

RESEARCH ARTICLE

PROGNOSTIC ROLE OF THE PRIMARY TREATMENT IN THE NATURAL HISTORY OF OVARIAN CANCER: A PILOT STUDY

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ABSTRACT

Epithelial Ovarian cancer is the most lethal and silent gynaecological tumor and relapses in about 75% of cases. Retrospective data supported the superiority of secondary cytoreduction surgery (SCS) plus chemotherapy versus chemotherapy alone; in order to best select patients for SCS literature established a clinical score based on ascites, performance status, and absence of residual disease to primary surgery. The present study analyzed the outcomes and pattern of relapse of a population with first relapse of ovarian cancer undergoing secondary surgery without residual tumor divided into two groups based on the type of treatment at the first diagnosis (primary debulking surgery

[PDS] or neoadjuvant chemotherapy followed by interval debulking surgery [IDS]).

This is an observational retrospective study carried out at the referred Centre of Oncologic Gynaecology of Bologna, Italy on patients who underwent SCS for ovarian cancer between January 2009 and December 2019 retrieved in an electronic database. Clinical surgical and pathological data were analyzed. Data about time and pattern of relapse and overall survival were evaluated.

Out of 270 ovarian cancer patients, 69 were enrolled in the study; 49 patients who at first received primary surgery (Group 1) and 20 patients at first received interval surgery (Group 2). The 5-year

Post Relapse Overall Survival in Group 1 was 76% and in Group 2 30% ($p = 0.0042$). The 5-year Post Relapse Disease Free Survival in Group 1 was 49% and in Group 2 30% ($p = 0.08$). Regarding the pattern of relapse, Group 2 relapsed more frequently as multifocal peritoneal disease (75%) respect to Group 1 (41%) ($p = 0.02$). Finally, relapse after pri-

mary debulking surgery resulted in a more favourable pattern of recurrent disease, and secondary surgery after PDS offered longer survival.

Our study lays the foundation for considering the primary treatment received by patients among the selection variables for secondary cytoreduction surgery.

KEY WORDS

Ovarian cancer; secondary surgery; interval debulking surgery; primary debulking surgery; recurrence.

IMPACT STATEMENT

In patients with advanced epithelial ovarian cancer, primary treatment impacted among the selection variables for secondary cytoreduction surgery and primary debulking surgery reported better outcomes.

INTRODUCTION

Epithelial ovarian cancer (EOC) is a relatively rare disease with the highest incidence rates in western countries such as Europe and North America (8 cases per 100.000). This cancer is the most lethal and silent gynaecological tumor with diagnosis in advanced stages (III-IV) in about 80% of cases and a five-year survival of only 20-30% (1, 2).

The standard approach is surgical cytoreduction and chemotherapy with platinum and taxane compounds (3-7). Surgery can be offered at diagnosis (primary debulking surgery, PDS) or after neoadjuvant chemotherapy (NACT) (interval debulking surgery, IDS), with the goal to obtain absent or minimal residual disease and optimal debulking surgery represents one of the major prognostic factors (4). Despite optimal surgery and appropriate chemotherapy, about 70%-80% of patients will develop recurrence that results in about 23% within 6 months, and 60% after 6 months to the last platinum administration. Based on these parameters, patients were defined platinum sensitive and platinum resistant (8, 9).

When disease relapse occurs, surgery is a possible option in platinum sensitive patients with the same objective of primary surgery: minimal or absent residual disease. Some retrospective data supported the superiority of secondary cytoreduction surgery (SCS) plus chemotherapy versus chemotherapy alone (10), however the use of SCS is controversial. Some Authors have reported that the improved outcomes may reflect selection bias rather than the superiority of SCS due to the ret-

rospective design of the studies. Some selection biases were explained by Gockely A *et al.* in 2019 (11) in a large retrospective study. They found that patients who underwent SCS were younger ($p = 0.001$), with an earlier stage disease at diagnosis ($p = 0.002$) and longer disease-free intervals ($p < 0.001$), compared with those taking chemotherapy alone, no significant differences in complication rates were found between patients receiving SCS versus those having chemotherapy only. According to the sensitivity analysis performed in the study, the survival benefit related to SCS could be explained by a lower incidence of multiple sites of relapse, ascites or carcinomatosis among women undergoing SCS.

The consensus of scientific community recognized that patients with the best outcomes were those submitted to SCS with minimal or absent residual disease and with long disease-free interval after adjuvant therapy (> 6-12 months) (12-15). In order to best select patients for SCS, European Researchers established in the AGO-DESKTOP studies designed and applied a clinical score for SCS (Arbeitsgemeinschaft Gynaekologische Onkologie, AGO score) (16): ascites < 500 ml, patients' performance status, absent residual disease to primary surgery. Presence of unresectable disease to imaging, contraindications to surgery and possibility to complete cytoreduction were also take into account. Recently, two randomized studies were published reporting different outcomes. In 2019, the GOG 213 randomized trial published in the New Eng-

land Journal of Medicine failed to demonstrate a surgery-determined advantage in both Progression Free Survival (PFS) and Overall Survival (OS) in recurrent ovarian cancer versus chemotherapy alone (17). Conversely, after one year, final analysis from the AGO DESKTOP III/ENGOT-ov20 study looking at the impact of SCS in recurrent ovarian reported a median of 16 months longer survival in around 75% of patients that had a complete resection respect to patients who did not receive surgery (18).

From an evaluation of the studies proposed in the literature, among the parameters used in the decision for secondary surgery, PDS adjuvant chemotherapy or neoadjuvant plus IDS were the types of treatment at diagnosis that were not considered. It is known that patients who undergo neoadjuvant chemotherapy and IDS are characterized by higher burden disease, selection of chemoreistant clone by drugs administered, different pattern of relapse respect to PDS and adjuvant chemotherapy (19). The association of results derived from PDS or IDS can lead to an incorrect analysis, risking to unify data that concern two different histories of disease and with different outcomes.

The main aim of the present study is to analyze the outcomes of a population with first relapse of EOC undergoing to SCS divided into two groups based on the type of treatment at the first diagnosis (PDS or IDS). Further evaluations will be the pattern of relapse (abdominal, extra-abdominal, single or multiple peritoneal, lymph node, hepatic, pelvic) and the incidence of post-surgical complications between two groups.

MATERIALS AND METHODS

This is an observational retrospective study carried out at the referred Centre of Oncologic Gynaecology of Bologna, Italy on patients who underwent SCS for ovarian cancer between January 2009 and December 2019 retrieved in an electronic database. Design of the study was reported in **figure 1 a**. The study is part of a larger study that was approved by local Ethical Committee.

Inclusion criteria were: EOC according to the WHO criteria, patients older than 18 years old, FIGO (International Federation of Gynaecology and Obstetrics) Stage III-IV, PDS or IDS with no residual macroscopic disease, SCS without residual macroscopic disease, follow up data after SCS at least six months.

Exclusion criteria were: borderline and no epithelial ovarian cancer, Stage FIGO at diagnosis I-II, Patients stage III-IV with no resected disease, residual macroscopic disease at first diagnosis, recurrent disease treated with chemotherapy; missing data about follow-up or surgical primary/secondary treatments, other neoplasia in the last 5 years.

Patients were divided into two groups: Group 1 includes patients with first relapse EOC submitted to SCS after PDS at first treatment; Group 2 includes patients with first relapse submitted to SCS after IDS at first treatment. At the time of the first diagnosis the decision-making process on whether to refer patients to PDS or NACT was taken after diagnostic laparoscopy by the two senior surgeons, to avoid selection bias.

Selection criteria for SCS were: AGO score (16) positive, imaging evaluation (computer tomography, CT or ¹⁸F-FDG PET/CT) showed resected disease and possibility to complete cytoreduction. Otherwise, patients were submitted for chemotherapy without surgery selected in according to the best treatment available. Patients scheduled for SCS were submitted to a diagnostic laparoscopy in order to confirm the surgical indication, if they were judged non cytoreducible to laparoscopy were selected for chemotherapy. Residual disease after surgery was classified in completeness of cytoreduction (CC): absence of disease (CC-0), minimal residual disease 0.1-0.5 cm (CC-1), and gross residual disease > 0.6-1.0 cm (CC-2) and > 1 cm (CC3). After surgery, patients were selected to receive chemotherapy with platinum and taxane compounds or other drugs based on oncologist evaluation, for a total of six cycles.

Follow-up was performed according to local guidelines of the hospital, in particular, physical examination, pelvic ultrasound, CA125 serum tumor marker (CA19-9 was tested only for mucinous tumors) CT scan were assessed every 4 months, ¹⁸F-FDG PET/CT was prescribed whenever there was a clinical suspicion of relapse or as confirmation of another instrumental examination such as CT. Planned follow up was modified, if required, according to patient's needs (suspect of relapse or request of clinical evaluation for symptoms).

Clinical and pathological data were collected and examined, including: age at diagnosis, body mass index (BMI), histological type, FIGO staging system (20), BRCA mutation if available, CA125 at recurrence, primary tumor treatment (surgery and/or chemotherapy), date of relapse, diagnosis meth-

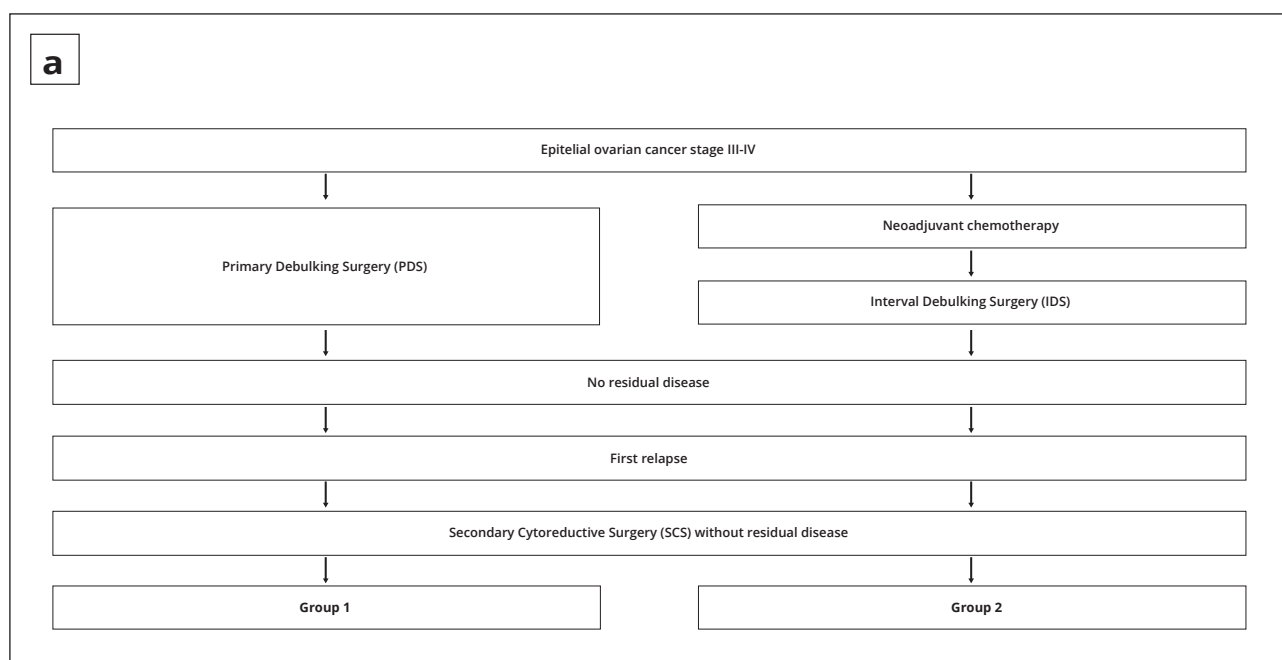


Figure 1 a. Shows the study design.

ods/system of relapse, site of relapse, date of relapse and secondary surgery, Aletti surgical complexity score (21), Peritoneal Cancer Index (PCI) (22), surgical complications (Dindo-Clavien classification) (23), other therapies performed in association with surgery (chemotherapy, radiotherapy), maintenance therapies, date of last follow-up, date of second relapse and date of death.

Statistical analysis

Standard descriptive statistics were used to evaluate the distribution of each variable. Continuous variables were reported as means $\pm$ standard deviation (SD) and categorical variables as frequencies or percentages. The distribution of variables between groups were compared with chi-square test or Fisher's exact test and Mann-Whitney *U* test or ANOVA test, as appropriate. Peri-operative complication rates were reported as the frequency and percentage of patients. All *p*-values reported are two-sided and a *p*-value < 0.05 was considered statistically significant. OS and PFS were estimated by the Kaplan-Meier method, and two groups survival curves were compared by the log-rank test.

OS, Post Relapse Disease Free Survival (PRDFS) and Post Relapse Overall Survival (PROS) were defined respectively as time in months from first diagnosis to last follow-up or death, months from first relapse diagnosis to second relapse or last follow-up, time from first relapse to last follow-up or death.

RESULTS

The recruitment flow chart is shown in **figure 1 b**. Briefly, 760 patients with EOC (stage III-IV) undergoing surgical staging were retrieved in the database, of these patients, 344 (45%) received PDS (Group 1) and 416 (55%) neoadjuvant chemotherapy and IDS (Group 2). In Group 1, the percentage of patients receiving primary surgery without residual disease was 76% (263/344), and in Group 2 69% (196/283). Of these patients optimally cytoreduced, a total of 207 patients relapsed after a median of 22 months (range 6-76) and were evaluated for SCS. Sixty-nine (33%) patients met the inclusion criteria (AGO score combined to imaging evaluation) and were enrolled in the study, 49 out of 120 (40%) for Group 1, and 20 out of 87 (23%) for Group 2 (**figure 1 b**). Of a total of 207 with first relapse, 138 (69%) were judged not amenable for surgery.

Patients' characteristics of the two groups are reported in **table I**. No differences were reported in age, BMI, stage, histology. Median of time relapse was shorter in Group 2, 28 months (range 12-67), respect to Group 1, 31 months (range 6-76), *p* = 0.05. BRCA status data are not available for all patients as BRCA mutation has been routinely checked in our Unit since 2015. A total of 49 (71%) patients in Group 1, and 14 (70%) in Group 2 were tested for mutations in BRCA genes. The mutation of both BRCA 1-2 genes was reported in 8 women (16%) of

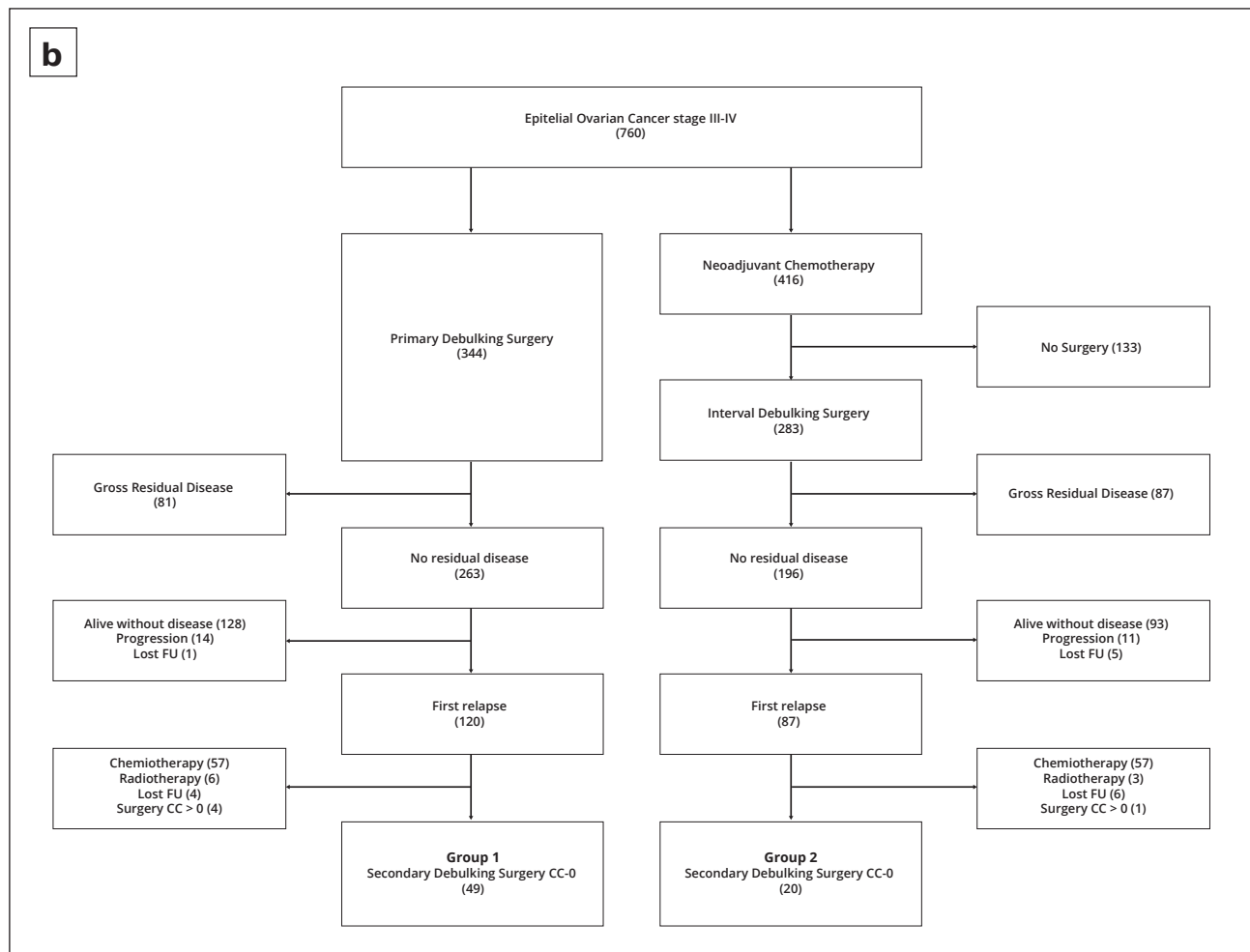


Figure 1 b. Shows the recruitment flow chart of the study with the number of patients evaluated and the patients excluded from our study population groups.

	GROUP 1		GROUP 2		<i>P</i> < 0.05
Total number	49		20		<i>ns</i>
	Median	(range)	Median	(range)	<i>ns</i>
Age	62	(24-83)	61	(39-85)	
Age at the diagnosis	56	(19-76)	55	(35-75)	<i>ns</i>
BMI (Kg/m²)	25	(15-39)	25	(17-47)	<i>ns</i>
	N	(%)	N	(%)	
FIGO Stage					
III	47	(96%)	18	(90%)	<i>ns</i>
IV	2	(4%)	2	(10%)	
Histology					
Serous	37	(76%)	16	(80%)	<i>ns</i>
Endometrioid	9	(18 %)	2	(10%)	
Mucinous	2	(4%)	1	(5%)	
Clear cell	1	(2%)	1	(5%)	

Table I. Clinical and pathological parameters of the study Population.

N = number; BMI = Body mass index; FIGO = International Federation of Gynecology and Obstetrics.

Group 1 and in 7 (35%) of Group 2. In Group 1, 5 patients (10%) had the BRCA1 mutation, 3 (6%) had the BRCA2 mutation, 24 (49%) were not mutated, and 17 (35%) had BRCA unavailable status. In group 2, 6 patients (30%) had the BRCA1 mutation, 1 (5%) had the BRCA2 mutation, 7 (35%) were not mutated, and 6 (30%) had the BRCA unavailable status.

Results about SCS are reported in **table II**. The value of CA 125 was significantly higher in Group 2 respect to Group 1 (median 68 U/ml, range 12-304 versus 38 U/ml, range 2-375; $p = 0.0206$), the levels of CA 125 were significantly lower ($p = 0.001$) in the relapse than in the first diagnosis. The other parameters did not differ between two groups except for PCI than was higher in Group 2 without reaching significance (**table II**). Surgical complexity (Aletti's score) was significantly lower ($p = 0.001$) in the relapse than in primary surgery.

There was no significant difference in post-surgical complication incidence between the two groups (**table II**). The incidence grade 3 complications were reported in two patients in Group 1 and grade 4 in one patient in Group 2. A death was reported in Group 2 for myocardial ischemia.

Pattern of first recurrence in both groups is re-

ported in **figure 2**. Lymph node recurrences and intraparenchymal metastasis was reported in both groups with no statistical significance, Group 2 relapsed more frequently as multifocal peritoneal disease (75%) respect to G1 (41%) ($p = 0.02$).

After SCS, both groups received systemic chemotherapy. In Group 1, 30 patients received chemotherapy with carboplatin and gemcitabine, 19 patients with carboplatin and taxane. In Group 2, nine patients received carboplatin and gemcitabine, 11 patients with carboplatin and taxane. In Group 1, two of the patients that underwent surgery for thoracic relapse received radiotherapy in association to carboplatin and gemcitabine.

Beside traditional chemotherapy, antiangiogenic drugs such as Bevacizumab and poly ADP-ribose polymerase inhibitors (PARPi) have been added. In Group 1, 33% (16/49) of patients received Bevacizumab and 20% (10/49) of patients received PARPi; of these, Olaparib was used in 5 patients with BRCA mutation and Niraparib in 5 patients with wild-type BRCA. In Group 2, 25% (5/20) of patients received Bevacizumab, 20% (4/20) received PARPi therapy, and 15% (3/20) received both therapies; in total 35% (7/20) of patients were treated with PARPi. Olapar-

	GROUP1		GROUP2		$P < 0.05$
	Median	(range)	Median	(range)	
DFS (months)	31	(6-76)	28	(12-67)	
	N	(%)	N	(%)	
CA-125 (U/ml)					
0-34	19	(39%)	3	(15%)	0.0206
35	22	(45%)	12	(60%)	
Not available	8	(16%)	5	(25%)	
PCI					
0	15	(31%)	5	(25%)	ns
1-10	20	(41%)	11	(55%)	
11-20	6	(12%)	2	(10%)	
20-39	2	(4%)	2	(10%)	
Not available	6	(12%)	0	(0%)	
Aletti complexity score					
Low (≤ 3)	36	(73%)	11	(55%)	ns
Intermediate (4-7)	13	(27%)	7	(35%)	
High (8)	0	(0%)	2	(10%)	
Dindo-Clavien classification					
No surgical complications	28	(57%)	13	(65%)	ns
Grade I-II	18	(37%)	6	(30%)	
Grade III-IV	2	(4%)	1	(5%)	
Grade V	1	(2%)	0	(0%)	

Table II. Surgical parameters of the secondary cytoreduction.

Legend: DFS = disease free survival; PCI = peritoneal cancer index.

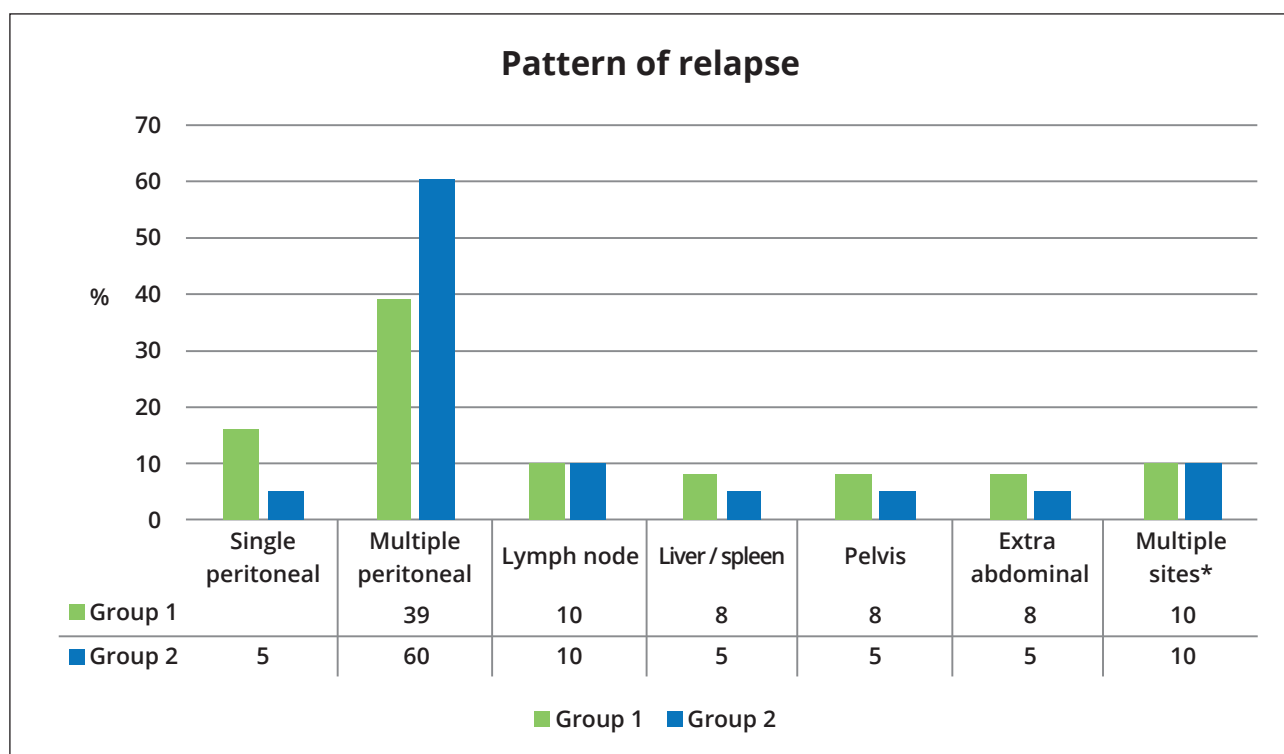


Figure 2. The figure shows the site and percentage of the pattern of relapse in our population study divided into the two study groups.

ib was used in 3 patients with BRCA mutation and Niraparib in 4 patients with wild-type BRCA.

The median of total follow up of our study population was 55 months (range 13-132), after SCS, 25 months (range 7-104). The 3-year OS was 94% and 80% in Group 1 and Group 2, and 5-year OS was 82% and 65% in Group 1 and Group 2 ($p = 0.0042$). The 3-year PROS in Group 1 was 82% (40/49) and in Group 2 65% (13/20), 5-year PROS in Group 1 was 76% (37/49) and in Group 2 30% (6/20) ($p = 0.0042$). The 3-year PRDFS in Group 1 was 51% (25/49) and in Group 2 30% (6/20); 5-year PRDFS in Group 1 49% (24/49) and in Group 2 30% (6/20) ($p = 0.08$) (**figure 3**).

DISCUSSION

This is a pilot study performed in a selected population of recurrent EOC patients that, to our knowledge, is the first of its kind to investigate the impact of the primary treatment on the natural history of the disease. Here, we reported different outcomes between PDS and neoadjuvant and IDS patients in the pattern of relapse and PROS. Results reported that Group 1 was characterized by better prognosis and a more surgical favorable pattern of relapse. Surgery represented a cornerstone in the treatment of EOC, maximal surgical effort without residual

disease combined to chemotherapy led to good prognosis (4, 24). This statement was translated to SCS and the favourable role of SCS on prognosis has been established for decades in retrospective studies and metanalysis (12, 17, 25) even if its effectiveness is closely related to a careful selection of patients to undergo surgery and more restrictive criteria about surgical complexity (AGO score) was applied to SCS. To confirm these data, two prospective randomized studies were proposed (GOG 213 and AGO-DESKTOP studies), however, opposite results were actually found. In 2019, results of one of the randomized studies, GOG 213, raised some concerns about the SCS survival improvement previously suggested. The study reported that SCS can be safely performed in these patients, but it did not improve overall survival. Some concerns about this study have been raised by European Scientists. The GOG 213 was designed to evaluate the impact of antiangiogenic treatment on OS in platinum-sensitive recurrent ovarian cancer (PSROC) and secondary aims were to explore the role of SCS; other bias reported were patient selection and the low percentage of CC-0 in the population analysed. Different results are reported from the second randomized study, DESKTOP III study, in which PSROC patients with positive AGO score reported an average increase of 5.6 months in progression-free survival (from 14.0

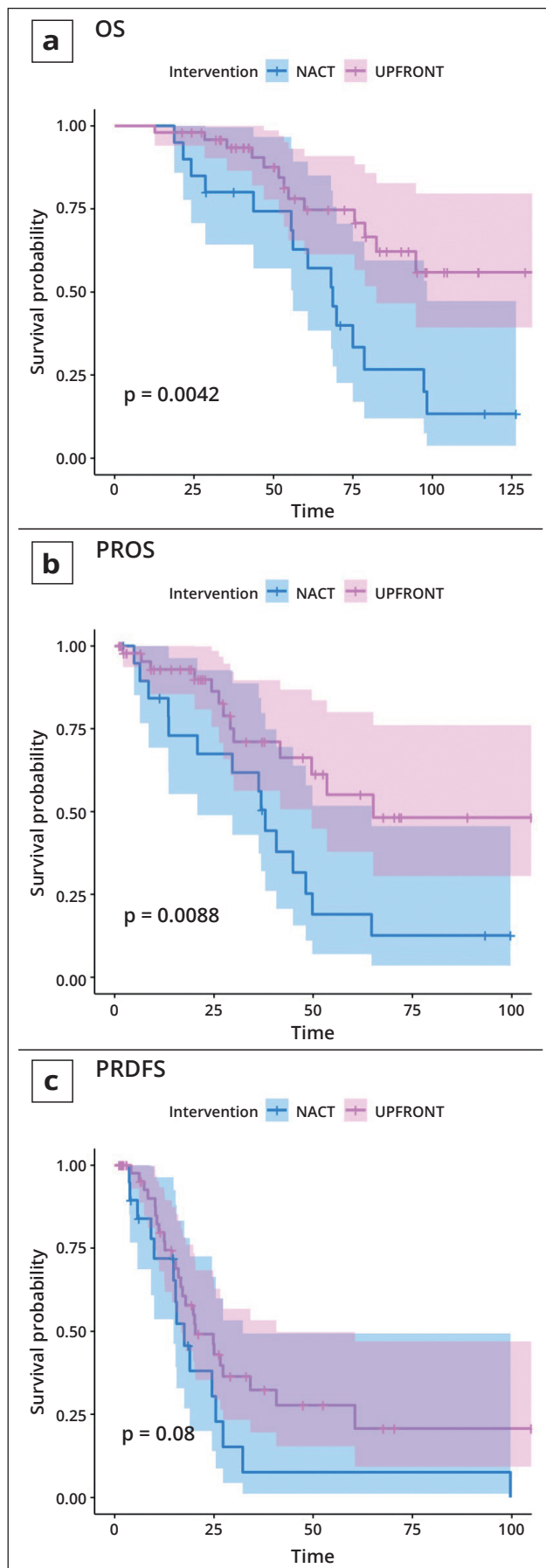


Figure 3. **a.** Kaplan-Meier curves of Overall Survival; **b.** Post Relapse Overall Survival; **c.** Post Relapse Overall Survival; in Group 1 (pink line) and Group 2 (blue line).

to 19.6 months) and a median survival greater than 16 months in approximately 75% of patients who had a complete cytoreduction compared to patients who received chemotherapy alone. The publication of SOLO 1 (26) study reporting a 3-year disease-free period due to target therapy with poly ADP ribose polymerase inhibitors (PARPi) in recurrent EOC BRCA-mutated patients raised further doubts about the role of SCS in these settings. Marchetti *et al.* (27) addressed this issue and subsequently reported a better OS in BRCA mutated patients undergoing SCS plus chemotherapy and PARPi compared to patients undergoing chemotherapy and PARPi alone (3-year PRS of 79% and 42%, $p = 0.02$). The results of Desktop III and the criticisms of GOG 213 have confirmed the indication to SCS even in the *era* of target therapy, such as PARPi. The key-points for a better prognosis for patients undergoing SCS were: patient's selection and the absence of residual disease after surgery. Patients recruited in our study were strictly selected using AGO score criteria, the review of imaging CT and/or ^{18}F -FDG PET/CT and finally diagnostic laparoscopy in order to confirm the first two parameters (**figures 4, 5**). With these modalities, our percentage of optimal debulking surgery was very high, 92% in Group 1 and 95% in Group 2. When comparing the two groups, a higher percentage of patients were scheduled for SCS in Group 1 (40%) respect to Group 2 (20%) associated to a better prognosis for the Group 1. Although both groups were without residual disease at the first surgery, the data seemed to indicate that another selection parameter could be the type of primary treatment. Based on these data and literature reports, it could be hypothesized that patients undergoing PDS who relapse but who have a positive AGO score are those who could obtain the greatest benefit from SCS if compared to the neoadjuvant group (Group 1). The reasons for this difference could be various. It could be the case that completely cytoreduced patients after NACT could have a higher incidence of residual microscopic lesions that are not surgically detectable because they are hidden by scar tissues, especially in the upper abdomen and diaphragmatic surfaces. Furthermore, after chemotherapy often whitish and flat areas are highlighted in the site of previous neoplastic nodules to which it is difficult to give a meaning: some theories suggest possible residual disease or outcomes of chemotherapy. After NACT, microscopic persistent neoplastic foci may contain chemotherapy-resistant clones. The process is directly proportional to the number of cycles, and

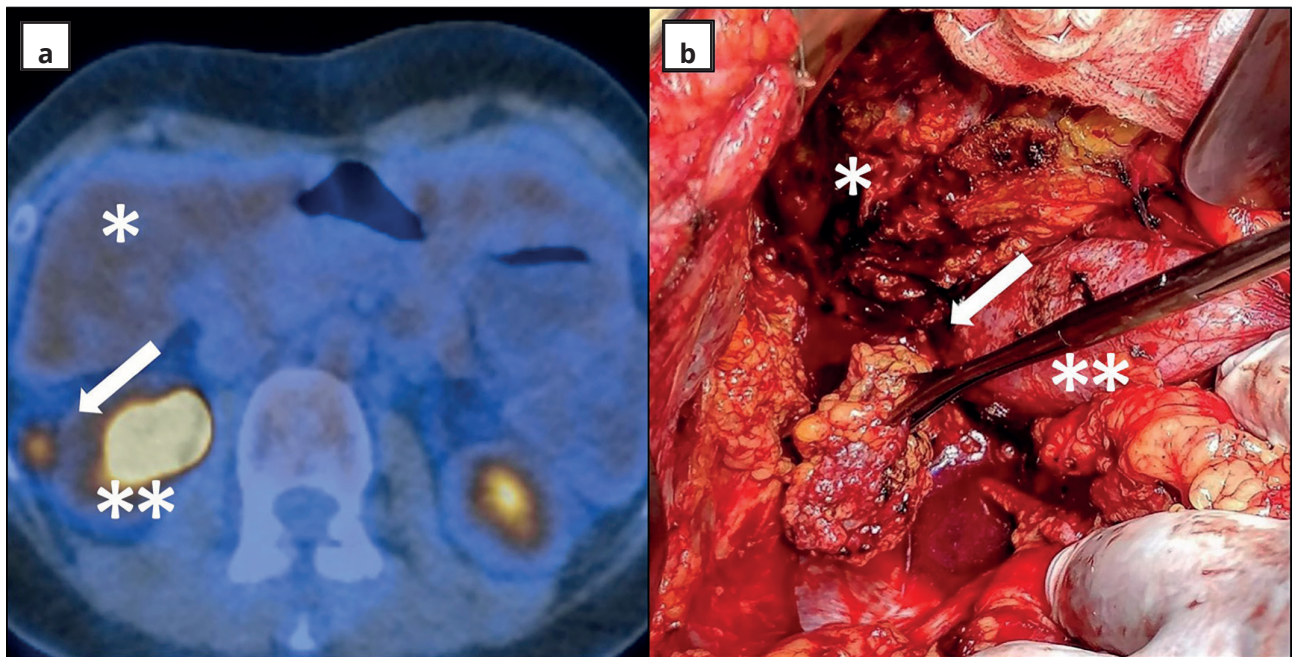


Figure 4. ^{18}F -FDG PET/CT image (4A) and surgical image (4B) show pararenal relapse of epithelial ovarian cancer (indicated by the arrows). * Liver; ** right kidney.

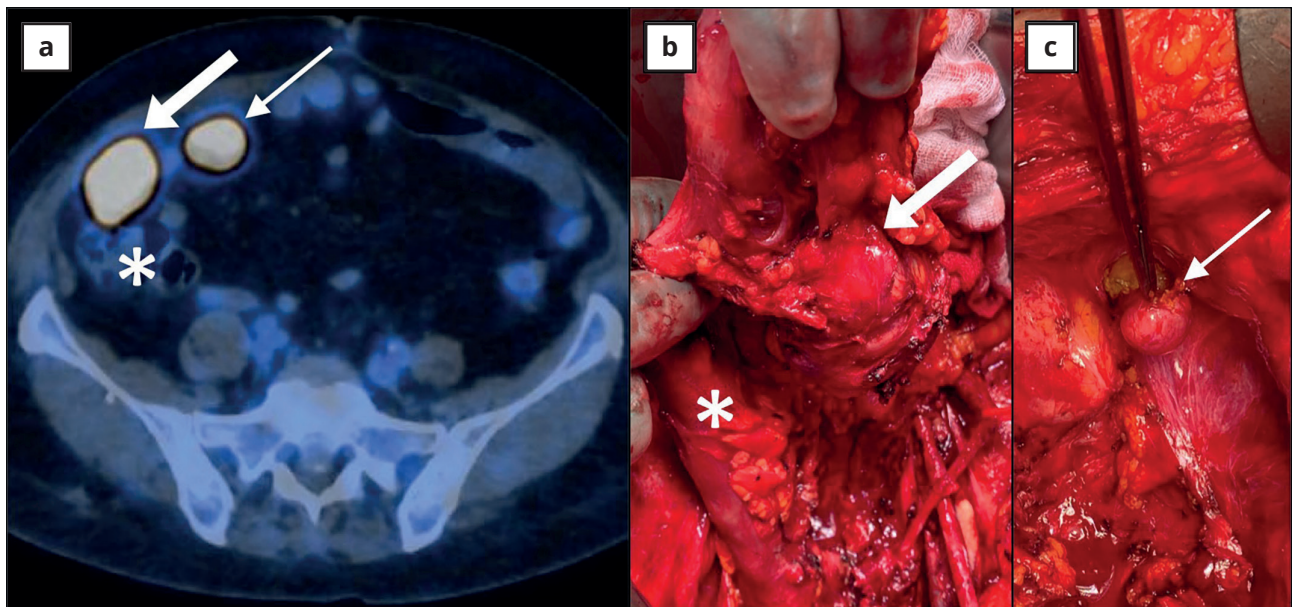


Figure 5. ^{18}F -FDG PET/CT (5A) and surgical (5B-5C) image of two bowel relapses of epithelial ovarian cancer (larger lesion is indicated by the bold arrows, smaller lesion is indicated by the slim arrows). * Descending colon.

many authors discuss the benefits of surgery after more than 6 cycles of chemotherapy. Literature data indicate that the presence of a larger and heterogeneous tumour burden at the time of initiation of chemotherapy could play an important role in the development of drug resistance, thus leading some authors to speculate that avoiding PDS in favour of

NACT could promote the selection of a major aggressive disease (17, 28).

On the other hand, no useful data are currently available to clarify whether and how the choice to administer PDS or NACT followed by IDS can change the natural history of recurrent ovarian cancer. However, some indications may be considered such as

the pattern of relapse or level of CA 125 or PCI to recurrence. In support of this diversity we have found that the modalities of relapse are different between the two groups. The IDS group tends to relapse more frequently as multifocal or peritoneal disease (carcinosis) than the PDS group which has intraparenchymal and paucifocal relapses. The characteristics of Group 2 reduce the surgical indications and the chances of optimal surgery. This is confirmed by higher levels of CA 125 and the PCI in Group 2. Therefore, in our study we did not find a higher surgical complexity score or increased post-operative complications in Group 2. Our results are supported by the study of Petrillo *et al.* (29). Here, the author reports that the two different approaches widely used in advanced ovarian cancer, PDS and NACT followed by IDS, are associated with significant differences in terms of presentation of recurrent disease. Papers reported that patients who relapse after NACT often have widely disseminated carcinomatosis and experience a higher incidence of platinum resistance compared with those who recur after PDS. The limitations of our work are the small sample size and the retrospective nature of our study. Patient selection criteria for NACT and therapies have changed over time, however in our center, diagnostic laparoscopy has been widely used since its onset in patients with high tumor burden and we are one of the first institutions that used diagnostic laparoscopy to select ovarian cancer patients. And again, the lack of differences in clinical and pathological characteristics at diagnosis between the two groups, as well as the absence of residual tumour after PDS and IDS, make the two series homogeneous and comparable. Biological genetics or biological components were not taken into account and this could be a bias of the study.

CONCLUSIONS

In conclusion, our study lays the foundation for considering the primary treatment received by patients

among the selection variables for SCS. Relapse after PDS results in a more favourable pattern of recurrent disease, and SCS after PDS offers longer survival if pre-existing criteria are selected (AGO scoring criteria) and diagnostic laparoscopy is performed. Certainly, further evaluations are needed to confirm our data and to clarify the impact of PDS and NACT on the natural history of ovarian cancer. However, it must be considered that the decision for the neoadjuvant must be the result of a careful evaluation and must be made in referral Centers in order not to reduce future surgical chances of patients with a disease where relapse occurs in about 75% of patients in the advanced stage.

ETHICS

Fundings

There were no institutional or private fundings for this article.

Conflict of interests

The authors have declared no conflict of interests.

Availability of data and material

The data underlying this article can be shared just before a reasonable request to the corresponding author.

Code availability

N/A

Authors' contribution

AMP: writing original article, formal analysis; MT: investigation; EDC: conceptualization; CAC: data collection; AB: visualization; SB: software; GD: data collection; SG: supervision; PDI: supervision.

Ethical approval and consent to participate

The study is part of a larger study that was approved by local Ethical Committee (number 160/2012/O/Sper).

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