cancer=39&type=0&statistic=5&prevalence=0&population_group=0. [Accessed 10 February 2022]. &ages_group%5B%5D=0&ages_group%5B%5D=17&group_cancer=1&include_nmsc=1&include_nmsc_other=1#collapse-group-1-4-0.

[2] Chobanian N, Dietrich 3rd CS. Ovarian cancer. Surg Clin 2008;88(2):285–99. https://doi.org/10.1016/j.suc.2007.12.002. vi.

[3] Ecis- European Cancer Information System [Internet], [cited 2021 Dec 16]. Available from: https://ecis.jrc.ec.europa.eu/explorer.php?$0-2$1-All$2-All$4-2$3-32$6-0,14$5-2000,2007$7-1$CRelativeSurvivalCountry$X0_15-RSC. [Accessed 16 December 2021].

[4] du Bois A, Reuss A, Pujade-Lauraine E, Harter P, Ray-Coquard I, Pfisterer J. Role of surgical outcome as prognostic factor in advanced epithelial ovarian cancer: a combined exploratory analysis of 3 prospectively randomized phase 3 multicenter trials: by the Arbeitsgemeinschaft Gynaekologische Onkologie Studiengruppe Ovarialkarzinom (AGO-OVAR) and the Groupe d'Investigateurs Nationaux Pour les Etudes des Cancers de l'Ovaire (GINECO). Cancer 2009;115(6):1234–44. https://doi.org/10.1002/cncr.24149.

[5] Winter 3rd WE, Maxwell GL, Tian C, Carlson JW, Ozols RF, Rose PG, et al. Prognostic factors for stage III epithelial ovarian cancer: a Gynecologic Oncology Group Study. J Clin Oncol 2007;25(24):3621–7. https://doi.org/10.1200/jco.2006.10.2517.

[6] Eisenkop SM, Friedman RL, Wang H-J. Complete cytoreductive surgery is feasible and maximizes survival in patients with advanced epithelial ovarian cancer: a prospective study. Gynecol Oncol 1998 May 1;69(2):103–8. https://doi.org/10.1006/gyno.1998.4955.

[7] Aletti GD, Dowdy SC, Gostout BS, Jones MB, Stanhope CR, Wilson TO, et al. Aggressive surgical effort and improved survival in advanced-stage ovarian cancer. Obstet Gynecol 2006;107(1):77–85. https://doi.org/10.1097/01.AOG.0000192407.04428.bb.

[8] Harter P, Muallem ZM, Buhrmann C, Lorenz D, Kaub C, Hils R, et al. Impact of a structured quality management program on surgical outcome in primary advanced ovarian cancer. Gynecol Oncol 2011;121(3):615–9. https://doi.org/10.1016/j.ygyno.2011.02.014.

[9] Lim MC, Yoo HJ, Song YJ, Seo SS, Kang S, Kim SH, et al. Survival outcomes after extensive cytoreductive surgery and selective neoadjuvant chemotherapy according to institutional criteria in bulky stage IIIC and IV epithelial ovarian cancer. J Gynecol Oncol 2017;28(4):e48. https://doi.org/10.3802/jgo.2017.28.e48.

[10] Raspagliesi F, Bogani G, Ditto A, Martinelli F, Chiappa V, Borghi C, et al. Implementation of extensive cytoreduction resulted in improved survival outcomes for patients with newly diagnosed advanced-stage ovarian, tubal, and peritoneal cancers. Ann Surg Oncol 2017;24(11):3396–405. https://doi.org/10.1245/s10434-017-6030-0.

[11] Dahm-Kähler P, Palmqvist C, Staf C, Holmberg E, Johannesson L. Centralized primary care of advanced ovarian cancer improves complete cytoreduction and survival - a population-based cohort study. Gynecol Oncol 2016;142(2):211–6. https://doi.org/10.1016/j.ygyno.2016.05.025.

[12] Chi DS, Eisenhauer EL, Zivanovic O, Sonoda Y, Abu-Rustum NR, Levine DA, 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(1):26–31. https://doi.org/10.1016/j.ygyno.2009.03.018.

[13] Eisenhauer EL, Abu-Rustum NR, Sonoda Y, Levine DA, Poynor EA, Aghajanian C, et al. The addition of extensive upper abdominal surgery to achieve optimal cytoreduction improves survival in patients with stages IIIC-IV epithelial ovarian cancer. Gynecol Oncol 2006;103(3):1083–90. https://doi.org/10.1016/j.ygyno.2006.06.028.

[14] Falconer H, Joneborg U, Krawiec K, Palsdottir K, Bottai M, Salehi S. Ultra-radical upfront surgery does not improve survival in women with advanced epithelial ovarian cancer; a natural experiment in a complete population. Gynecol Oncol 2020;159(1):58–65. https://doi.org/10.1016/j.ygyno.2020.07.009.

[15] Rafii A, Stoeckle E, Jean-Laurent M, Ferron G, Morice P, Houvenaeghel G, et al. Multi-center evaluation of post-operative morbidity and mortality after optimal cytoreductive surgery for advanced ovarian cancer. PLoS One 2012;7(7):e39415. https://doi.org/10.1371/journal.pone.0039415.

[16] Aletti GD, Eisenhauer EL, Santillan A, Axtell A, Aletti G, Holschneider C, et al. Identification of patient groups at highest risk from traditional approach to ovarian cancer treatment. Gynecol Oncol 2011;120(1):23–8. https://doi.org/10.1016/j.ygyno.2010.09.010.

[17] Prat J. FIGO Committee on Gynecologic Oncology. Staging classification for cancer of the ovary, fallopian tube, and peritoneum. Int J Gynaecol Obstet 2014;124(1):1–5. https://doi.org/10.1016/j.ijgo.2013.10.001.

[18] Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 2004;240(2):205–13. https://doi.org/10.1097/01.sla.0000133083.54934.ae.

[19] Aletti GD, Dowdy SC, Podratz KC, Cliby WA. Surgical treatment of diaphragm disease correlates with improved survival in optimally debulked advanced stage ovarian cancer. Gynecol Oncol 2006;100(2):283–7. https://doi.org/10.1016/j.ygyno.2005.08.027.

[20] Chi DS, Eisenhauer EL, Lang J, Huh J, Haddad L, Abu-Rustum NR, et al. What is the optimal goal of primary cytoreductive surgery for bulky stage IIIC epithelial ovarian carcinoma (EOC)? Gynecol Oncol 2006;103(2):559–64. https://doi.org/10.1016/j.ygyno.2006.03.051.

[21] Polterauer S, Vergote I, Concin N, Braicu I, Chekerov R, Mahner S, et al. Prognostic value of residual tumor size in patients with epithelial ovarian cancer FIGO stages IIA-IV: analysis of the OVCAD data. Int J Gynecol Cancer 2012;22(3):380–5. https://doi.org/10.1097/IGC.0b013e31823de6ae.

[22] Chang S-J, Hodeib M, Chang J, Bristow RE. Survival impact of complete cytoreduction to no gross residual disease for advanced-stage ovarian cancer: a meta-analysis. Gynecol Oncol 2013;130(3):493–8. https://doi.org/10.1016/j.ygyno.2013.05.040.

[23] Turnbull HL, Akrivos N, Wemyss-Holden S, Maiya B, Duncan TJ, Nieto JJ, et al. The impact of ultra-radical surgery in the management of patients with stage IIIC and IV epithelial ovarian, fallopian tube, and peritoneal cancer. Arch Gynecol Obstet 2017;295(3):681–7. https://doi.org/10.1007/s00404-016-4265-9.

[24] Winter 3rd WE, Maxwell GL, Tian C, Sundborg MJ, Rose GS, Rose PG, et al. Tumor residual after surgical cytoreduction in prediction of clinical outcome in stage IV epithelial ovarian cancer: a Gynecologic Oncology Group Study. J Clin Oncol 2008;26(1):83–9. https://doi.org/10.1200/JCO.2007.13.1953.

[25] Harter P, Sehouli J, Lorusso D, Reuss A, Vergote I, Marth C, et al. A randomized trial of lymphadenectomy in patients with advanced ovarian neoplasms. N Engl J Med 2019;380(9):822–32. https://doi.org/10.1056/NEJMoa1808424.

[26] Chi DS, Zivanovic O, Levinson KL, Kolev V, Huh J, Dottino J, et al. The incidence of major complications after the performance of extensive upper abdominal surgical procedures during primary cytoreduction of advanced ovarian, tubal, and peritoneal carcinomas. Gynecol Oncol 2010;119(1):38–42. https://doi.org/10.1016/j.ygyno.2010.05.031.

[27] Phillips A, Sundar S, Singh K, Pounds R, Nevin J, Kehoe S, et al. The NICE classification for “Ultra-radical (extensive) surgery for advanced ovarian cancer” guidance does not meaningfully predict postoperative complications: a cohort study. BJOG 2019;126(1):96–104. https://doi.org/10.1111/1471-0528.15423.

[28] Vergote I, Tropé CG, Amant F, Kristensen GB, Ehlen T, Johnson N, et al. Neo-adjuvant chemotherapy or primary surgery in stage IIIC or IV ovarian cancer. N Engl J Med 2010;363(10):943–53. https://doi.org/10.1056/NEJMoa0908806.

[29] Kehoe S, Hook J, Nankivell M, Jayson GC, Kitchener H, Lopes T, 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(9990):249–57. https://doi.org/10.1016/S0140-6736(14)62223-6.

[30] Fagotti A, Ferrandina MG, Vizzielli G, Pasciuto T, Fanfani F, Gallotta V, et al. Randomized trial of primary debulking surgery versus neoadjuvant chemotherapy for advanced epithelial ovarian cancer (SCORPION-NCT01461850). Int J Gynecol Cancer 2020;30(11):1657–64. https://doi.org/10.1136/ijgc-2020-001640.

[31] Hynninen J, Lavonius M, Oksa S, Grénman S, Carpén O, Auranen A, et al. Is perioperative visual estimation of intra-abdominal tumor spread reliable in ovarian cancer surgery after neoadjuvant chemotherapy? Gynecol Oncol 2013;128(2):229–32. https://doi.org/10.1016/j.ygyno.2012.11.007.