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Original Research

Real-world clinical practice patterns and outcomes for advanced ovarian cancer in Spain (GEICO-42-R study)

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Objective: To assess epidemiological, pathological and clinical characteristics, therapeutic management patterns and outcomes in the management of advanced ovarian cancer (AOC) in clinical practice. *Methods*: Multicenter, retrospective, epidemiological, observational real-world study reviewing clinical records from 277 patients diagnosed with AOC between January 2008 and December 2010 who were treated and followed in 31 Spanish hospitals belonging to the Spanish Ovarian Cancer Research Group (GEICO). Survival curves were estimated by Kaplan–Meier and differences analyzed by the log-rank test. *Results*: Median age at diagnosis was 62 years (range 26–96), 62% of patients had a high-grade serous carcinoma, and 64% and 21% of patients had stage IIIC and stage IV disease, respectively. Overall, 46% of patients underwent primary debulking surgery (PDS), with complete cytoreduction in 63% of procedures, and 34% underwent interval debulking surgery, with complete cytoreduction in 71% of them. Overall, 96% of patients received at least one cycle of front-line chemotherapy. Recurrence occurred in 77% of patients, and 90% of them (69% of total) received a second-line chemotherapy. Median progression-free survival (PFS) was 14 months (95% CI: 13–17) and median overall survival (OS) was 41 months (95% CI: 34–49). PDS and complete cytoreduction had a statistically significant correlation with PFS and OS. *Conclusions*: This retrospective study provides real-world data of clinical characteristics, therapeutic management, and outcomes in Spanish AOC patients. Primary debulking surgery and complete cytoreduction were favorable prognostic factors in this series.

Keywords

Ovarian cancer; Real-world data; Primary debulking surgery; Complete cytoreduction

1. Introduction

Ovarian cancer (OC) is the most lethal gynecological cancer. It has been estimated that 313,959 women developed OC in 2020 worldwide and 207,252 died from the disease [1].

The overall 5-year survival rate for women with OC is approximately 45%, but it is strongly related to the stage at diagnosis, ranging from $>$90% for stage IA tumors to $\leq$30% at advanced stages. Unfortunately, fewer than 20% of OCs are confined to the ovaries at diagnosis [2].

The standard front-line treatment of advanced OC (AOC) involves primary debulking surgery (PDS) followed by platinum-based chemotherapy, usually carboplatin in combination with paclitaxel, with or without bevacizumab [3, 4]. Neoadjuvant chemotherapy (NACT) followed by interval debulking surgery (IDS) is an alternative, usually chosen when PDS is not possible. More recently, PARP inhibitors have shown interesting results as maintenance therapy after first-line chemotherapy [4].

Even though most tumors respond to first-line chemotherapy, relapse will occur in many cases. Appropriate therapy for the recurrent-disease setting is based on the timing and nature of the relapse and is individually assessed according to disease- and patient-related factors [5].

In Spain, a well-established official registry for OC is lacking, and data on the disease mainly come from population-based general cancer registries that have been developed in a limited number of regions. Therefore, there is a need for real-world data regarding the disease characteristics, pathological and clinical features, therapeutic strategies, and outcomes, re-

flecting real-life clinical practice in Spain. This information is key not only for the proper assessment and improvement of therapeutic strategies, but also to help with the development and support of research programs, and ultimately to determine priorities for patient care planning. With this in mind, the objective of the present study was to describe the epidemiological, pathological and clinical characteristics, therapeutic management patterns, and treatment outcomes in Spanish patients with AOC in a routine clinical practice setting.

2. Material and methods

2.1 Study design

This was a retrospective, multicenter, observational study performed in a real-world practice setting. Clinical records were reviewed for 277 patients from 31 hospitals belonging to the Spanish Ovarian Cancer Research Group (GEICO) (**Supplementary Table 1**).

The study included women aged ≥18 years, newly diagnosed with confirmed advanced ovarian, fallopian tube, or primary peritoneal carcinoma (FIGO stages III or IV) between January 2008 and December 2010 inclusive.

The data collection period lasted 9 months, from June 2014 to January 2015, and was done using an electronic case report form. The following variables were extracted from clinical records: age, ethnicity, gynecological history, family history of ovarian and/or breast tumors; clinical information regarding the initial diagnosis, including baseline CA-125, staging, European Cooperative Oncology Group (ECOG) performance status, imaging technique used for staging; data on treatment, including date and type of debulking surgery, outcomes of the surgical procedure (complete/optimal or suboptimal), tumor histology and grade, information regarding each chemotherapy or treatment received, from first until last chemotherapy line; and progression-free survival (PFS), and overall survival (OS).

The local Ethics Committee from each participating hospital approved the protocol, and all living patients signed a written informed consent form prior to participation. The study was conducted in accordance with the Declaration of Helsinki (1964) and its later amendments.

2.2 Statistical methods

To avoid sampling bias or selection of patients based on arbitrary or subjective reasons, physicians were initially instructed to obtain a list of all patients meeting the inclusion criteria, and to rank them according to the date of diagnosis. Afterwards, patients were included into the study starting from the most recent in the list (from December 2010) and working backwards in a consecutive and chronological order until completing a maximum of 9 allotted patients per participating site.

Frequencies and percentages were used for descriptive analysis of categorical variables, whereas continuous variables were presented with measures of central tendency and dispersion. Results were analyzed by the intent-to-treat approach. The Kaplan–Meier method was used to estimate PFS and OS survival times, and differences were analyzed using the log-rank test. All statistical analyses were performed using the computing environment R, and a result was considered statistically significant at $p < 0.05$.

3. Results

3.1 Patient and clinical characteristics

277 women were included. The majority (n = 209; 76%) had been diagnosed in 2010, with the remaining patients diagnosed in 2009 (n = 55; 20%) and 2008 (n = 13; 5%). Patients' demographic and clinical characteristics are summarized in Table 1. The median age at diagnosis was 62 years (range 26–96 years). With respect to hormonal risk factors, the mean (± standard deviation) age at menarche was 13 (±2) years, mean age at menopause was 49 (±5) years, and patients had had 2 (±2) pregnancies on average. 26% of patients (n = 56) had a family history of breast and/or OC.

Table 1. Patients' demographic and clinical characteristics.

Demographic and clinical characteristics	N	n (%)
Age at diagnosis, years, mean (SD)	277	62 (13)
Ethnic group, n (%)	268	
Caucasian		263 (98)
Hispanic		2 (1)
Black		3 (1)
Family history of breast and/or ovarian cancer, n (%)	220	56 (26)
Brest cancer		41 (19)
Ovarian cancer		6 (3)
Both		9 (4)
Performance status (ECOG score)	259	
0		116 (45)
1		94 (36)
2		37 (14)
3		11 (4)
4		1 (0)
Histology subtypes	277	
High grade serous		173 (62)
Low grade serous		10 (4)
Endometrioid		17 (6)
Clear cell		10 (5)
Mixed		13 (5)
Mucinous		8 (3)
Squamous		3 (1)
Undifferentiated		9 (3)
Transitional cells		2 (1)
Other		29 (10)
NA		3 (1)
Histological grade	174	
Grade 1		10 (6)
Grade 2		28 (16)
Grade 3		136 (78)
FIGO stage	277	
IIIA		17 (6)
IIIB		27 (10)
IIIC		176 (64)
IV		57 (21)

ECOG, European Cooperative Oncology Group; FIGO, Fédération Internationale de Gynécologie et d'Obstétrique; SD, standard deviation.

Table 2. Initial type of surgical procedure by FIGO stage.

Stage	Primary debulking surgery (PDS)	Interval debulking surgery (IDS)	No surgery
IIIA (n = 17)	13 (76)	2 (12)	2 (12)
IIIB (n = 27)	17 (63)	8 (30)	2 (7)
IIIC (n = 176)	89 (51)	68 (39)	19 (11)
IV (n = 57)	9 (16)	16 (28)	32 (56)

Data are n (%).

Regarding histological subtypes, high grade serous carcinoma was diagnosed in 62% of cases, and the remaining subtypes did not individually exceed frequencies of 10%. 64% of patients had FIGO stage IIIC and 21% had FIGO stage IV. At diagnosis, 60% and 25% of patients had ascites and pleural effusion, respectively, and 45% and 36% had an ECOG performance status score of 0 or 1, respectively.

The most commonly used imaging technique for diagnosis and staging was Computed Tomography (CT) (87% of cases), while Magnetic Resonance Imaging (MRI) and Positron Emission Tomography (PET) were used in less than 10% cases (9.8% and 5%, respectively). In 92% of patients, CA-125 at diagnosis was above the upper limit of normal.

3.2 Treatment

Overall, 46% of patients (n = 128) underwent PDS, with optimal cytoreduction achieved in 63% of procedures; 34% of patients (n = 94) underwent IDS, with optimal cytoreduction achieved in 71% of cases; and 20% of patients (n = 55) did not have any cytoreductive surgery. The median number of chemotherapy cycles before IDS was 4. Table 2 shows the distribution of each surgical intervention by FIGO stage.

95.7% of patients (n = 265) received at least one cycle of front-line chemotherapy. The most common was the combination of carboplatin and paclitaxel (80% of treatments), with the addition of bevacizumab being very infrequent (3.2%) outside of a clinical trial.

204 patients (77%) experienced a relapse: 40% of patients had a treatment-free interval of platinum (TFIp) <6 months, 27% had a TFIp between 6 and 12 months, and 33% had a TFIp >12 months. 20 patients with a relapse (11%) underwent secondary cytoreduction, and subsequent cytoreductions were very infrequent. 183 (89.7% of relapsed patients; 69.1% of total) received a second line of chemotherapy. Among all treated patients, 50.9% received a third line, 28.7% a fourth line, and 18.1% a fifth line of chemotherapy. Only 8.7%, 2.3% and 1.1% received a sixth-, seventh- or eighth-line systemic treatment, respectively. Table 3 shows the PFS, TFIp and patients treated at the time of progression after each line of therapy, and Fig. 1 summarizes the chemotherapy regimens (only those >5% of administered treatments) received in each line. 43% and 20% of patients received a platinum regimen (outside of a clinical trial) in second and third line, respectively.

3.3 Survival analysis

Among the 277 patients, 90 (32%) were alive at the time informed consent was obtained, and 39 (14%) were alive without disease. The most frequent cause of death was related to disease progression (88%).

For the entire cohort, median PFS was 14.3 months (95% CI: 13–17) and median OS was 40.6 months (95% CI: 33.7–48.6). PFS and OS for patients who underwent PDS (median 17.5 and 61.6, respectively) were statistically significantly longer than for those who underwent IDS (median 14.1 and 40.6, respectively) (Fig. 2).

Complete cytoreduction resulted in statistically significantly longer PFS and OS vs suboptimal cytoreduction in the entire population (PFS: 18.1 vs 13.7 months, and OS: 57.7 vs 40.5 months respectively). Moreover, complete cytoreduction achieved a PFS benefit both in patients with PDS and IDS, and an OS benefit only in patients with IDS (Fig. 3).

From second-line treatment, median PFS was 7.5 months (95% CI: 5.9–8.4). Median PFS progressively decreased in successive treatment lines (Table 2). Among patients receiving platinum-based chemotherapy, PFS and OS were better in those patients who had a longer TFIp in treatment lines 1 through 3 (**Supplementary Figs. 1** and **2**).

4. Discussion

This study served primarily to document the real-world patterns of treatment and outcomes in AOC patients treated in a large group of Spanish hospitals belonging to GEICO. A great amount of information from front-line treatment onwards has been gathered which will be useful for analyzing and optimizing the approach to managing patients with AOC in Spain.

The clinical characteristics and rates of PFS and OS of the patients included in our study were generally in line with other series of patients with AOC described previously in the literature [6–10]. It should be noted that *BRCA* mutational status was not available in our series, as the current recommendation to test all patients was not in place during the period when the study population was treated.

Initial treatment for AOC includes debulking surgery and systemic treatment, with PDS followed by platinum-based chemotherapy being the preferred option. Nevertheless, a recent pooled analysis of two randomized trials shows that NACT could be a valuable treatment option for patients with stage IIIC-IV, particularly in those with a high tumor burden at diagnosis or poor performance status, for whom PDS is not advisable [11]. However, these two trials have been criticized due to a low rate of optimal cytoreduction; moreover, another randomized trial failed to demonstrate non-inferiority of NACT vs PDS [12]. Therefore, NACT may not always

Table 3. Patients treated and tumor progression data by each line of treatment.

Chemotherapy line	1 L	2 L	3 L	4 L	5 L	6 L	7 L	8 L
Chemotherapy received								
Frequency, n (%)*	265 (100)*	183 (69)	135 (51)	76 (29)	48 (18)	23 (9)	6 (2)	3 (1)
Number of cycles, median (IQR)	6 (6–8)	6 (3–7)	4 (3–6)	4 (3–6)	4 (2–7)	3 (2–6)	5 (3–6)	3 (3–7)
Progression–free survival								
Months, median (95% CI)	14 (13–17)	8 (6–8)	4 (3–7)	4 (3–6)	4 (3–6)	4 (3–6)	3 (2–nr)	3 (3–nr)
TFIp after each line**, n (%)								
TFIp <6 months	77 (40)	44 (56)	25 (71)	12 (92)	2 (67)	3 (100)	NA	NA
TFIp 6–12 months	53 (27)	26 (33)	9 (26)	1 (8)	1 (33)	0 (0)	NA	NA
TFIp >12 months	65 (33)	8 (10)	1 (3)	0 (0)	0 (0)	0 (0)	NA	NA
Progression after treatment								
Frequency, n (%)	204 (77)	155 (85)	103 (76)	62 (82)	38 (79)	17 (74)	5 (83)	3 (100)
Patients treated, n (%)	183 (90)	134 (87)	77 (75)	48 (77)	23 (61)	7 (41)	3 (60)	0 (0)
Surgery for tumor progression, n (%)	20 (11)	3 (2)	4 (5)	1 (2)	1 (4)	0 (0)	0 (0)	NA

IQR, interquartile range; L, line of therapy; NA, not applicable; nr, not reached; TFIp, treatment-free interval of platinum. *Percentages are based on patients who received at least 1L (a total of 12 patients did not receive it). **Only calculated for patients who received platinum in each line.

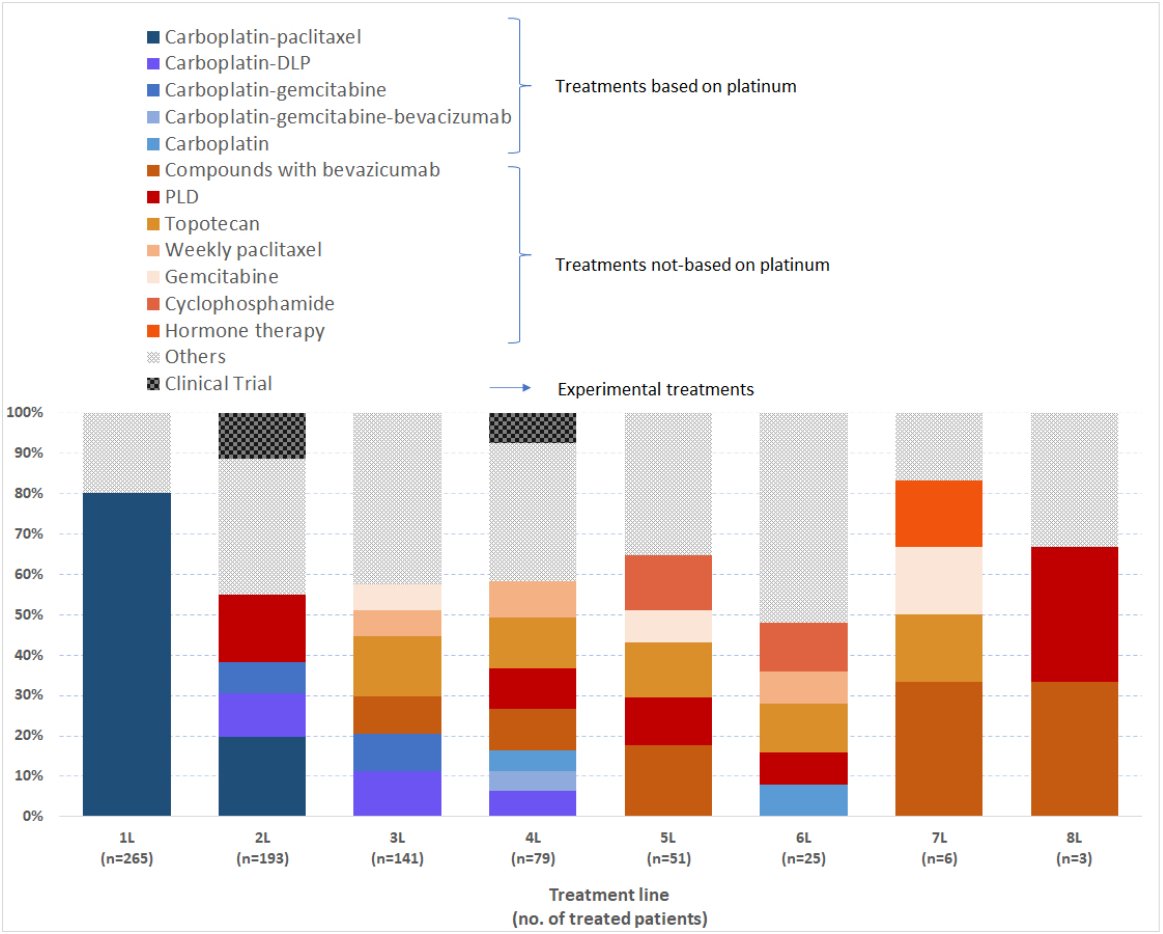

Fig. 1. Treatment modalities (only those >5%) administered at each treatment line.

be a substitute for PDS, at least until the results of another randomized trial (TRUST study, NCT02828618), performed only in hospitals with high-quality surgery, are available. In a publication of data from 24 non-randomized studies, median PFS and OS were significantly longer after PDS compared with NACT (PFS: 17 vs 14 months; OS: 43 vs 33 months) [9]. These results are in line with ours, probably due to the worse prognosis of patients who received NACT (usually with high FIGO stage, high tumor burden or poor performance status). In our series, 20% of patients did not undergo surgery, similar

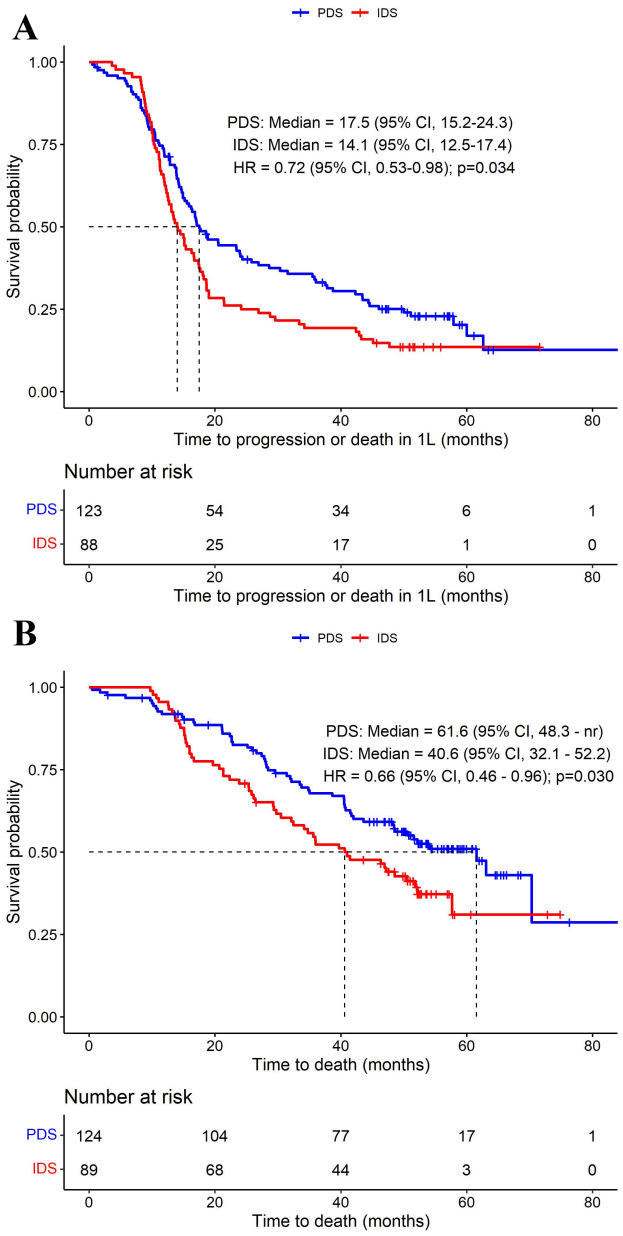

Fig. 2. Kaplan–Meier curves for progression-free survival. (A) And overall survival (B) by type of surgery. PDS, primary debulking surgery; IDS, interval debulking surgery; 1L, first-line treatment.

to the results of a retrospective cohort, with 24.8% of almost 8000 patients only receiving chemotherapy [13].

Complete cytoreduction has been correlated with a better PFS and OS in many studies [10, 14, 15], and results from our series are consistent with this finding. Randomized trials have shown higher rates of complete cytoreduction in IDS than in PDS (73% vs 41% in the CHORUS study, and 81% vs 42% in the EORTC study), but this observation did not correlate with any differences in PFS and OS [14, 16]. The complete cytoreduction rate achieved in our study is similar to the rate of these randomized trials in the case of IDS (71%), but better than theirs in the case of PDS (63%). Interestingly, in our study patients achieving a complete cytoreduction at IDS obtained a clear benefit in OS, highlighting the importance of complete cytoreduction not only in PDS but also at IDS. Patients with high tumor load, affecting the upper abdomen, will require much more radical surgery in order to achieve complete cytoreduction. Ultra-radical surgery encompasses several procedures, such as extensive peritonectomies, bowel resection, splenectomy, liver resection and diaphragmatic stripping. This surgery should be performed by expert gynecologic oncologists to achieve favorable outcomes, as some studies have shown [17, 18]. A higher specialization of gynecologist oncologists dedicated to ovarian cancer surgery and a centralization of complex cases in expert centers could have an impact on the survival of these patients in the future.

With respect to systemic therapy, the addition of bevacizumab to carboplatin-paclitaxel was very uncommon in our study and no patients received PARP inhibitors as maintenance in first-line therapy. This is because at the time the study participants were treated, bevacizumab was not yet approved in first line in Spain, and patients could almost exclusively receive it within clinical trials. Recently, several clinical trials have shown that maintenance treatment with PARP inhibitors (olaparib, niraparib, or the combination olaparib-bevacizumab) in first line achieves a clinically relevant increase in PFS in patients with BRCA mutation or Homologous Recombination Deficiency (HRD) in the tumor [19–21]. Therefore, they are currently being incorporated into the therapeutic armamentarium. When we can analyze long-term real-life results with the use of these therapies, we will probably observe an improvement in the rates of PFS and OS that we have shown in this study.

The rate of secondary cytoreduction of our series (11%) could be considered low but, again, we have to take into consideration that, at the time patients were treated, we did not have the results of any randomized trials addressing this topic. Currently, final results from the DESKTOP III trial have been communicated at the last ASCO congress, showing that secondary cytoreduction can achieve a PFS and OS benefit when patients are selected by AGO score [22].

The use of the 6-month cutoff of TFIp for defining platinum sensitivity or resistance has been abandoned after the 2019 ESMO-ESGO consensus. Currently, there is a more therapeutic-oriented definition that classifies patients into two groups: those for whom platinum might or might not be the best option [5]. However, TFIp continues to be an important factor for selecting therapy at disease recurrence, and it has been shown to be a predictor of OS [23–25], as also corroborated by our study.

The heterogeneity of systemic therapies administered beyond the first line clearly reflects the diversity of treatment options that are available, as well as the heterogeneity of the treated patients. In another retrospective real-world study, Bookman et al. found similar results to ours. For example, in second line, they described at least 6 different regimens of

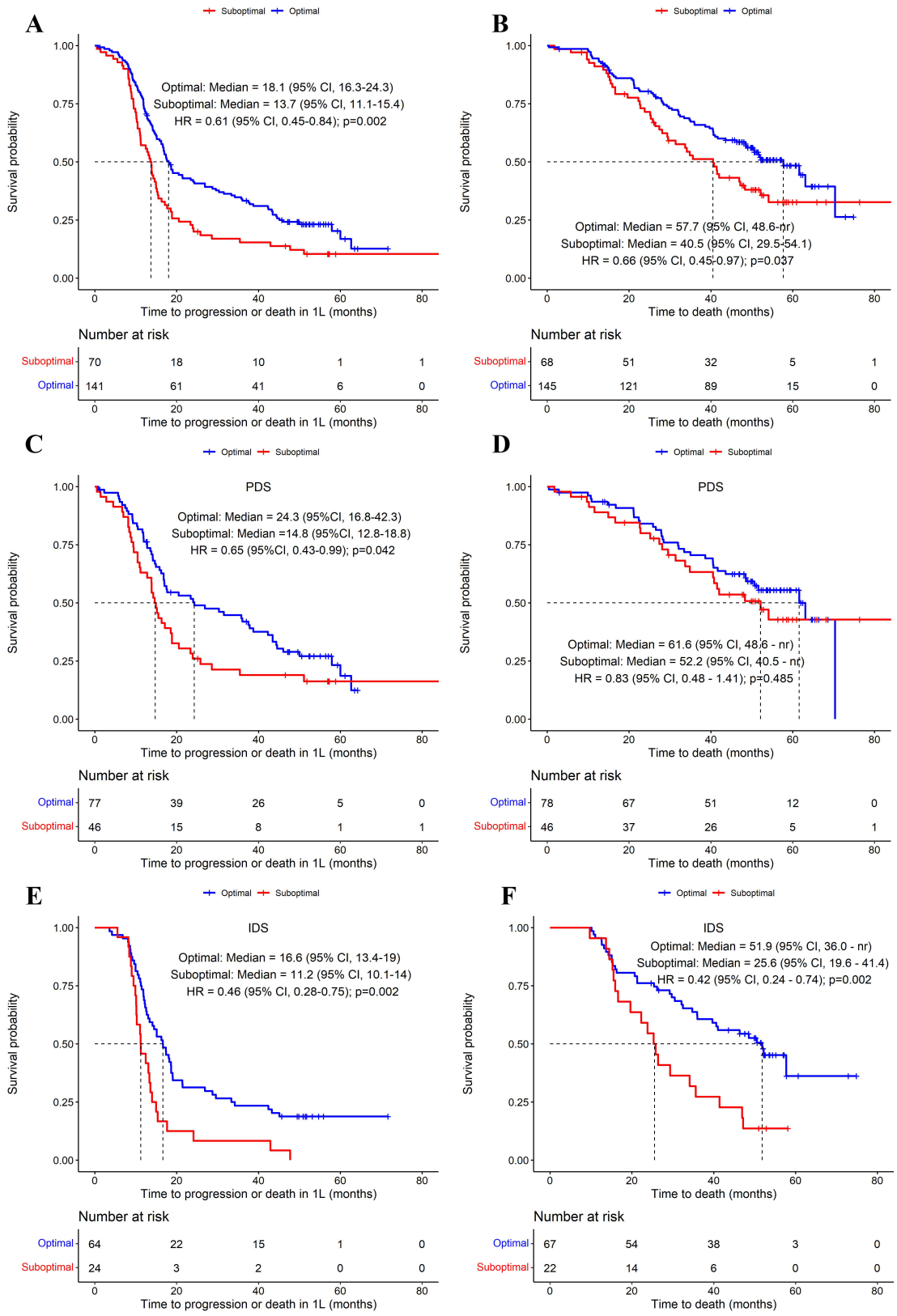

Fig. 3. Kaplan–Meier curves by outcomes of optimal (complete) or suboptimal cytoreduction for progression-free survival. (A) And overall survival (B) in the entire population, and in the cohorts of primary debulking surgery (C and D, respectively), and interval debulking surgery (E and F). 1L, first-line treatment; IDS, interval debulking surgery; PDS, primary debulking surgery.

chemotherapy and with more than 20% of patients with other additional schemes [6]. In our series, the proportions of patients who received a platinum combination at the first and second tumor progression (43% and 20%, respectively) were relatively low, although patients who could receive platinum within a clinical trial were not included. Nowadays, in the PARP inhibitor era and with a higher rate of patients who received a maintenance treatment at first line (and, therefore, with a longer TFIp), the rate of platinum re-challenge in the recurrent setting may have probably increased.

The study had some limitations, the main one being its retrospective nature. Data were not primarily collected for research purposes and we cannot exclude the influence of unmeasured confounding factors on the PFS and OS outcomes. To reduce selection bias, investigators had to rank their patients according to the date of diagnosis and start the inclusion of patients from the most recent in the list and working backwards in a consecutive order. The potential contribution of the limited sample size to uncertainty around the results should be considered; however, it is not a small size for such a study. Another limitation is that treatment of AOC has experienced some important changes in recent years, and some drugs that are currently used frequently did not have any approval at the time that patients were treated.

Nevertheless, it is important to highlight the major strength of this study, which is that it was based on real-world data from a heterogeneous population with this disease, including patients with different histological subtypes, ages, performance status and comorbidities, and so reflects routine clinical practice. Until now, appropriate real-world data on the patterns of therapy and outcomes in patients with AOC have not been available in Spain. It is interesting to know which therapies are used in the real-world population of patients with AOC, a population not always represented in clinical trials which often exclude older patients or those with poor performance status.

5. Conclusions

Therefore, this retrospective study is the first to provide multicenter real-world data from Spanish patients with AOC. It provides a picture of the different therapeutic approaches used in routine clinical practice and the associated outcomes, highlighting the correlation of PDS and complete cytoreduction with the survival of AOC patients.

Author contributions

AR and AGM—data collection and management, data analysis, manuscript writing, editing and approval; RG, NR, MI, CM, AS, AM, MJR and PM—data collection and critical revision and approval. MVT and MJ—design and planning of the study, data analysis, manuscript writing, editing. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The local Ethics Committee from each participating hospital approved the protocol, and all living patients signed a written informed consent form prior to participation. The study was conducted in accordance with the Declaration of Helsinki (1964) and its later amendments. The Ethics Committee from Hospital Arnau de Vilanova de Valencia approved the study post-authorization EPA-OD, Promotor Protocol Code: MSD-OVA-2013-01. All living patients signed a written informed consent form prior to participation.

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Conflict of interest

AR reports honoraria and advisory/consultancy (MSD, AstraZeneca, Roche, GSK, Clovis, PharmaMar, Lilly, Amgen), research grant/funding to his institution (Eisai, PharmaMar, Roche), travel/accommodation/expenses (AstraZeneca, Tesaro, PharmaMar, Roche), and speakers bureau (MSD, AstraZeneca, Roche, GSK, Clovis, PharmaMar), outside the submitted work. RG reports advisory/consultancy (BMS, Sanofi, Pfizer, EUSA, Roche), speakers bureau (Roche, Abbot, Angelini, Pfizer, BMS, Sanofi), and travel/accommodation/expenses (Abbot, Angelini, Pfizer, Riche, Sanofi). NR reports travel/accommodation/expenses (PharmaMar) and speakers bureau (MSD, AstraZeneca, Tesaro), outside the submitted work. MI reports advisory/consultancy (Roche, GSK, Tesaro, PharmaMar) travel/accommodation/expenses (Novartis, AstraZeneca, MSD, Tesaro, PharmaMar, Roche, GSK, Pfizer, Eisai), and speakers bureau (AstraZeneca, Roche, GSK, Tesaro, Eisai, Clovis, PharmaMar), outside the submitted work. AS reports honoraria and advisory/consultancy (MSD, Astra Zeneca, Roche, GSK, Clovis, Pfizer, Pierre-Fabre), travel/accommodation/expenses (MSD, Pfizer, Roche), and speakers bureau (MSD, AstraZeneca, Roche, GSK, Clovis, PharmaMar, Pfizer, Pierre Fabre), outside the submitted work. AM reports speakers bureau (AstraZeneca, PharmaMar, Roche, Sanofi), outside the submitted work. MJR reports honoraria and advisory/consultancy (MSD, AstraZeneca, Roche, GSK, Clovis, PharmaMar), travel/accommodation/expenses (AstraZeneca, PharmaMar,

Roche), and speakers bureau (MSD, AstraZeneca, Roche, GSK, PharmaMar), outside the submitted work. AGM reports honoraria and advisory/consultancy (Amgen, AstraZeneca, Clovis Oncology, Genmab, GSK, ImmunoGen, MSD, Novartis, Oncoinvent, Pfizer/Merck, PharmaMar, Roche, Sotio), speakers bureau (AstraZeneca, PharmaMar, Roche, GSK), research grant/funding (Roche, Tesaro), and travel/accommodation/expenses (AstraZeneca, PharmaMar, Roche, Tesaro). CM, PM, MVT, and MJ, report no conflicts of interest.

Supplementary material

Supplementary material associated with this article can be found, in the online version, at https://ejgo.imrpress.com/EN/10.31083/j.ejgo4206163.

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