Initial Incomplete Surgery Modifies Prognosis in Advanced Ovarian Cancer Regardless of Subsequent Management

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Abstract. *Background: Prognosis in ovarian cancer is determined by completeness of cytoreduction and proper management by specialized oncological gynecologists. Incomplete initial debulking surgery in non-specialized Centers is, however, a reality and there is ongoing discussion about the best subsequent management of such patients. Patients and Methods: Patients with advanced ovarian cancer (International Federation of Gynecology and Obstetrics - FIGO FIGO stages IIIC-IV) who had biopsy by laparotomy or incomplete cytoreduction followed or not by chemotherapy further referred to our Institution between January 2002 and May 2014 were included. The two groups of incomplete cytoreduction [followed by upfront surgery or followed by chemotherapy and interval debulking surgery (IDS)] were compared and also compared against a cohort of 197 patients with similar characteristics who underwent upfront maximal surgery according to the standard at our Iinstitution during the same period. Results: A total of 99 eligible patients were identified. Sixty-seven of them underwent biopsies by laparotomy and 32 underwent incomplete cytoreduction in other institutions. Twenty-eight patients underwent direct re-operation while 71 patients underwent neoadjuvant chemotherapy followed by IDS. The mean overall survival duration for patients with upfront reoperation was 31 months and 54 months for patients with neoadjuvant chemotherapy and IDS, considerably lower than the 72 months obtained for the group of 197 patients with maximal up-front complete cytoreduction at our Institution. Conclusion: Primary biopsy or incomplete cytoreduction reduces survival regardless of the subsequent approach. However, if incomplete cytoreduction has occurred, neoadjuvant chemotherapy followed by IDS is preferable to up-front reoperation.*

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Key Words: Advanced ovarian cancer, biopsy, neoadjuvant chemotherapy, interval debulking surgery, IDs, incomplete cytoreduction.

Ovarian cancer is the leading cause of death due to gynecological malignancies in both the United States of America and Europe (1). Most patients are diagnosed with disease at advanced stages, and lacking effective screening strategies, optimizing current treatment in those with advanced-stage disease is the only current solution for prolonging survival (2).

Survival in advanced ovarian cancer depends on the extent of residual disease after primary surgery; the concept was proposed in 1934 by Meiggs (3) and constantly evolved until the study by Griffiths (4) which demonstrated, in an objective manner, the relationship between remaining disease and survival. The notion of optimal debulking surgery has changed over time from 2 cm to 1 cm and currently to no macroscopic remaining tissue. Although the concept of maximal cytoreduction is currently accepted and completeness of surgery is warranted to maximize survival, current practice varies widely, with an important number of patients receiving treatment below standard (5-8).

Although evidence about management of ovarian cancer in general is abundant, there exist few articles regarding the rather frequent situation of patients who underwent biopsy or incomplete surgery in non-specialized services and who are subsequently referred to tertiary centers.

Patients and Methods

All patients with advanced epithelial ovarian cancer (stages IIIC-IV according to FIGO classification) surgically treated at Fundeni Clinical Hospital between January 2002 and May 2014 were retrospectively reviewed. In order to be considered eligible for this

study, the patients had to meet the following criteria: (a) primary diagnosis of IIIC-IV epithelial ovarian cancer after histopathological examination of the biopsy specimen or of the incomplete resection specimen; (b) re-operation with radical intent at the time of study. Both patients who were submitted to neoadjuvant chemotherapy after initial biopsy or incomplete cytoreduction and those who were re-operated on directly were introduced in this study. The number of cycles of chemotherapy widely varied. In cases in which chemotherapy was associated, the indication of oncological treatment was established by the clinician who had performed the biopsy. At the time of enrolment into our study, chemotherapy had been already performed at other centers in all cases. Patients with non-epithelial ovarian tumors or borderline tumors were excluded.

Survival results were compared with data obtained from a cohort of 197 patients with IIIC epithelial ovarian cancer who were submitted to *per-primam* complete cytoreductive surgery. Date of death was confirmed with the National Register. Statistical analysis was performed using the application Sigma Plot version 12.1 (www.sigmaplot.com – Systat Software Inc, distributed by Stira Electronic SRL, Sighisoara, Romania). Survival curves of overall survival and disease-free survival were generated using the Kaplan–Meier method. A *p*-value of less than 0.05 was considered statistically significant.

Results

Overall, 99 patients with a mean age of 54.58 years (range=19-77 years) were eligible for this study. All patients had been previously submitted to biopsy or incomplete cytoreduction and were presumed to have residual disease at the time of enrolment into our study. Twenty-eight patients underwent direct re-operation after biopsy, while 71 of them underwent neoadjuvant chemotherapy. The mean time between biopsy and re-operation was 73 days (range=7-158 days) for patients who did not undergo chemotherapy and 186 days (range=49-368 days) for those who underwent neoadjuvant chemotherapy. The mean number of chemotherapy cycles was 6 (range=3-12 cycles), the most frequent chemotherapeutic protocol consisted of taxane–platinum salt association. Sixty-four out of 71 patients were re-operated on immediately after ending the chemotherapeutical protocol, while seven cases initially formerly refused surgery; they self-referred to our Institution when symptoms reappeared, at a mean interval of 12 months (rang=8-24 months) after ending neoadjuvant chemotherapy. At the time of the initial surgery at other institutions, 67 patients underwent biopsies by laparotomy only, while 32 underwent incomplete cytoreduction.

The most often encountered stage at re-operation was IIIC (82 patients), while 9 patients were diagnosed with stage IV ovarian cancer; in 8 cases no residual disease was found during re-operation. The main characteristics are shown in Table I.

The associated resections at the time of re-operation are shown in Table II. In 60 out of the 71 cases who underwent chemotherapy after biopsy, complete resection was achieved at re-operation. Residual disease less than 1 cm (R1 resection) was encountered in one case, while in three cases, the remnant tumor measured more than 1 cm (R2 resection). Surgery was limited to being palliative in seven cases. In cases who were submitted to direct re-operation, R0 resection was achieved in 23 cases; in one case an R1 resection was performed, while two other cases presented residual disease of more than 1 cm (R2 resection); palliative surgery was performed in two cases presenting visceral peritoneal carcinomatosis with retraction of the mesentery (Table III). In 38 cases, hyperthermic intraperitoneal chemotherapy (HIPEC) was associated to the debulking procedure.

Table I. *Initial characteristics of the two cohorts of patients.*

Criterion	Direct reoperation	Interval debulking surgery	Total=99
FIGO stage			
IIIC	21 (75.0%)	61 (85.9%)	82 (82.8%)
IV	4 (14.3%)	5 (7.05%)	9 (9.1%)
No residual tumor	3 (10.7%)	5 (7.05%)	8 (8.1%)
Histopathological type			
Serous	27 (96.4%)	58 (81.8%)	85 (85.8%)
Endometroid	1 (3.6%)	4 (5.6%)	5 (5.1%)
Mucinous	-	3 (4.2%)	3 (3.0%)
Clear cell	-	1 (1.4%)	1 (1.0%)
Other type	-	5 (7.0%)	5 (5.1%)
Differentiation grade			
G1	10 (35.7%)	20 (28.2%)	30 (30.3%)
G2	5 (17.8%)	32 (43.6%)	37 (37.4%)
G3	12 (46.5%)	20 (28.2%)	32 (32.3%)

The postoperative mortality was 7.1% in cases who underwent direct re-operation and 5.6% in cases who underwent interval debulking surgery (IDS). The main postoperative complications are shown in Table IV. Classification of postoperative morbidity according to the Clavien–Dindo scale is presented in Table V.

Disease-free survival was 27 months in cases with immediate re-operation and 29 months in cases submitted to neoadjuvant chemotherapy. The median overall survival was 43 months in cases submitted to neoadjuvant chemotherapy and only 33 months in cases with immediate re-operation, while the mean overall survival was 54 months in patients with neoadjuvant chemotherapy and only 31 months for those with direct re-operation (p=0.048) (Figure 1).

When studying the influence of age at diagnosis on overall survival in both studied groups, elderly patients had a better prognosis although statistical significance was not obtained. In the group pre-treated with chemotherapy, patients aged over 60 years had a mean survival of 51 months, while in the younger patient group, the mean survival was 48 months (p=0.56) (Figure 2). When studying the same parameter (age cut-off of 60 years) in the group who underwent direct re-

Table II. *Associated resections at the time of re-operation.*

	Direct re-operation	Interval debulking surgery
Total hysterectomy with bilateral adnexectomy	11 (39.3%)	41 (57.7%)
Omentectomy	19 (67.8%)	47 (66.2%)
Parietal peritonectomy (including diaphragmatic peritoneum)	18 (64.3%)	47 (66.2%)
Colic resections	8 (28.6%)	17 (23.9%)
Splenectomy	4 (14.3%)	6 (8.5%)
Atypical hepatectomy	1 (3.6%)	2 (2.8%)
Pelvic lymph nodes	1 (3.6%)	2 (2.8%)
Partial cystectomy	2 (7.1%)	4 (5.6%)
Partial gastrectomy	1 (3.6%)	3 (4.2%)
Appendectomy	2 (7.1%)	3 (4.2%)
Partial frenectomy	1 (3.6%)	7 (9.9%)
Distal pancreatectomy	-	1 (1.4%)

Table III. *Main types of surgical resections at the time of re-operation.*

Type of resection	Direct re-operation	Interval debulking surgery
R0	23 (82.1%)	60 (84.5%)
R1	1 (3.5%)	1 (1.4%)
R2	2 (7%)	3 (4.2%)
Palliative	2 (7%)	7 (9.8%)
Total	28	71

Table IV. *Main postoperative complications.*

Complication	Direct re-operation	Interval debulking surgery
Re-laparotomy		
Hemoperitoneum	-	2 (2.8%)
Intra-abdominal abscess	4 (14.3%)	4 (5.6%)
Conservative treatment		
Pancreatic fistula	2 (7.1%)	2 (2.8%)
Pleural effusion	-	2 (2.8%)
Pulmonary embolism	2 (7.1%)	-
Upper digestive hemorrhage	1 (3.6%)	-
Renal failure	1 (3.6%)	-
Minor complications		
Fever	1 (3.6%)	2 (2.8%)
Digestive intolerance	1 (3.6%)	2 (2.8%)
Acute urine retention	-	1 (1.4%)

Table V. *Clavien–Dindo scale of postoperative-related morbidity.*

Clavien-Dindo scale	Direct re-operation	Interval debulking surgery
1	2 (7.1%)	4 (5.6%)
2	3 (10.7%)	2 (2.8%)
3	3 (10.7%)	4 (5.6%)
4	2 (7.1%)	2 (2.8%)
5	2 (7.1%)	4 (5.6%)

operation, the mean survival for elderly patients was 34 months, while younger patients had an overall survival of 28 months. However, this fact did not have statistical significance (p=0.823) (Figure 3).

The two groups (represented by patients with IIIC epithelial ovarian cancer who underwent direct re-operation and those who underwent neoadjuvant chemotherapy and IDS, respectively, in whom R0 resection was acheived) were retrospectively compared with a group of 197 patients with IIIC ovarian cancer who benefitted from per-primam complete cytoreduction. (Figure 4). The median survival time in this last category was 51 months, while the mean overall survival was 72 months. Comparison of the overall survival of cases who underwent *per-primam* complete cytoreduction and those who underwent direct re-operation after biopsy was statistically significantly different: the mean overall survival was 72 months in the first group and only 31 months in the latter (p=0.001) (Figure 5). When comparing the other two groups, *i.e.* patients who underwent complete cytoreduction at initial surgery and those who underwent chemotherapy after biopsy and IDS, differences were also obtained (mean overall survival of 72 months for the former and only 54 months for the latter) but with no statistical significance (p=0.437).

Discussion

The standard treatment for advanced ovarian cancer consists of up-front maximal surgery followed by taxane/platinum-based chemotherapy (9). The amount of residual disease is the most important factor impacting on survival (10). The strict adherence to current protocols is correlated with improved survival (8).

Removal of all macroscopic disease gives the best possible chance to these patients (11-13). Neoadjuvant chemotherapy prior to radical surgery has been studied as an attractive alternative to up-front surgery in order to improve the percentage of maximal cytoreduction and survival; the results were, however, disappointing (14, 15). The review by Bristow *et al.* concludes that survival outcomes were inversely proportional to the increased number of preoperative chemotherapy cycles (8). Preoperative chemotherapy seems beneficial for a subcategory of patients (stage IV with metastatic tumors >45 mm) as revealed by the

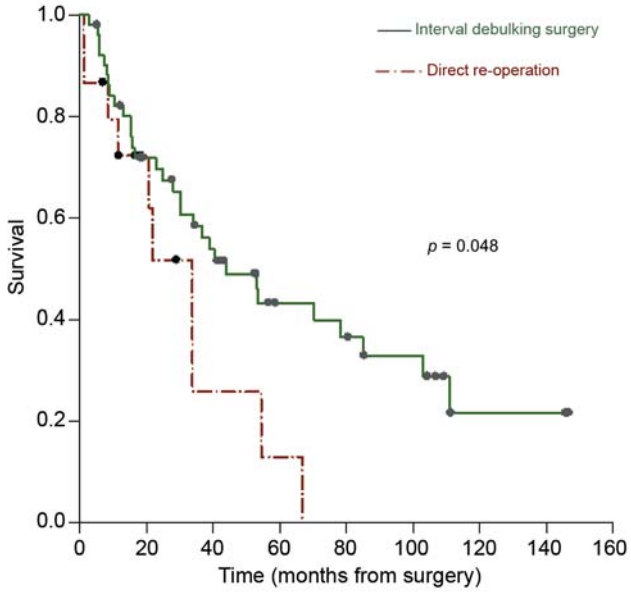

Figure 1. *Overall survival for patients who underwent interval debulking surgery and direct re-operation.*

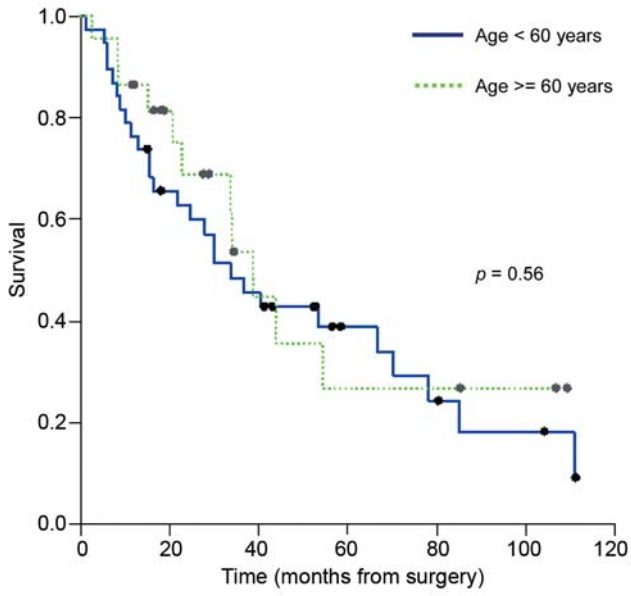

Figure 2. *Correlation between age and overall survival for the group of patients treated with interval debulking surgery.*

European Organization for Research and Treatment of Cancer (EORTC) 55971 (16).

If dealing with newly diagnosed treatment-naive patients with ovarian cancer is well documented and evidence-based, the standard of care for patients who underwent biopsy alone or incomplete cytoreduction surgery outside specialized

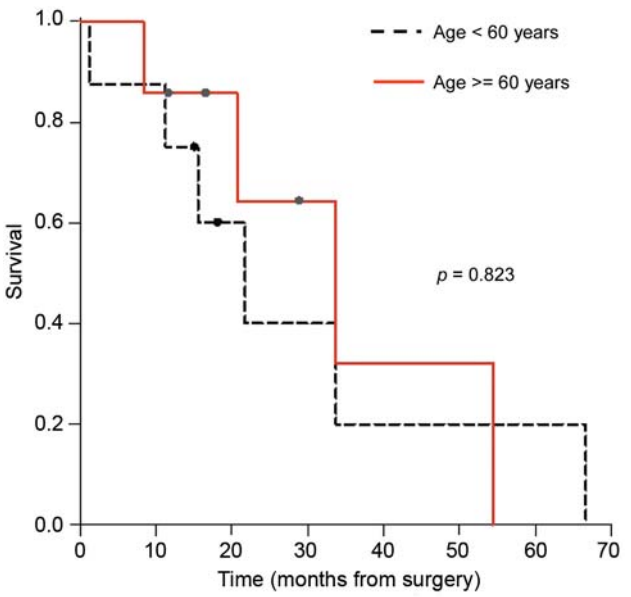

Figure 3. *Correlation between age and overall survival for the group who underwent direct re-operation.*

centers does not seem to have drawn as much attention, although the situation is not rare.

Several studies have shown the feasibility of maximal IDS after initial suboptimal resections but failed to show a survival advantage (17-19). An EORTC trial did, however, show an advantage of IDS (20). Grabowski *et al*. in a study of 48 patients concluded that up-front surgery after incomplete debulking is feasible and can improve outcome (21).

In many of the 99 patients with biopsy or incomplete cytoreduction, R0 resection was achievable both for those who underwent up-front surgery and those who underwent IDS after neoadjuvant chemotherapy following incomplete surgery; the rate of maximal cytoreduction was comparable between the two groups (82.1% *versus* 84.5%) and also comparable with the 197 patients who underwent *per primam* radical surgery at our Center.

Maximal survival was achieved with up-front maximal surgery (mean survival of 72 months), while patients who underwent biopsy or incomplete cytoreduction outside specialized centers failed to reach the same survival, regardless of the subsequent approach at a tertiary center. Patients who underwent chemotherapy followed by IDS had a mean survival of 54 months, while those with immediate maximal debulking following biopsy or incomplete surgery had an even worse outcome, with a mean overall survival of just 31 months (p=0.048) when compared to patients with up-front maximal surgery at specialized centers. We therefore conclude that any kind of surgical procedure, be it biopsy or incomplete cytoreduction, for advanced-stage ovarian cancer

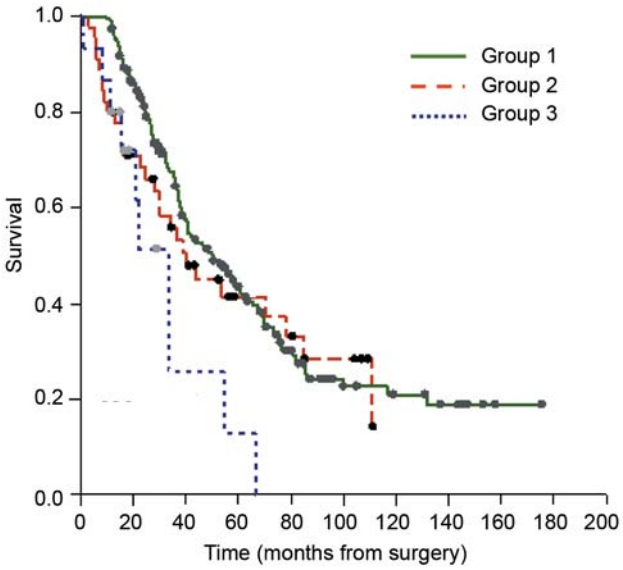

Figure 4. *Kaplan-Meier curves showing the survival differences between the three patient groups: group 1: patients who underwent complete cytoreduction for IIIC ovarian cancer; groups 2: patients who underwent complete cytoreduction after biopsy and neo-adjuvant chemotherapy; group 3: patients who underwent direct reoperation and R0 resection after biopsy.*

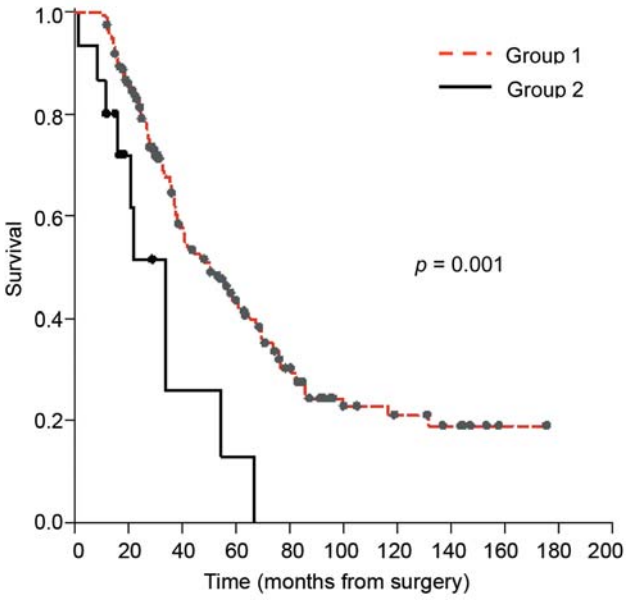

Figure 5. *Kaplan-Meier curves showing the survival differences between the two patient groups: group 1: patients who underwent complete cytoreduction for IIIC ovarian cancer; group 2: patients who underwent direct reoperation and R0 resection after biopsy.*

reduces survival when compared to up-front maximal cytoreduction according to the standard and this situation cannot be corrected regardless of the subsequent management at a specialized center. Maximal cytoreduction can still be obtained and at a rate comparable to up-front surgery, but the survival will be lower; however, if such a patient underwent incomplete surgery, neoadjuvant chemotherapy prior to reintervention with radical intent will improve improve survival compared to up-front reintervention.

The initial procedures for the 67 patients who underwent biopsy were performed by 46 physicians, 15 of them general surgeons and 31 gynaecologists. Only two out of the 67 patients (0.03%) were referred to an oncological surgeon, the rest being referred to medical oncologists. Thirty out of the 46 physicians were contacted and questioned about the reasons for their management of these patients. Surprisingly, 25 of them (54%) considered the extent of the disease to exceed feasibility of R0 resection, therefore the purpose of chemotherapy was to maximize the percentage of maximal debulking. All of them considered their choice of therapy as the best way to maximize survival.

Conclusion

Patients who undergo biopsy by laparotomy or incomplete cytoreduction have a shorter survival than those who undergo up-front surgery at a specialized clinic, regardless of the subsequent treatment approach in the former two groups of patients, although achievability of an R0 resection is comparable and does not seem to be affected by initial incomplete surgery. Nevertheless, for a patient who underwent incomplete procedures, neoadjuvant chemotherapy followed by IDS brings survival benefit as compared to up-front reintervention. Non-expert surgeons and gynecologists tend to underestimate the possibility of complete debulking for advanced ovarian cancer, which leads to the decision of biopsy and incomplete cytoreduction, with further indication for chemotherapy.

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Received February 3, 2015
Revised February 18, 2015
Accepted February 22, 2015