

# Complete cytoreductive surgery, the key factor for survival in advanced ovarian cancer. Experience of an intermediate volume hospital

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## Summary

**Introduction:** We aimed to analyze the outcome in a series of women with primary advanced ovarian cancer in an Intermediate Volume Hospital where new surgical and chemotherapy treatments were implemented over a period of 14 years. **Material and Methods:** One hundred and twenty-seven women with stage IIIB-IV disease underwent primary (76.4%) or interval debulking surgery (23.6%). Fifty-seven were operated on from 2000 to 2005 (Group 1) and 70 from 2006 to 2014 (Group 2). **Results:** No gross residual disease was achieved in 51.5% and 43.3% of women who underwent primary and interval surgery, respectively. For no gross and < 1cm residual disease, median overall and progression-free survival were 94.7 vs. 60.6 months ( $p = 0.001$ ) and 25.3 vs. 20.0 months, respectively ( $p = 0.02$ ). The rate of no gross residual (36.8 to 60.0%) and 5-yr median overall survival (56.3 to 73.7 months) increased between 2000-2005 (Group 1) and from 2006 to 2014 (Group 2). On multivariate analysis, interval surgery, multiple peritoneal implants and residual disease were predictive of overall and progression-free survival. **Conclusions:** Survival after primary and interval debulking surgery progressively correlates with decrease in residual disease. Increasing rates of successful primary surgery are possible through standardization and adoption of best practices without increasing morbidity.

**Key words:** Ovarian cancer; Cytoreduction; Neoadjuvant chemotherapy; Bevacizumab; Hospital volume.

## Introduction

Optimal cytoreduction after primary debulking surgery (PDS) followed by adjuvant chemotherapy (CT) with Carboplatin and Paclitaxel is currently considered the standard treatment for primary epithelial advanced ovarian cancer (AOC) [1-4]. Neoadjuvant chemotherapy (NACT) followed by interval debulking surgery (IDS) with optimal cytoreduction is an alternative for those women in whom complete cytoreduction is not expected to be attained during PDS [5, 6]. Many studies have found that oncological outcome is better for women treated by high-volume surgeons and centers.

However, other studies have found that results are equally good when treatment is provided by experts in gynecologic oncology and treatment guidelines are rigorously adhered to in Intermediate-volume hospitals [7].

The aim of this study is to analyze our oncological results in a series of women with primary epithelial AOC who were treated in our institution for this malignancy over a period of 14 years comparing two timeline periods.

## Material and Methods

Four hundred and ten women with epithelial ovarian cancer visited our Gynecologic Oncology unit during the study period (January 2000 to December 2014). After Institutional Review Board approval was obtained, we reviewed clinical and surgical records from 127 women that met the selection criteria. These inclusion criteria were as follows:

1. Having undergone either PDS or IDS surgery followed by a combination of Platinum derivatives and Taxanes in our hospital (Bevacizumab (BV) or intraperitoneal CT (IP) was administered based on a case-by-case decision),
2. A follow-up of at least two years from the end of treatment.

Fifty-seven patients were operated on from 2000 to 2005 (Group 1) and 70 from 2006 to 2014 (Group 2).

Radical surgical was defined as *Simple* if surgical procedures included hysterectomy, salpingo-oophorectomy, subcolic omentectomy, pelvic and/or aortic lymphadenectomy and/or single small bowel resection or *Radical* in the case of pelvic exenteration, total omentectomy, two or more

bowel resections, diaphragm resection, partial liver, gastric or pancreas resection and/or splenectomy [8]. In addition to preoperative imaging by CT scan, a laparoscopic evaluation of intraperitoneal disease was performed in most cases. All patients were operated on by the same team (Gynecologic oncologists: MJ, JLA and JAM; and surgical oncologists: FMR and GZL), throughout the study period.

Relative contraindications to PDS included an ASA score > 4, tumor distribution precluding an attempt at optimal resection (extensive tumor infiltration of the small bowel mesenteric root, extensive small bowel serosa implants, celiac axis nodal involvement, unresectable involvement of the porta hepatis, large volume ( $\geq 1$  cm) unresectable extra-abdominal metastasis (e.g., lung), and/or multiple unresectable parenchyma liver metastases.

Multiple peritoneal implants was defined as > 20 implants, and ascites was defined as > 500 mL of free peritoneal fluid. Both parameters were recorded from the surgical report.

Complications occurring during the first 30 days after surgery were registered and graded according to the Clavien-Dindo scale [9].

Follow-up consisted of history and physical examination, routine biochemical and hematologic laboratory assessment including CA-125. Computed tomography or PET-CT scan were also utilized.

Overall survival (OS) was measured in months from the date of primary surgery or diagnosis to the time of death or last follow-up appointment and progression-free survival (PFS) was measured from the date of surgery or the beginning of NACT to the time of the first failure or death.

### Statistical analysis

Statistical analysis was performed with the statistical package for the social sciences (SPSS) for Windows 20 (SPSS Inc. Chicago, IL, USA). Continuous data are presented as means with standard deviation and ranges or medians with interquartile range (IQR) depending on data distribution. Categorical data are presented as the number of cases and percentages. Categorical data were compared using two-tailed Fisher's exact test where appropriate. The Kruskal-Wallis test was used for comparing two or more independent samples of equal or different sample sizes. Continuous data were compared using the Mann-Whitney U test when data distribution was not normal and one-way analysis of variance when distribution was normal.

Odd ratios with 95% confidence intervals (CIs) for predicting morbidity were calculated for several prognostic factors by using a binary logistic regression analysis, choosing a forward stepping model procedure.

Survival analysis was performed with the Kaplan-Meier method, compared by the long-rank and the Breslow statistical method. Univariate and multivariate Cox proportional hazard ratio (HR) analyses were performed to identify potential prognostic factors choosing a forward stepping model procedure.

A *p* value of less than 0.05 was considered statistically

significant for all tests. Neither Confidence Interval or *p* values are shown in the text when results are given in tables.

## Results

Demographic data for the subjects are summarized in Table 1. Patients' median age was 57.8 years (range 28 to 82 years). Most women had high-grade serous histology ( $n = 88$ , 69.3%) and ASA = 1-2 ( $n = 86$ , 67.7%). Ninety-seven patients (76.4%) underwent PDS and 30 (23.6%) NACT followed by IDS. NACT consisted of 3 cycles before IDS followed by at least three more cycles.

Optimal debulking surgery ( $\leq 1$  cm residual disease (RD)) was achieved in 84.3% of cases (83.5% in PDS and 86.0% in IDS group). Indeed, complete resection was achieved in 49.6% of patients (51.5% and 43.3% in the case of PDS and IDS, respectively).

Adjuvant CT with a combination of Platinum and Taxol was administered to 122 women (96%). Forty-two women (33%) received IP/IV CT, whereas 80 women received only IV CT. The proportion of women who received adjuvant IP/IV CT was similar in the PDS and IDS groups (32.0% vs. 36.7%) ( $p = 0.61$ ), and in Group 1 and Group 2 (28.1% vs. 37.2%) ( $p = 0.35$ ). Most patients who received adjuvant IP/IV had complete or optimal resection (79%). Patients who received IP/IV CT had similar characteristics to those who only received IV CT (data not shown).

Bevacizumab (BV) was administered in 10.5% and in 30.4% of women in these Groups ( $p = 0.008$ ). Twelve women (9.4%) received maintenance CT with cyclophosphamide (CPM)  $\pm$  BV, more frequently in Group 2 than in Group 1 (14.3% vs. 3.5%) ( $p = 0.06$ ), and at a similar rate in PDS and IDS (8.3% and 13.3%, respectively ( $p = 0.47$ )).

The surgical procedures performed are shown in Table 2. There was no significant difference between the PDS and IDS groups, except for lymphadenectomies and hysterectomies that were more frequently performed in patients who underwent PDS. Upper abdominal surgery was performed in 15.7% of women (18.6% in PDS and 6.7% in IDS), and increased from 5.3% ( $p = 0.01$ ). Intestinal surgical procedures also increased from 24.3% in Group 1 to 38.5% in Group 2. The rate of no gross residual disease (NGR) increased from 36.8% in Group 1 to 60.0% in Group 2.

After a median follow-up of 56.2 months (IQR: 71.7), OS and PFS for the whole series was 53.7% and 20.9%, respectively. Median overall survival (mOS) and median progression-free survival (mPFS) were 63.4 and 21.8 months, respectively.

According to residual disease status (NGR, RD < 1 cm, RD  $\geq 1$  cm), mOS was 94.7, 60.6, and 34.3 months, respectively. In contrast, mPFS was 25.3, 20.0 and 13.2 months, respectively. Survival in IDS was shorter than in PDS (mOS 44.8 and 73.7 months respectively). However, it was similar (88.5 vs. 94.6 months) ( $p = 0.22$ ) when NGR was achieved. Median five-year PFS in PDS was 23.3 months while in IDS it was 16.7 months at three years.

Table 1. — General Characteristics of the patients.

| N = 127                              | N (%)        |
|--------------------------------------|--------------|
| <b>Age</b> , mean (range)            | 57.8 (28-82) |
| <b>BMI</b> , mean (range)            | 23.6 (13-52) |
| <b>ASA%</b>                          |              |
| 1-2                                  | 86 (67.7)    |
| > 3                                  | 41 (32.3)    |
| <b>FIGO Stage</b>                    |              |
| III b-c                              | 105 (82.7)   |
| IV                                   | 22 (17.3)    |
| <b>Histology n (%)</b>               |              |
| Serous                               | 111 (87.4)   |
| High grade                           | 88 (79.3)    |
| Low grade                            | 23 (20.7)    |
| Endometrioid                         | 6 (4.7)      |
| Mucinous                             | 4 (3.1)      |
| Clear Cell                           | 4 (3.1)      |
| Mixed/Other                          | 2 (1.6)      |
| <b>Grade n (%)</b>                   |              |
| 1                                    | 6 (5.3)      |
| 2                                    | 21 (18.6)    |
| 3                                    | 86 (76.1)    |
| <b>Diagnosis Tool</b>                |              |
| Image + Ca-125 + pathology*          | 37 (29.1)    |
| Laparoscopy/Laparotomy               | 90 (70.9)    |
| <b>Surgery</b>                       |              |
| Primary                              | 97 (76.4)    |
| Interval                             | 30 (23.6)    |
| CA-125 × 10 <sup>3</sup> , mean (SD) | 1.4 (2.7)    |
| Log Ca-125, mean (SD)                | 6.2 (1.6)    |
| <b>Ascites n (%)</b> , mL            |              |
| < 500                                | 23 (18.1)    |
| > 500                                | 50 (39.3)    |
| <b>Carcinomatosis</b>                |              |
| No (or < 20 implants)                | 39 (29.9)    |
| Yes                                  | 89 (70.1)    |
| <b>Degree of Cytoreduction</b>       |              |
| Optimal (0 to < 1 cm)                | 107 (84.3)   |
| Complete                             | 63 (49.6)    |
| <b>Residual disease</b>              |              |
| No visible                           | 63 (49.6)    |
| 1-10 mm                              | 44 (34.6)    |
| > 10 mm                              | 20 (15.7)    |
| <b>Adjuvant CT, n (%)</b>            |              |
| Carbo-Taxol                          | 99 (78.0)    |
| Cisplatin-Taxol                      | 23 (18.1)    |
| Other                                | 5 (3.9)      |
| Cycles, mean (range)                 | 6.2 (5-10)   |
| <b>Bevacizumab</b>                   |              |
| Yes                                  | 27 (21.4)    |
| No                                   | 99 (78.6)    |
| <b>Neoadjuvant CT</b>                |              |
| Carbo-Taxol                          | 30 (23.6)    |
| Cisplatin-Taxol                      | 24 (85.7)    |
| Other                                | 4 (14.3)     |
| Other                                | 2 (6.7)      |
| Cycles, mean (range)                 | 4 (3-6)      |
| <b>Primary IV/IP</b>                 |              |
| Carbo-Taxol                          | 42 (33.0)    |
| Cisplatin-Taxol                      | 20 (50.0)    |
| Cisplatin-Taxol                      | 16 (40.0)    |
| Carboplatin                          | 5 (10.0)     |
| Cycles, median (range)               | 5 (1-10)     |

\*FNB = fine needle biopsy or Cytology.

Women with multiple peritoneal implants (MPI) had shorter mOS and mPFS compared to No/isolated peritoneal implants (56.3 months vs. not reached,  $p = 0.01$ ; and 19.3 vs. 75.2 months ( $p = 0.001$ ), respectively). Although NGR was achieved in the MPI group, OS and PFS remained similar (58.8 and 19.3 months, respectively). Group 2 showed an improvement in mOS over Group 1 (73.7 vs. 56.3) (Figure 1).

Intraperitoneal CT did not improve either OS (64.2 vs. 63.4 months) ( $p = 0.740$ ) or PFS (22.4 vs. 20.1) ( $p = 0.632$ ) compared with the IV regimen alone. Nevertheless, in the case of NGR, IP CT provided a crude advantage of 31 months of mOS (106 vs. 75 months), although this was not statistically significant ( $p = 0.352$ ). In RD < 1 cm there was a 25-month advantage of mOS (55 vs. 80 months).

Table 3 shows the overall results of the regression analysis. Risk of death (overall survival) was increased in MPI, IDS, and RD  $\geq 1$  cm, while more radical surgery and use of BV decreased that risk. In multivariate analysis, independent variables were MPI, IDS and RD  $\geq 1$  cm. The risk of PFS was increased in MPI, IDS, RD  $\geq 1$  cm, CA-125 > 500 IU/mL. In the multivariate analysis, only MPI, IDS and RD remained significant.

In women treated with BV, the HR for death decreased by a 50% (HR: 0.5). After controlling for NGR, any RD, or MPI, the HR for death was 0.3 (CI, 0.12-0.58) ( $p = 0.001$ ), 0.7 (CI, 0.35-1.6) ( $p = 0.49$ ) and 0.6 (CI, 0.32-1.0) ( $p = 0.06$ ) respectively.

Overall, rate of major complications (Clavien-Dindo  $\geq 3$ ) was 35%. Major complications occurred in 13.3% and 16.7% of cases in the PDS and IDS groups respectively ( $p = 0.52$ ). Specifically, such major complications were: moderate-severe pleural effusion in nine women (7.1%, all in PDS and seven of these related to diaphragmatic resection); bowel fistula in two women (1.5%); abdominal abscess in three women (2.3%); evisceration in one woman (0.78%); pulmonary embolism in three women (2.3%); severe renal failure in one woman (0.78%); and relaparotomy for bleeding in five women (3.9%).

The probability of major complications was lower for IDS (OR: 0.6) although it did not reach statistical significance ( $p = 0.44$ ). The implementation of more radical procedures did not increase morbidity.

In the multivariate analysis, only pleural effusion remained statistically significant (Table 4).

There were two readmissions, one for prolonged Ileus and the other for vaginal bleeding, both of which were managed conservatively. Intraoperative complications occurred in 11 (9.5%) women: Liver injury (n = 1), Spleen injury (n = 1), Ureter injury (n = 1), Bladder injury (n = 1), small bowel injury (n = 2), epigastric artery lesion (n = 1), external iliac artery lesion (n = 1), vena cava lesion (n = 1), and two diaphragmatic lesions. No ninety-day mortalities occurred.

Table 2. — Characteristics of surgical procedures.

| Procedure                         | All (n = 127)  | PDS (n = 97)  | IDS (n = 30)  | p     |
|-----------------------------------|----------------|---------------|---------------|-------|
| Total Hysterectomy                | 119 (93.7)     | 83 (93.3)     | 23 (76.7)     | 0.019 |
| Adnexectomy                       | 126 (99.0)     | 96 (98.9)     | 30 (100)      | 0.98  |
| Radical Oophorectomy              | 22 (17.3)      | 18 (18.6)     | 4 (1.3)       | 0.59  |
| Lymphadenectomy any               | 50 (39.4)      | 45 (46.4)     | 5 (16.7)      | 0.005 |
| Omentectomy                       |                |               |               |       |
| Subcolic                          | 108 (85.0)     | 82 (84.5)     | 26 (86.7)     | 0.77  |
| Total                             | 19 (15.2)      | 15 (15.5)     | 4 (13.3)      |       |
| Intestinal Resection              |                |               |               |       |
| Small Bowel any                   | 10 (7.9)       | 6 (6.2)       | 4 (13.3)      | 0.24  |
| Large Bowel any                   | 39 (30.7)      | 32 (33.0)     | 7 (23.3)      | 0.23  |
| Colostomy                         | 0              |               |               |       |
| Ileostomy                         | 0              |               |               |       |
| Others                            |                |               |               |       |
| Appendectomy                      | 31 (24.4)      | 25 (25.8)     | 6 (20.0)      | 0.24  |
| Splenectomy                       | 7 (5.5)        | 5 (5.1)       | 2 (6.7)       | NA    |
| Partial Hepatectomy               | 4 (3.1)        | 4 (4.1)       | -             |       |
| Distal Pancreatectomy             | 1 (0.78)       | 1 (1.0)       | -             |       |
| Cholecystectomy                   | 7 (5.5)        | 5 (5.2)       | 2 (6.7)       | NA    |
| Ureterectomy/cystectomy           | 3 (2.4)        | 3 (3.1)       | -             |       |
| Peritonectomies                   |                |               |               |       |
| Pelvic                            | 61 (48.0)      | 49 (50.5)     | 12 (40.0)     | 0.4   |
| Abdomen                           | 29 (23.0)      | 23 (23.7)     | 6 (20.7)      | 0.8   |
| Diaphragm (+/-resection)          | 11 (8.7)       | 11 (11.5)     | -             | NA    |
| Surgical Radicality               |                |               |               |       |
| Simple                            | 90 (70.9)      | 70 (72.2)     | 20 (66.7)     | 0.64  |
| Radical                           | 37 (29.1)      | 27 (27.8)     | 10 (33.3)     |       |
| Surgery Time, hours, mean (range) | 3.8 (1.10-9.6) | 3.9 (1.2-9.8) | 3.4 (1.3-6.0) | 0.37  |

\*Median (range) of Lymph Nodes retrieved.

§ includes Radical Oophorectomy.

Table 3. — Overall OUTCOME (Univariate and Multivariate Cox Regression.)

|                      | OS | HR  | 95% CI  | p     | PFS | HR   | 95% CI  | p     |
|----------------------|----|-----|---------|-------|-----|------|---------|-------|
| <b>Univariate</b>    |    |     |         |       |     |      |         |       |
| Age > 70 y           |    | 1.5 | 0.9-2.7 | 0.1   |     | 1.1  | 0.7-1.8 | 0.68  |
| BMI                  |    | 1   | 0.9-1.0 | 0.98  |     | 1    | 0.9-1.0 | 0.76  |
| ASA $\geq$ 3         |    | 1.5 | 0.9-2.4 | 0.06  |     | 1.1  | 0.7-1.7 | 0.51  |
| FIGO III b-C         |    | 1.2 | 0.7-2.1 | 0.41  |     | 1.2  | 0.7-2.0 | 0.44  |
| FIGO IV              |    | 1.5 | 0.9-2.7 | 0.12  |     | 1.3  | 0.8-2.1 | 0.29  |
| HG serous            |    | 1   | 0.8-2.9 | 0.15  |     | 1.2  | 0.7-2.1 | 0.4   |
| Multiple implants    |    | 2.6 | 1.4-4.6 | 0.001 |     | 3.1  | 1.8-5.1 | 0     |
| IDS vs. PDS          |    | 2   | 1.2-3.2 | 0.003 |     | 2.1  | 1.4-3.3 | 0.001 |
| Surgical Radicality  |    | 0.5 | 0.3-0.9 | 0.02  |     | 0.7  | 0.4-1.1 | 0.14  |
| RD 0 vs. > 1 cm      |    | 2.2 | 1.2-4.1 | 0.007 |     | 1.7  | 1.1-2.6 | 0.023 |
| I.V/IP vs. IV        |    | 1   | 0.7-1.7 | 0.7   |     | -0.9 | 0.6-1.3 | 0.62  |
| CA-125 > 500 IU/mL   |    | 1.5 | 0.9-2.4 | 0.06  |     | 1.6  | 1.0-2.4 | 0.02  |
| Bevacizumab          |    | 0.5 | 0.3-0.8 | 0.01  |     | 0.7  | 0.4-1.1 | 0.13  |
| <b>Multivariate*</b> |    |     |         |       |     |      |         |       |
| Multiple implants    |    | 2.2 | 1.2-4.0 | 0.008 |     | 3.1  | 1.8-5.2 | 0     |
| IDS                  |    | 1.9 | 1.0-2.8 | 0.009 |     | 1.7  | 1.1-2.7 | 0.03  |
| RD 0 vs. > 1 cm      |    | 2.3 | 1.2-4.4 | 0.008 |     | 1.8  | 1.0-3.2 | 0.04  |

\*Variables with  $p \leq 0.10$ .

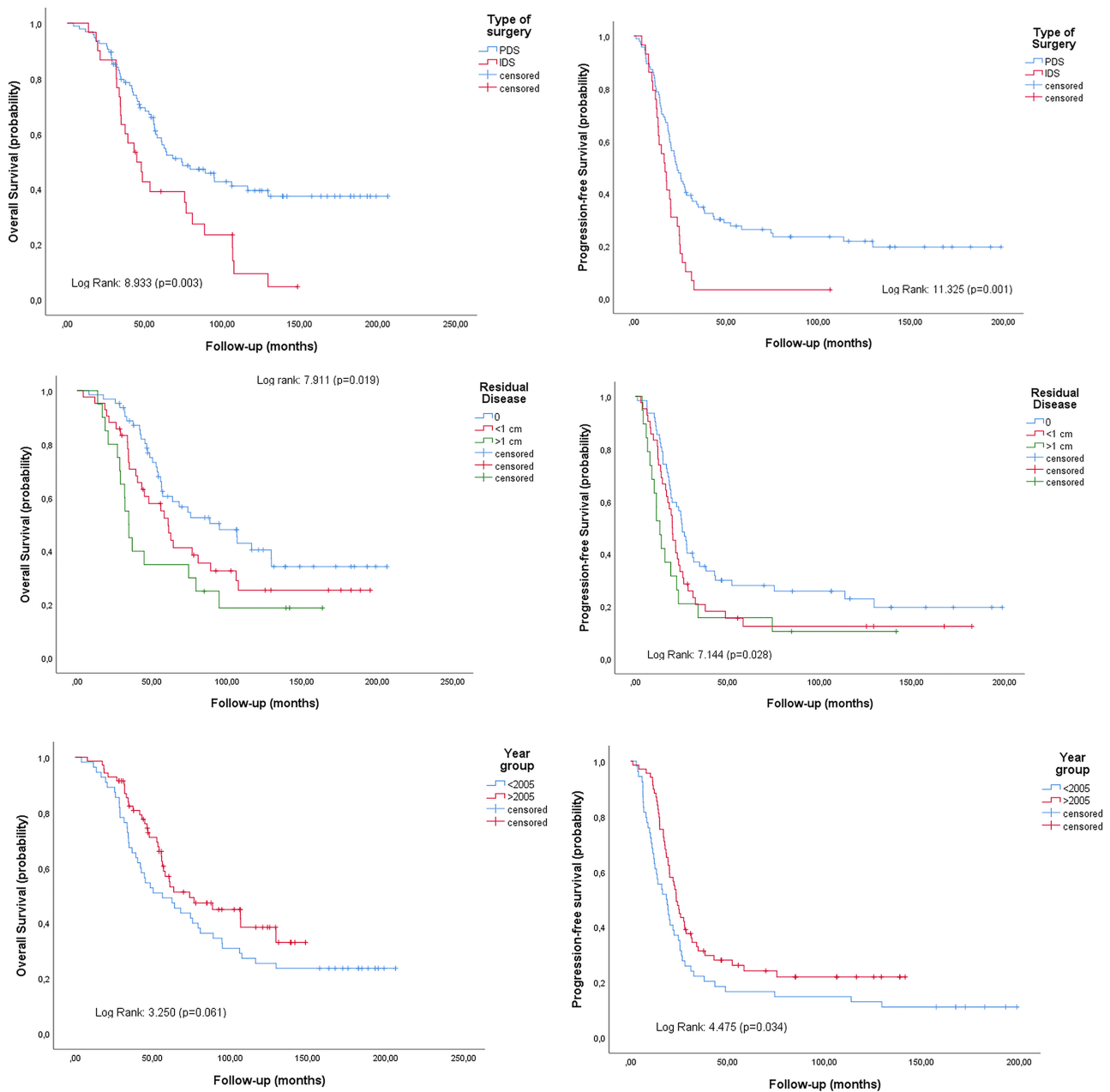


Figure 1. — Overall and Progression Free Survival according to Type of Surgery (A); Residual disease (B) and period of treatment (C).

**Discussion**

Several studies have demonstrated that women without any visible macroscopic disease after primary cytoreduction have the best survival [10]. Nevertheless, women left with gross but  $\leq 1$  cm RD still have a significant survival advantage over those left with  $> 1$  cm. Chiva *et al.* found a weighted rate of complete resection of 25%, with an mOS and mPFS of 70 and 30 months respectively [11]. For the group of 1-10 mm RD it was 42% with mOS and mPFS of 40 and 16 months, and for suboptimal surgery ( $> 1$  cm) mOS and mPFS were 30 and 12 months respectively [11].

Training of dedicated surgical teams for surgery for

ovarian cancer is paramount and results in better optimal debulking rates and survival [12-19] According to the definition of Wright *et al.* [11] and Bristow *et al.* [16] with a cutoff of 20 new cases treated per year, our Department can be considered an Intermediate volume center during the period of study. Our study confirms a significant association between survival and RD after PDS and IDS in AOC that is also significant after resection to RD  $\leq 1$  cm in PDS. This improvement could be attributed to the implementation of more extensive surgical approaches from 2006 onwards, mainly due to a higher rate of upper abdominal and intestinal surgery procedures as other authors have found [17]. Despite the implementation of new surgical techniques, the

Table 4. — Risk of Morbidity (Clavien-Dindo  $\geq 3$ ) (Logistic regression).

| Univariate                       | ORs | 95% CI    | p     |
|----------------------------------|-----|-----------|-------|
| Age > 70 year                    | 1.4 | 0.33-6.7  | 0.64  |
| ASA > 3                          | 1.5 | 0.40-5.9  | 0.52  |
| IMC > 30                         | 1.1 | 0.2-5.4   | 0.9   |
| Carcinomatosis                   | 1.9 | 0.65-7.2  | 0.3   |
| Residual Disease > 1 cm          | 2   | 0.7-6.0   | 0.18  |
| Small bowel resection, any       | 3.4 | 0.72-14.7 | 0.1   |
| Large bowel resection, any       | 3   | 0.8-11.0  | 0.09  |
| Multiple GI resections $\geq 2$  | 3.4 | 0.9-13.3  | 0.07  |
| Pleural Effusion (postoperative) | 7.7 | 1.6-24.0  | 0.008 |
| Diaphragm resection              | 4.9 | 1.2-19.0  | 0.02  |
| Fever (> 38 °C > 2 days)         | 11  | 3.0-30    | 0     |
| Total N° of BU*                  | 1.4 | 1.1-1.6   | 0.002 |
| Surgery length hr. (continuous)  | 1.7 | 1.2-2.4   | 0.001 |
| Ascites                          | 2.4 | 0.7-7.1   | 0.14  |
| IP chemotherapy                  | 1.3 | 0.4-3.5   | 0.72  |
| Interval Surgery                 | 0.6 | 0.2-2.0   | 0.44  |
| Radical surgery                  | 2.8 | 0.97-8.2  | 0.05  |
| Upper-abdomen surgery            | 4.1 | 1.3-13.2  | 0.01  |
| Year-group                       | 1.2 | 0.4-3.6   | 0.66  |
| <b>Multivariate</b>              |     |           |       |
| Pleural Effusion                 | 6.7 | 1.6-34    | 0.02  |

\*Intra + postoperative.

perioperative morbidity rate did not increase in our study and therefore, when resection to minimal RD is likely, PDS followed by CT remains the preferred treatment [4, 17].

A question that remains controversial concerns the negative prognostic impact of initial disease volume despite optimal cytoreduction. Horowitz *et al.* found that initial disease volume was predictive of survival despite NGR or optimal cytoreduction thus casting doubt on the role of surgical complexity to overcome tumor biology [18]. Although our study found that NGR had the best outcome, it seems that complete resection of gross disease did not overcome tumor load as mentioned above. Nevertheless, complete removal of gross disease should continue to be the goal of primary cytoreduction [1, 10, 15, 19, 20, 21].

The review by Timmermans *et al.* of the value of residual disease after NACT (6) showed that mOS was 41, 27 and 21 months for patients with no NGR, 0.1-1 cm, and > 1 cm RD, respectively. Despite this evidence there is still much controversy regarding NACT [20, 22]. In our study, mOS was 30 months shorter, and all women had suffered relapse during the three first years of follow-up. Nevertheless, in women with NGR, survival was similar to PDS which confirms that resection of all macroscopic disease at IDS is also the strongest independent predictor [6, 23]. Results from the TRUST study are expected to give a better view of the role of NACT [24].

The benefit of intraperitoneal (IV/IP) over IV CT in AOC with low volume has been already demonstrated [25-

27]. Our results agree with these findings since there was an advantage of 16 months in favor of IP/IV but the decrease in risk of death was irrelevant (HR: 0.93;  $p = 0.78$ ). Although mature results are still expected, the phase III trial GOG 252 in optimally resected ( $\leq 1$  cm) tumors has reported negative results [27].

As increased angiogenesis has been linked with the progression of ovarian cancer, BV has gained approval for the front-line treatment of AOC in combination with carboplatin and paclitaxel. The ICON 7 study found that HR for PFS improved irrespectively of FIGO stage or RD and that front-line BV-containing treatment is beneficial when there is NGR [28]. The GOG-0218 trial of BV in women with primary AOC if only RD remained after PDS found no survival differences for women who received BV compared with chemotherapy alone [29]. Our data show that the addition of BV to CT seems to play a positive role in survival but not in the risk of progression after complete resection.

Limitations of this study include the retrospective nature of the analysis with its inherent biases, and the low number of women recruited. Inclusion of women treated with NACT could affect outcomes although its use over the periods of study is similar (21% vs. 25%) and there were no significant differences between general features.

Strengths of the study include the same surgical and medical oncology team throughout the period of study in a high Complexity Center, and the progressive implementation of new surgical techniques and chemotherapeutical treatments that made our treatment a qualified competitive program.

## Conclusions

In conclusion, OS after PDS and IDS for AOC progressively correlates with gradual decrease in RD and that increasing rates of successful PDS are possible through standardization and adoption of best practices without increasing morbidity, when treatment is provided by experts in gynecologic oncology, with a rigorous adherence to treatment guidelines and an institutional commitment to quality.

## Ethics approval and consent to participate

All subjects gave their informed consent for inclusion before they participated in the study. The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of Clinica Universidad de Navarra (approval number: 2018.001).

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## Conflict of Interest

All the authors declare no conflict of interest.

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