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The paradigm shift in advanced ovarian cancer: Outcomes of extensive primary cytoreductive surgery. A single-center retrospective analysis

Tommaso Bianchi [a,b,1], Tommaso Grassi [b,1], Luca Bazzurini [b], Filippo Testa [a,b], Jasmine Corti [a,b], Giorgia Pecis Cavagna [a,b], Martina Bombelli [a,b], Andrea Alberto Lissoni [a,b], Giampaolo Di Martino [b], Gaetano Trezzi [b], Elena De Ponti [c], Robert Fruscio [a,b,*], Fabio Landoni [a,b]

[a] Department of Medicine and Surgery, University of Milano-Bicocca, Milano, Italy
[b] Clinic of Obstetrics and Gynecology, IRCCS Fondazione San Gerardo dei Tintori, Monza, Italy
[c] Medical Physics, IRCCS Fondazione San Gerardo dei Tintori, Monza, Italy

A B S T R A C T

Objective: The standard surgical treatment of advanced ovarian carcinoma is primary debulking surgery (PDS) aiming to complete cytoreduction. The need to achieve complete cytoreduction has shifted the surgical paradigm to more complex procedures, whose impact on morbidity is controversial. The objective of this retrospective analysis is to explore the impact of extensive PDS on morbidity and oncologic outcomes in a real-world scenario.

Methods: A retrospective single-center analysis was performed on 137 patients with advanced high-grade ovarian carcinoma (HGOC) who received PDS in 2015–2020. Patients treated in 2015–2017 (Group 1) were compared to patients treated in 2018–2020 (Group 2). The two periods were chosen according to the higher complexity of surgical procedures introduced in 2018.

Results: The increase in complete cytoreduction observed in Group2 (RD 0: 33 % vs 61 %, p = 0,008) was related to a higher surgical complexity (Aletti Score: 4 vs 6, p = 0,003) and did not reflect an increase in peri-operative complications (CCI: 20,9 vs 20,9, p = 0,11). After a median FUP of 44 months, PFS and OS at 24 months were 33,60 % vs 47,33 % (p = 0,288) and 72,10 % vs 80,37 % (p = 0,022) in Group 1 and 2, respectively.

Conclusions: An extensive surgical effort leads to a significant increase in complete cytoreduction with acceptable morbidity. Arm-in-arm with novel maintenance therapies, it contributes to increasing the outcomes of patients with advanced HGOC.

1. Background

Ovarian cancer (OC) represents the most lethal gynecologic malignancy, with a 5-years survival rate of 50 % [1,2]. The mainstay of advanced OC treatment is primary debulking surgery (PDS) aiming to complete cytoreduction followed by adjuvant platinum-based chemotherapy [3,4]. In patients not fit enough to receive PDS and those in whom disease extension does not allow optimal cytoreduction, interval debulking surgery (IDS) after platinum-based neoadjuvant chemotherapy (NACT) was not inferior to PDS in three randomized clinical trials (RCTs) [5–8].

The main goal of cytoreductive surgery has changed over decades. Optimal cytoreduction progressively evolved from debulking with less than 1–2 cm of residual disease (RD) to complete resection of all macroscopically visible tumor with no evidence of RD [9,10]. Several high-quality studies and metanalyses showed an advantage in both disease-free-survival (DFS) and overall-survival (OS) in patients who received complete cytoreduction compared to those who underwent optimal (RD < 1 cm) or suboptimal (RD > 1 cm) debulking [10–13]. Consequently, the need to achieve complete resection of all visible tumor has shifted the surgical paradigm to more complex surgical procedures, including systematic removal of pelvic and abdominal peritoneum, multiple bowel resections, upper abdomen, supra-diaphragmatic and extra-abdominal procedures [14–16].

Whilst the prognostic significance of complete cytoreduction is supported by robust evidence, the impact of extensive surgical procedures on intra- and postoperative morbidity, and ultimately on oncological outcomes is less clear [17]. In our Institution, with the change of the department's Chief in 2018, there has been an increase in the PDS choice and a shift towards a more aggressive surgery. Therefore, we were able to perform this retrospective analysis to explore the impact of the change in the surgical paradigm on oncological radicality, morbidity, and

* Corresponding author. Department of Medicine and Surgery, University of Milano-Bicocca, Milano, Italy.
E-mail address: robert.fruscio@unimib.it (R. Fruscio).
[1] These authors contributed equally to this work.

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survival outcomes in a real-world scenario.

2. Methods

2.1. Study design

This is a single-institution retrospective study with the primary objective to compare surgical radicality during two different periods in the treatment of FIGO IIIA-IVB high-grade ovarian carcinoma (HGOC). For this purpose, patients were divided into two groups: i) Group 1, patients who received PDS in years 2015–2017; ii) Group 2, patients who received PDS in years 2018–2020. The definition of the two time periods was chosen according to the change in the surgical philosophy that occurred at our institution in 2018, when higher surgical complexity and debulking completeness were introduced. Secondary endpoints were incidence of intra- and post-operative complications, DFS and OS. DFS was defined as time from surgery to relapse; OS was defined as time from surgery to death, data cut off or lost follow-up.

2.2. Study population

Patients were eligible if they were referred to our institution for surgery from 1st January 2015 to 31st December 2020. All patients with newly diagnosed FIGO stage IIIA-IVB, non-mucinous HGOC who received PDS were included. Patients operated with only diagnostic intent and those receiving IDS after NACT were excluded. The primary treatment selection was determined by our institution's tumor board based on tumor resectability according to pre-operative CT scan and patient eligibility for a major surgical procedure. For the whole cohort of patients, pre-operative imaging was revised by an onco-radiologist dedicated to gynecologic oncology imaging. In both Group 1 and Group 2, all cytoreductive procedures were performed or directly supervised by an experienced surgical gynecologic oncologist with peculiar expertise in ovarian cancer surgery. Adjuvant treatment and subsequent maintenance treatment were administered according to the ESGO-ESMO-ESP guidelines [3] based on histology, FIGO stage, molecular biology, and patients' comorbidity. Following I-line adjuvant treatment, patients were scheduled for follow-up with clinical and CA125 evaluation every 3–4 months for the first 3 years and then 6 monthly for the next 2 years. A chest and abdomen CT scan was performed annually or in case of suspected recurrence. Informed consent was collected for each patient at the time of diagnosis.

Patient's clinicopathological data were collected from internal clinical records. Demographic and clinical data included age at surgery, ECOG Performance Status, ASA score, Body Mass Index (BMI), pre-operative hemoglobin (Hb) and platelet count, BRCA status, histotype, and tumor stage according to FIGO 2014 classification [18]. Intra- and postoperative data included tumor extension assessed with the Peritoneal Cancer Index (PCI) [19], length of surgery, surgical complexity, blood loss, RD, and surgical complications. The number of upper abdomen surgical procedures and the number and type of bowel resections were also recorded. RD was defined as follows: i) R0 if complete resection was achieved; ii) infracentimetric if < 1 cm; iii) suboptimal if > 1 cm. Surgical complexity was defined according to the Aletti Surgical-Complexity-Score (SCS) [20]. Surgical complications were defined as any intra- and post-operative adverse events occurring within 30 days after surgery. Each complication was classified according to the Clavien-Dindo Classification [21]. For each patient, the burden of surgical complications was calculated according to the Comprehensive-Complication-Index (CCI) [22].

2.3. Statistical analysis

Statistical analysis was performed by the Medical Physics Department of our institution. Discrete variables were expressed in fractions and compared using Fisher's Exact or Chi-Square Test. Continuous variables were expressed as medians and compared using the Sum Rank Test. Survival curves were estimated by the Kaplan-Meier method and were compared with the Log-rank test. Cox regression models were used to evaluate the impact of different covariates on PFS and OS. All statistical tests were two-sided. *Stata software 9.0* was used to perform all statistical analyses and a level of $p < 0.05$ was adopted for significance.

3. Results

3.1. Study population

Among the 211 patients with newly diagnosed FIGO stage IIIA-IVB, non-mucinous HGOC referred to our institution for primary surgical treatment during 2015–2020, 137 received PDS and were included in the study. Of these, 60 patients received surgical treatment during 2015–2017 (Group 1) and 77 during 2018–2020 (Group 2).

Table 1 reports patients' baseline characteristics. No statistical differences in the selected covariates were found between the two groups. Median age at diagnosis was 66 and 65 in Group 1 and Group 2, respectively, and most patients (93 % and 96 %, respectively) had a good performance status (ECOG 0–1). As expected, high-grade serous ovarian carcinoma was the most common histologic subtype in both groups. Concerning BRCA mutations, the difference in the availability of BRCA mutational status approached statistical significance. Mutational status was unavailable in 52 % and 37 % of patients in Groups 1 and 2, respectively ($p = 0{,}053$). Among patients with known BRCA status, mutation incidence was comparable in the two groups.

3.2. Surgical radicality and complications

Table 2 reports surgical, post-operative treatment, and morbidity parameters. No difference in disease distribution was observed between the two groups. Median PCI was 12,5 and 12 in Group 1 and Group 2, respectively ($p = 0{,}317$). FIGO stage distribution was comparable in the

Table 1
Patients' baseline characteristics by surgery time period.

		Group I (n: 60)	Group II (n: 77)	p
Age	Median (IQ range)	66 (55–73)	65 (58–72)	0,891
ECOG	0	38 (63 %)	54 (70 %)	0,599
	1	18 (30 %)	20 (26 %)	
	2	4 (7 %)	3 (4 %)	
ASA	1	2 (3 %)	1 (1 %)	0,489
	2	38 (63 %)	55 (71 %)	
	3	19 (32 %)	21 (28 %)	
	4	1 (2 %)	0 (0 %)	
BMI	Median (IQ range)	24.5 (20,6–28,2)	23,1 (20,3–26.6)	0,453
Hb (g/dL)	Median (IQ range)	12.5 (11.5–13.5)	12,7 (11,4–13,4)	0,888
PLT (U/uL x10^3)	Median (IQ range)	350 (257–435)	342 (263–432)	0,979
BRCA Status	N/A	31 (52 %)	28 (37 %)	0,053
	wtBRCA1-2	13 (22 %)	31 (40 %)	0,200
	s-gBRCA1	11 (18 %)	10 (13 %)	
	s-gBRCA2	5 (8 %)	8 (10 %)	
	s-gBRCA1 + s-gBRCA2	0 (0%)	0 (0 %)	
Histotype	high-grade serous	49 (82 %)	69 (90 %)	**0,011**
	high-grade endometrioid	6 (10 %)	1 (1 %)	
	clear cell	2 (3 %)	1 (1 %)	
	carcinosarcoma	0 (0%)	5 (7 %)	
	undifferentiated	3 (5 %)	1 (1 %)	
FIGO Stage	IIIA	3 (5 %)	6 (8 %)	0,615
	IIIB	4 (7 %)	5 (7 %)	
	IIIC	39 (65 %)	55 (71 %)	
	IVA	3 (5 %)	4 (5 %)	
	IVB	11 (18 %)	7 (9 %)	

Table 2
Patients' Surgical, post-operative treatment, and morbidity parameters by surgery time period.

		Group I (n: 60)	Group II (n: 77)	
PCI	Median (IQ range)	12,5 (8–20)	12 (8–16)	0,317
Surgical Approach	LPS	7 (12 %)	3 (4 %)	0,081
	LPT	53 (88 %)	74 (96 %)	
Lenght of surgery (min)	Median (IQ range)	195 (171–255)	246 (192–328)	**0,001**
Aletti SCS	Median (IQ range)	4 (3–7)	6 (4–9)	**0,003**
Patients receiving at least 1 bowel resection		23 (38 %)	34 (44 %)	0,305
Patients receiving recto-sigmoid resection		19 (32 %)	29 (38 %)	0,292
Patients receiving large bowel resection		5 (8 %)	9 (12 %)	0,364
Patients receiving small bowel resection		5 (8 %)	12 (16 %)	0,155
Patients receiving at least 1 upper abdomen procedure		16 (27 %)	34 (44 %)	**0,026**
Patients receiving diaphragmatic stripping/resection		9 (15 %)	28 (36 %)	**0,004**
Patients receiving splenectomy		4 (7 %)	4 (5 %)	0,495
Patients receiving liver resection/ tumorectomy		6 (10 %)	1 (1 %)	**0,028**
RD	NED	20 (33 %)	47 (61 %)	**0,008**
	1–4 mm	15 (25 %)	15 (19 %)	
	5–10 mm	8 (13 %)	6 (8 %)	
	<10 mm	43 (72 %)	68 (88 %)	**0,012**
	>10 mm	17 (28 %)	9 (12 %)	
Blood Loss (mL)	Median (IQ range)	500 (300–1000)	500 (300–800)	0,456
Patients without any complications		31 (52 %)	38 (49 %)	0,461
Patients with at least one complication	Total	29 (48 %)	39 (51 %)	
	CDC 1	5 (8 %)	5 (6 %)	0,652
	CDC 2	25 (42 %)	30 (39 %)	
	CDC 3	2 (3 %)	4 (5 %)	
	CDC 4	0 (0 %)	0 (0 %)	
	CDC 5	3 (5 %)	1 (1 %)	
CCI	Median (IQ range)	20,9 (20.9–29.6)	20,9 (20.9–20.9)	0,117
Patients receiving adjuvant CT	yes	53 (88 %)	75 (97 %)	**0,041**
	no	3 (5 %)	2 (3 %)	
	n/a	4 (7 %)	0 (0 %)	
Patients receiving maintenance therapy after I line CT	no	49 (82 %)	51 (66 %)	**0,004**
	Bevacizumab	6 (10 %)	13 (17 %)	
	PARP-i	0 (0 %)	10 (13 %)	
	other	1 (2 %)	2 (3 %)	
	n/a	4 (7 %)	1 (1 %)	
Patients receiving maintenance therapy after II line CT	Relapsed patients	41 (68 %)	47 (61 %)	0,241
	no	26 (63 %)	25 (53 %)	0,289
	Bevacizumab	5 (13 %)	14 (30 %)	
	PARP-i	5 (13 %)	5 (11 %)	
	other	1 (2 %)	1 (2 %)	
	n/a	4 (9 %)	2 (4 %)	
FUP (months)				
PFS	Median	19	19	0,288
	at 24 months	33,60 %	47,33 %	
OS	Median	38	>68	**0,022**
	at 24 months	72,10 %	80,37 %	

two groups, with most patients presenting with stage IIIC disease (65 % and 71 %, respectively; p = 0,615).

A significant increase in complete cytoreduction was observed in Group 2. 33 % and 61 % of patients in Groups 1 and 2 had no RD after surgery (p = 0,008), and 38 % and 27 % had infra-centimetric RD, respectively. Suboptimal cytoreduction was performed in 28 % of patients in Group 1 and 12 % of patients in Group 2. Comprehensively, RD was < 1 cm in 72 % and 88 % of patients in Groups 1 and 2, respectively (p = 0,012). The higher rate of complete cytoreduction in Group 2 was related to the higher surgical complexity of PDS in Group 2. The median Aletti SCS was 4 and 6 in Group 1 and Group 2, respectively (p = 0,003). This difference did not derive from an increase in the number of patients receiving small or large bowel resections (38 % and 44 % in Group 1 and Group 2, respectively [p = 0,305]) but was secondary to a significant increase in upper abdomen surgical procedures. Diaphragmatic stripping and/or resection, splenectomy, partial gastrectomy, liver tumorectomy, or a combination of these were performed in 27 % and 44 % of patients in Group 1 and Group 2, respectively (p = 0,026). Particularly, a significant increase in diaphragmatic surgical procedures was observed in Group 2 (15 % vs 36 %, p = 0,004). Despite a longer median duration of surgery (246 vs 195 min, p = 0,001), the more aggressive surgical approach of Group 2 was not associated with an increase in the median intra-operative blood loss nor with higher rates of surgical complications. Intra- and postoperative complications occurred comprehensively in 48 % and 51 % of patients in Groups 1 and 2, respectively. Median CCI was 20,9 in both groups (p = 0,117). Grade II complications were the most frequently recorded (42 % vs 39 %, respectively [p = 0,652]), whereas only 3 % and 5 % experienced at least one Grade III complication, respectively. Post-operative death occurred in 3 patients in Group 1 and 1 patient in Group 2. Intravenously administered platinum-based adjuvant chemotherapy was administered in 88 % and 97 % of patients in Groups 1 and 2 (p = 0,041), respectively. No patients received HIPEC or intraperitoneal chemotherapy. First-line maintenance treatment was administered in 18 % and 34 % of patients in Group 1 and 2, respectively (p = 0,004): 10 % of patients in Group 1 and 17 % in Group 2 received Bevacizumab, whereas no patients in Group 1 and 13 % of patients in Group 2 received a PARP-inhibitor as first-line maintenance therapy. 37 % of patients in Group 1 and 47 % of patients in Group 2 received second-line maintenance therapy for relapsed disease: Bevacizumab was administered in 13 % and 30 % of patients, whereas 13 % and 11 % of patients of Group 1 and 2 received PARP-inhibitors, respectively.

3.3. Oncologic outcomes

Median follow-up was 44 months in the entire cohort. Two different patients' stratifications were designed to analyze oncologic outcomes.

First, patients were stratified according to RD irrespective of the surgical Group. As expected, Fig. 1 shows a significantly better PFS (p = 0.014) and OS (p < 0,001) in patients with RD = 0 compared to patients with so-called optimal RD (<1 cm) and suboptimal debulking. Compared with those with larger RD, a lower but still consistent benefit on both PFS and OS was observed in patients with infra-centimetric RD.

Second, patients were stratified according to the surgical Group (Group 1 vs Group 2). Median DFS was 19 months in both groups. DFS at 24 months was 33,60 % in Group 1 and 47,33 % in Group 2 (p = 0,288). Albeit a trend of better DFS in Group 2, these differences did not reach statistical significance. Conversely, a statistically significant better OS was observed in Group 2 (Fig. 2). The median OS was 38 months in Group 1, whereas it was not reached in Group 2 at the time of data cut-off. OS at 24 months was 72,10 % in Group 1 and 80,37 % in Group 2 (p = 0,022).

Residual disease, surgery group, FIGO stage, histotype, and first-line maintenance therapy were the selected covariates included in univariate and multivariate analysis for PFS. RD at PDS was a significant detrimental prognostic factor for PFS at both univariate (OR 1,69; 95%CI 1,05-2,73; p = 0,031) and multivariate analysis (OR 2.02; 95%CI 1.13–3.59; p = 0,017), whereas administration of first-line maintenance therapy was associated with improved PFS at both univariate (OR 0,32; 95%CI 0,14-0,75; p = 0,008) and multivariate analysis (OR 0,29; 95%CI 0,12-0,72; p = 0,007). RD, surgery group, FIGO stage, histotype, first-line, and second-line maintenance were the selected covariates included in univariate and multivariate analysis for OS. At univariate analysis, RD at PDS (OR 2,53; 95%CI 1,55-4,14; p < 0,001), stage IIIC-IV (OR 9,62; 95%CI 1,24–74,80; p = 0,031) and administration of second-line maintenance (OR 0,08; 95%CI 0,02-0,28; p < 0,001) impacted significantly on OS. At multivariate analysis, only the administration of maintenance therapy, both first- and second-line, remained a significant prognostic factor for OS (Table 3).

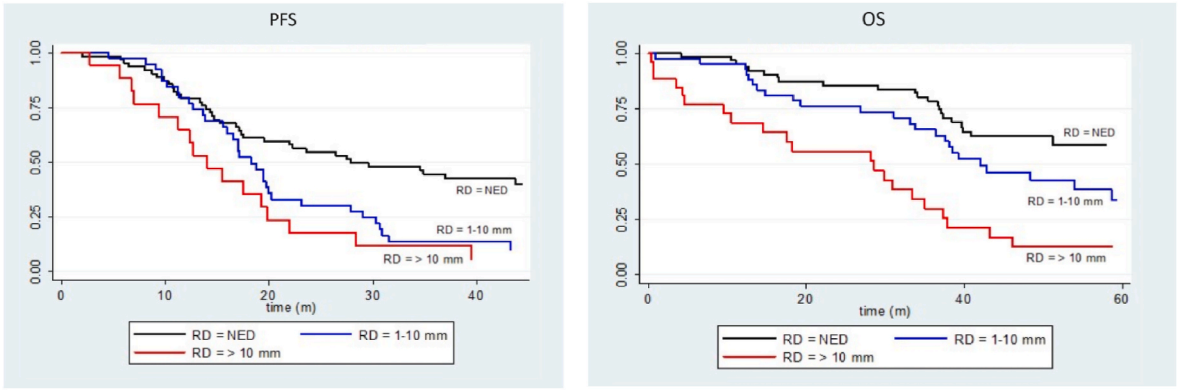

Fig. 1. Kaplan-Meyer plots for DFS and OS in the entire study cohort stratified per RD.

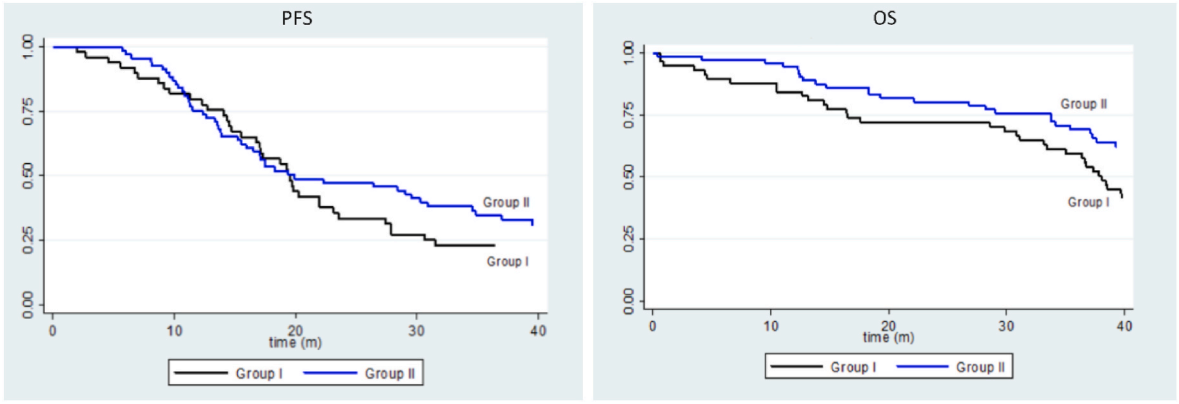

Fig. 2. Kaplan-Meyer plots for DFS and OS in the entire study cohort stratified per surgery Group.

Table 3
Univariate and multivariate Cox Regression Models of PFS and OS at 24 months.

Progression Free Survival				
	Univariate analysis		Multivariate analysis	
	OR (IC 95 %)	P - value	OR (IC 95 %)	P - value
RD > 10 mm vs RD < 10 mm vs RD = 0	1.69 (1.05–2.73)	**0.031**	2.02 (1.13–3.59)	**0.017**
Group 2 vs Group 1	0.65 (0.32–1.30)	0.223	0.79 (0.35–1.78)	0.566
Figo Stage	1.42 (0.52–3.85)	0.496	1.18 (0.40–3.50)	0.764
Histotype	1.59 (0.59–4.24)	0.358	1.41 (0.47–4.21)	0.536
I line maintenance therapy	0.32 (0.14–0.75)	**0.008**	0.29 (0.12–0.72)	**0.007**
Overall Survival				
	Univariate analysis		Multivariate analysis	
	OR (IC 95 %)	P - value	OR (IC 95 %)	P - value
RD > 10 mm vs RD < 10 mm vs RD = 0	2.53 (1.55–4.14)	**<0.0001**	1.76 (0.72–4.26)	0.213
Group 2 vs Group 1	0.60 (0.29–1.24)	0.171	2.74 (0.66–11.45)	0.167
Figo Stage	9.62 (1.24–74.80)	**0.031**	6.09 (0.57–65.28)	0.135
Histotype	1.03 (0.36–2.92)	0.957	0.24 (0.03–1.75)	0.160
I line maintenance therapy	0.39 (0.15–1.05)	0.061	0.18 (0.03–0.96)	**0.044**
II line maintenance therapy	0.08 (0.02–0.28)	**<0.0001**	0.06 (0.01–0.27)	**<0.0001**

4. Discussion

In this single-center retrospective analysis, we evaluated the impact of extensive upfront cytoreductive surgery on surgical radicality, morbidity, and survival outcomes in 137 patients with newly diagnosed FIGO stage IIIA-IVB, non-mucinous HGOC who received PDS during two different three-year periods. The choice of these two distinct cohorts was made according to the change in surgical paradigm that occurred at our institution in 2018, when a more aggressive systematic abdominal debulking approach including upper abdominal procedures and extensive removal of the peritoneum was introduced in routine surgical practice.

This change in the philosophy of surgical treatment of advanced HGOC mainly occurred thanks to the firm belief of the new department's Chief of our institution about the beneficial role of maximal surgical effort on oncologic outcomes.

Since it is well established that NACT reduces the burden of disease, surgical complexity is lower in patients undergoing IDS and complete cytoreduction is likely to be more often achieved when IDS is performed compared to PDS, only patients who received PDS were included in our analysis.

Despite similar disease and FIGO stage distribution between the two groups, a higher surgical complexity was observed in Group 2, mainly attributable to the global increase in the incidence of upper abdomen surgical procedures. Conversely, the incidence of bowel resections was slightly comparable in the two groups. As expected, higher surgical complexity reflected in better surgical outcomes with a higher rate of complete tumor resection; on the other hand, more aggressive surgery was not associated with a significant increase in surgical morbidity.

The increase in upper abdominal surgery in Group 2 was mainly attributable to the consistent increase in diaphragmatic stripping and

resections. Contrarily, liver procedures were more frequent in Group 1 (10 % vs 1 %, p = 0,028) and this might reflect a different algorithm in the selection of patients considered suitable for adequate PDS between the two groups.

The increased rate of complete cytoreduction in Group 2 did not correlate with a higher complication rate, nor with greater complication severity based on the Clavien-Dindo Classification, nor with a higher burden of complications assessed using the CCI. This is of extreme importance since surgical complications make hospitalization longer and the subsequent delay in the start of adjuvant chemotherapy is associated with worse oncologic outcomes [23,24]. Our data are in line with Yalcin et al. [25], who found no increase in the complication rate of patients undergoing upper abdominal surgery in the treatment of advanced OC. Conversely, our results contrast with the previous series by Benedetti Panici et al. [26] who reported diaphragmatic resection as an independent predictor of severe complications. The way complications were recorded may have influenced our results. The CTC Version 4.03 classification [27] used by Benedetti Panici et al. stratifies complications in a 4-tier grading according to the severity of clinical manifestations, whereas the Clavien-Dindo Classification relies on the type of treatment, either medical or surgical, used to manage each complication.

The goal of surgery has changed over decades, and optimal cytoreduction progressively evolved from debulking with less than 1–2 cm of residual disease (RD) to complete resection of all visible tumor with no evidence of RD. In 2009 Du Bois et al. [10] showed the "tremendous impact" on both PFS and OS of complete cytoreduction with no RD and the lower but still significant impact of small RD (<1 cm) compared to gross macroscopic RD. In line with the results of that practice-changing study and other similar series [13,15,28], we showed that complete tumor resection at PDS is one of the most important prognostic factors in the treatment of advanced HGOC. Particularly, the absence of RD and optimal cytoreduction (RD < 1 cm) were associated with a significant improvement in both PFS and OS in our cohort compared to gross RD (RD > 1 cm).

We expected that the more extended surgical radicality of Group 2 would have resulted in significantly better PFS and OS compared to Group 1. Unexpectedly, the difference in PFS between the two groups did not reach statistical significance. However, a trend of better PFS was observed in Group 2, and RD at PDS was an independent prognostic factor for PFS in both univariate and multivariate analysis. One possible explanation for this finding may be the relatively small number of our patients' cohort, probably underpowered to detect any difference in PFS after stratification for the surgery group. Additionally, despite similar FIGO stage distribution and median PCI in the two groups, we hypothesize that some differences in abdominal disease distribution between the two groups may exist, as neither FIGO Stage nor PCI can fully capture tumor spread within the abdominal cavity. For instance, FIGO Stage IVB comprises both patients with bowel transmural invasion and patients with distant parenchymal metastases, whereas PCI assesses peritoneal spread but not intra-abdominal parenchymal invasion. Thus, Group 2 might present a more complex peritoneal distribution and a more unfavorable metastatic FIGO IVB disease, reflecting a higher risk of relapse.

Contrary to PFS, OS was significantly higher in Group 2. At univariate analysis, improved OS was related to the absence of RD, FIGO stage, and administration of maintenance therapy, whereas at multivariate analysis only administration of first-line and second-line maintenance remained an independent prognostic factor for OS. Therefore, the enhanced OS in Group 2 was not solely due to increased surgical radicality and complete cytoreduction rates but likely derived from higher maintenance therapy usage in both first-line and post-relapse settings. Additionally, the greater surgical effort and the lower RD rates observed in Group 2 might have reduced the probability of developing chemoresistance after first-line and subsequent lines of treatment, since the number of tumor cells exposed to chemotherapy-induced selective pressure was lower. Furthermore, the two cohorts of our series are metachronous; the significant increase of OS observed in Group 2 despite similar PFS might reflect the increased use of maintenance therapy in patients treated more recently. In the last decade, the practice-changing results of several phase III randomized clinical trials [29–36] have led to the approval of VEGF inhibitors and PARP inhibitors as maintenance therapies both in the recurrent and first-line setting with consistent benefit for PFS and/or OS. Contrary to Bevacizumab, which received approval from the Italian drug agency in 2013 and whose effect on OS is controversial [29,30], Olaparib was approved as maintenance therapy after second- and first-line platinum-based CT only in 2018 and 2020, respectively, displaying a significant advantage for both PFS and OS in BRCA1-2 mutated patients [32,37]. Consequently, patients of Group 2 received maintenance more frequently compared to Group 1 and were more likely to receive PARP inhibitors as first-line maintenance therapy.

Comprehensively, our cohort shows that an extensive surgical effort not only improves the oncological outcome of advanced-stage HGOC patients but is also safe in terms of morbidity. One of the major strengths of this study is its "real-life" nature; all consecutive patients treated surgically with cytoreductive intent at our institution in years 2015–2020 were included irrespective of morbidity, treatment choice, and discontinuation. Second, the choice of the two time periods and the more extensive surgical procedures performed in 2018–2020 reflected the change in surgical philosophy that occurred at our institution in 2018. The main limitation of our analysis is the metachronous nature of our cohorts. This led to a significant disparity in follow-up duration between the two groups, as well as in the frequency and specific drug utilized for maintenance treatment.

5. Conclusions

In contrast to those enrolled in clinical trials, patients encountered in daily routine clinical practice are usually older of age, have less favorable performance status, and have more comorbidities. Thus, they are exposed to a higher probability of postoperative complications and might benefit less from extensive surgical procedures. Our data show that the absence of RD at surgery is one of the most important prognostic factors in the treatment of advanced ovarian cancer not only in the highly selected population of clinical trials but also in the real-life clinical practice of an ESGO-accredited large university hospital. Optimal cytoreduction with RD < 1 cm is still of benefit compared to larger RD and might be an option in patients with HGOC in whom complete debulking is unaffordable. An extensive surgical effort with routine systematic removal of the peritoneum and implementation of upper abdomen procedures leads to a significant increase in complete cytoreduction and the results of this maximal surgical effort are even more valuable considering that a more aggressive surgical approach was not associated with an increase in surgical morbidity. Arm-in-arm with novel maintenance therapies, complete cytoreduction contributes to increasing the outcomes of patients with advanced HGOC and should represent the standard of care in real-life clinical practice.

Ethics approval and consent to participate

The study was approved by IRB Comitato Etico Brianza, IRCCS San Gerardo dei Tintori, Monza, Italy, and was conducted in accordance with the Declaration of Helsinki. Informed consent was collected for each patient at the time of diagnosis.

Data availability

The raw data that support the findings of this study are not openly available due to reasons of sensitivity and are available from the corresponding author upon reasonable request.

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CRediT authorship contribution statement

Tommaso Bianchi: Conceptualization, Study design, Data acquisition, Quality control of data and algorithms, Formal analysis, Formal analysis, Manuscript preparation, Writing – review & editing, Writing – review & editing, Manuscript revision. **Tommaso Grassi:** Conceptualization, Study design, Data acquisition, Quality control of data and algorithms, Formal analysis, Formal analysis, Manuscript preparation, Writing – review & editing, Manuscript review, Manuscript revision. **Luca Bazzurini:** Conceptualization, Study design, Data acquisition, Quality control of data and algorithms, Formal analysis, Formal analysis, Writing – review & editing, Manuscript review. **Filippo Testa:** Data acquisition, Writing – review & editing, Manuscript review. **Jasmine Corti:** Data acquisition, Writing – review & editing, Manuscript review. **Giorgia Pecis Cavagna:** Data acquisition, Writing – review & editing, Manuscript review. **Martina Bombelli:** Data acquisition, Writing – review & editing, Manuscript review. **Andrea Alberto Lissoni:** Data acquisition, Writing – review & editing, Manuscript review. **Giampaolo Di Martino:** Data acquisition, Writing – review & editing, Manuscript review. **Gaetano Trezzi:** Data acquisition, Writing – review & editing, Manuscript review. **Elena De Ponti:** Formal analysis, Formal analysis. **Robert Fruscio:** Conceptualization, Study design, Quality control of data and algorithms, Formal analysis, Formal analysis, Manuscript preparation, Manuscript revision. **Fabio Landoni:** Conceptualization, Study design, Quality control of data and algorithms, Formal analysis, Formal analysis.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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