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ORIGINAL ARTICLE – GYNECOLOGIC ONCOLOGY

Which Surgical Attitude to Choose in the Context of Non-Resectability of Ovarian Carcinomatosis: Beyond Gross Residual Disease Considerations

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ABSTRACT

Background. In ovarian cancer, the increased rate of radical surgery comprising upper abdominal procedures has participated to improve overall survival (OS) in advanced stages by increasing the rate of complete cytoreductions. However, in the context of non-resectability, it is unclear whether radical surgery should be considered when it would lead to microscopic but visible disease ($\leq$1 cm). We aimed to compare the survival outcomes among patients with incomplete cytoreduction according to the extent of surgery.

Methods. Overall, 148 patients presenting with advanced stage ovarian carcinomas were included in this retrospective study, regardless of treatment schedule. These patients were stratified according to the extent of surgery (standard or radical). Complete cytoreduction at the time of debulking surgery could not be carried out in all cases.

Results. Among our study population ($n = 148$), 96 patients underwent standard procedures (SPs) and 52 underwent radical surgeries (RP). Patients in the SP group had a lower Peritoneal Index Cancer (PCI) at baseline (12.6 vs. 14.9; $p = 0.049$). After PCI normalization, we observed similar OS in the SP and RP groups (39.7 vs. 43.1 months; $p = 0.737$), while patients in the SP group had a higher rate of residual disease >10 mm ($p < 10^{-3}$). Patients in the RP group had an increased rate of relapse ($p = 0.005$) but no difference in disease-free survival compared with the SP group (22.2 for SP vs. 16.3 months; $p = 0.333$). Residual disease status did not impact survival outcomes.

Conclusions. In the context of non-resectable, advanced stage ovarian cancer, standard surgery seems as beneficial as radical surgery regarding survival outcomes and should be considered to reduce surgery-associated morbidity.

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Due to the lack of effective screening, ovarian cancer spreading to the peritoneum often results in an advanced stage diagnosis [International Federation of Gynecology and Obstetrics (FIGO) stages IIIC and IV].[1] It is thus associated with poor outcomes and is considered the leading cause of death from gynecologic cancer in developed countries.

In patients presenting with advanced stage, the mainstay of treatment involves a combination of cytoreductive surgery and paclitaxel and platinium-based chemotherapy.[2,3] Surgery can be performed either primarily or after courses of neoadjuvant chemotherapy, depending on the extent of the initial disease and the possibility of a complete debulking.[4] This cytoreductive surgery aims to remove the bulk of the tumor with the ideal purpose of complete resection as the amount of residual disease is a major prognosis parameter.[2,5,6] Hence, radical procedures involving multiple digestive tract resections, peritoneum stripping, and upper abdominal surgery (UAS) are sometimes required to achieve complete cytoreduction.[5,7]

Unfortunately, in some cases complete gross resection cannot be achieved. Several studies have observed an inverse correlation between the amount of residual disease and survival.[8] Nevertheless, the threshold effect is still not well determined; some authors have defined a cutoff of 1 cm[9] and others have defined a cutoff of 2 cm,[10,11] while current research tends to only distinguish complete from incomplete surgeries.[3] Extensive abdominal cytoreduction is associated with a higher complication rate, therefore the benefit of such a procedure should be carefully evaluated.[12] This poses the question of whether radical surgery should be prioritized over standard procedures (SPs) to minimize postoperative tumor residues.

This study aims to assess survival outcomes in women experiencing advanced stage ovarian cancer where complete cytoreduction could not be carried out. Our main goal was to define whether these patients would benefit from more extensive procedures.

PATIENTS AND METHODS

Study Population

This study received the agreement of the local Institutional Review Board. A total of 527 patients with advanced stage ovarian cancers (FIGO stages IIIC and IV with pleural invasion only) treated from January 2003 to December 2007 were included, and patients were treated in seven French referral gynecologic oncology units. All patients with complete cytoreductive surgery were excluded; hence, only patients who underwent incomplete cytoreductive surgery were enrolled, independently of the amount of residual disease and the treatment schedule. Upfront debulking surgeries, as well as interval procedures after neoadjuvant chemotherapy, were thus considered. The decision in treatment schedule was defined in tumor board review and was based on clinical assessment and laparoscopic evaluation of disease extension, concordantly with French and international guidelines. In each referral center, a senior surgeon mentored all surgeries and made the decision regarding surgical extent at the time of debulking surgery. Therefore, surgical attitudes were homogenous in a specific center.

Subgroup Definition

Our study population was stratified according to the extent of surgery. Standard surgery was defined as a procedure involving hysterectomy, bilateral salpingo-oophorectomy, rectosigmoid resection, infragastric omentectomy, pelvic and aortic lymphadenectomy and, when applicable, appendectomy. Radical surgery was defined as a procedure involving standard surgery plus a combination of UAS, multiple digestive tract resections, abdominal organ resections (splenectomy, partial gastrectomy, and others), coeliac lymph node dissection, and total abdominal peritoneum stripping. All events, demographic characteristics, histological subtypes, Peritoneal Cancer Index (PCI), and patterns of treatment were collected retrospectively.

Residual Disease Nomenclature

The terminology proposed by Chang and Bristow was used to define residual disease.[8] Residual disease measuring $\leq$10 mm in maximal diameter was defined as gross residual-1 (GR1), and residual disease >10 mm was defined as gross residual-bulky (GRB). Reasons for incomplete cytoreduction were unresectable carcinomatosis of bowel surface, deep mesenteric infiltration, or node and coeliac involvement.

Statistical Analysis

XLSTAT software (Addinsoft®, USA) was used to perform statistical analysis. Overall survival (OS) and disease-free survival (DFS) were computed from the date of initial diagnosis. The first event corresponded to death of any cause for OS, and to relapse or death for DFS. OS and DFS curves were achieved using Kaplan–Meier or parametric analysis. All statistical tests were two-sided and differences were considered significant when $p < 0.05$. The Cox proportional model was used to compute hazard ratios (HRs).

RESULTS

Demographics

Of 527 patients, 152 met our inclusion criteria as they had residual disease after undergoing cytoreductive surgery. We excluded the remaining patients, 374 in whom complete cytoreduction was achieved and 1 in whom residual disease status was unknown. Among the 152 patients with incomplete cytoreduction, 4 were secondarily excluded due to missing data.

Considering our study population ($N = 148$), 96 patients underwent a standard procedure (SP group) and 52 underwent a radical surgery (RP group) (for further details regarding surgical procedures refer to electronic supplementary Tables 1 and 2). No significant differences were observed in patient age, FIGO stages, and patterns of treatment between the two groups (Table 1). Mean PCI value was higher in the RP group than in the SP group ($p = 0.049$). The amount of residual disease was greater after standard surgery: GRB rate in the SP group was 45.8 versus 17.3 % in the RP group ($p < 10^{-3}$).

Surgical Extent Does Not Impact Survival Outcomes

The median follow-up was 49 months, and median DFS and OS was 19.9 and 41.9 months, respectively (Table 1). Both the SP and RP groups exhibited similar OS (40.2 vs. 42.7 months, respectively; $p = 0.711$) (Fig. 1), and there was a trend towards reduced DFS in the RP group (16.5 vs. 22.1 months in women in the SP group; $p = 0.068$). Noteworthy, patients who underwent radical procedures were more likely to develop a relapse ($p = 0.021$), with an HR for recurrence of 1.46 ($p = 0.05$).

TABLE 1 Comparative statistics considering the whole population

	Total ($N = 148$)	SP group ($N = 96$)	RP group ($N = 52$)	p-Value
Age [mean (SD)]	61.1 (9.8)	61.2 (9.8)	60.9 (9.9)	0.853
PCI [mean (SD)]	13.5 (6.2)	12.6 (6.6)[a]	14.9 (5.2)[b]	0.049*
DFS [mean (SD)]	19.9 (14.3)	22.1 (15.5)	16.5 (11.8)	0.068
OS [mean (SD)]	41.9 (18.5)	40.2 (18.1)	42.7 (19.4)	0.711
OS after relapse [mean (SD)]	–	19.2 (13.5)	27.4 (15.8)	0.125
FIGO stage				0.795
IIIC	112 (75.7)	72 (75.0)	40 (76.9)	
IV	36 (24.3)	24 (25.0)	12 (23.1)	
Neoadjuvant CT				0.187
Yes	86 (58.1)	52 (54.2)	34 (65.4)	
No	62 (41.9)	44 (45.8)	18 (34.6)	
Histological type				0.079
Serous papillary	105 (70.9)	65 (67.7)	40 (76.9)	
Endometrioid	18 (12.2)	13 (13.6)	5 (9.6)	
Undifferentiated	18 (12.2)	15 (15.6)	3 (5.8)	
Other	7 (4.7)	3 (3.1)	4 (7.7)	
Residual disease, mm				$<10^{-3}$*
≤ 10	95 (64.2)	52 (54.2)[a]	43 (82.7)[b]	
>10	53 (35.8)	44 (45.8)	9 (17.3)	
Relapse				0.005*
No	15 (12.4)	14 (19.2)[a]	1 (2.1)[b]	
Yes	106 (87.6)	59 (80.1)	47 (97.9)	
Condition				0.92
Alive	46 (38.0)	28 (38.4)	18 (37.5)	
Dead	75 (62.0)	45 (61.6)	30 (62.5)	

Data are expressed as n (%) unless otherwise specified

SP standard procedure, *RP* radical procedure, *SD* standard deviation, *PCI* Peritoneal Cancer Index, *DFS* disease-free survival, *OS* overall survival, *FIGO* International Federation of Gynecology and Obstetrics, *CT* chemotherapy

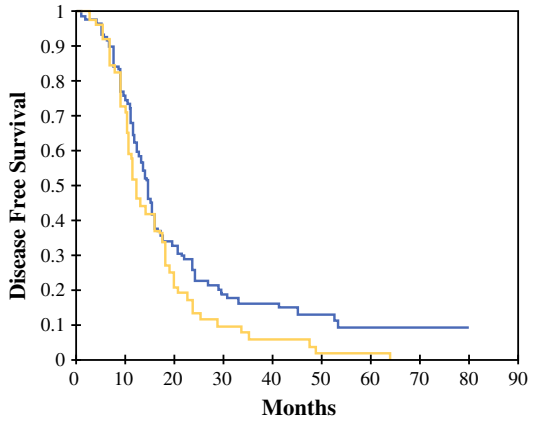
* Statistical significance

[a,b] A statistical significance is observed in the comparison between the groups marked with a different letter

(A) Disease Free Survival

	Standard surgery group *N= 96*	Radical surgery group *N= 52*	*ρ*-value
Disease free survival, months (SD)	**22.1** (15.5)	**16.5** (11.8)	*0.068*

SD = standard deviation



(B) Overall Survival

	Standard surgery group *N= 96*	Radical surgery group *N= 52*	*ρ*-value
Overall survival, months (SD)	**40.2** (18.1)	**42.7** (19.4)	0.711

SD = standard deviation

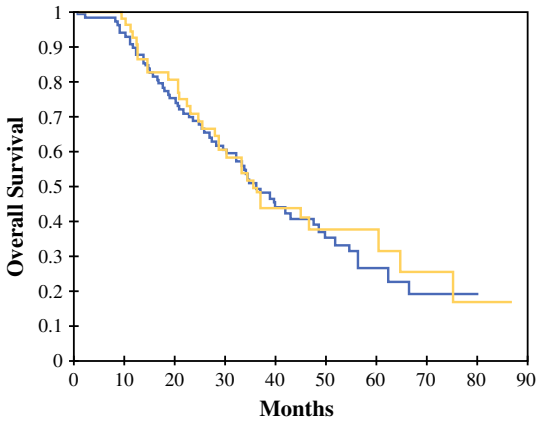


FIG. 1 Comparative outcomes between the standard procedure and radical surgery groups for (**a**) disease-free survival, and (**b**) overall survival

Subgroup Analysis

To avoid possible bias due to the significant difference of disease extent between the two groups, we only included patients with a PCI ≥10 (Table 2). We observed similar results regarding the volume of residual disease: patients in the SP group displayed more GRB than patients in the RP group (60.3 vs. 16.7 %, $p < 10^{-4}$). The treatment patterns were slightly different between the two groups, with a trend toward more neoadjuvant chemotherapy in patients in the RP group (62.5 vs. 46.6 %; $p = 0.09$).

Median OS and DFS were 42 and 19.5 months, respectively, in the subpopulation with a PCI ≥10 ($N = 121$). Similarly to non-adjusted analysis, more recurrences were observed in the RP group ($p = 0.005$), but the corresponding HR did not reach significance (HR 1.319; $p = 0.158$). No significant difference regarding DFS between the two groups was observed despite a substantial gap of 5.9 months (22.2 months in the SP group vs. 16.3 months in the RP group; $p = 0.156$) (Fig. 2). Conversely, patients in the RP group seemed to exhibit improved OS (43.1 vs. 39.7 months) but the difference was still not significant ($p = 0.575$).

Defining a cutoff at 20 for PCI, we noticed a significant difference between the two groups regarding treatment schedule; the rate of upfront debulking surgery was higher in the SP group ($p = 0.04$) (Table 3). Furthermore, the increased rate of relapse observed in the RP group ($p = 0.033$) was associated with a significant HR for recurrence of 2.013 ($p = 0.026$). In parallel, patients in the RP group had a decreased DFS compared with the SP group (13.6 vs. 25.4 months, respectively; $p = 0.031$) (electronic supplementary Figure 1); however, both groups displayed similar OS (37.9 months for the RP group and 35.5 months for the SP group; $p = 0.55$).

Residual Disease and Treatment Schedule Do Not Modulate Prognosis

Residual disease status did not impact survival outcomes in the study population. HR associated with GRB was 1.146 ($p = 0.41$) and 1.045 ($p = 0.058$) for OS and DFS, respectively. Similarly, the treatment schedule did not modulate patients' prognosis. HR associated with neoadjuvant chemotherapy was 1.072 ($p = 0.74$) and 1.15 ($p = 0.43$) for OS and DFS, respectively.

TABLE 2 Comparative statistics after PCI adjustment (≥10)

	Total ($N = 121$)	SP group ($N = 73$)	RP group ($N = 48$)	p-Value
Age [mean (SD)]	62 (9.8)	62 (10)	62(9.6)	0.93
PCI [mean (SD)]	16 (4.8)	17 (5.1)	16 (4.4)	0.43
DFS [mean (SD)]	19.5 (14.4)	22.2 (16.1)	16.3 (11.3)	0.156
OS [mean (SD)]	42.0 (19.9)	39.7 (19.7)	43.1 (19.9)	0.575
OS after relapse [mean (SD)]	–	19.5 (14.8)	28.4 (16.1)	0.126
FIGO stage				0.35
IIIC	93 (76.9)	54 (74.0)	39 (81.2)	
IV	28 (23.1)	19 (26.0)	9 (18.8)	
Neoadjuvant CT				0.09
Yes	64 (52.9)	34 (46.6)	30 (62.5)	
No	57 (47.1)	39 (53.4)	18 (37.5)	
Histological type				0.79
Serous papillary	90 (74.4)	53 (72.6)	37 (77.1)	
Endometrioid	15 (12.4)	10 (13.7)	5 (10.4)	
Undifferentiated	9 (7.4)	6 (8.2)	3 (6.2)	
Other	7 (5.8)	4 (5.5)	3 (6.3)	
Residual disease, mm				$<10^{-4}$*
≤10	69 (57.0)	29 (39.7)[a]	40 (83.3)[b]	
>10	52 (43.0)	44 (60.3)	8 (16.7)	
Relapse				0.005*
No	15 (12.4)	14 (19.2)[a]	1 (2.1)[b]	
Yes	106 (87.6)	59 (80.1)	47 (97.9)	
Condition				0.92
Alive	46 (38.0)	28 (38.4)	18 (37.5)	
Dead	75 (62.0)	45 (61.6)	30 (62.5)	

Data are expressed as *n* (%) unless otherwise specified

SP standard procedure, *RP* radical procedure, *SD* standard deviation, *PCI* Peritoneal Cancer Index, *DFS* disease-free survival, *OS* overall survival, *FIGO* International Federation of Gynecology and Obstetrics, *CT* chemotherapy

* Statistical significance

[a,b] There is a statistical significance in the comparison between the groups marked with a different letter

Overall, 86 patients received neoadjuvant chemotherapy (58.1 %). Within this subgroup, DFS and OS was 18.9 and 43.4 months, respectively. The surgical approach (standard or radical) did not affect prognosis; no significant differences were observed in OS (37.9 months for SP vs. 49.6 months for RP; $p = 0.22$) and DFS (20.2 months for SP vs. 16.5 months for RP; $p = 0.25$). HR associated with radical surgery was 1.12 ($p = 0.51$) for DFS and 0.68 ($p = 0.27$) for OS. Patients who underwent radical procedures did not develop more recurrences compared with the SP subgroup ($p = 0.15$).

A total of 62 patients underwent upfront debulking surgery (41.9 %). DFS and OS was 22.2 and 42.5 months, respectively. Similar to the subgroup with neoadjuvant chemotherapy, the extent of surgery did not impact OS (45.1 months for SP vs. 36.9 months for RP; $p = 0.23$) and DFS (24.8 months for SP vs. 17.3 months for RP; $p = 0.27$). HR associated with radical surgery was 1.1 ($p = 0.82$) for DFS and 1.37 ($p = 0.52$) for OS. The RP subgroup did not display more relapses ($p = 0.07$).

Finally, the comparison in survival outcomes between the four subgroups, defined according to surgical extent and treatment schedule, showed no significant differences ($p = 0.15$ and $p = 0.9$ for DFS and OS, respectively).

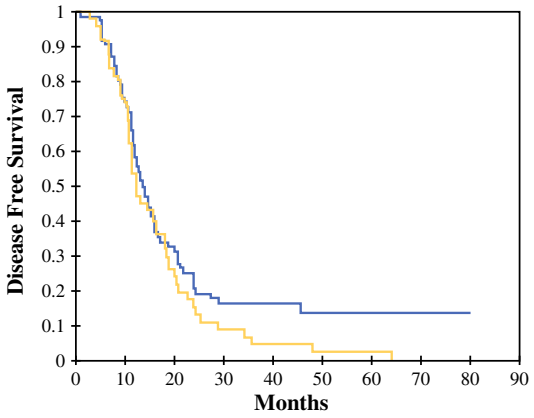
Intercenter Comparison

In all centers, maximal surgical effort was performed to achieve complete cytoreduction whenever applicable. In the case of non-fully resectable disease, we observed a great heterogeneity among centers regarding surgical extent (electronic supplementary Table 1). Two departments prioritized aggressive surgeries (100 and 73.7 %, respectively) and reached the lowest rates of GRB disease

(A) Disease Free Survival

	Standard surgery group *N= 73*	Radical surgery group *N= 48*	*ρ*-value
Disease free survival, months (SD)	**22.2** (16.1)	**16.3** (11.3)	*0.156*

SD = standard deviation



(B) Overall Survival

	Standard surgery group *N= 73*	Radical surgery group *N= 48*	*ρ*-value
Overall survival, months (SD)	**39.7** (19.7)	**43.1** (19.9)	*0.575*

SD = standard deviation

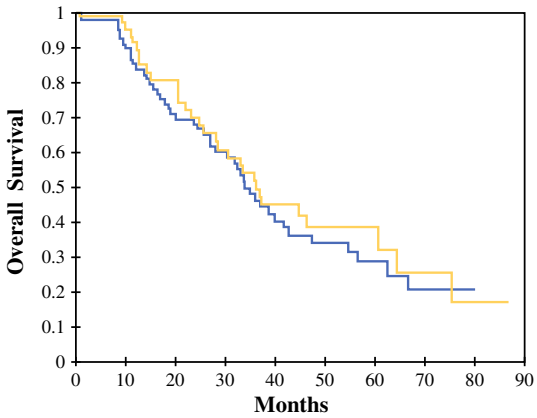


FIG. 2 Comparative outcomes between the standard procedure and radical surgery groups for (**a**) disease-free survival, and (**b**) overall survival, after Peritoneal Cancer Index adjustment (≥10)

(11.8 and 10.5 %, respectively); however, there was no significant difference in OS between the seven departments. Pooling the patients according to the type of surgical strategy of each center (aggressive vs. less aggressive) led to similar results: mean OS was 50.4 months in the two teams prioritizing aggressive approach, and 40.1 months in the others departments ($p = 0.15$).

DISCUSSION

Our results suggest that, in the context of non-resectable, advanced stage ovarian cancer, standard surgery is just as beneficial as radical surgery regarding survival outcomes.

Complete cytoreduction is the main objective in the surgical management of advanced stage ovarian cancer.[6] Considering our whole population ($N = 527$), complete resection was achieved in most patients (71 %) requiring upper abdominal procedures in 185 cases. This perfectly illustrates the paradigm shift toward more extensive debulking surgeries described by Chi et al. in order to improve survival outcomes.[13] The wider acceptability of extended surgical procedures has thus contributed to an increase in the rate of complete cytoreductions.[13,14]

Despite tremendous progress in the imaging of peritoneal carcinomatosis, the visual evaluation at the time of laparoscopy and surgery provides the most accurate information regarding the feasibility of disease resection.[15] It is not always possible to completely remove bulky disease; however, two different approaches can be discussed: (i) minimizing the extent of surgery in the removal of bulky masses in order to decrease pre- and postoperative morbidity, albeit with the risk of increasing residual disease; (ii) minimizing the amount of residual disease with radical procedures despite a higher risk of surgical morbidity. To date, it is unclear whether radical surgery should be considered when it would shift GRB disease to GR1.[8] Nevertheless, several studies have pointed out the survival benefit associated with optimal, but visible, cytoreduction (GR1) in comparison to suboptimal resection (GRB). Eisenhauer et al. have reported that additional UAS to achieve complete or GR1 resection led to similar survival outcomes than patients without the need for UAS, yet with identical tumor residue.[16] In comparison, women who did

TABLE 3 Comparative statistics defining a cutoff at 20 for PCI

	Total ($N = 50$)	SP group ($N = 34$)	RP group ($N = 16$)	p-Value
Age [mean (SD)]	61 (10.5)	61 (11.4)	60(8.5)	0.60
PCI [mean (SD)]	23 (2.8)	24 (2.7)	23 (3.0)	0.24
DFS [mean (SD)]	21.3 (15.3)	25.4 (17.5)	13.6 (6.7)	0.03*
OS [mean (SD)]	39.0 (18.6)	35.5 (17.9)	37.9 (20.4)	0.52
OS after relapse [mean (SD)]	–	15.9 (12.1)	22.8 (18.9)	0.48
FIGO stage				0.15
IIIC	46 (92.0)	30 (88.2)	16 (100)	
IV	4 (8.0)	4 (11.8)	0 (0.0)	
Neoadjuvant CT				0.04*
Yes	21 (42.0)	11 (32.4)[a]	10 (62.5)[b]	
No	29 (58.0)	23 (67.6)	6 (37.5)	
Histological type				0.79
Serous papillary	34 (68.0)	23 (67.7)	11 (68.7)	
Endometrioid	10 (20.0)	8 (23.5)	2 (12.5)	
Undifferentiated	2 (4.0)	1 (2.9)	1 (6.3)	
Other	4 (8.0)	2 (5.9)	2 (12.5)	
Residual disease, mm				0.104
≤10	26 (52.0)	15 (44.1)	11 (68.7)	
>10	24 (48.0)	19 (55.9)	5 (31.3)	
Relapse				0.034*
No	8 (16.0)	8 (23.5)[a]	0 (0.0)[b]	
Yes	42 (84.0)	26 (76.5)	16 (100)	
Condition				0.12
Alive	17 (34.0)	14 (41.2)	3 (18.8)	
Dead	33 (66.0)	20 (58.8)	13 (81.2)	

Data are expressed as *n* (%) unless otherwise specified

SP standard procedure, *RP* radical procedure, *SD* standard deviation, *PCI* Peritoneal Cancer Index, *DFS* disease-free survival, *OS* overall survival, *FIGO* International Federation of Gynecology and Obstetrics, *CT* chemotherapy

* Statistical significance

[a,b] There is a statistical significance in the comparison between the groups marked with a different letter

not benefit from UAS and only underwent GRB resection displayed a poorer prognosis. Notwithstanding, the group with UAS comprised 23 % of complete cytoreductions, which has probably impacted the gap observed between survival outcomes. More recently, Barlin et al. observed similar survival in patients with GR1 resection, regardless of the use of UAS to complete the desired cytoreduction.[17] They did not provide any comparison with GRB patients, therefore it was not possible to estimate the specific survival impact yielded by radical surgery.

According to our data, both surgical approaches led to similar outcomes, although patients who underwent a standard surgery had greater residual disease ($p < 10^{-3}$). Patients with radical procedures were more likely to develop a recurrence within the study follow-up. They also displayed a trend toward decreased DFS compared with the SP group, with a gap of almost 6 months (16.5 vs. 22.1 months, respectively; $p = 0.068$). Regarding OS, we observed an opposite trend (42.7 vs. 40.2 months), with a less striking gap. Such a discrepancy prompted us to propose further hypothesis. (i) The apparent gap in DFS is due to the difference in tumor extent between the two groups of patients; however, a similar gap was observed in the subgroup with a higher PCI. (ii) A more extended cytoreduction might positively impact recurrence sensitivity to second-line treatments. Indeed, OS after relapse was apparently improved in the RP group, with an absolute difference of 9 months after PCI adjustment (28.4 vs. 19.5 months), but once again this was not significant.

Defining a cutoff at 20 for PCI, the difference between interval and relapse became significant—DFS was 25.4 months in the SP group and 13.6 months in the RP group ($p = 0.03$); however, both groups had similar OS, supporting the lack of evidence regarding surgical benefit provided by radical procedures, in particular in the context of wide peritoneal spread of cancer.

Contrary to previous reports, we have included both primary and delayed surgeries. This was justifiable for two reasons. First, treatment schedule did not impact prognosis on Cox proportional analysis (HR = 1.15, $p = 0.43$), agreeing with conclusions of the recent EORTEC randomized trial.[3] Second, making a decision concerning the surgical approach in a patient where the disease cannot be completely removed despite the use of neoadjuvant chemotherapy is difficult, and we aimed to provide some relevant information that could be applied to routine surgical practice. According to our data, the surgical decision did not affect patients' outcome in this specific context.

In our study population, the amount of residual disease after debulking surgery did not impact survival (HR 1.045; $p = 0.058$). Such a finding goes against usual considerations but proving its accuracy is beyond the scope of this article. We can hypothesize that prognosis, in the context of non-resectable, advanced stage ovarian cancer, is also modulated by biological features participating in disease therapeutic response and kinetics, far beyond surgical considerations.

Due to the nature of the study, it does suffer limitations. Its retrospective design exposes the study to potential risks of selection bias and confounding risk factors. The small-sized population might have hindered the strength of our analysis. Data on second-line treatments were not available and, consequently, are not able to be discussed.

Nevertheless, the study brings additional and practical information on an unexplored topic. While we and others support that complete cytoreduction should be performed whenever possible, there is no consensus in the context of surgical failure. The great heterogeneity among the seven centers regarding surgical attitude supports that, in such cases, proverbs and personal feelings are more customary than evidence of science. Some will vow by *primum non nocere* and reduce the extent of the resection to circumvent surgery-associated morbidity in order not to delay systemic treatment. Others will support *the more the better*, preferring a more radical approach. Despite increased morbidity, most patients are able to receive postoperative chemotherapy after UAS;[18] however, delayed initiation of chemotherapy is associated with poorer outcomes. Wright et al. have reported that women who began therapy more than 12 weeks after surgery were 32 % more likely to die from their tumors.[19] In this study, we highlight the fact that, in the context of non-resectability, surgical management is not binary, with an attitude superior to another. Expected disease sensitivity to first- and second-line treatment should also participate in the decision through the screening of individual biological tumor features.

DISCLOSURES Fabien Vidal, Haya Al Thani, Pascale Haddad, Mathieu Luyckx, Eberhard Stoeckle, Philippe Morice, Eric Leblanc, Fabrice Lecuru, Emile Daraï, Jean-Marc Classe, Christophe Pomel, Ziyad Mahfoud, Gwenael Ferron, Denis Querleu, and Arash Rafii have declared no conflicts of interest.

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