Chapter 6

Treatment Decisions and Survival in Ovarian Cancer

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Abstract

Objective: to review the most recent data on the impact of the primary treatment and individual factors on ovarian cancer patient survival and to study it in a real world population. **Methods/materials:** retrospective analysis of 147 consecutive ovarian cancer patients treated with platin-based chemotherapy, either after primary debulking surgery (PDS) (n = 94, 64%) or as neoadjuvant (NACT) treatment (53, 36%). **Results:** NACT patients were older (64.3 vs. 58.2 years), with radiologically unresectable disease (74%) and/or comorbidities (26%). Fifty-five percent of pts. submitted to PDS were staged III/IV. Serous carcinomas were equally distributed (PDS-57% vs. NACT-60%) but endometrioid (20 vs. 4%) and carcinomas not otherwise specified (6 vs. 30%) were more frequently diagnosed in the PDS and NACT group, respectively. Genetic diagnosis (24.4%): 11 BRCA1/2 and 1 RAD51C carriers identified. Residual disease after surgery was the only significant prognostic factor for both relapse (HR = 2267) and death (HR = 1847). Primary debulking surgery was associated with a significantly better PFS (HR = 0.541; p = 0.012) and with a trend to a better OS (HR = 0.714; p = 0.296). For pts. with III/IV disease OS was significantly superior in the PDS group. **Conclusion:** residual disease was the only significant prognostic factor. Primary surgery was associated with a significantly better PFS. The difference in OS was significant in stage III/IV patients. This reinforces the importance of maximal cytoreduction.

Keywords: epithelial ovarian cancer, neoadjuvant therapy, primary surgery

1. Introduction

Ovarian cancer (OC) is the most lethal gynaecological malignancy in developed countries, with over 225.000 new cases and more than 140.000 deaths every year worldwide [1].

Epithelial OC is currently divided into seven main subtypes: serous, endometrioid, clear cell, mucinous, transitional cell, mixed and undifferentiated and unclassified OC [2]. Due to inadequate screening and a lack of early clinical symptoms, 70% of women with OC present with advanced disease, associated with high morbidity and mortality [1, 3]. The standard of care for OC treatment comprises maximal cytoreductive resection aiming to remove all visible tumour tissue, followed by platinum-taxane chemotherapy [4]. However, most patients relapse within the first 5 years after diagnosis, with a median progression-free survival (PFS) of 11 to 18 months and a median overall survival (OS) of 24 to 38 months [5, 6]. Data from the EUROCARE show a 5-year age-standardised relative survival of 37.6% [7]. Data from the National Cancer Institute show a 5-year survival of 46.2% [8].

Many OC patient characteristics are associated with survival, like stage [9, 10], histology [10–14], residual disease and debulking status after cytoreductive surgery [10, 12, 14, 15], type of chemotherapy [6, 10, 13, 16] and BRCA status [17, 18]. Maximal surgery, even when total absence of residual disease cannot be obtained, seems to relate to survival advantage [19]. The expertise of the surgical team is important in providing optimal cytoreduction without compromising post-operative morbidity [20].

A subgroup of OC patients is found to have surgically unresectable cancer and prediction criteria for suboptimal cytoreduction are important in treatment decisions. Studies using computed tomography (CT) suggested that the presence of an omental cake extending to the spleen, a diaphragm coated by tumour or lesions >2 cm in the suprarenal, para-aortic lymph-nodes and porta hepatis, among others [21], were predictors of unresectable disease. Other features predicting the outcome of cytoreduction correspond to traditionally difficult anatomic locations, such as extensive upper abdominal disease [22]. Recently, the Society of Gynecologic Oncology and the American Society of Clinical Oncology published the latest guidelines on neoadjuvant chemotherapy (NACT), stating the predictors of suboptimal cytoreduction. These include radiological predictors, such as retroperitoneal lymph-nodes above the renal hilum >1 cm, diffuse small bowel adhesions or thickening, small bowel mesentery lesions >1 cm, root of the superior mesenteric artery lesions >1 cm, perisplenic lesions >1 cm, lesser sac lesions >1 cm, and ascites on at least two-thirds of CT scan slices; and clinical predictors such as age ≥ 60 years and CA-125 ≥ 500 U/mL [23].

Interval debulking surgery (IDS) after NACT for patients with unresectable disease criteria is still controversial. A meta-analysis [24] suggested that NACT was associated with a worse outcome, but in 2010 a study concluded that it was not inferior to primary debulking surgery (PDS) in bulky stage IIIC or IV OC [25]. Moreover, it was associated to significantly lower adverse effects, such as postoperative infections, venous complications, fistula and haemorrhage, as well as lower postoperative mortality rates [25–27]. Other studies, such as the SCORPION and the JCOG0602 trials, seem to confirm these findings [23]. Some phase III trials suggested that NACT would also lead to improved quality of life [28–30]. Preoperative predictors for complete cytoreduction and outcomes from NACT are needed and subject of research [31].

The decision of treating advanced OC patients with NACT became more frequent [32], but there are still unsolved issues. Staging is surgical and based on laparotomy findings. Residual

disease after surgery is a major prognostic factor for survival [14, 25] and visual evaluation by the surgeon is critical to conclude about intra-abdominal tumour spread. Whether the surgeons' statement of complete tumour resection is equal in primary surgery and in IDS remains unclear. Microscopically carcinomatous areas may have a benign visual appearance after NACT [33] interfering with the visual evaluation of tumour extension and potentially leading to incomplete cytoreduction. Also, the possibility that NACT may induce platinum resistance [34, 35] remains unclear. A recent study revealed that although the proportion of platinum-resistant recurrence after NACT and IDS was superior, this difference was not significant. A significant difference was only observed when women who had a recurrence were retreated with platinum-based chemotherapy [36].

The highest risk associated with NACT may be that patients with significant side effects and refractory disease will lose the opportunity for debulking surgery [37], although it has been suggested that these patients have a poor prognosis and should be encouraged to participate in clinical trials or to discontinue active cancer therapy [23]. Another limitation of NACT is the insufficient data supporting the use of intraperitoneal (IP)/intravenous (IV) chemotherapy as adjuvant treatment after NACT [23]. Recent results from the OV21/PETROC trial seem to support that a carboplatin-based IP regimen, after NACT and debulking surgery, is well tolerated and associated with a higher PFS compared to IV therapy (immature data) [38].

Besides patient characteristics, survival depends on treatment decisions and questions remain about the reproducibility of study data in routine clinical practice. We tried to review the most recent data on the primary treatment of OC and the factors that have impact on the survival of these patients. Therefore, our objective was to characterise a consecutive series of OC patients treated in our centre and to analyse the effect of patient variables and decision criteria on efficacy outcomes for patients treated with either PDS or primary NACT.

2. Material and methods

This study is a retrospective analysis. It includes all patients with epithelial OC observed in the Gynaecological Oncology multidisciplinary group of our centre and registered in the South Portuguese Cancer Registry (ROR-Sul), between January 2006 and December 2011. Medical records were reviewed, and demographic, clinical, surgical, pathologic, molecular and follow-up information obtained. Optimal cytoreduction was defined as no macroscopic residual disease at the end of surgery. Pathology data were collected from the pathology report after citoreductive surgery. The chemotherapy regimen used was the doublet of carboplatin (AUC = 6) and paclitaxel (175 mg/m^2 of body surface). Progression data were obtained from clinical notes: most were confirmed by CT scan and CA125 measurement criteria. In less than 5% of cases, progression was assumed by CA125 measurement and clinical examination. Information concerning molecular testing was obtained from patients previously counselled and given informed consent through procedures and forms approved by the Ethics Committee.

2.1. Statistics

Statistical analysis was performed with IBM SPSS Statistics software (version 23). Continuous data (presented as the means ± SD) that were normally distributed were analysed using Student's t-test, while data that were not normally distributed were analysed using the Mann–Whitney U test. The Pearson's exact chi-square or Fisher's exact test were used to compare the proportions between groups. Progression-free survival was defined as the time interval between the end of primary treatment and the date of progression. If there was no documented recurrence, PFS was calculated from the end of primary treatment to the date of last follow-up or death. Platinum-resistant relapse was defined as recurrence within 6 months of primary treatment. Overall survival was defined as the time interval between date of diagnosis and date of death or last follow-up. Progression free survival and OS were analysed by the log-rank test and the results were expressed as Kaplan–Meier plots. A Cox proportional hazards model was estimated to assess the impact of different prognostic variables on survival. A p value <0.05 was defined as statistically significant.

3. Results

3.1. Cases

Two hundred and fifty-seven patients were registered in the ROR-Sul database and 147 (58%) of those received systemic treatment and were included in this analysis. Excluded patients either were not submitted to surgery or chemotherapy in our centre, died without any specific treatment, had non-eligible neoplasia after surgery (3 mucinous adenocarcinomas of the appendix) or were diagnosed with early stage disease with low-risk features (**Figure 1**).

Demographic and clinical characteristics are summarised in **Table 1**. All 147 patients were treated with platin-based chemotherapy: either following primary surgery (n = 94, 64%) or in the neoadjuvant setting (n = 53, 36%). The mean age at diagnosis was 60.4 years (25–89; IC95% = [58.4–62.4]); patients in NACT group were older (64.3 vs. 58.2; p = 0.002) and we did not observe age differences between advanced versus non-advanced stages, different histologic subtypes or between platinum-resistant versus platinum-sensitive patients (p = 0.318; p = 0.108; p = 0.774, respectively). More cases of advanced disease were treated with NACT (6% stages IIIB, 83% IIIC-IV) as compared with primary surgery (27% stages IA-IC, 36% IIA-IIIB, 37% IIIC-IV). The median number of chemotherapy cycles was superior in the NACT group (8 vs. 6; p = 0.000). Macroscopic residual disease after debulking surgery (PDS or IDS) was present in 46% of all cases (IC95% = [37%; 54%]) and was not associated with the treatment modality (Pearson X2 = 0.001; p = 1.000). Most cases were serous, endometrioid or carcinomas not otherwise specified (NOS) (58.5, 14.3 and 15%, respectively); 9 patients (6%) had cancers with mucinous/clear cell histology. The proportion of serous carcinomas was similar between groups. In the PDS group, a significantly higher proportion of endometrioid tumours was observed (20 vs. 2%; p = 0.021) while carcinomas NOS were more frequent in the NACT group (16 vs. 6%; p = 0.021). Thirty-six patients (24.4%) had information of molecular testing: 23 in the PDS (7 BRCA carriers) and 13 in the NACT (4 BRCA carriers and 1 RAD51C carrier) groups.

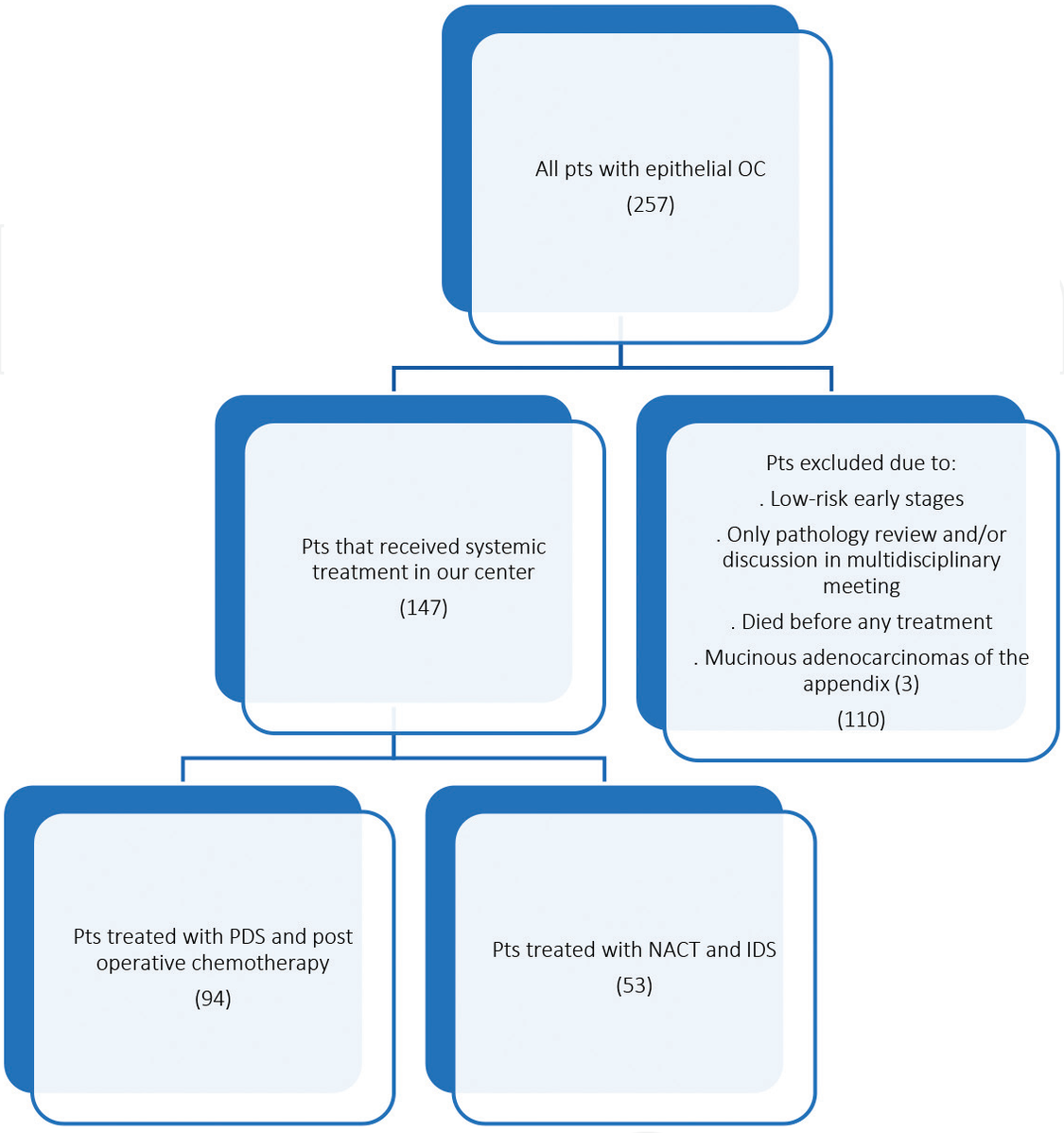

Figure 1. Study design. OC: Ovarian cancer; PDS: Primary debulking surgery; NACT: Neoadjuvant chemotherapy; IDS: Interval debulking surgery.

	PDS (*N* = 94)	**NACT–IDS (*N* = 53)**	***P***
Age (mean, years)	58 (±12)	64 (±10)	0.002
Histology [*N*(%)]			
Serous	54 (57.4)	32 (60.4)	0.021
Endometrioid	19 (20.4)	2 (3.8)	
Mucinous	3 (3.2)	1 (1.9)	
Clear cell	4 (4.3)	1 (1.9)	
Mixed	2 (2.1)	0 (0)	
Poorly differentiated	6 (6.4)	1 (1.9)	
Carcinoma NOS	6 (6.4)	16 (30.2)	

	PDS (*N* = 94)	NACT–IDS (*N* = 53)	*P*
FIGO Stage [*N*(%)]			
IA-IC	25 (26.6)	—	0.000
IIA-IIC	17 (18.1)	—	
IIIA	5 (5.3)	—	
IIIB	12 (12.8)	3 (5.7)	
IIIC	21 (22.3)	15 (28.3)	
IV	14 (14.9)	29 (54.7)	
Unknown	—	6 (11.3)	
Nr of cycles (median)	6 (±1.3)	8 (±2.7)	0.000
Residual disease after debulking surgery [*N*(%)]	60 (64)	29 (55)	1.000

Table 1. Demographic and clinical characteristics of the study population. PDS: Primary debulking surgery; NACT-IDS: Neoadjuvant chemotherapy and interval debulking surgery; NOS: Not otherwise specified; Values for continuous measurements are means, unless otherwise specified; FIGO: International Federation of Gynecology and Obstetrics.

3.2. Treatment decision

The decision for NACT was due mainly to radiological criteria: implants >2 cm outside the pelvis (18 pts; 34%), lymphadenopathies above renal hilum (12 pts; 23%), subcapsular or Parenchymal liver metastasis (8; 15%) or pre-sacred retroperitoneal disease (1 pt; 2%). In 14 pts (26%), comorbidities that contraindicated upfront surgery were also considered in the decision for NACT.

3.3. Efficacy analysis

For the total cohort, the median PFS and OS were 13.4 (IC95%= [9,3-17,5]) and 44.0 (IC95% = [29.7–58.3]) months, respectively. In the PDS group, PFS was significantly superior (23.4 vs. 13.8 months; p = 0.010), even when restricting analysis to advanced stages (21.4 vs. 12.5 months; p = 0.040). Patients with no macroscopic residual disease after debulking surgery had superior PFS (27.0 vs. 14.0 months; p = 0.000).

For patients treated with PDS, OS was significantly superior (48.4 vs. 30.9 months; p = 0.001), even when restricting the analysis to advanced stages (44.4 vs. 28.2 months; p = 0.014) (**Figure 2**).

Patients with no macroscopic residual disease after debulking surgery had superior OS (52.7 vs. 36.0 months; p = 0.002) (**Figure 3**), as well as those with non-advanced stage disease (52.5 vs. 37.1 months; p = 0.009). Moreover, patients with platinum-sensitive relapse (>6 months) had significantly superior OS (56.0 vs. 12.3 months; p = 0.000) (**Figure 4**), as compared to platinum resistant patients.

The Cox proportional hazards model (**Table 2**) allowed estimating the impact in survival of factors such as age at diagnosis, histology, stage, platinum free interval, residual disease after debulking surgery and therapeutic modality. Adjusting for these variables, the

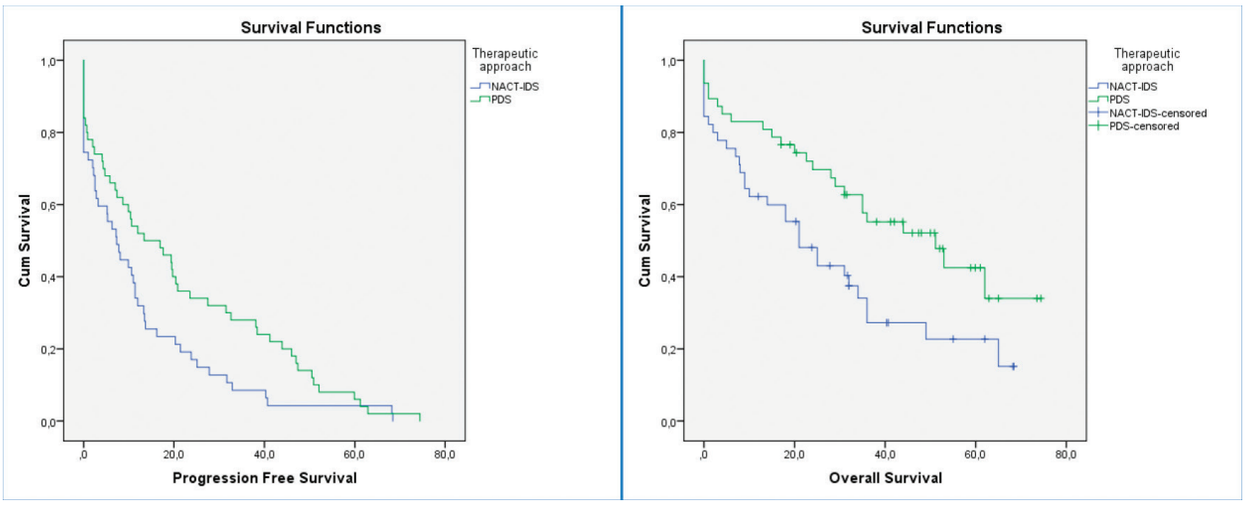

Figure 2. Kaplan–Meier survival curves showing the PFS and OS rates of patients in the NACT/IDS *vs.* PDS groups (only advanced stages) (7.3 *vs.* 13.4 months; p = 0.010 and 21.0 *vs.* 55.1 months; p = 0.001, respectively).

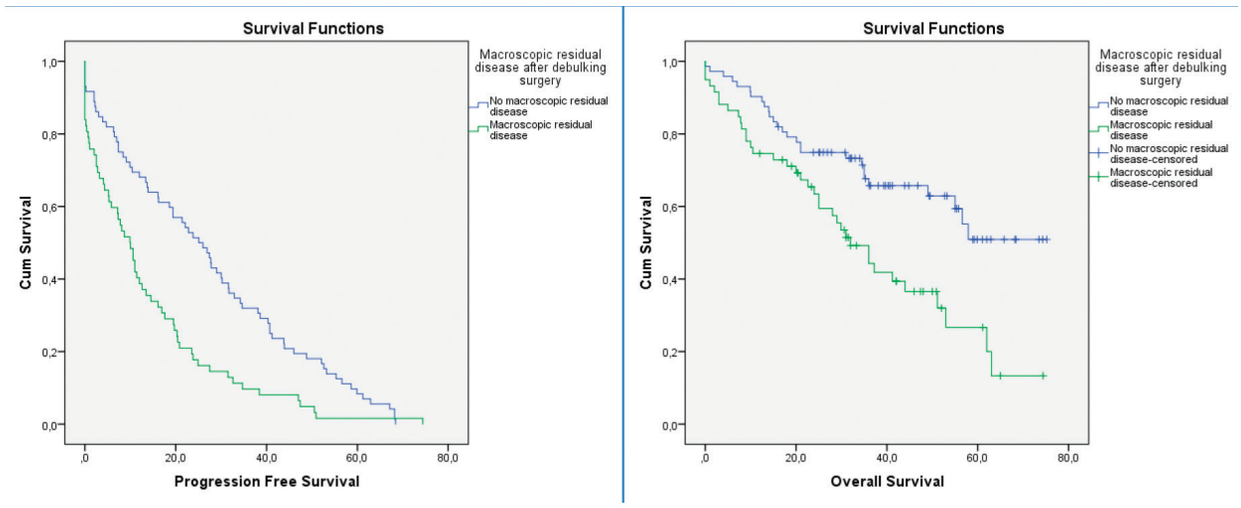

Figure 3. Kaplan–Meier survival curves showing the PFS and OS rates of patients with *vs.* without macroscopic residual disease after debulking surgery (PFS: 9.9 *vs.* 25.1 months, p = 0.000; as it did not fall below 50% at the time of the analysis, it is not possible to estimate median OS, p = 0.002).

only statistically significant prognostic factor for both relapse and death was the presence of macroscopic residual disease after surgery, with more than 2-fold higher risk of relapse (HR = 2267; p = 0.000) and 80% higher risk of death (HR = 1847; p = 0.036). Primary debulking surgery was associated to a significantly better outcome, but only in terms of PFS (HR = 0.541; p = 0.012), with no significant gain in OS compared to NACT, although there is a trend to a better outcome (HR = 0.714; p = 0.296). Other factors, such as age, histology or advanced stage did not have a significant effect on relapse. Platinum-resistant disease was associated with a 9-fold higher risk of death (HR = 8964; p = 0.000). There is a trend towards a worse prognosis of advanced stage disease (HR = 1293; p = 0.468) and towards a better outcome of serous histology (HR = 0.847; p = 0.560).

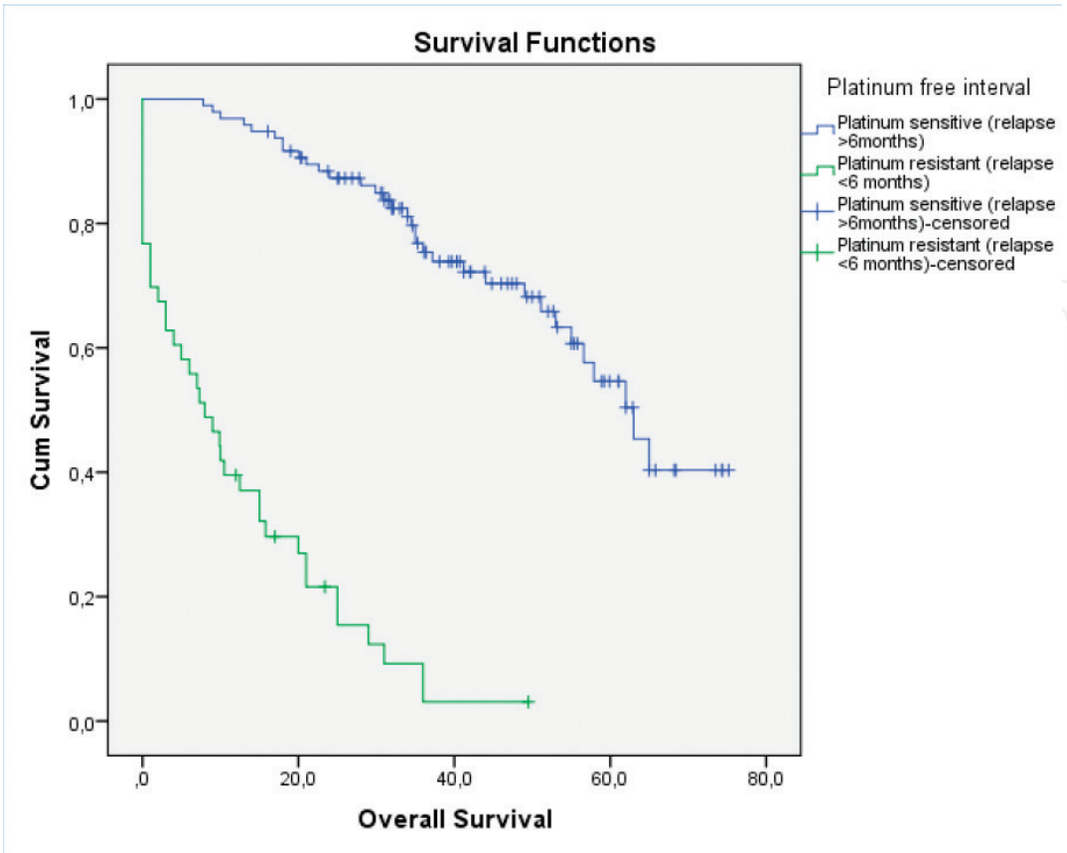

Figure 4. Kaplan–Meier survival curves showing OS rates of patients with platinum-sensitive *vs.* platinum-resistant relapse after primary treatment (63.0 *vs.* 8.0 months, p = 0.000).

	OS				PFS			
	Coefficient	**SE**	**P**	**HR (95% CI)**	**Coefficient**	**SE**	**P**	**HR (95% CI)**
Age	0.021	0.012	0.097	1021 (0.996–1046)	0.004	0.008	0.559	1004 (0.990–1020)
Serous histology (*vs* nonserous)	−0.166	0.285	0.560	0.847 (0.484–1481)	0.323	0.194	0.096	1381 (0.944–2020)
Advanced stage (stage III-IV *vs.* I-II)	0.257	0.354	0.468	1293 (0.646–2590)	−0.315	0.243	0.195	0.730 (0.453–1176)
Residual disease	0.603	0.293	0.036	1847 (1040–3278)	0.818	0.219	0.000	2267 (1504–3416)
PDS (*vs* NACT)	−0.337	0.322	0.296	0.714 (0.380–1344)	−0.615	0.244	0.012	0.541 (0.335–0.873)
Platinum resistant disease	2193	0.300	0.000	8964 (4976–16.147)	—	—	—	—

Table 2. Multivariate Cox regression model. OS: overall survival; PFS: progression-free survival; SE: standard error; HR: hazard ratio; CI: confidence interval; PDS (vs NACT): primary debulking surgery (vs neoadjuvant chemotherapy).

Ninety seven percent (97%) of patients relapsed and almost 1/3 of these (46 pts) had platinum-resistant disease (31%; IC95% = [23%; 39%]). The treatment strategy (NACT vs. PDS) and residual disease after debulking surgery were not associated with the occurrence of relapse (Pearson X2 = 2318 and p = 0.297; Pearson X2 = 0.708 and p = 0.625, respectively).

At the time of this analysis, all BRCA carriers (7/7) in the PDS and 75% of BRCA carriers in the NACT (3/4) group were alive as compared to 54 and 36% of patients with unknown BRCA status, respectively.

4. Discussion

Between 2006 and 2011, NACT was decided as primary approach for advanced OC, mostly for patients with radiologically determined unresectable disease and for older patients with comorbidities. Independently of the therapeutic modality, non-advanced stage at diagnosis and absence of residual disease after surgery were associated with progression free survival. Adjusting for age at diagnosis, histology, stage, platinum free interval, residual disease after surgery and therapeutic modality (either NACT or PDS), the only statistically significant prognostic factor for both relapse and death was the presence of macroscopic residual disease after surgery. Primary debulking surgery was associated with a significantly better outcome only in terms of PFS, although a trend to a better OS was also observed. When analysis was restricted to stages III and IV OS was significantly superior in the PDS group, as compared with the NACT group. BRCA status was known for a small proportion of patients in both groups, which limits statistical analysis and conclusions. However, it's interesting to note that all known BRCA carriers in the PDS group were alive at the time of this analysis, compared to only 75% after NACT-IDS. That happens for unknown BRCA status patients as well, but with a smaller difference between groups (54 vs. 36%). Recent observations suggest a selection of tumour cell clones without somatic loss of heterozygosity (LOH) for the wild-type allele of BRCA genes, during neoadjuvant therapy [39].

Patients treated with PDS had better outcome in terms of PFS. This is not unexpected since this group included patients with less advanced disease, but suggests that the cytotoxic treatment before primary surgery in the NACT group could not counteract the bad prognosis associated with advanced stage. This was observed even if patients in the NACT group received a higher number of chemotherapy cycles (8 vs. 6; p = 0.000). Some authors have expressed concern about the selection of resistant clones in patients submitted to NACT [34–36] but we did not observe an association between the platinum free interval and the chosen treatment approach (Pearson X2 = 3955 and p = 0.058). Patients with platinum-sensitive relapse (>6 months) had significantly superior OS (56.0 vs. 12.3 months; p = 0.000), as compared to platinum resistant patients. This was confirmed in the multivariate survival analysis, with Cox model showing that platinum-resistant disease was associated with a 9-fold higher risk of death (HR = 8964; p = 0.000). These findings should be carefully interpreted, since further lines of treatment widely vary between platinum-sensitive and platinum-resistant populations.

There is evidence that longer platinum-chemotherapy-free interval is associated with better survival (especially PFS after further lines of treatment) [40], but although the platinum-free interval is defined as the period of time from the last date of platinum dose until progressive disease is documented, it does not take into account how progression is defined (CA125 alone, radiological and symptomatic recurrence) [41].

The PDS group had a significantly higher number of patients with endometrioid histology. This factor and more advanced cases in the NACT group, may have contributed to the better outcomes in patients submitted to upfront surgery. The higher proportion of carcinoma NOS in NACT group (16 vs. 6%; p = 0.021) is a limitation of our study, since consecutive pathology review was not done. However, this finding is not unexpected in pathology reports of surgical specimens after NACT.

We did not observe an improvement of optimal debulking rates with NACT, as macroscopic residual disease after debulking surgery (PDS or IDS) was not associated with the treatment strategy (Pearson X2 = 0.001; p = 1.000). In the 2010 EORTC-NCIC trial, no gross residual tumour after PDS was achieved in 19% of patients and after IDS in 51% of patients [25]. Progression-free survival and OS for both arms were 12 and 30 months, respectively. In our cohort, cytoreduction was higher (36%) in the PDS group, as well as PFS and OS (13.4 and 55.1 months, respectively). Cytoreduction rate for our NACT group (45%) was closer to the rate described in the EORTC trial but our observations for PFS and OS were lower (7.3 and 21.0 months, respectively). Besides the expected differences between a randomised trial and an observational study, stage IV patients were well-balanced between arms in the EORTC trial but predominated in the NACT group (55 vs. 15%) of our study. In the CHORUS trial the complete cytoreduction rate was inferior to the one in our cohort, both in PDS and NACT groups (15 vs. 35%) but PFS and OS outcomes with NACT were better (10 and 23 months, respectively) than with PDS (12 and 25 months, respectively) [42]. However, a recent observational trial [32] showed NACT to be inferior to PDS in stage IIIC but superior in stage IV. It is important to remember that, for this analysis, we considered complete cytoreduction as the absence of macroscopic residual disease, even if, this was not the case for other studies [25, 32, 42].

Although retrospective, our study reflects how decisional criteria for both modalities were applied in a group of consecutive, non-selected OC patients. Statistical methodologies were selected according to the retrospective nature of the study: univariate analysis first identified factors influencing the outcomes of these patients (other than primary treatment); these factors were then integrated in the multivariate analysis (Cox regression model), to ascertain the efficacy of each strategy, adjusting to variables previously identified as an influence to prognosis. Limitations to this study are possible selection and recall bias, as well as unknown confounding variables that may have a negative impact on the accuracy of the results. One example is the limited accuracy in determining performance status and comorbidities as criteria for the decision of upfront treatment, although notes from multidisciplinary meetings were carefully reviewed. As for the assessment of residual disease after debulking surgery, heterogeneity was observed due to changing criteria for the classification of ideal resection during the period covered by our study.

In conclusion, the only significant prognostic factor for both relapse and death was the presence of macroscopic residual disease after surgery, which enhances the importance of

maximal cytoreduction in the primary treatment. As for the influence of treatment modality on outcomes, PDS was associated to a significantly better PFS and a non-significant trend to a better OS. Other factors, such as age, histology or advanced stage did not have a significant effect on relapse. Our findings are in agreement with other studies [19, 20, 25, 32, 42, 43] about the impact of optimal debulking surgery in survival of OC patients. This is observed whether complete debulking is attained with easily resectable disease or extensive surgery. It has also been shown that the impact of potentially negative biologic factors such as grade and histology can be overcome by surgical debulking [43]. This is why surgical expertise plus supportive management (antibiotics, blood banking, and intensive care) should parallel the development of better systemic therapies.

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