Does the Diagnosis Center Influence the Prognosis of Ovarian Cancer Patients Submitted to Neoadjuvant Chemotherapy?

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Abstract. *Aim: To compare prognosis of advanced epithelial ovarian cancer (AEOC) patients based on where the first surgical assessment was performed. Patients and Methods: Retrospective analysis of primary AEOC patients was performed and three groups were formed based on where the decision of primary treatment was taken: Internal, if the decision was carried out at our Institution (PDS (Primary Debulking Surgery), I-IDS (Internal- Interval Debulking Surgery)) and Referred in case women were referred after neoadjuvant chemotherapy (NACT) from other Centers (R-IDS (Referred- Interval Debulking Surgery)). Results: Among 573 AEOC, 279 (48.7%) were PDS and 294 (51.3%) IDS. In particular, 134 of 294 (45.6%) were R-IDS and 160 (54.4%) were I-IDS. Median progression-free survival (PFS) was 26 months in PDS, 14 months in I-IDS and 17 months in R-IDS. The difference was statistically significant ($p<0.05$) among all groups. Conclusion: IDS can represent a suitable approach only when the first complete debulking is not achievable in a tertiary referral hospital.*

The completeness of tumor removal is the most important prognostic factor in advanced epithelial ovarian cancer (AEOC) (1-4). A recent analysis of the GOG 182 study reported a median overall survival of 54.6 months in patients with complete resection compared to 40.4 months for patients with residual tumor greater than 1 cm (5). However, the EORTC-NCT00003636 randomized clinical trial showed that approximately 40% of AEOC patients are operated with remaining lesions of more than 1 cm in diameter (6). Indeed, comprehensive surgery for AEOC requires for appropriate skills and training, as well as optimized infrastructures, which are often not available outside of expert Centers (7, 8). Consequently, the rate of optimal primary debulking, resulting in macroscopic complete resection, is still very heterogeneous between the centers and incomplete cytoreduction or explorative surgery are not uncommon occurrences.

In this context, it might be possible that women admitted to neoadjuvant chemotherapy (NACT) in some peripheral centers would have benefited of a primary optimal debulking surgery (PDS) in a tertiary level hospital with a significant improvement in terms of prognosis. On the contrary, patients assessed for NACT in a referral center with high rates of primary optimal cytoreduction might suffer from a very aggressive and diffused disease with a very unfavorable prognosis.

To test such a hypothesis, we retrospectively compared clinical characteristics, peri-operative outcome and prognosis of patients admitted to surgery at our tertiary-level Center, based on where the decision of primary treatment was performed: Internal, if the decision was carried-out at our Institution (PDS and I-IDS) and Referred in case women were referred after NACT from other centers (R-IDS).

Patients and Methods

The medical records of patients with AEOC (International Federation of Gynecology and Obstetrics stage IIIC–IV disease) admitted to surgery (both PDS and IDS) at the Catholic University of Sacred Heart (CUSH) of Rome and Campobasso from January 2006 to December 2012, were retrospectively analyzed. This study period encompasses the time to reach at least 24 months of follow-up for the whole population. Women receiving either exploratory laparotomy/laparoscopy or unexplored, based on clinical and/or

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Key Words: Ovarian cancer, interval debulking surgery, cytoreduction, prognosis.

Table I. *Patients' characteristics*.

Variable	PDS N (%)	I-IDS N (%)	R-IDS N (%)	*p*-Value
All cases	279	160	134	n.a.
Median age, years (range)	60 (26-90)	63 (31-83)	63 (33-90)	0.08
ECOG Performance status				
<2	259 (92.8)	149 (93.1)	124 (92.5)	0.981
≥2	20 (7.2)	11 (6.9)	10 (7.5)	
FIGO surgical stage				
IIIC	230 (82.4)	124 (77.5)	114 (85.1)	0.222
IV	49 (17.6)	36 (22.5)	20 (14.9)	
Histology[a]				
Type I	19 (6.8)	11 (6.9)	4 (3.0)	0.256
Type II	260 (83.2)	149 (93.1)	130 (97.0)	
Median courses of NACT (range)	--	4 (3-6)	6 (3-10)	0.001
Clinical response (RECIST)				
Complete/Partial		124 (77.5)	111 (82.8)	0.306
No-change/Progression	--	36 (22.5)	23 (17.2)	
Serological response (GCIG)				
Complete/Partial		151 (94.4)	125 (93.3)	0.808
No-change/Progression	--	9 (5.6)	9 (6.7)	

[a]According to Kurman *et al*. (22). n.a.: Not applicable. PDS: Primary Debulking Surgery. I-IDS: Internal - Interval Debulking Surgery. R-IDS: Referred - Interval Debulking Surgery. ECOG: Eastern Cooperative Oncology Group.NACT: Neoadjuvant chemotherapy. RECIST: Response Evaluation Criteria In Solid Tumors. GCIG: Gynecologic Cancer InterGroup.

radiological data, were submitted to three or more courses of neoadjuvant platinum-based chemotherapy. A dedicated radiologist reviewed computed tomography (CT) scans at the time of diagnosis and after NACT (9) according to our previously published criteria (10). After NACT, clinical response was assigned according to both Response Evaluation Criteria In Solid Tumors (RECIST) (11) and Gynecologic Cancer InterGroup (GCIG) criteria (12) and the response has been classified as complete/partial or stable/progressive. According to our previously published data (13), patients were suitable for IDS in case of (i) complete/partial radiological or serological response; (ii) stable radiological disease in the presence of serological response and good performance status (Eastern Cooperative Oncology Group (ECOG) < 1). A laparoscopic exploration and subsequent laparotomy were performed according to our model (13-16).

The same team, trained in gynecologic oncology surgery, performed surgery over the study period. The type and extent of the procedures were recorded according to the surgical complexity score by Aletti *et al*. (17) considering the intermediate and high scores (*i.e.*: score >3) as major surgical procedures. The decision of performing autologous blood transfusion was made during or after surgery according to the patient's hemodynamic conditions and hemoglobin levels. Post-operative recovery was calculated starting from the first post-operative day to the day of hospital discharge. Surgical complications were graded according to the Memorial Sloan Kettering Cancer Center (MSKCC) grading system (18). After surgical evaluation, women received 3 courses of platinum-based chemotherapy every 3 weeks in case of cytoreduction or started a 2nd-line of chemotherapy in case of not resectable tumor burden and/or intra-operative evaluation of progressive disease. Date of progression (progression-free survival (PFS)) was based on doubling of cancer antigen 125 (CA-125) serum levels (12) and/or the first appearance of one or more new lesions or increased size of existing lesions at CT according to the RECIST criteria (19).

Statistical analysis. Cases were divided into three groups based on where the decision of primary treatment was taken: PDS or I-IDS if the decision was carried-out at CUSH and R-IDS in case women were referred after NACT from other peripheral centers. Peripheral centers were defined as low surgical case volume (<9 AEOC cases/year) (7).

Univariate analysis included Chi-square analysis or Fisher's exact test for categorical variables and Student's *t*-test and Mann–Whitney test for continuous variables. Survival time was measured from the day of histological diagnosis to the date of recurrence. Mean and life tables were computed using the product-limit estimate by the Kaplan–Meier method and analyzed by the log-rank test (20-21). All statistical tests were two-sided and differences were considered significant at the level of $p<0.05$. The SPSS statistical software program (SPSS Inc., Chicago, IL, USA) was used.

Results

During the study period, 573 primary AEOC were submitted to surgery at CUSH. Among them, 279 (48.7%) received PDS and 294 (51.3%) IDS after NACT. In particular, 134 cases of 294 (45.6%) IDS were referred from other Centers (R-IDS) and 160 cases (54.4%) were internal (I-IDS).

Patients' characteristics, divided into three groups based on their first assessment and primary treatment (PDS, I-IDS, R-IDS), are shown in Table I. No statistically significant clinical differences were observed, except for a higher number of

Table II. *CT-scan parameters at diagnosis*.

CT – scan parameters[a]	PDS N (%)	I-IDS N (%)	R-IDS N (%)	*p*-Value[b]	*p*-Value[c]
All cases	279	160	134	n.a.	n.a.
Peritoneal thickening, peritoneal implants >2 cm					
Yes	178 (63.8)	125 (80.6)	97 (72.4)	0.001	0.09
No	101 (27.6)	30 (19.4)	37 (27.6)		
Bowel mesentery involvement					
Yes	45 (16.1)	72 (45.0)	15 (11.2)	0.0001	0.233
No	234 (83.9)	88 (55.0)	119 (88.8)		
Pelvic side-wall involvement and/or hydroureter					
Yes	38 (13.6)	30 (18.8)	10 (7.5)	0.171	0.07
No	241 (86.4)	130 (81.2)	124 (92.5)		
Infrarenal paraaortic lymph nodes > 2 cm					
Yes	36 (12.9)	37 (23.1)	20 (14.9)	0.008	0.645
No	243 (87.1)	123 (76.9)	114 (85.1)		
Suprarenal paraaortic lymph nodes > 1 cm					
Yes	37 (13.3)	35 (21.9)	26 (19.4)	0.023	0.110
No	242 (86.7)	125 (78.1)	108 (80.6)		
Large volume ascites (500 ml)					
Yes	187 (67.0)	135 (84.4)	100 (74.6)	0.0001	0.138
No	92 (33.0)	25 (15.6)	34 (25.4)		
Diaphragmatic disease (infiltrating carcinosis or confluent nodules)					
Yes	37 (13.3)	58 (36.2)	13 (9.7)	0.0001	0.337
No	242 (86.7)	102 (63.8)	121 (90.3)		
UAD (Spleen, stomach, lesser sac)[d]					
Yes	13 (4.7)	28 (17.5)	5 (3.7)	0.0001	0.800
No	266 (95.3)	132 (82.5)	129 (96.3)		
Superficial liver metastases >2 cm and/or intraparenchymal liver metastases of any size					
Yes	26 (9.3)	31 (19.4)	11 (8.2)	0.003	0.854
No	253 (90.7)	129 (80.6)	123 (91.8)		
Overall radiologic score (median) (range)	0 (0-4)	2 (0-6)	0 (0-4)	0.001	0.392

[a]According to Ferrandina *et al*. (10). PDS: Primary Debulking Surgery. I-IDS: Internal - Interval Debulking Surgery. R-IDS: Referred - Interval Debulking Surgery. [b]I-IDS vs. PDS. [c]R-IDS vs.PDS. [d]UAD= Upper Abdominal Disease. n.a.: Not applicable.

cycles of NACT in the referred patients with respect to the internal cases (6 cycles *vs*. 4 cycles; p=0.0001). However, all NACT women presented at IDS with similar percentages of radiological and serologica response independently from the Center of disease primary assessment and number of cycles.

The up-front judgment of unresectability was made on both radiological and surgical evaluation in all women assessed at our tertiary-level Center, whereas 32/134 (23.9%) referred patients (R-IDS) were firstly defined as unresectable on the bases of radiological criteria only.

Tumor extension at diagnosis, assessed by CT scan, is shown in Table II. As expected, women driven to NACT in our center (I-IDS) showed a much more diffused disease than those submitted to PDS, in terms of bowel and mesentery involvement, diaphragm infiltration, upper disease (*i.e*. spleen, lesser omentum, stomach) and liver metastases. However, as shown in Table II, similar differences were observed comparing I-IDS women with patients submitted to NACT in peripheral Centers (R-IDS). In fact, in these latter cases, the tumor load was of the same magnitude than in PDS cases treated at the referral center.

Among 279 PDS patients, 217 (77.8%) gained complete cytoreduction at the end of surgery, at the cost of major surgical procedures in 79.2% of the cases. As expected, these patients had a longer operative time and hospital stay, higher blood loss and more frequent major post-operative complications with respect to IDS women (Table III). Regarding IDS, macroscopically-absent residual tumor was achieved in comparable rates of patients, according to Centre of primary diagnosis (58.8% I-IDS *vs*. 66.4% R-IDS, p=0.186), but with a different rate of major surgical procedures utilized (39.4% I-IDS *vs*. 24.6% R-IDS; p=0.007). Regarding peri-operative parameters, the two IDS groups did not show any statistically significant difference in terms of operative time or blood loss resulting in a comparable length of stay. The overall high-grade (3 to 5) complication rate was less than 5 % in both groups (Table III).

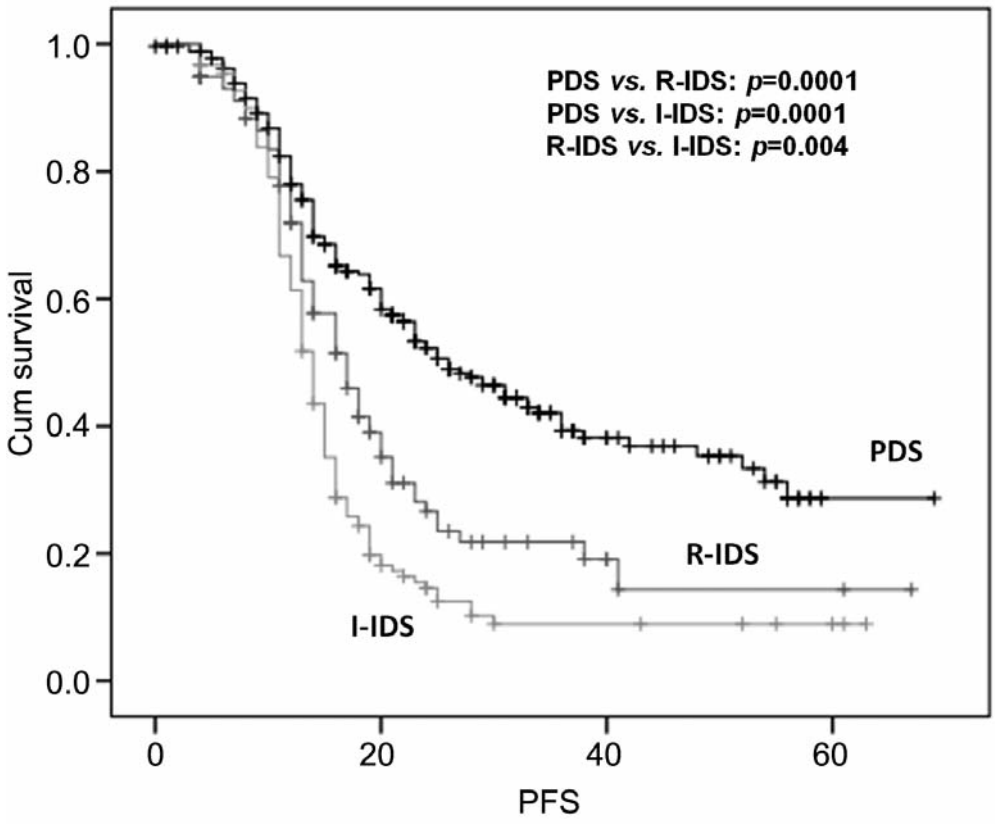

Figure 1. *Progression-free survival (PFS) of AEOC patients submitted to surgery at CUSH. Black line, Primary Debulking Surgery (IPDS); dark grey line, Referred IDS (R-IDS); light grey line, Internal IDS (I-IDS). PFS is expressed in months.*

Table III. *Surgical outcome and peri-operative morbidity.*

Variable	PDS N (%)	I-IDS N (%)	R-IDS N (%)	*p*-Value[a]
All cases	279	160	134	n.a.
Absent residual tumor				
Yes	217 (77.8)	94 (58.8)	89 (66.4)	0.186
No	62 (22.2)	66 (41.2)	45 (33.6)	
Surgical complexity score groups[b]				
1	58 (20.8)	97 (60.6)	101(75.4)	0.007
2-3	221 (79.2)	63 (39.4)	33 (24.6)	
Median blood loss (ΔHb g/dl)° (range)	3.7 (0-5)	1.5 (0-5)	2.7 (0-5)	0.180
Median operative time (min) (range)	320 (100-660)	200 (60-420)	230 (60-430)	0.668
Median length of ICU stay (days) (range)	1 (0-3)	0 (0-2)	0 (0-1)	0.438
Median length of hospitalization (days) (range)	7 (4 - 26)	5 (2-18)	5 (2-15)	0.604
Major post-operative complications[c]				
Grade 3	18 (6.4)	5 (3.1)	2 (1.4)	0.880
Grade 4	11 (3.9)	2 (1.2)	1 (0.7)	
Grade 5	0	0	0	

PDS: Primary debulking surgery. I-IDS: Internal - Interval debulking surgery. R-IDS: Referred - Interval Debulking Surgery. ICU: Intensive Care Unit. °ΔHb g/dl: largest variation in Hb levels between pre-operative and post-operative day 1. [a]I-IDS vs. R-IDS. [b]According to Aletti *et al*. (17). [c]According to MSKCC grading system (18). n.a. Not applicable.

With a median follow-up of 27 months (95% CI=8-82), median PFS was 26 months (95% CI=21.0-30.9) in PDS, 14 months (95% CI=13.0-14.9) in I-IDS and 17 months (95% CI=14.5-19.4) in R-IDS (Figure 1). The difference was statistically significant between all the groups (PDS *vs*. I-IDS p=0.0001; PDS *vs*. R-IDS p=0.0001; I-IDS *vs*. R-IDS p=0.004).

Discussion

In the present study, we report on the outcome of women submitted to surgery at our tertiary referral medical center depending on the hospital in which they received their primary disease assessment. The main result of this retrospective analysis is that women primarily assessed for NACT at a peripheral Center (R-IDS) have the same tumor burden at diagnosis than cases submitted to PDS in a referral Center. Moreover, when selected in a referral centre (I-IDS), they show a lower tumor load than patients receiving the same approach (NACT+IDS).

This finding clearly supports the idea that if R-IDS patients received their primary assessment in a tertiary referral center, they were offered optimal PDS. Indeed, only about 20% of patients in the R-IDS group have extensive tumor in the upper quadrants and only about 10% have mesenteral retraction at pre-operative CT scan. In other words, based on imaging data and the high rate of ECOG PS <2 patients, a vast majority of R-IDS women could achieve a significant improvement in their median PFS, which rose from 17 up to 26 months, if admitted to PDS.

Moreover, although the incomplete tumor removal is a possible occurrence in AEOC, especially in case of emergency in a peripheral Centre for presumed bowel obstruction or ovarian torsion, up-front re-surgery before the start of chemotherapy may be still feasible and successful in more than half of these patients (23). Referring women to a certified Center of expertise may offer an immediate re-surgery option (24) in most cases and the use of a minimally invasive approach, such as laparoscopy, to assess the chance of complete cytoreduction is an interesting opportunity in these pre-operated cases (15).

On the other hand, in the case R-IDS, patients would not benefit of a different primary treatment; however, they maintain a small but statistically significant advantage in terms of PFS over I-IDS women. The higher rate of complex surgical procedures in the I-IDS *vs*. R-IDS women (39.4 *vs*. 24.6; p=0.007) to obtain super imposable rates of optimal cytoreduction (58.8% *vs*. 66.4%, p=0.186) once more underlines the differences between the groups in terms of a larger initial tumor burden, as well as a lower median number of cycles of NACT administered.

Despite the retrospective nature of the study, we do believe it is unique in supporting, from a different point of view never analyzed before, the well-known issue that AEOC patients should be treated in a tertiary referral centre. These data, together with the observation that disease presentation and survival rates at the time of recurrence are very different between PDS *vs*. IDS (25), confirm that the primary approach to ovarian cancer plays a crucial role in defining the prognosis of these patients. As a consequence, NACT followed by IDS can represent a suitable approach only in women in whom primary complete debulking is not achievable in tertiary referral hospital.

Conflicts of Interest

No conflicts of interest is declared by the Authors.

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