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Improved survival after implementation of ultra-radical surgery in advanced epithelial ovarian cancer: Results from a tertiary referral center

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HIGHLIGHTS

- Implementation of ultraradical surgery resulted in significantly longer overall survival.
- The median overall survival was increased by 21 months.
- The survival benefit was mostly seen in FIGO stage III patients.
- Overall survival was influenced by residual tumor and Clavien-Dindo complication grade.

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ABSTRACT

Objective. To compare survival rates of surgically treated advanced epithelial ovarian cancer patients before and after a programmatic change in surgical approach from standard surgery towards ultra-radical surgery.

Methods. 247 patients with FIGO stage IIIB-IV ovarian, tubal, and primary peritoneal carcinoma were operated during 2013–2019 either by primary or interval cytoreduction in Tampere University Hospital, Finland. Group 1 ($n = 122$) patients were operated during 2013 and February 2016. Group 2 patients ($n = 125$) were operated between March 2016 and March 2019, when a systematic change in surgical approach towards more extensive surgery was implemented.

Results. The complete resection (R0) rate increased significantly from 17.2% (21/122) to 52.0% (65/125) within the study period ($p < 0.001$). The median progression-free survival (PFS) was 15.6 months vs 19.3 months ($p = 0.037$), and the median overall survival (OS) was 33.5 months vs 54.5 months in Groups 1 and 2, respectively ($p = 0.028$). Median OS for stage III patients in Group 1 was 36.1 months (95% CI 27.4–44.8) but could not be reached in Group 2 ($p = 0.009$). In Stage IV patients, OS was 32.0 months (16.4–47.7) and 39.3 months (24.8–53.8) in Group 1 and 2, respectively ($p = 0.691$). Multivariable Cox regression analysis revealed that OS was independently affected by the amount of residual tumor and complication grade.

Conclusions. The change of surgical approach towards maximal surgical effort improved both progression-free and overall survival. The survival benefit was unquestionable for stage III patients but did not reach statistical significance in stage IV patients.

1. Introduction

Epithelial ovarian cancer is the 8th most common cancer among women with 310,000 new cases worldwide annually and presents the worst survival of gynecologic malignancies [1]. Most patients are diagnosed at advanced stage with a poor prognosis due to widespread disease. Primary cytoreductive surgery aiming at resection of all visible tumor remains the cornerstone of the treatment in advanced ovarian cancer. Numerous studies have shown improved survival rates with complete cytoreduction, which is the most important prognostic factor for survival and should always be the objective of surgery [2–8].

To achieve this goal, more extensive procedures, compared to standard surgery, have been introduced into ovarian cancer surgery. These ultraradical procedures have enabled operating patients with

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widespread disease, previously ending up with suboptimal surgical outcome, to macroscopically complete resection. The effect of programmatic change in surgical approach to more extensive surgery has improved cytoreduction rates and survival according to previous studies, but these analyses have mainly focused on stage III with low proportion of stage IV patients, and opposite results have also been presented [4,9–13].

The objective of this retrospective study was to evaluate the impact of change of surgical approach on progression-free survival (PFS) and overall survival (OS) in women with advanced epithelial ovarian cancer operated in a tertiary referral center, Tampere University Hospital, Finland.

2. Material and methods

This retrospective study was performed by analyzing the complete patient records of 247 consecutive patients operated in Tampere University Hospital (TAUH) between January 2013 and March 2019. TAUH is a tertiary referral center for a population of 1 million people. Gynecological cancer patients are treated by specialist gynecological oncology team, consisting of certified Gynecologic Oncologists. Inclusion criteria for this analysis were as follows: FIGO (Federation of Gynecology and Obstetrics) 2014 stage IIIB–IVB ovarian, Fallopian tube or primary peritoneal cancer, epithelial histology and having either primary or interval debulking surgery. Patients with explorative laparotomy aimed for debulking but were declared unresectable at the time of surgery were included in the analysis. Patients with non-epithelial histology or concomitant other malignancy were excluded.

2.1. Data collection

This retrospective, registry-based study approach was approved by the administration of the Tampere University Hospital. Individual patient characteristics, clinical variables, site of metastases at the diagnosis, surgical findings and procedures, histopathological reports and postoperative data including given chemotherapy and other medication, complications, follow-up data, recurrences and death were collected from the patient records. The final follow-up data was collected in November 2020. No approval of the Ethics Committee was necessary for this retrospective analysis.

2.2. Study groups

Patients were categorized into two groups according to the operation date. Group 1 consisted of 122 patients operated between January 2013 and February 2016. All patients underwent standard surgery with the intent to reach maximal cytoreduction. In this group, patients with tumor involving upper abdomen including diaphragmatic peritoneum and parenchymal metastases in liver or spleen were most likely considered as unresectable leaving these patients suboptimally debulked. There was no standardized protocol on patient selection during these years.

Group 2 consisted of 125 patients operated between March 2016 and March 2019. The change in surgical approach towards maximal surgical effort was initiated in March 2016, hence this was decided to be the division point between groups. This change was preceded by internal educatory sessions of the Gynecologic Oncology team and a visit for surgical training in a European accredited ovarian cancer center in 2015. Gastrointestinal and thoracic surgeons, affiliated with the team, were also educated about the change in surgical approach. After March 1st, 2016, ultra-radical procedures as total peritonectomy, diaphragm resection, splenectomy, distal pancreatectomy, liver resection, cholecystectomy and multiple bowel resections were performed during surgery when considered applicable. Gastrointestinal surgeons performed all the bowel resections when it seemed necessary after the surgical plan was made together with the gynecologic oncologist. All the other procedures were performed by gynecologic oncologist. Thoracic surgeons were involved in the first five operations to consult in diaphragmatic and cardiophrenic lymph node resections, after which the gynecologic oncologist performed these independently in following operations.

Patient selection for extensive surgery was structured with the criteria of ASA class ≤2, age under 75 years and preoperative albumin level over 30 g/l. If albumin level was suboptimal at the time of diagnosis, a preoperative nutritional support was initiated to reach the required level of 30 g/l. If the patient did not fill these criteria, standard surgery or neoadjuvant chemotherapy followed by interval debulking surgery was chosen.

2.3. Treatment

In both periods, primary debulking surgery (PDS) was the preferred surgical approach. If optimal cytoreduction was deemed impossible to achieve according to the preoperative work-up, the treatment was started with neoadjuvant chemotherapy (NACT) and interval debulking surgery (IDS) was reconsidered if tumor load showed response to treatment after three cycles of chemotherapy. NACT-IDS was also selected if patient's performance status or pre-operative albumin level was low. All patients in both groups were operated only by a trained gynecologic oncologist.

The complexity of the surgery was evaluated retrospectively from the operative records by surgical complexity score (SCS) by Aletti [14]. Total SCS points 3 or under was defined as low, between 4 and 7 as intermediate and 8 or over as high surgical complexity and patients were assigned to the groups based on these points.

Surgical adverse events occurring within 30 days after surgery were graded according to Clavien-Dindo classification system [15]. Grades 1, 2 and 3A, which are relatively common after ovarian cancer surgery and infrequently have a major effect on the recovery of the patient, were considered as “minor complications” in the analyze to include only grades 3B to 5 to the “major complications” group.

Chemotherapy given after surgery or as neoadjuvant was recorded. Also, treatment with bevacizumab or PARP-inhibitors (olaparib or niraparib) was documented. BRCA mutation status was systematically analyzed after year 2016.

2.4. Outcome measures

Complete cytoreduction or R0 was defined as no visible residual disease at the end of the surgery. Cytoreduction was defined as R1 when residual tumor measured less than 10 mm in maximal dimension and R2 if the residual tumor diameter exceeded 10 mm.

All recurrences of the disease and deaths were recorded. PFS was defined as the date from PDS or the first infusion of chemotherapy in the NACT group to the date of first documented recurrence or progression of the disease. Recurrence was defined radiologically from CT scans based on RECIST 1.1. criteria or the CA12–5 criteria by the Gynecological Cancer Intergroup [16,17]. Second-line chemotherapy treatment was considered as progression, excluding changes in the first-line treatment due to adverse events. If the patient didn't have these, PFS was calculated as a time interval from surgery to the date of last follow-up or death, whichever occurred first. OS was defined as the time interval from the date of PDS or the first infusion of chemotherapy for patients undergoing IDS to the date of death or the last follow-up. Patients were followed up to November 2020.

2.5. Statistical methods

Distributions between categorial variables were compared with Chi square or Fisher's exact test. Differences between continuous variables were compared using Mann Whitney *U* test. Univariate survival analyses were performed using the Kaplan-Meier method and differences

in survivals were analyzed with the log-rank test. Multivariate survival analyses and adjusted hazard ratios for death and their 95% confidence intervals were estimated with Cox regression. The following independent variables were included in the multivariable analysis: date of treatment (Group 1 vs Group 2), FIGO stage (IIIB, IIIC, IVA, IVB), timing of surgery (primary vs interval surgery), surgical complexity score (low, medium, high), tumor residual (R0, R1, R2), age (18–49, 50–75, >75), histology (high grade serous, low grade serous, other) and complications (no vs minor vs major complications). All statistical tests were two-sided, and differences were considered significant with *p*-values <0.05. The analyses were performed with IBM SPSS Statistics version 27 (IBM Corp., Armonk, N.Y., USA).

3. Results

3.1. Patient characteristics

Patient characteristics are presented in Table 1. There were no statistical differences between groups in median age, ASA class or BMI. The most common tumor histology was high grade serous in both groups (83.6% and 84.8%). Among those with BRCA status known, BRCA mutation was found in 19% and 16.3% in Group 1 and 2. There was a minor increase in proportion of stage IV patients from 31.1% in Group 1 to 40.8% in Group 2, but the stage distribution between groups in stage III and IV was not statistically significant, $p = 0.145$ (Table 1).

In Stage IV patients, the proportion of Stage IVA with positive pleural cytology was 42.1% (16/38) in Group 1 and 19.6% (10/51) in Group 2. Distant lymph node metastasis as the most common distant metastatic site were found in 59.1% and 48.8%, liver metastasis in 31.8% and 17.1% and lung metastasis in 9.1% and 9.8% of Stage IVB patients in Group 1 and Group 2, respectively. Other metastatic sites in study groups were spleen, infiltration of bowel, umbilicus, and bone. Two or more metastatic sites were found in 18.2% and 19.5% of the patients in Group 1 and 2 (Table S1).

3.2. Surgical outcomes

The rate of primary debulking surgery increased from 58% to 69% in Group 1 and Group 2, respectively, but the difference was not statistically significant ($p = 0.08$; Table 2). The rate of complete resection (R0) increased from 17.2% (21/122) to 52.0% (65/125) within the study period ($p < 0.001$), whereas the rate of suboptimal (R2) cytoreduction decreased from 62.3% (76/122) to 15.2% (19/125). The proportional rate of extensive surgical procedures increased significantly in Group 2 (Table 3).

Median operation time (161 vs 342 min) and blood loss in surgery (300 vs 1000 ml) were significantly higher in Group 2. The median of Surgical Complexity Score was 2 and 7 in Groups 1 and 2, respectively ($p < 0.001$). When categorized in groups "low, intermediate and high SCS" groups, the rate of high SCS increased from 4.1% to 44.8% after the change in surgical approach, while the rate of low complexity surgeries decreased from 71.3% to 19.2%. There was a slightly higher number of patients who had complications related to surgery in the second group (82 vs 107), but the rate of minor vs major complications according to Clavien-Dindo classification in patients who had any complication, was similar between groups ($p = 0.298$), including one postoperative death in Group 1 and two in Group 2.

Despite the marked rise in surgical complexity, there was no difference in the number of patients able to receive chemotherapy (92.6% vs 93.6% in groups 1 and 2, respectively). The most used combination was six cycles of paclitaxel and carboplatin in both groups (Table 2). The median time from surgery to first infusion of chemotherapy was 35 and 36 days ($p = 0.010$), and the number of patients for whom the chemotherapy could not be initiated despite the original treatment plan, was nine and eight patients in Group 1 and Group 2, respectively. Patients were treated with bevacizumab more often in Group 1 (61.5% vs 47.2%, $p = 0.030$). PARP-inhibitors were more commonly used in

Table 1
Patient characteristics.

Variable	Group 1 (N = 122)	Group 2 (N = 125)	P value
Median age (range)	'67 (24–87)	68 (31–89)	0.908
ASA class N (%)			0.179
1	47 (38.5%)	40 (32.0%)	
2	56 (45.9%)	54 (43.2%)	
3	19 (15.6%)	31 (24.8%)	
FIGO stage N (%)			0.145
III	84 (68.9%)	74 (59.2%)	
IIIB	5 (4.1%)	14 (11.2%)	
IIIC	79 (64.8%)	60 (48.0%)	
IV	38 (31.1%)	51 (40.8%)	
IVA	16 (13.1%)	10 (8.0%)	
IVB	22 (18.0%)	41 (32.8%)	
Pre-operative albumin (g/l)	28 (19–45)	36 (15–47)	0.013
BRCA tested N (%)	36 (29.5%)	86 (69.0%)	<0.001
1/2 positive	7 (19%)	14 (16.3%)	
1/2 negative	29 (81%)	72 (83.7%)	
Histology N (%)			0.190
High grade serous adenocarcinoma	102 (83.6%)	106 (84.8%)	
Low grade serous adenocarcinoma	4 (3.3%)	9 (7.2%)	
Endometrioid adenocarcinoma	5 (4.0%)	2 (1.6%)	
Mucinous adenocarcinoma	4 (3.3%)	2 (1.6%)	
Carcinosarcoma	3 (2.5%)	4 (3.2%)	
Other (transitional cell, mixed cell)	1 (0.8%)	2 (1.6%)	

ASA, American Society of Anesthesiologists; BRCA, breast cancer gene; FIGO, International Federation of Gynecology and Obstetrics.

Table 2
Surgical outcomes.

Variable	*Group 1*	*Group 2*	*P value*
Cytoreduction N (%)			<0.001
R0	21 (17.2%)	65 (52.0%)	
R1	25 (20.5%)	41 (32.8%)	
R2	76 (62.3%)	19 (15.2%)	
Stage III R0	12 (14.3%)	40 (54.1%)	<0.001
R1	17 (20.2%)	23 (31.1%)	
R2	55 (65.5%)	11 (14.9%)	
Stage IV R0	9 (23.6%)	25 (49.0%)	<0.001
R1	8 (21.1%)	18 (35.3%)	
R2	21 (55.3%)	8 (15.7%)	
PDS	71 (58%)	86 (69%)	0.083
IDS	51 (42%)	39 (31%)	
Surgical complexity score			<0.001
Low ≤3	87 (71.3%)	24 (19.2%)	
Intermediate 4–7	30 (24.6%)	45 (36.0%)	
High ≥8	5 (4.1%)	56 (44.8%)	
Blood loss (ml)	300 (10−3000)	1000 (20–4350)	<0.001
Operation time (min)	161 (59–393)	342 (83–734)	<0.001
Clavien-Dindo grade			
No complication	40 (32.8%)	18 (14.4%)	0.002
I-IIIA	73 (59.8%)	89 (71.2%)	
IIIB-V	9 (7.4%)	18 (14.4%)	
Days from surgery to first cycle of chemotherapy	35 (7–57)	36 (15–71)	0.010
Patients receiving chemotherapy after surgery	113 (92.6%)	117 (93.6%)	0.762
Taxan-carboplatin	93 (82.3%)	93 (79.5%)	
Other platinum-based	17 (15.0%)	24 (20.5%)	
Other chemotherapy	3 (2.7%)	0 (0%)	
Number of chemotherapy cycles	6 (1–17)	6 (1−10)	<0.001
Second-line chemotherapy	83 (68.0%)	62 (49.6%)	0.004
Bevacizumab (first or second line)	75 (61.5%)	59 (47.2%)	0.030
PARP-inhibitor	7 (5.7%)	18 (14.9%)	0.021

IDS, interval debulking surgery; PARP, Poly (ADP-ribose) polymerase; PDS, primary debulking surgery; R0, complete cytoreduction; R1, optimal cytoreduction; R2, suboptimal cytoreduction.

Table 3
Cytoreductive procedures performed.

Procedure	Group 1	Group 2	P value
Hysterectomy	74 (60.7%)	87 (69.6%)	0.145
Salpingo-oophorectomy	114 (93.4%)	114 (91.2%)	0.635
Resection of omentum	104 (85.2%)	116 (92.8%)	0.067
Pelvic lymphadenectomy	18 (14.8%)	43 (34.3%)	<0.001
Para-aortic lymphadenectomy	17 (13.9%)	47 (37.6%)	<0.001
Peritonectomy	5 (4.1%)	86 (68.8%)	<0.001
Large bowel resection	16 (13.1%)	52 (41.6%)	<0.001
Isolated sigmoid/rectosigmoid resection	16 (13.1%)	11 (8.8%)	0.277
En-bloc resection	0 (0%)	41 (32.8%)	<0.001
Splenectomy	1 (0.8%)	33 (26.4%)	<0.001
Small bowel resection	1 (0.8%)	9 (7.2%)	0.019
Superficial liver resection	0 (0%)	13 (10.4%)	<0.001
Non-anatomic liver resection	0 (0%)	6 (4.8%)	0.029
Diaphragm resection	0 (0%)	15 (12.0%)	<0.001
Large bowel stoma	4 (3.3%)	44 (35.2%)	<0.001
Small bowel stoma	10 (8.2%)	14 (11.2%)	0.521
Cholecystectomy	0 (0%)	10 (8.0%)	0.002
Cardiophrenic lymph node resection	0 (0%)	12 (9.6%)	<0.001

Group 2 (5.7% vs 14.9%, $p = 0.021$). The surgical outcomes and the subsequent therapies are summarized in Table 2.

3.3. Survival outcomes

The median follow-up time was 34 months for the Group 1 and 27 months for the Group 2. PFS and OS rates were significantly improved in the Group 2. The median PFS in Group 1 was 15.6 months (13.6–17.5) and in Group 2 19.3 months (17.8–20.9), $p = 0.037$. OS rates for Group 1 vs Group 2 were 33.5 months (95% CI 26.2–40.8) and 54.5 months (95% CI 35.2–73.8), respectively ($p = 0.028$) (Fig. 1).

Cox multivariable analysis showed that OS was independently influenced by the amount of residual tumor and Clavien-Dindo complication grade: optimal cytoreduction (R1) HR for death 3.6 (95% CI 2.07–6.10), and suboptimal cytoreduction (R2) HR for death 3.9 (95% CI 2.17–7.08) compared to no residual disease, and Clavien-Dindo complication grade IIIB to IV HR for death 2.5 (95% CI 1.53–3.93) compared to Clavien-Dindo complication grade < IIIB. In the multivariate analysis, there was no significant difference between the stages (Table S2).

Survival comparisons between stages are shown in Fig. 2. PFS for stage III patients was 17.5 months (95% CI 13.1–21.9) in Group 1 and 19.8 months (95% CI 18.0–21.6) in Group 2, but the difference was not statistically significant ($p = 0.085$). Median OS for stage III patients in Group 1 was 36.1 months (95% CI 27.4–44.8) but could not be reached in Group 2 ($p = 0.009$). In Stage IV patients, the change in surgical approach did not associate with improved survival: PFS was 14.8 months (12.5–17.1) and 16.8 months (14.3–19.2) in Group 1 and 2, respectively ($p = 0.144$). OS was 32.0 months (16.4–47.7) and 39.3 months (24.8–53.8) in Group 1 and 2, respectively ($p = 0.691$). There were no statistically significant differences in OS or PFS between PDS and IDS/NACT patients in either study group. Survival times and curves are found in supplementary material (Fig. S1).

For group 2 patients, we analyzed the survival outcomes in stage III and IV separately for completely debulked patients and patients with residual tumor >0. In Group 2, 54.1% of Stage III and 49.0% of Stage IV patients were completely debulked. In these patients, the number of major complications (12.2% vs 17.6%, $p = 0.39$), ASA grade ($p = 0.306$), time from surgery to first infusion of chemotherapy (36.5 vs 35.0, $p = 0.841$) and the proportion of PDS vs IDS ($p = 0.943$) were similar. Median OS for completely cytoreduced patients in Stage III was not reached, whereas it was 54.5 months in stage IV (25.6–83.5), $p = 0.018$ (Fig. 3). There was no OS benefit seen in Stage IV patients with residual tumor >0 cm after the surgical paradigm change: OS was 26.7 months (95% CI 22.6–30.7) and 30.1 months (21.8–38.4) in Group 1 and Group 2, respectively ($p = 0.85$).

4. Discussion

This single center retrospective study shows that the change in ovarian cancer surgery towards maximal surgical effort has led to both significantly improved complete cytoreduction rates, as well as improved progression-free and overall survival. When the time periods 2013–2016 (Group 1) and 2016–2019 (Group 2) were compared, an increase of 21 months in median OS was observed, but the survival benefit seemed to be limited to FIGO Stage III patients.

There were no significant differences in the patient characteristics between the study groups. Despite the more aggressive surgery in Group 2, there was no increase in major morbidity rate and therefore, the number of patients receiving chemotherapy was similar and the time interval from surgery to initiation of chemotherapy was not delayed. During the study years, oncological treatments have practically remained unchanged. Treatment with bevacizumab was more common in the first group thus it is not an explanation for the better survival in the latter group. In fact, the use of bevacizumab in group 1 reflects the local practice of using bevacizumab only in suboptimally debulked patients according to results of ICON7 trial. [18] As shown in recent trials, PARP-inhibitors have improved survival rates to a great extent. [19–21] The effect of PARP-inhibitors in our study population may not be seen

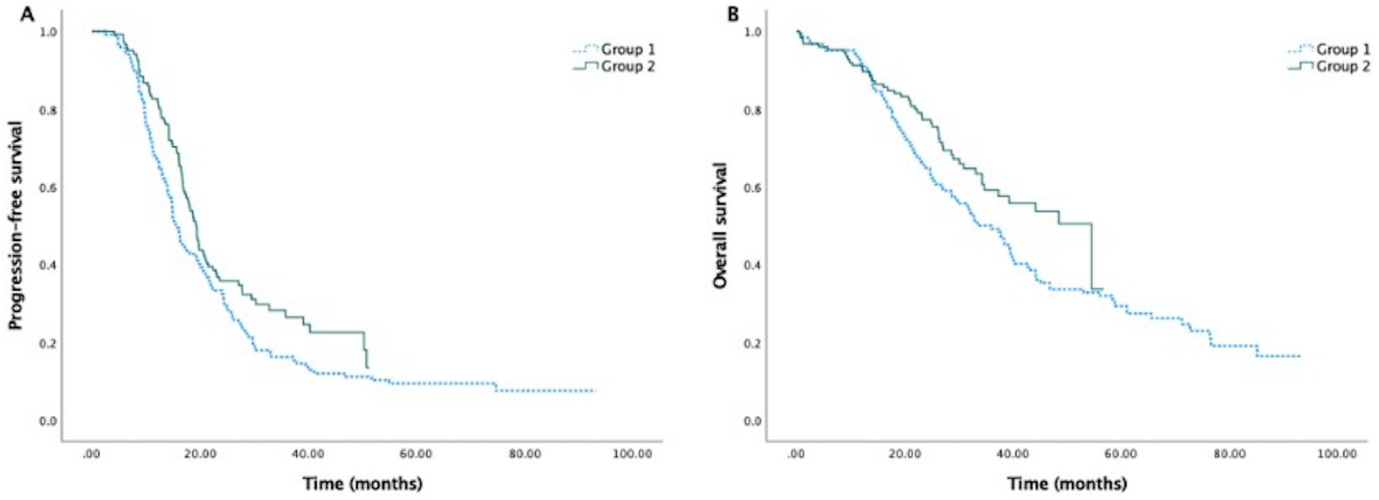

Fig. 1. A. Progression-free survival in Group 1 and Group 2, all stages combined ($p = 0.037$). B. Overall survival in Group 1 and Group 2, all stages combined ($p = 0.028$).

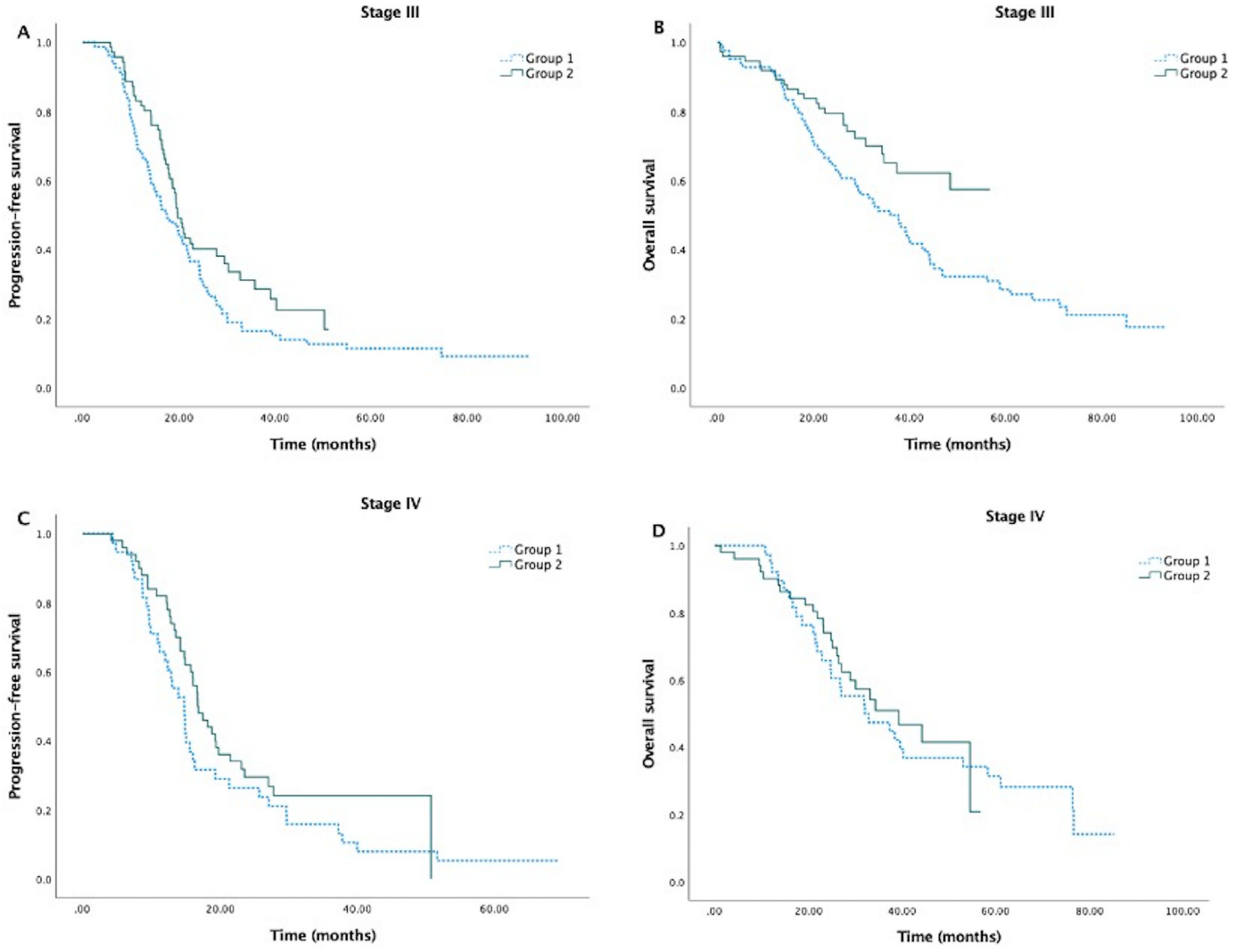

Fig. 2. A. Progression-free survival in Stage III patients by groups ($p = 0.085$). B. Overall survival in Stage III patients by groups ($p = 0.009$). C. Progression-free survival in Stage IV by groups ($p = 0.144$). D. Overall survival in Stage IV patients by groups ($p = 0.691$).

yet because the introduction of PARP-inhibitors took place at the end of the study period and the number of PARPi-treated patients was low due to low prevalence of BRCA1/2 mutations in Finland, and the use of PARPis was mainly limited to recurrent setting. Considering these aspects, we presume that the improved survival associated with the Group 2 patients is mainly resulting from the change in the surgical approach.

The positive survival effect of programmatic change in surgery of advanced ovarian cancer has been demonstrated in many studies previously. Chi et al. showed improvement in five-year PFS (31% vs 14%) and five-year OS (47% vs 35%) after the change in surgical paradigm in their institution, and OS was significantly longer (54 vs 43 months, $p = 0.03$) compared to previously operated patients. [9] However, their proportion of Stage IV patients were only 12% and 17% in study groups.

When assessing our survival results by subgroups, OS benefit was detected only in Stage III patients. Previous studies showing improved survival after introducing maximal surgical effort in ovarian cancer surgery have mainly focused on stage III patients with low proportion of stage IV and survival results have often been presented combining stage III ja IV together. [4,9] Therefore, the benefit of programmatic surgical change regarding stage IV patients has remained somewhat unclear. Recently, a Swedish study by Falconer et al. showed no improved survival in women with advanced epithelial ovarian cancer after implementation of ultra-radical surgery in their institution, with study cohort including 34% stage IV patients. [22] However, their survival results or rates of complete cytoreduction were not specified according to FIGO stage.

More advanced disease is shown to be associated with poorer survival even when complete resection has been reached also in preceding studies. [23,24] Gynecologic Oncology Group 182 study by Horowitz et al. showed that even when the complete cytoreduction is achieved, patients with advanced epithelial ovarian cancer with high disease burden before the surgery (tumor affecting upper abdominal organs) had worse PFS (18.3 months vs 32.3 months, $p < 0.001$) and OS (50.1 vs 82.8 months) compared to patients with low or moderate disease burden. [23] However, their study only included patients having PDS and the proportion of stage IV was low (11%).

Ataseven et al. studied the impact of primary debulking surgery and residual disease on survival in Stage IV patients. [25] R0 was achieved in 54.9% of patients with median OS being 50 months. Their conclusion was that FIGO Stage IV patients do benefit from extensive debulking surgery if the tumor residual <10 mm is achieved. Patients with suboptimal cytoreduction would have done better without any surgery, with OS 16 months vs 19 months in patients with no surgery. Also, Sørensen et al. found that achieving residual disease <1 cm increases overall survival in stage IV patients but this study did not assess the effect of

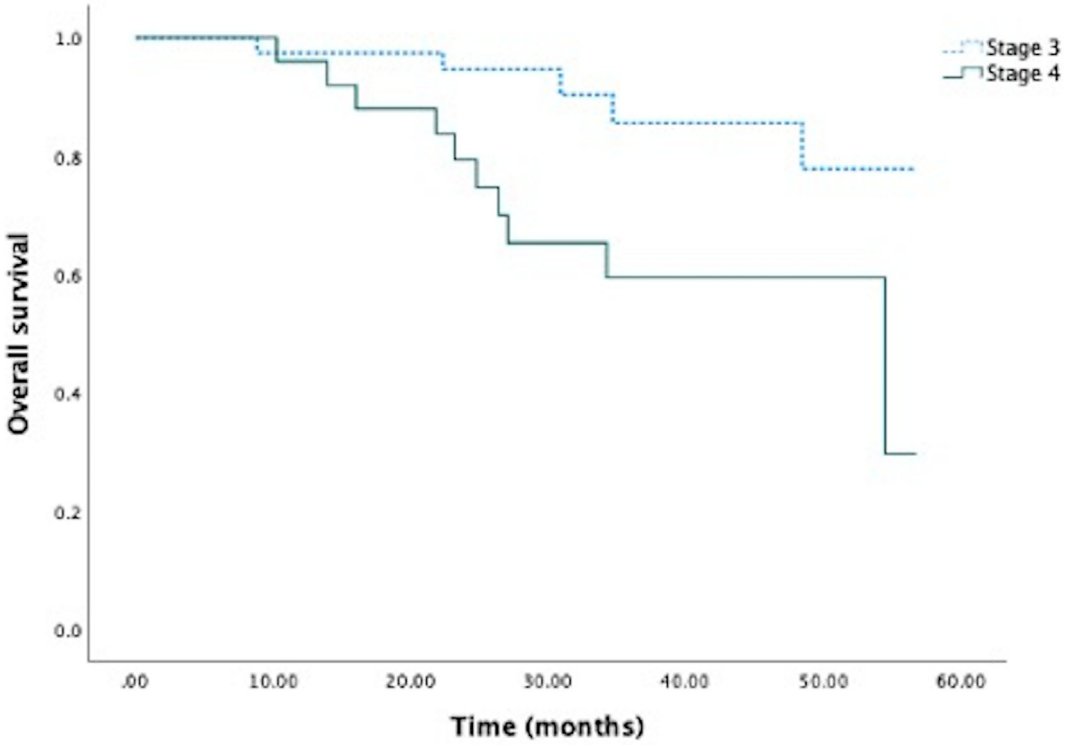

Fig. 3. Overall survival in Group 2 patients with complete cytoreduction in Stage III and Stage IV.

aggressive surgery. [26] Winter et al. stated that selected stage IV patients might benefit from ultra-radical procedures if complete cytoreduction is achieved. In our study, the rate of optimal debulking almost doubled (44.7% vs 84.3%) in stage IV patients with the protocol change without a significant improvement in overall survival. However, our findings from Stage IV patients do not directly imply that these patients do not benefit from extensive surgery but emphasizes the role of careful patient selection for extensively radical surgery. It is not known if the distant metastases, tumor biology or both impact the poorer survival of stage IV patients compared to stage III patients when complete cytoreduction is achieved. Worse prognosis of stage IV patients has been presented to result from extra-abdominal metastases and poorer overall health due to advanced disease. [26]

The prognosis of stage IV patients has been proposed to differ according to the site of metastasis, but our study population was too small to assess this aspect. [27–29] Ataseven et al. stated that as a heterogenous group, stage IV patients with different metastatic patterns should be separated into subgroups of good and poor prognosis, for example resectable extra-abdominal lymph node metastases vs multiple lung metastases. [30] Their suggestion was that stage IV may be associated with a distinct biology only in few cases. Contrarily, extensive spreading of tumor cells and poorer prognosis of stage IV patients has been contemplated to result from more aggressive tumor biology as the aspect that cannot overcome by surgery. Falconer et al. speculated possible explanations for that to be the inflammatory response after surgery that diminishes the positive effects of complete resection, and that surgical stress could affect the sensitivity of remaining cancer cells to following chemotherapy resulting in poorer prognosis [22,31,32] Chang et al. concluded on their review that "surgical expertise at least partly counteracts the effects of underlying tumor biology" and surgery resulting in complete cytoreduction leads to best survival. [33] Our results imply that the survival benefit of extensive debulking surgery in stage IV patients may be limited, thus emphasizing the importance of patient selection to undergo procedures with increased morbidity and for whom complete cytoreduction is achievable. Therefore, more studies, especially prospective ones, are needed to assess this topic. Also, the small sample size limits the statistical power to analyze stage IV more specifically.

The weaknesses of the present study are the retrospective setting and relatively short follow-up time, which was right censored especially in Group 2. Due to small sample size and the rapid change in surgical approach, we decided not to define a wash-out period between the groups, so there may be some patients operated at the beginning of the second period who were not treated with the novel extensive surgical protocol.

The strength of our study is that it presents high-quality data from a tertiary referral center with certified Gynecologic Oncologists, who are responsible for the complete treatment and follow-up of these patients. This is the study with one of the largest proportions of stage IV patients analyzed when evaluating the impacts of extensive ovarian cancer surgery and it represents the real-world evidence with unselected patient material. Also, our study included both PDS and IDS, which is a different design compared to previous studies investigating the impact of surgical shift, as they have been including only PDS. [4,9–11]. However, we feel that the design of the current study including both PDS and IDS patients reflects better the real-world evidence setting and is most probably less prone to selection bias. PDS has shown to be preferable choice for surgery over NACT-IDS, which has more often been chosen for patients with poorer performance status and comorbidities and this may affect the worse prognosis of these patients. [34–36] Therefore, our results are not directly comparable to these previously presented, but on the other hand, the PDS/IDS rate did not change during the study period, so the study groups were similar in this regard. In addition, so far there have been only few studies from Scandinavia on this subject and no previous studies from Finland.

In summary, this retrospective analysis shows that implementing maximal surgical effort to treatment of advanced epithelial ovarian cancer results in an increased rate of complete cytoreduction and improves both progression-free and overall survival, when considering stage III and IV as a same entity. [9,37] In the sub-analysis of the present data,

the benefit of programmatic change from standard surgery towards maximal surgical effort was limited to FIGO Stage III patients. Further studies are needed to evaluate the survival effects of maximal surgical effort among stage IV women. We suggest that ovarian cancer patients with FIGO Stage III and Stage IV should be considered as separate entities in future research.

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Declaration of Competing Interest

The authors declare no conflict of interest.

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