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ORIGINAL RESEARCH

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Review of neoadjuvant chemotherapy characteristics in advanced epithelial ovarian cancer: experience from two cancer centers

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Abstract

Background: This study aimed to review the characteristics and survival of patients with Advanced Epithelial Ovarian Cancer undergoing neoadjuvant chemotherapy (NACT) and the impact of timing of surgery and post-operative adjuvant chemotherapy (CCT). **Methods**: Retrospective multicentre study, of patients with an initial diagnosis of advanced high-grade epithelial ovarian carcinoma, considered inoperable at diagnosis and treated with NACT. **Results**: Eighty-six patients were analyzed. Fifty-seven underwent surgery, with significantly higher median overall survival (mOS) versus those who were never operated. The percentage of complete surgery (R0) was 74%, with a median progression-free survival (mPFS) of 45 months and mOS of 67 months versus mPFS of 27 months and mOS of 28 months in patients with residual disease. Of the operated patients, 21 underwent 3–4 cycles of NACT and 36 5–6 cycles of NACT, with a mOS of 64 months and 38 months respectively. Patients with almost complete/complete NACT response had significantly improved PFS and OS compared with patients with partial/minimal/absent response. Twenty-two patients underwent 2–3 cycles CCT with no significant differences in terms of PFS or OS. COX regression showed that both the increase in time between NACT and surgery and the chemotherapy response score are related to the risk of death. **Conclusions**: Complete surgery and Chemotherapy Response Score (CRS) were the most important prognostic factors for survival in this population. The use of CCT showed no advantage in survival outcomes. Prospective studies are needed to evaluate new therapeutic strategies for patients with inoperable ovarian cancer at diagnosis.

Keywords

Ovarian neoplasms; Neoadjuvant therapy; Adjuvant chemotherapy

1. Introduction

Ovarian cancer is the 8th most frequent cancer in Europe and the 5th with the highest mortality rate in women, being a leading cause of death from gynaecologic malignancy [1]. Cytoreductive surgery and platinum-based chemotherapy, in some cases followed by maintenance therapy (bevacizumab and/or poly-ADP ribose polymerase [PARP] inhibitors), are the basis of treatment of newly diagnosed advanced ovarian cancer [2, 3]. Complete macroscopic resection remains the most important prognostic factor in advanced epithelial ovarian cancer, and primary debulking surgery (PDS) should be offered in patients who are surgical candidates and in whom removal of macroscopic disease appears feasible [4, 5]. However in clinical practice it's not always possible to perform primary surgery, particularly in patients clinically unsuitable and/or with low probability of complete cytoreduction after rigorous evaluation of resectability. In these cases starting with neoadjuvant chemotherapy (NACT) followed by interval debulking surgery (IDS) should be considered. There are several randomized trials that compared NACT/IDS/postoperative chemotherapy versus standard treatment (PDS/postoperative chemotherapy), that demonstrated improved surgical outcomes with NACT approach but no significant differences in terms of survival outcomes [6–9]. These trials included essentially patients with FIGO stage IIIC-IV, and all of them tested regimens of 3–4 NACT followed by IDS and 3–4 cycles of postoperative chemotherapy. Nevertheless in clinical practice there is often a need to delay surgery until after 6 cycles of NACT, due to the low response to chemotherapy (CT) and anticipation of suboptimal surgery after 3 cycles. The optimal timing of interval surgery was never established, as was the need for post-operative adjuvant CT when the 6 established CT cycles were all performed previously.

Our primary objective was to review the characteristics of patients with advanced epithelial ovarian cancer undergoing neoadjuvant chemotherapy (NACT) and the survival outcomes

according to the timing of interval surgery and post-operative adjuvantchemotherapy (CCT).

2. Materials and Methods

2.1 Design and Patients

This study was a retrospective observational and multicentre study. We retrospectively identified patients from two Portuguese institutions with an initial diagnosis of advanced high-grade epithelial ovarian/fallopian tube/primary peritoneal carcinoma (International Federation of Gynecology and Obstetrics (FIGO) 2014 stage III-IV), considered inoperable at diagnosis and treated with chemotherapy with neoadjuvant intent initiated between October 2015 and October 2020. Inoperability was decided in a multisdiciplinary team meeting with a gynecologic oncologists.

2.2 Study Data

We reviewed data from the electronic health records including: demographic variables, diagnosis (FIGO stage, histology and BRCA status), treatment characteristics (chemotherapy and surgery), presence of residual disease, pathology response to chemotherapy, disease progression, death and last follow-up. Histology was confirmed with tumor biopsy before starting NACT.

Survival outcomes were analyzed according to surgery, residual disease, number of NACT cycles, adjuvant chemotherapy, pathological chemotherapy response score (CRS), timing between last cycle of NACT and surgery and timing between surgery and postoperative chemotherapy.

For the purpose of this study the term adjuvant chemotherapy (AdCT) will be used for patients who have undergone 5-6 cycles of NACT and who after IDS had another 2-3 cycles of postoperative chemotherapy. Complete surgical resection (R0) refers to no macroscopic residual disease after surgery. All other patients will be categorized as R1. CRS was assigned based on the original publication by Böhm and colleagues in 2015 that stratifies patients into complete/near-complete (CRS3), partial (CRS2), and no/minimal (CRS1) response based on omental examination [10].

2.3 Statistics

Data were summarized by frequency and percentage for categorical variables and by median and range for continuous variables. Progression free survival (PFS) was defined as the time from diagnosis until disease progression or last follow-up visit. Overall survival (OS) was defined as the time from diagnosis until death from any cause or last follow-up visit.

Kaplan-Meier survival curves were used to estimate PFS and OS. Two-sided log-rank tests were used to compare the subgroups. Cox proportional-hazards regression analysis was used to univariable and multivariable analysis of survival outcomes. Significance level of the test results was set at 0.05. Statistical analyses were conducted using IBM SPSS Statistics 26 software.

3. Results

Eighty-six patients met the inclusion criteria and were included in the analysis. Baseline patient characteristics are presented in Table 1. Median age at diagnosis was 67 years (36–88). Most patients had FIGO stage IIIC-IV and high grade serous histology. We had access to BRCA 1 and 2 status in 54 patients, of whom 13 (24%) had a pathogenic mutation (6 germline and 7 somatic). All but one were treated with Carboplatin/Paclitaxel regimen, mostly on the 3-week schedule.

57 patients (66%) underwent IDS, of whom 42 (74%) had complete surgery (R0), Of the operated patients (n = 57), 21 (37%) had 3–4 cycles of NACT and 36 (63%) 5–6 cycles of NACT. 22 (61%) underwent CCT. Considering patients with known BRCA status (n = 54), 41 underwent IDS (11 with BRCA mutation and 30 BRCA wild type). No statistically differences were found in survival outcomes (PFS and OS) according to the BRCA status. Nonetheless there was a trend favoring BRCA mutated patients in terms of OS, with a mOS of 64 months (95% CI 26.8–101.2) in the BRCA wild type subgroup versus a mOS that was not reached in the BRCA mutated subgroup.

The CRS was evaluated in 43 patients (75% of the operated patients), with complete or almost complete response in 11 patients. Median time between the last NACT cycle and surgery was 5 weeks, and between surgery and post-operative CT 5.5 weeks. In the subgroup of patients where BRCA status was identified, 41 underwent IDS, of which 7 had a CRS3, all without BRCA mutations.

Survival analysis was done with 74 (86%) events for PFS and 56 (65%) events for OS.

Median OS (mOS) was significantly higher in operated patients (n = 57), with a mOS of 48 months (95% CI 20.7–75.3) versus 18 months (95% CI 14.5–21.5) in the subgroup of patients who never underwent surgery (n = 29 patients) (log-rank $p = 0.000$) (Fig. 1).

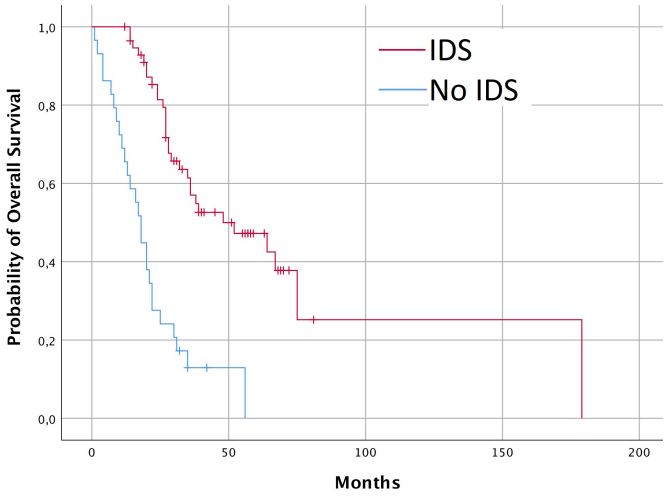

FIGURE 1. OS according to the performance or not of IDS. IDS, interval debulking surgery; OS, overall survival.

Regarding the presence of residual disease, patients with R0 surgery had a median progression-free survival (mPFS) of 45 months (95% CI 33.8–56.2) and mOS of 67 months (95% CI

TABLE 1. Baseline characteristics of patients.

Variables	
Age: median (range)	67, 36–88
FIGO Stage	IIIB – 11 / IIIC – 38 / IVA – 20 / IVB – 17
Histology (Tumor Biopsy)	High grade serous: 79
	Endometrioid: 4
	Clear Cell: 2
	Other: 1
Chemotherapy regimen	Carboplatin/Paclitaxel 3 weeks schedule: 75
	Carboplatin/Paclitaxel Weekly schedule: 10
	Carboplatin monotherapy:1
Interval Debulking Surgery (IDS) versus No surgery	57 (66%) versus 29 (34%)
BRCA status*	BRCA 1 and/or 2 mutation: 13 of the 54 evaluated patients (24%)
	6 germline/7 somatic
Complete Surgery (%)†	Overall population: 74%
	Patients with 3–4 NACT cycles: 86%
	Patients with 5–6 NACT cycles: 64%
Number of NACT cycles (n, %)‡	3–4: 21, 37%
	5–6: 36, 63%
Adjuvant Chemotherapy (AdCT) after 5–6 NACT cycles§	22, 61%
Chemotherapy Response Score‖	CRS1: 15
	CRS2: 17
	CRS3: 11

*Footnote: * Only available in 54 patients. †‡ Considering the 57 patients that had interval debulking surgery (n=57). § Considering patients that had 2–3 postoperative chemotherapy cycles after having 5–6 cycles in the neoadjuvant setting. ‖ Only available in 43 patients. CRS1: no or minimal tumour response. CRS 2: appreciable tumour response with viable tumour that is readily identifiable. CRS3: complete or near complete response with no residual tumour or minimal irregularly scattered tumour foci seen as individual cells, cell groups, or nodules of up to 2-mm maximum size.*

51.6–82.4) versus mPFS of 27 months (95% CI 19.4–34.6) and mOS of 28 months (95% CI 20.8–35.2) in patients R1 (Log-rank *p* PFS = 0.06; log-rank *p* OS = 0.04) (Fig. 2).

Comparing patients who underwent 3–4 cycles of NACT (21/57) versus those who had 5–6 cycles of NACT (36/57), mPFS was 15 months versus 13 months (log-rank 0.09), and mOS 64 months (95% CI 35.6–92.4) versus 38 months (95% CI 29.4–46.6) respectively (log rank *p* = 0.2) (Fig. 3).

Twenty-two of the 36 patients who underwent 5–6 NACT cycles had 2–3 cycles of CCT, with a mPFS of 16 months and mOS of 36 months (95% CI 23.3–48.7) versus mPFS of 14 months and mOS of 39 months (95% CI 27.5–50.5) in patients who did not undergo CCT (log-rank *p* = 0.6 for PFS and *p* = 0.5 for OS) (Fig. 4).

Taking the CRS into account, patients with almost complete/complete NACT response (11 patients) versus partial/minimal/absent response, had a mPFS and mOS that were not reached versus mPFS of 14 months (95% CI 11.3–16.7) and mOS 35 months (95% CI 27.3–48.7) (logrank *p* = 0.000 for PFS and *p* = 0.035 for OS) (Fig. 5).

Multivariable cox regression analysis showed that both CRS (HR 0.32; 95% CI, 0.124–0.839; *p* = 0.020) and the time in weeks between the last cycle of NACT and surgery (HR 1.46; 95% CI 1.131–1.882; *p* = 0.004) are related with the risk of death.

4. Discussion

With regard to the characteristics of the patients, it is important to highlight the percentage of BRCA mutation (24%), interestingly with half of them being somatic mutations. The prevalence of germline BRCA mutation varies among different ovarian cancer subtypes, but it's highest in high grade serous subtype which was reported up to 20–25% [11, 12]. The incidence of somatic mutations is reported to be much lower, approximately 5%–7% of ovarian cancer cases [13]. In our population the balance between germline and somatic is atypical.

The majority of patients (66%) responded to NACT allowing patients to be submitted to IDS. As expected, operated patients had significantly better prognosis. The percentage of complete surgery (74%) is in line or higher compared with previously published randomized clinical trials, which may indicate a good selection of patients [6–9]. If we look at the R0 rate according to the number of NACT cycles we can see that it's highest in those who respond and are able

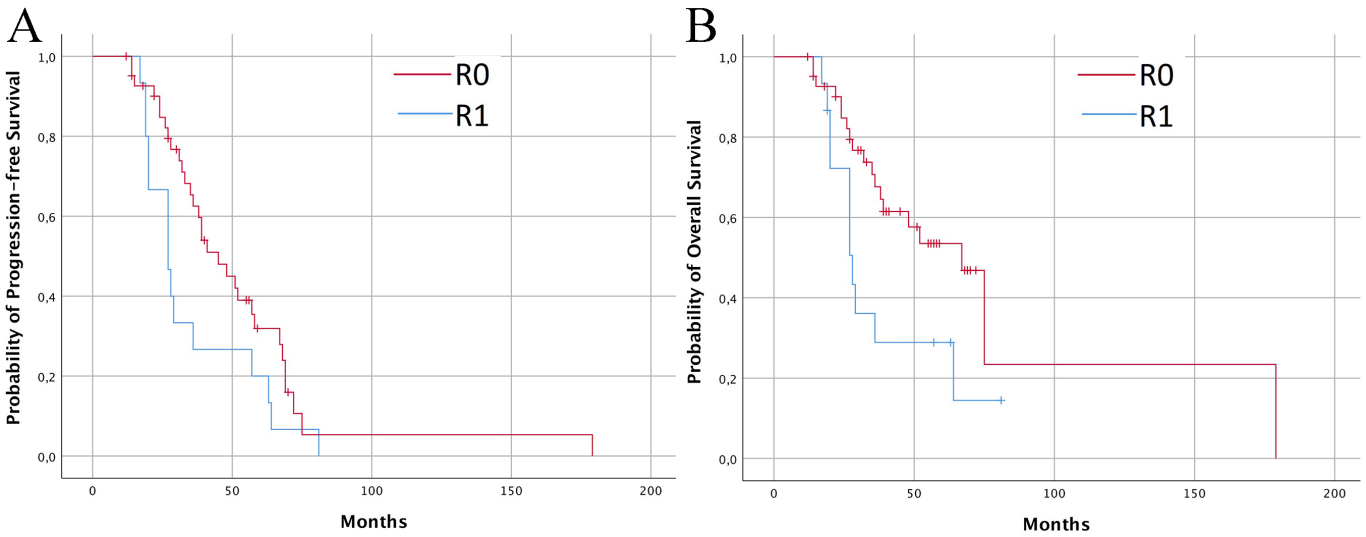

FIGURE 2. Survival according to residual disease after surgery. (A) PFS according to residual disease after IDS. (B) OS according to residual disease after IDS. R0, complete resection/no macroscopic residual disease; R1, presence of residual disease; PFS, progression free survival; IDS interval debulking surgery; OS, overall survival.

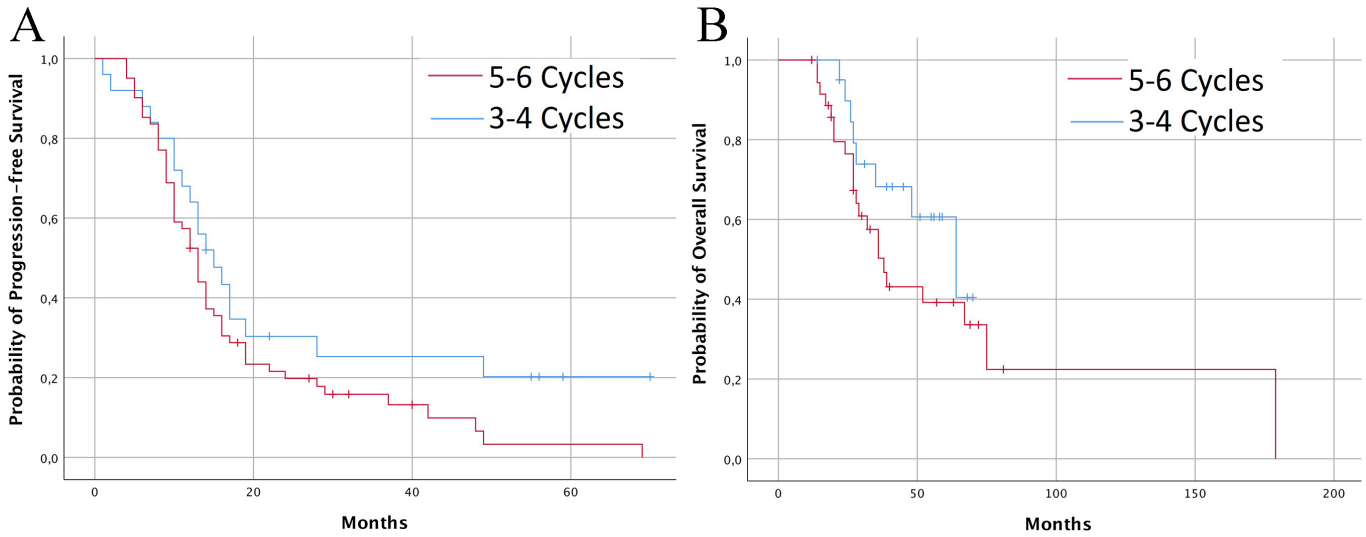

FIGURE 3. Survival according to the number of neadjuvant chemotherapy cycles. (A) PFS according to the number of NACT cycles. (B) OS according to the number of NACT cycles. NACT, Neoadjuvant chemotherapy; PFS, progression free survival; OS, overall survival.

to undergo surgery after 3–4 cycles. Also, the OS although not statistically significant, is clinically superior in patients operated after 3–4 cycles (64 versus 38 months). This might be a reflection of both the higher rate of R0 in this subgroup and the higher response rate to platinum compared to those who need to delay surgery until after 6 cycles. Another explanation is that gradual chemoresistant disease might occur with the cumulative number of NACT.

Some reports have evaluated the impact of late IDS performed after more than four cycles of NACT with contradictory results [14, 15]. Yoneoka *et al*. [14] and Akladios found that the number of NAC cycles (≤4 or ≥5 cycles of NACT) does not seem to play a role in the OS of patients with advanced ovarian cancer. On the contrary, Colombo *et al*. [16] and Xu *et al*. [17] found that patients with advanced EOC receiving complete IDS after more than 4 cycles of NAC have poor prognosis.

As mentioned above, post-operative residual tumor is one of the most important independent prognostic factor for survival [4, 5, 18]. In our analysis there was a statistically significant impact on OS favoring R0 patients compared to R1. This strengthens the idea that the goal of surgery should be complete resection. Most randomized trials of NACT found that this approach increased the likelihood of complete resection compared with PDS. However, despite improved surgical outcomes and less residual disease after surgery, no significant differences were found in OS or PFS when compared with PDS approach [6–9]. Can we speculate that in the neoadjuvant setting, the higher rate of R0 does not have such a preponderant impact on survival? Or it should reinforce once again the idea that whenever possible PDS should be carried out, reserving the NACT strategy only for those in

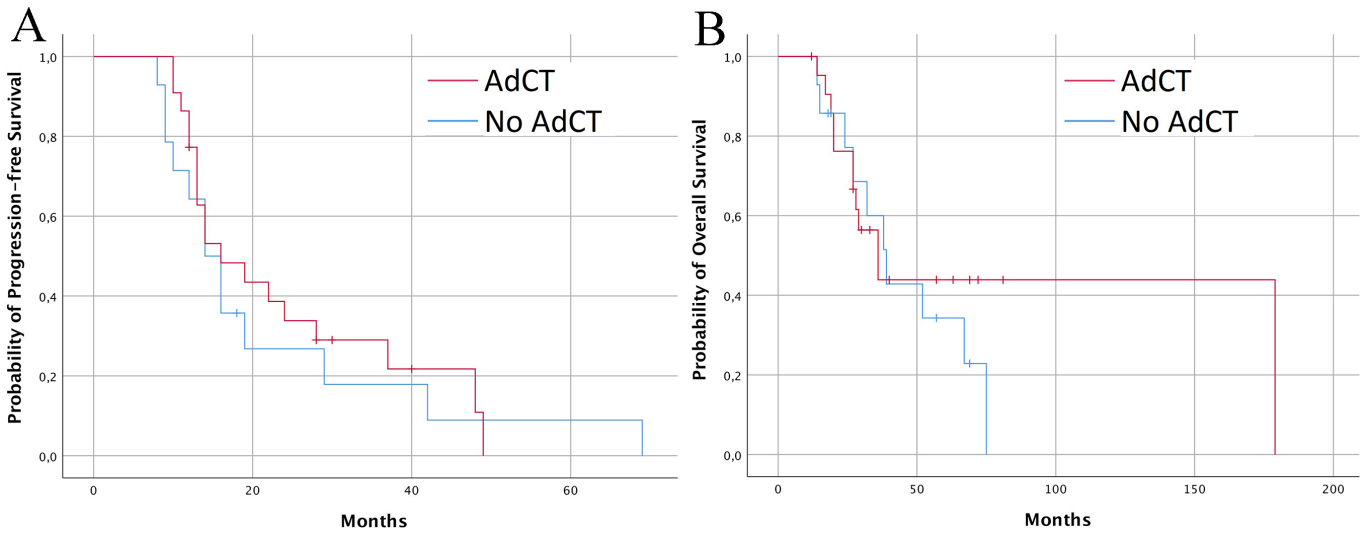

FIGURE 4. Survival according to adjuvant chmeotherapy. (A) PFS according to performance of AdCT. (B) OS PFS according to performance of AdCT. AdCT, Adjuvant chemotherapy; PFS, progression free survival; OS, overall survival.

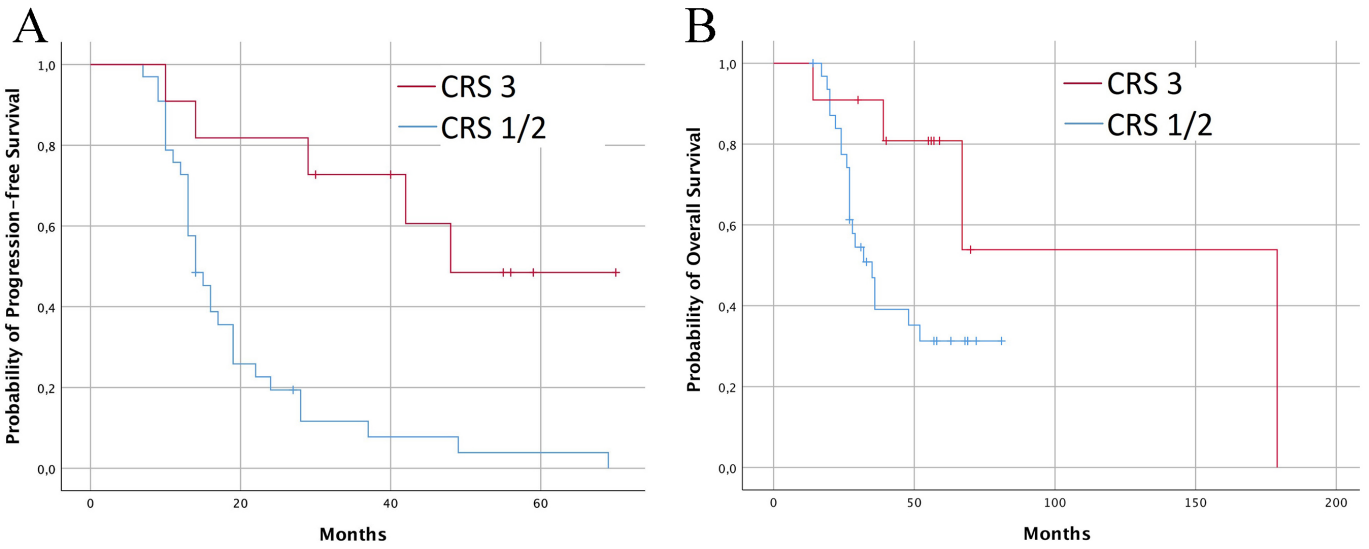

FIGURE 5. Survival according to chemotherapy response score. (A) PFS according to pathological response to CT. (B) OS according to pathological response to CT. CRS1/2, no/minimal/partial pathologic response; CRS3, complete/near-complete pathological response; PFS, progression free survival; OS, overall survival.

which macroscopic resection isn't possible.

Another objective of this analysis was to verify whether the use of postoperative adjuvant chemotherapy (AdCT) in patients who underwent 5–6 cycles of NACT had an impact on patient survival. If we consider the adjuvant setting after PDS, the number of chemotherapy cycles is well established, with the standard 6 cycles of carboplatin/paclitaxel. In the context of NACT and IDS, particularly in patients undergoing the 6 cycles of NACT, we do not have clinical trial data regarding the need and number of cycles of postoperative CCT. All randomized trials of NACT tested 3–4 cycles of NACT followed by IDS and 3–4 cycles of adjuvant chemotherapy, indicating that the total number of cycles should be 6 to 8 [6–9]. Regarding this issue, there is heterogeneity in clinical practice. The NCCN guidelines recommend that regardless of the number of cycles of NACT received, IDS should always be followed by adjuvant chemotherapy [3]. The ESMO–ESGO consensus and Portuguese National consensus do not address this issue, and the global recommendation is 3 cycles of NACT followed by IDS if possible, followed by 3 cycles of adjuvant chemotherapy [2, 19]. In our analysis we have 22 patients in this situation, who completed a total of 8–9 cycles of chemotherapy, having undergone 5–6 in the NA context. Our results show no impact from the point of view of PFS or OS of performing more chemotherapy cycles after surgery when 5–6 cycles are given in the NA context. We recognize the limitations of the study and the small number of the sample, but it would be important to realize the real need to administer more chemotherapy considering the potential toxicities inherent to this treatment. If we look at the situation from another perspective, and thinking that the patients who need 5–6 cycles of NACT will be those with the least chemosensitivity, do we need to offer them CCT? Or is it better to think about maintenance therapies? As such, we

must integrate the potential maintenance treatments we have available (iPARP and bevacizumab). Bevacizumab safety with NACT was shown in two randomized phase II clinical trials (ANTHALYA and GEICO 1205/NOVA), however its role in improving surgical outcomes and survival is yet to be demonstrated [20, 21]. To date, first-line iPARP is only validated as a maintenance treatment after response to platinum-based chemotherapy. Currently, PARP inhibitors combined with chemotherapy are being tested in the neoadjuvant setting in order to improve tumor response [22, 23].

We also tried to see if there was any prognostic correlation of the pathological response to chemotherapy (via CRS) and the time between chemotherapy and surgery, and between surgery and chemotherapy restart. The multivariate analysis showed that better pathological response to NACT and the shorter the time between the last NACT cycle and surgery are related to better survival in our population. It is important to recognize these factors in order to improve our clinical practice. Assessment of response to chemotherapy should be described in all pathological anatomy reports in patients who underwent NACT. To date this criterion has no impact on the treatment decision after IDS, but its prognostic factor has already been described in other studies [10, 24]. Regarding the time between the last cycle of chemotherapy and surgery, it is important to optimize the articulation between clinicians from different specialties, the request for reassessment tests and the discussion about the surgical possibility. There are often logistical and functional limitations in hospitals that make it difficult to comply with these timings, but it is crucial that we strive to overcome them.

The main limitation of the study is its retrospective design with the intrinsic risk of selection bias.

Considering that this is a retrospective study, it was not possible to determine or establish criteria for the selection of patients for either NACT or CCT. It is not clear why some patients perform CCT after 5–6 cycles of NACT and others do not. Another important limitation is related to the sample size, which limits the analysis of important subgroups, namely separate assessment of stages III and IV. The main strength is that it represents the real clinical practice of two Portuguese clinical centers, which allows us to share and improve our clinical practice.

In conclusion, in this population, the possibility of performing IDS, complete surgery and complete or near complete pathological response to chemotherapy were the most important prognostic factors for survival for patients who underwent NACT and surgery. The use of CCT showed no advantage in survival outcomes. For R1 patients and those who never undergone surgery, the prognosis is clearly unfavorable. We need prospective studies to evaluate new therapeutic optimization strategies and better tumor response to NA treatment for patients with inoperable ovarian cancer at diagnosis.

AUTHOR CONTRIBUTIONS

FFS—conceptualization, data curation, formal analysis, investigation, methodology, project administration, resources, software, supervision, validation, visualization, writing – original draft, writing – review & editing; SBA—conceptualization, formal analysis, methodology, writing – original draft; MLB—data curation, supervision, validation, writing – original draft, writing – review & editing; SB—data curation, supervision, writing – original draft, writing – review & editing; HN—methodology, validation, writing – original draft, writing – review & editing.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

ACKNOWLEDGMENT

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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