ANTICANCER RESEARCH *40*: 5869-5875 (2020)
doi:10.21873/anticanres.14606

Radical Surgical Procedures in Advanced Ovarian Cancer and Differences Between Primary and Interval Debulking Surgery

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Abstract. *Background/Aim: We aimed to identify differences in cytoreduction rates and procedures performed in patients with advanced ovarian cancer undergoing primary (PDS) or interval debulking surgery (IDS). Patients and Methods: Data were collected prospectively on 110 consecutive patients from June 2016 to Mar 2020. Results: Forty-nine patients (44.5%) underwent diaphragmatic peritonectomy (34 in PDS and 15 in IDS, p=0.005), while 38 (34.5%) underwent large bowel resection (29 in PDS and 9 in IDS, p<0.001). Complete cytoreduction was achieved in 39 patients in PDS and 29 in IDS (65% vs. 58%, p=0.22). Longer operations with more blood loss and extended hospital stay were performed in the PDS group. Ten patients (9.1%) experienced severe complications and in eight patients (7.2%) chemotherapy was delayed. Conclusion: More bowel resections and diaphragmatic stripping were performed in the PDS group. End surgical results were similar between groups, with a trend for more complete cytoreduction in PDS.*

Ovarian cancer is the second most common malignancy of the female genital tract with approximately 80% of new cases presenting with advanced stage (FIGO Stage III-IV) disease (1). At time of diagnosis, half of these patients will present with bulky upper abdominal disease of which only 30% is estimated to be completely resectable (2-3). The standard treatment is surgery in combination with platinum-based chemotherapy. The aim of surgery is complete cytoreduction with no macroscopic residual tumor as this is associated with significantly improved outcomes when compared to sub-optimal cytoreduction (4-5). The surgical effort required for complete resection of all macroscopic disease during primary debulking surgery (PDS) is often challenging and demands advanced surgical skills. This is also associated with significant risk of perioperative morbidity and mortality (3).

In patients where complete cytoreduction is not considered achievable or patients with limited performance status, administration of three or four cycles of neo-adjuvant chemotherapy is recommended in order to reduce the tumor burden prior to interval debulking surgery (IDS). The latter has gained popularity over the last decade after the publication of two relevant randomized studies which showed that IDS was not inferior to PDS in relation to overall survival (4, 5). Despite these recent studies, there is still controversy in relation to IDS (6, 7) and results of further randomized trials emphasizing on surgical radicality (TRUST study) are eagerly awaited, as the main criticism of the previous randomized studies was the low complete cytoreduction rate in the PDS group (8).

Despite the controversies between PDS and IDS, maximum surgical effort towards complete cytoreduction or minimal residual is undoubtedly the cornerstone for the best survival outcomes with both approaches (9). Complete cytoreduction can be achieved with radical procedures in the pelvis, mid and upper abdomen. These include liver mobilization and diaphragmatic stripping, splenectomy, small and large bowel resections, lesser omentectomy, Morrison's pouch peritonectomy, extensive abdominal and pelvic peritonectomy and excision of disease from the surface of the liver, porta hepatis, duodenum and stomach, or even liver resection and gastrectomy.

We sought to assess the type and extend of surgical procedures required to achieve complete cytoreduction in patients with FIGO Stage IIIC-IV ovarian cancer as well as to identify differences in surgical procedures performed between PDS and IDS. The morbidity and mortality generated with these procedures as well as other perioperative factors were also captured and analyzed.

Patients and Methods

All patients with FIGO Stage IIIC-IV epithelial ovarian cancer who underwent cytoreductive surgery between July 2016 and Mar 2020

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Key Words: Debulking for ovarian cancer, primary debulking, complete cytoreduction, upper abdominal surgery, morbidity, interval debulking surgery.

Table I. *Characteristics of the population.*

Variable	Total (%)	PDS (%)	NAC (%)	*p*-Value
Number	110	60	50	
Age, median (IQR)	66.5 (57-72)	65.5 (54.2-72)	67 (60-72.2)	0.444
Histology				0.156
Serous	103 (93.6%)	53 (88.3%)	50 (100%)	
Carcinosarcoma	3 (2.8%)	3 (5%)	0	
Clear cell	2 (1.8%)	2 (3.3%)	0	
Endometrioid	1 (0.9%)	1 (1.7%)	0	
Mucinous	1 (0.9%)	1 (1.7%)	0	
Grade				**0.004**
High grade	101 (91.8%)	51 (85%)	50 (100%)	
Low grade	9 (8.2%)	9 (15%)	0	
FIGO stage				**0.003**
IIIC	67 (60.9%)	44 (73.3%)	23 (46%)	
IV	43 (39.1%)	16 (26.7%)	27 (54%)	
ASA score				0.106
1-2	94 (88.7%)	54 (93.1%)	40 (83.3%)	
3	11 (10.4%)	3 (5.2%)	8 (16.7%)	
4	1 (0.9%)	1 (1.7%)	0	
CA125 pre-op, median (IQR)	164 (53-507)	350 (116-1076)	61 (26-218)	**<0.001**
Albumin pre-op, median (IQR)	42 (38-44)	42 (38-45)	42 (39-44)	0.934
BMI, median (IQR)	25.2 (22.8-28.2)	25.2 (23.2-30.9)	25.1 (22.6-28)	0.333

Statistically significant results are indicated in bold.

at Poole Hospital NHS Foundation Trust, a tertiary referral cancer center in the UK, were prospectively enrolled to our gynecological oncology database. Patients with non-epithelial or borderline tumors were excluded from the study.

Our data registry amongst others included the following: age, FIGO stage, histological type and grade, body mass index (BMI) (kg/m^2), American Society of Anesthesiologists (ASA) score, pre- and post-operative serum Ca-125, pre-op serum albumin, type of surgery (PDS or IDS), number of cycles of neo-chemotherapy in case of IDS, description of surgical procedures, duration of operation, estimated blood loss, intra- or post-operative transfusion, end result of surgery (complete: no macroscopic residual/optimal: less than 1cm maximum residual/suboptimal: more than 1cm maximum residual/open-close), site of residual disease, intraoperative complications/injuries, admissions to High Dependency Unit or Intensive Care Unit, post-operative complications, length of hospitalization, morbidity and mortality 30 days after operation, long term morbidity and adjuvant treatment.

All patients had an initial evaluation with a CT scan of the chest, abdomen and pelvis, along with serum Ca-125 and a Multidisciplinary team review where staging of the tumor and resectability was assessed. Cases with pleural effusions and suspicious axillary, mediastinal or groin nodes were considered as stage 4 with no confirmatory cytology/biopsy needed. Patients with potentially resectable disease on imaging were selected for PDS and assessed in an outpatient clinic appointment in relation to their fitness for surgery. Patients deemed not fit to undergo extensive radical surgery (*e.g.* poor performance or nutritional status, large pleural effusions causing shortness of breath) with significant co-morbidities, patients not likely to achieve complete cytoreduction (suspected large volume disease on small bowel surface/small bowel mesentery, large volume of disease at the porta hepatis, liver metastasis) or patients with extensive lymphadenopathy (axillary, mediastinal subclavian) were considered candidates for neo-adjuvant chemotherapy. The response to the latter was assessed with a further CT scan and serum Ca-125 after 3 cycles of chemotherapy. If there was evidence of biochemical and radiological response, patients were considered for IDS after being assessed for their fitness for surgery. If no biochemical or radiological response was evident then chemotherapy either stopped or continued for further 3 cycles according to tumor board recommendations. In some cases, debulking surgery was considered and performed for patients that had completed 6 cycles of neo-adjuvant chemotherapy and showed biochemical and radiological response.

All patients signed an informed consent during consultation in the outpatient's clinic and all possible complications were explained. On theatre day they underwent a midline laparotomy and the extent of disease was systematically assessed by a consultant gynecological oncologist, who performed the operation. The surgery was continued if complete or very minimal residual was anticipated, otherwise it was abandoned. All procedures in this study were performed by three gynecological oncologists.

Several descriptive statistics were used based on the type of variables in order to describe the distribution (*i.e.* continuous data were described by their median and interquartile range (IQR), while categorical data were described as frequencies and percentages) across the total population and between treatment groups. Comparisons were performed using two sample *t*-test or Mann-Whitney test for continuous variables, as appropriate. Comparisons were performed using chi-square test or Fisher's exact test for qualitative variables. Overall, all statistical analyses were performed using IBM SPSS Statistics 26.0 (IBM, Armonk, NY, USA). All the aforementioned statistical tests were two-sided and were performed at a 0.05 significance level.

Table II. *Radical procedures during cytoreductive surgery for advanced ovarian cancer in relation to PDS and NAC.*

Name of procedure	Total 110 (%)	PDS 60 (%)	IDS 50 (%)	*p*-Value
Large bowel resection	38 (34.5%)	29 (48.3%)	9 (18%)	**<0.001**
MPE	27 (24.5%)	23 (38.3%)	4 (8%)	
Total colectomy	3 (2.7%)	3 (5%)	0	
Right hemicolectomy	3 (2.7%)	1 (1.7%)	2 (4%)	
Sigmoidectomy	3 (2.7%)	2 (3.3%)	1 (2%)	
Transverse colectomy	2 (1.8%)	0	2 (4%)	
Diaphragmatic peritonectomy (right/both)	49 (44.5%)	34 (56.6%)	15 (30%)	**0.005**
With partial diaphragmatic excision	9 (8.2%)	5 (8.3%)	4 (8.0%)	
Splenectomy	15 (13.6%)	11 (18.3%)	4 (8%)	0.116
Pelvic/Paraaortic/Groin[1] lymphadenectomy	16 (14.5%)	12 (20%)	4 (8%)	0.075
Other upper abdominal procedures[1]	20 (18.2%)	13 (21.7%)	7 (14%)	0.299
Lesser omentectomy	8	6	2	
Duodenal nodules excision	5	3	2	
Excision of disease from Glisson's fascia	5	4	1	
Excision of disease from porta hepatis	7	7	0	
Excision of nodules from stomach/pylorus	5	4	1	
Cholecystectomy	3	3	0	
Excision of tail of pancreas/nodules	1	0	1	

PDS: Primary debulking surgery, NAC: neoadjuvant chemotherapy, MPE: modified posterior exenteration (en-block hysterectomy+bilateral salpingoophorectomy+rectosigmoid colectomy and anastomosis or total colectomy+pelvic peritoneal excision). Statistically significant results are indicated in bold. [1]Some patients had more than one procedure.

As the operations included in this study were according to the standard management for advanced ovarian cancer and the patients signed an informed consent, no ethical approval was required.

Results

Between June 2016 and Mar 2020, 110 patients underwent surgery for FIGO Stage IIIC-IV ovarian cancer in our department. The median (IQR) age of the patients was 66.5 years (range=57-72 years) with median (IQR) BMI 25.2 kg/m^2 (22.8-28.2). Approximately 67 patients had Stage IIIC disease (60.9%) whereas 43 (39.1%) had Stage IV. More patients with FIGO stage IIIC had PDS compared to those treated with IDS (73.3% *vs*. 46%, p=0.003). Serous histology was predominant, accounting for 103 (93.6%) cases. In total, 60 (54.6%) patients underwent PDS, while 50 (45.4%) had IDS including the ones having an operation after completing 6 cycles of neo-adjuvant chemotherapy. Table I summarizes patients' characteristics.

Table II presents the surgical procedures performed, overall and by treatment group (PDS *vs*. IDS). In total, 38 out of 110 (34.5%) patients underwent large bowel resection, the majority of whom had a modified posterior exenteration (27 patients, 24.5%). Amongst them, we performed a prophylactic loop ileostomy in 6 (22.2%). This was reversed after completion of chemotherapy in 5 patients. Three patients had a permanent end colostomy and three had an end ileostomy due to total colectomy performed. Approximately half of the patients (44.5%) underwent diaphragmatic peritonectomy (right/both); while in nine of them a partial diaphragmatic excision was required. The frequency of large bowel resection (18% *vs*. 48.3%, p<0.001) and diaphragmatic peritonectomy (30% *vs*. 56.6%, p=0.005) was lower in the IDS group. In total, fifteen patients (13.6%) required splenectomy, whereas in 20 patients (18.2%) other upper abdominal surgical procedures were performed. The number of patients in these last two categories was similar in both groups with a trend towards more procedures being performed in the PDS group.

Details regarding the most important perioperative characteristics of our population are summarized in Table III. The median (IQR) operation time was 300 min (195-394), with the duration of surgery in the PDS group being longer [360 min (192-430)] compared to IDS [270 min (199-334)] (p=0.047). The later had less intraoperative estimated blood loss (500 ml (range=300-1000 ml)) compared to PDS group [820 ml (400-1525)] (p=0.013). Overall, 22 patients (20%) required at least one unit of blood perioperatively and 77 patients (70%) were electively admitted to HDU post-operatively. The median hospital stay was significantly higher in the PDS group than in the NAC group (7 days *vs*. 6 days, p=0.050). Nine patients (8.2%) stayed in ITU intubated for the first night postoperatively, while one stayed intubated for 2 nights. In total, 10 (9.1%) Grade III-IV complications, according to the Clavien-Dindo classification of surgical complications, were noted in the first 30 days following the operation. These complications led to surgical (2 patients had a re-operation, the first to repair a small

Table III. *Perioperative results, related morbidity and time to chemotherapy.*

Variable	Total N=110	PDS N=60	NAC N=50	*p*-Value
Duration of operation median, (IQR)	300 mins (195-394)	360 mins (192-430)	270 mins (199-334)	**0.047**
Estimated blood loss median, (IQR)	800 mls (325-1375)	820 mls (400-1525)	500 mls (300-1000)	**0.013**
Number of patients who needed blood transfusion perioperatively	22 (20%)	13 (21.7%)	9 (18%)	0.632
Hospital stay median, (IQR)	7 days (5-9)	7 days (5-10)	6 days (5-8)	**0.050**
ICU/HDU admissions	77 (70%)	43 (71.7%)	34 (68%)	0.676
ICU/HDU stay median, (IQR)	1 day (0-2)	1 day (0-2)	1 day (0-2)	0.744
30-day Grade III-IV complications*	10 (9.1%)	6 (10%)	4 (8%)	0.365
Patients received adjuvant chemotherapy within 8 weeks	98 (89.1%)	54 (90%)	44 (88%)	0.738
Delay of chemotherapy due to surgical morbidity	8 (8%)	5 (8.8%)	3 (7%)	0.826

*According to Clavien-Dindo classification. Statistically significant results are indicated in bold.

bowel injury and the second due to evisceration) or radiological intervention, HDU admission for single or multiple organ dysfunctions or death (Table III). Some patients experienced more than one complication. Amongst all 35 patients that had any kind of large bowel resection and anastomosis no leaks were identified. One patient developed a ureteric fistula and urinoma that needed stenting and nephrostomy. Seven patients (6.3%) required re-admission mainly due to sepsis. One patient in the IDS group died on postoperative day 5 of unclear etiology.

Eight patients (7.2%) were unable to have chemotherapy within 8 weeks post-surgery due to postoperative morbidity. Overall, only 3 (2.7%) patients from the entire cohort did not receive any kind of adjuvant chemotherapy.

In total, as shown in Table IV, complete surgical cytoreduction was achieved in 61.8% of the 110 patients, followed by optimal surgical results in 27 (24.6%). In both groups the combined rate of complete and optimal cytoreduction was 81.7% and 92%, respectively. In eleven patients of the PDS group (18.3%) and 4 of the IDS (8%) suboptimal or open/close procedure was performed. No significant differences were found in relation to end surgery result between patients undergoing PDS or IDS, however there is a trend for more complete cytoreduction and suboptimal/open and close result in the PDS group.

Table IV. *Complete, Optimal and Suboptimal surgical results and their allocation in PDS and NAC group.*

Cytoreduction rate	Complete (N)	Optimal (N)	Complete & Optimal (N)	Suboptimal/ Open and close (N)
Total (N=110)	68 (61.8%)	27 (24.6%)	95 (86.4%)	15 (13.6%)
PDS (N=60)	39 (65%)	10 (16.7%)	49 (81.7%)	11 (18.3%)
NAC (N=50)	29 (58%)	17 (34%)	46 (92%)	4 (8%)
p-Value	0.225	0.178	0.758	0.071

Discussion

It is well established that complete cytoreduction is one of the most important prognostic factors in patients with advanced ovarian cancer irrespective of whether the surgery is offered upfront or following cycles of chemotherapy (9-13). To achieve the best surgical outcomes maximum surgical effort with extensive procedures in the upper abdomen and the pelvis is required. Most studies have focused in comparing PDS and IDS in terms of survival, while less is known in relation to the actual number and type of surgery performed in these 2 groups. In this single centre study, we demonstrate that even though radical surgical procedures can be performed with reasonable morbidity and mortality there are differences in bowel resections and diaphragmatic stripping between PDS and IDS.

The value of radical surgery for advanced ovarian cancer has been a matter of debate. In a large multicenter US study, Rodriguez *et al*. reviewed 2655 cases of advanced epithelial ovarian cancer where complete or optimal cytoreduction was achieved after incorporating radical procedures in the upper abdomen (14). They reported better progression-free survival and overall survival rates in patients that did not require upper abdominal surgery and were optimally cytoreduced compared to patients with the same surgical outcome and no upper abdominal surgery. However, in the subgroup of patients that had UAS, the overall survival of the 141 patients who achieved complete resection was 54.6 months compared to 40.4 months of the 341 patients who had residual disease <1 cm (p=0.0005). The authors concluded that UAS should be performed when complete cytoreduction is anticipated. In our series 18.2% of our patients had at least one upper abdominal procedure performed, besides splenectomy and in all but one complete cytoreduction could be achieved. In another single centre retrospective analysis,

Chi *et al*. reported improved survival in advanced ovarian cancer as a result of a change in surgical paradigm towards an aggressive surgical approach in PDS. In this study, the group that received extensive UAS had improved PFS and OS in comparison to the group that underwent more conservative surgical treatment (12).

Morbidity and mortality as well as their consequences, like delayed chemotherapy, are always an important factor when considering whether to perform radical procedures for patients with advanced ovarian cancer. In our series a 30-day mortality rate of 0.9% was observed and 9.1% of the patients suffered Grade III-V complications, which are both comparable with previously published data (10, 15-17). Fotopoulou *et al*. reported a higher severe complication rate of 18.6%, however in their series the complete cytoreduction rate was 89%, reflecting even more radical and complex procedures that may potentially confer more morbidity (16). Similarly, the same was observed in our series in terms of morbidity after PDS compared to IDS. The 30-day severe complication rate in PDS patients tended to be higher (10% *vs*. 8%) compared to IDS reflecting the higher number of radical procedures performed in the former group. It is unknown whether these unfavorable effects of PDS have a negative impact on survival or whether the high rate of complete cytoreduction in the PDS group could overcome any possible negative effects. The TRUST study, which is the third randomized trial aiming to show whether PDS has a survival advantage compared to IDS has already stopped recruiting and the first results, will hopefully provide adequate evidence on whether PDS should be the preferred method of managing patients with advanced ovarian cancer when adequate radical surgery is performed.

Large bowel resection mainly in the form of modified posterior exenteration is commonly performed during cytoreductive surgery to achieve pelvic clearance and aid towards complete cytoreduction. Most of the time this is followed by a primary end to end anastomosis with or without a prophylactic loop ileostomy. The latter however has a lot of disadvantages in terms of clinical sequelae as well as psychological consequences. The risk of anastomotic leak has been reported to be around 4-6%, mainly from colorectal research (18). Ovarian cancer is mainly intraperitoneal disease and when a modified posterior exenteration is performed the anastomosis lies approximately 10 cm from the anal verge in the mid-rectum. For this reason, the risk of anastomotic leak should be considerably lower compared to lower anastomosis performed for rectal cancers. This is also supported by the results of a large retrospective analysis in women with ovarian cancer showing that as the distance of the anastomosis from the anal verge increases the risk of anastomotic leak decreases (19). In our series amongst 27 patients that underwent modified posterior exenteration we did not observe a case of anastomotic leak. Nevertheless, our numbers are still small and this might change in the future as we enroll more patients. Early in our series we performed 6 prophylactic loop ileostomies; however, this was later abandoned in favor of a simple primary anastomosis. Others have also emphasized on the acceptable rate of serious complications with primary anastomosis in ovarian cancer and we strongly believe that if this is performed by an experienced gynecological oncologist is safe and spares the patient from unnecessary discomfort and reduced quality of life (20).

The main criticism of both the EORTC and CHORUS trials was the complete cytoreduction rate achieved for the group of patients undergoing surgery for advanced ovarian cancer. For the CHORUS trial this was around 30% for patients undergoing both PDS and IDS, while in the EORTC trial the complete cytoreduction rate in the PDS group was only 19.4% (4, 5). These rates of complete cytoreduction are similar to the ones that would have been achieved in our series if only the minimal operation was performed and emphasize on the weaknesses of both these trials and the need for more data in relation to surgery in advanced ovarian cancer and its possible positive impact on survival. In addition, radical surgery for advanced ovarian cancer is demanding and needs long operating times. In the CHORUS trial the median time for debulking operation was around 120 min, while in the EORTC this was increased to around 180 min. We believe that in both of these studies the operations performed are likely to be limited in radicality based on the median time spent in theatre. This might explain why the non-inferiority margin was reached for the IDS group. In our series the median operating time for the whole cohort was 300 minutes, (significant difference between PDS and IDS) similar to other published series and reflects the percentage of complete cytoreduction achieved.

During these 45 months of our practice it is evident that more radical procedures were performed in the PDS group compared to IDS. This has led to comparable rates of complete resection, however, with a trend for better results in the former group (65% *vs*. 58%). This might reflect the effect of chemotherapy in reducing the tumor burden in the latter group and is also emphasized by a trend for more open and close procedures in the PDS group. A closer look at our database and examination of the site of residual disease in both groups showed that in the IDS group there were more patients having residuals at the surface of the small bowel and the small bowel mesentery. We believe that this was the result of our selection to give NAC in patients presenting with a large volume of ascites meaning having more chances of generalized carcinomatosis that could not be cytoreduced completely with IDS. Therefore, there was a trend towards more optimal results in the IDS group.

Our study has certain limitations, mainly the non-randomized nature causing selection bias. Its strengths are that

it consists of consecutive patients with advanced disease and that all data were collected prospectively in our centres database. We believe that our results further encourage young gynecological oncologists to pursue adequate training and become experienced in performing radical surgery for women with advanced ovarian cancer. We have shown that this can be achieved with acceptable morbidity and mortality and could potentially increase the desirable complete cytoreduction rates.

Conflicts of Interest

The Authors declare that they have no conflicts of interest towards this study.

Authors' Contributions

V. Mitsopoulos: Data collection, Project development, Manuscript writing; I. Biliatis: Project development, Data collection, Manuscript writing; A. Innamaa: Data collection, Manuscript editing; J. Lippiatt: Data collection, Manuscript editing; N. Plevris: Data collection, Manuscript editing.

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Received June 23, 2020
Revised July 13, 2020
Accepted July 14, 2020