Survival and prognostic factors in patients with recurrent low-grade epithelial ovarian cancer: An analysis of five prospective phase II/III trials of NOGGO metadata base

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HIGHLIGHTS

- Platinum-sensitivity according to platinum-free interval has no prognostic value in low-grade recurrent ovarian cancer.
- Low-grade non-serous histology is associated with poorer outcome than serous histology in recurrent disease.
- Ascites and incomplete secondary surgical cytoreduction negatively influence the PFS in recurrent low-grade ovarian cancer.

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ABSTRACT

Objective. Low-grade epithelial ovarian cancers (EOC), constitute the minority among all epithelial cancers. Our study objective was to focus on low-grade recurrent EOC and compare the survival with high-grade disease, as well as in regard to "platinum-sensitive" and "-resistant" recurrences according to platinum-free interval.

Methods. This is an exploratory analysis within the North-Eastern German Society of Gynecological Oncology (NOGGO) database including five randomized phase II/III trials comparing different chemotherapy regimens in recurrent EOC. We conducted survival analyses and cox-proportional regression models.

Results. Out of 1050 patients having the first recurrence, 42 (4%) patients had low-grade and 1008 (96%) patients had high-grade disease. In the subgroup of platinum-sensitive recurrences, progression-free survival (PFS) (8.7 m vs 9.7 m, $p = 0.7$) and overall survival (OS) (23.9 m vs 24.8 m, $p = 0.9$) did not differ between low-grade and high-grade diseases. In platinum-resistant recurrences, patients with low-grade ovarian cancer had significantly better PFS (7.6 m vs 3.6 m, $p = 0.03$) and OS (41.9 m vs 9.5 m $p = 0.002$) in comparison to those with high-grade cancer. At low-grade EOC, there were no significant PFS ($p = 0.91$) and OS ($p = 0.25$) differences between platinum-sensitive and –resistant recurrences. Patients with low-grade non-serous histology had lower PFS with compared to those with low-grade serous histology ($p = 0.004$). At cox regression analysis presence of ascites and residual disease after secondary cytoreductive surgery were independently associated with poor PFS within low-grade recurrent EOC.

Conclusion. Our study indicates, platinum-free interval does not have any prognostic significance at recurrent low-grade EOC and non-serous histology is associated with poorer outcome in recurrence. Secondary surgical cytoreduction to no-gross residual disease and ascites are independently associated with disease progression.

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1. Introduction

Epithelial ovarian cancer is a heterogeneous disease across distinct histological types and grades. Differences between tumor types are based on different genetic and molecular features, clinical behavior and evolution [1,2]. The heterogeneity of histological types and grades has substantial clinical impact on surgical outcome and chemotherapy response, hence the survival per stage [3]. Despite understanding diverse features over the last decades, epithelial cancer continues to be

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treated irrespective of histology with the same treatment strategy including surgical debulking and platinum-based chemotherapy at the first-line [4]. Current evidence for the management strategy is mostly based on the clinical trials predominantly enrolled patients with high-grade serous epithelial cancer, which has a good initial chemoresponse, but poor survival after five-years [5]. On the other hand, either as a consequence of slow cell proliferation or activated MAP-kinase signaling pathway, which provide growth-factor independent growing and surviving signals, response to chemotherapy of tumor cells in low-grade epithelial cancer is limited [6,7]. Indeed, low-grade serous, mucinous and endometrioid cancers are considered to be less-chemoresponsive and have different prognosis [8]. In 2016 published analysis of metadata base of four randomized trials has revealed that the objective response rate to chemotherapeutics is considerably low in low-grade serous ovarian cancers (LGSOC) [9]. However, progression-free and overall survival is significantly better in LGSOC compared to high-grade disease and closely associated with residual disease after surgery [10].

In recurrent disease, treatment approaches are generally managed considering the length of treatment-free interval after the most recent platinum-based chemotherapy line. Until recently, patients experiencing disease progression based on a treatment-free interval ≤ 6 months or >6 months have been classified as "platinum-resistant" or "platinum-sensitive" disease. The term of "platinum sensitivity" based on strictly-defined platinum-free interval is outdated according to GCIG and ESMO-ESGO consensus, given being clinically not very informative and dependent on histological type, patient surveillance as well as the sensitivity of diagnostic tools [11]. Nevertheless, it should be separated from clinically observed platinum sensitivity, which is of crucial importance when tailoring the second-line treatment. Survival is poor in patients with high-grade epithelial cancer with a platinum-free interval ≤ 6 months, but no survival data in recurrent situation specifically for low-grade subtypes is available. Indeed, due to relatively low responsiveness to chemotherapy in low-grade cancers, platinum sensitivity according to platinum-free interval may not be as prognostic as it is in their high-grade counterparts [12].

Due to the rarity of low-grade epithelial cancers, organizing clinical trials in primary and recurrent disease is quite challenging. Using data collected within prospective phase II/III clinical studies, we aimed to investigate the outcome of patients with recurrent low-grade epithelial cancer according to platinum-free interval and histological subtypes, and to compare the survival with high-grade disease. Our secondary aim was to reveal patient and tumor characteristics associated with progression-free survival in recurrent low-grade epithelial ovarian cancer (EOC).

2. Patients and methods

We conducted an exploratory analysis within the metadata base of North-Eastern German Society of Gynecological Oncology (NOGGO) and merged five randomized phase II/III trials comparing chemotherapy regimens in recurrent EOC.

All of the trials had been fully published and included patients with recurrent EOC who had been treated with platinum-containing chemotherapy at the first-line. ECOG performance status was ≤2 in all five studies. All trials included patients at least 18 years of age and excluded patients with serious and uncontrolled medical comorbidities.

2.1. Topotecan Phase III study-nonplatinum topotecan combinations versus topotecan alone for recurrent ovarian cancer (n = 502) [13]

This randomized phase III trial compared the topotecan monotherapy with two nonplatinum topotecan combinations chemotherapy [(1) topotecan monotherapy 1.25 mg/m²/d vs (2) topotecan 1.0 mg/m²/d plus etoposide 50 mg/d vs (3) topotecan 0.5 mg/m²/d plus gemcitabine 800 mg/m² on day 1 and 600 mg/m² on day 8 every 3 weeks] in recurrent ovarian cancer patients after radical surgery and

platinum-based chemotherapy. The trial enrolled 502 patients, who were stratified as platinum-sensitive or -refractory according to treatment-free interval.

2.2. TOWER study-Topotecan weekly versus conventional 5-day schedule in patients with platinum resistant ovarian cancer (n = 194) [14]

The aim of this randomized phase II trial was to compare two independent protocols of topotecan [(1) weekly administration 4.0 mg/m² on days 1, 8 and 15 of a 28-day cycle, vs (2) conventional administration of 1.25 mg/m² on days 1–5 of a 21-day cycle] in platinum-resistant recurrent epithelial ovarian or primary peritoneal cancer after radical surgery and first-line platinum-containing chemotherapy.

2.3. HECTOR study-Topotecan plus carboplatin versus standard therapy with paclitaxel plus carboplatin or gemcitabine plus carboplatin or pegylated liposomal doxorubicin plus carboplatin (n = 550) in platinum-sensitive recurrent ovarian cancer [15]

This randomized phase III trial compared topotecan plus carboplatin chemotherapy (topotecan 0.75 mg/m²/d days 1–3 and carboplatin AUC 5 on day 3, every 3 weeks) versus three standard platinum-based combinations: paclitaxel plus carboplatin (PC); gemcitabine plus carboplatin (GC); pegylated liposomal doxorubicin plus carboplatin (PLDC) in platinum sensitive recurrent ovarian, peritoneal or fallopian tube carcinoma after the end of platinum-containing primary or secondary chemotherapy [(PC) paclitaxel 175 mg/m² and carboplatin AUC 5 on day 1, every 3 weeks; (GC) gemcitabine 1000 mg/m²/d on days 1and 8, and carboplatin AUC 4 on day 1, every 3 weeks; (PLDC) pegylated doxorubicin 30 mg/m² and carboplatin AUC 5 on day 1, every 4 weeks].

2.4. TRIAS study-Sorafenib plus topotecan versus placebo plus topotecan for platinum-resistant ovarian cancer (n = 174) [16]

The aim of this randomized phase II trial was to introduce topotecan (1.25 mg/m² on days 1–5) plus either oral sorafenib 400 mg or placebo (twice daily on days 6–15, repeated every 21 days for six cycles, followed by daily maintenance for up to 1 year or until disease progression) and compare in platinum-resistant recurrent or platinum-refractory ovarian cancer.

2.5. Treosulfan Phase III study-oral vs intravenous treosulfan in heavily pretreated recurrent ovarian cancer (n = 250) [17]

This randomized phase III trial compared two formulations of treosulfan chemotherapy (treosulfan i.v. 7000 mg/m² d1 q4w or treosulfan p.o. 600 mg/m² d1–28 q8w) in recurrent platinum-sensitive or -resistant ovarian cancer patients having received at least two previous lines of chemotherapy.

Among 1543 patients in the selected studies from the metadata base, only the patients having first recurrence were included to study and sorted according to available FIGO grade into two subgroups: Low-grade (FIGO grade 1) and high-grade (FIGO grades 2 and 3) disease. Two groups were compared for the following criteria: Age, ECOG score, FIGO stage at the first diagnosis, presence of ascites at recurrence, histological subtype (serous or non-serous), treatment-free interval after the first-line platinum-containing chemotherapy as >6 months or ≤6 months, residual disease after secondary cytoreductive surgery (SCRS) and completed cycles of second-line chemotherapy.

2.6. Statistical analysis

Associations between low- and high-grade disease groups, patients and disease characteristics were assessed by using the Mann–Whitney U test for continuous variables and chi-square test or the Fisher's exact

test was used for categorical factors. Progression-free survival (PFS) is calculated from the first day of second-line chemotherapy to disease progression. Overall survival (OS) was defined from the first day of second-line chemotherapy to the death. Patients who were without progressive disease or still alive, were censored at the date of last follow-up. Survival analysis was performed by using the log-rank test and survival curves were computed by using Kaplan-Meier method. The following variables were examined by univariate Cox regression: Age, Body mass index (BMI), ECOG score, histology, FIGO stage at the first diagnosis, platinum-free interval at recurrence, presence of ascites, amount of concurrent drugs prescribed due to concomitant diseases or symptom control and outcome of secondary cytoreductive surgery, if it is performed. Stepwise Cox proportional hazards regression with $p_{in} = 0.10$ was used to evaluate the impact of clinical variables on PFS at the patients with recurrent low-grade EOC. A two-sided p value of 0.05 was considered statistically significant. The statistical software IBM SPSS Statistics 24 (SPSS Inc., Chicago) was used for the analysis.

3. Results

3.1. Patients and disease characteristics

Among 1543 patients in the meta-database consisting of recurrent EOC, 1161 patients with the first recurrence were identified. Patients whom histologic grade could not be assessed ($n = 17$) or unknown ($n = 73$) or survival data is not available ($n = 21$) were excluded. Finally a total number of 1050 patients were considered eligible for study analysis. Among those, 42(4%) patients had low-grade EOC and 1008(96%) patients had high-grade EOC. Table 1 depicts the detailed patient and tumor characteristics.

Patients with low-grade EOC were younger than those with high-grade cancer (median age 56 vs 62 years, $p = 0.02$). Serous histology was the most frequent subtype in each group, however it was observed more often at high-grade disease compared to low-grade disease ($p < 0.001$). Patients with low-grade EOC were presented more frequently at stage I-II disease at the first diagnosis compared to patients with high-grade EOC ($p < 0.001$). Disease characteristics at the recurrence were well balanced for high- and low-grade cancers. Most of the patients have platinum-free interval > 6 months in both low-grade (80.9%) and high-grade groups (64.1%) ($p = 0.07$). Complete cytoreduction rate was similar in two groups. In low-grade EOC, 21 (50%) patients underwent SCRS and complete cytoreduction (no-gross residual disease) was achieved in 8(38.1%) patients. In high-grade EOC, 373(36.9%) patients underwent SCRC and complete cytoreduction was achieved in 180(48.3%) patients ($p = 0.62$). There was no difference in completed second-line chemotherapy cycles and ECOG scores between two groups ($p = 0.23$ and $p = 0.07$, respectively). Similarly, no difference was observed in regard to presence of ascites in recurrence between low- and high-grade diseases (23.8% vs 33.6%, $p = 0.18$).

3.2. Survival analysis

After a median follow-up of 14.5 months (range: 0–79), 396(37%) patients were still alive. Median survival in whole patient population was 18.9 months [95% CI; 17.2–20.5] and median PFS was 7.6 months [95% CI; 7.1–8.0]. We observed 34 (81%) recurrences and 22 (52%) deaths in low-grade patients, 783 (76%) recurrences and 642 (62%) deaths in high-grade patients.

3.2.1. Low-grade recurrent EOC vs high-grade recurrent EOC

Overall survival was longer in patients with low-grade EOC. The median OS was 24 months [95% CI; 14.3–33.6] in low-grade and 18.6 months [95% CI; 16.8–20.3] in high-grade EOC ($p = 0.02$). However, we did not find any significant difference in regard to PFS between low- and high-grade diseases. The median PFS was 8.1 months [95% CI;

Table 1
Patients and disease characteristics in the study cohort.

Characteristic	Low-grade EOC N (%)	High-grade EOC N (%)	P value
	42 (4%)	1008 (96%)	
Age (y)			**p = 0.02**
Median(range)	56 (36–77)	62 (24–84)	
ECOG score			p = 0.07
0	23 (54%)	419 (40.8%)	
1	16 (38.1%)	532 (51.8%)	
2	2 (4.8%)	72 (7%)	
3	0	1 (0.1%)	
Unknown	1 (2.4%)	3 (0.3%)	
FIGO stage			**p < 0.001**
I–II	16 (38.1%)	112 (10.9%)	
III–IV	24 (57.1%)	902 (87.7%)	
Unknown	2 (4.8%)	15 (1.5%)	
Ascites			p = 0.18
Yes	10 (23.8%)	339 (33.6%)	
No	29 (69.1%)	555 (55.1%)	
Unknown	3 (7.1%)	114 (11.3%)	
Histology			**p < 0.001**
Serous	25 (59.5%)	771 (76.5%)	
Non-serous	16 (40.5%)	216 (23.5%)	
Mucinous	9 (21.4%)	24 (2.4%)	
Endometrioid	3 (7.1%)	80 (7.9%)	
Others*	4 (9.5%)	112 (11.1%)	
Platinum status			p = 0.07
Platinum-sensitive	34 (80.9%)	646 (64.1%)	
Platinum-resistant	7 (16.7%)	278 (27.6%)	
Unknown	1 (2.4%)	84 (8.3%)	
Secondary cytoreductive surgery (SCRS)			p = 0.10
No	21 (50%)	635 (63.1%)	
Yes	21 (50%)	373 (36.9%)	
Disease status at the end of SCRS			p = 0.62
No gross residual	8 (38.1%)	180 (48.3%)	
Gross residual	12 (57.1%)	170 (45.5%)	
Unknown	1 (4.8%)	23 (6.2%)	
Received chemotherapy cycles			p = 0.23
Median(range)	6 (2—13)	6 (0–26)	

ECOG, Eastern Cooperative Oncology Group; FIGO, International Federation of Gynecology and Obstetrics. Histology, others* include undifferentiated, clear cell, transitional carcinoma.

6.2–9.9] in low-grade and 7.6 months [95% CI; 7.1–8.0] in high-grade disease ($p = 0.23$).

In the subgroup of platinum-sensitive recurrences (TFI >6 months), PFS and OS did not differ between low- and high-grade EOC (8.7 months [95% CI; 6.7–10.6] vs 9.7 months [95% CI; 9.1–10.2] $p = 0.7$, and 23.9 months [95% CI; 17.5–30.2] vs 24.8 months [95% CI; 22.6–26.9] $p = 0.9$, respectively). (Fig. 1A-B).

In platinum-resistant disease (TFI ≤6 months), PFS was significantly longer in low-grade EOC (7.6 months [95% CI; 6.8–8.3]) in comparison to high-grade EOC (3.6 months [95% CI; 3.0–4.1]) ($p = 0.03$). Similarly, in platinum-resistant group we observed longer OS in patients with low-grade EOC (41.9 months [95% CI; 10.7–73.0]) than those with high-grade disease (9.5 months [95% CI; 8.1–10.8]) ($p = 0.002$). (Fig. 1.C-D).

Subsequently, we compared survival rates of patients with serous histology according to the grade of the disease. Patients with low-grade serous cancer had longer PFS (11.3 months [95% CI; 7.6–14.9]) and OS (41.9 months [95% CI; 19.5–64.2]) than those with high-grade serous cancer (7.7 months [95% CI; 7.2–8.1] and 19.5 months [95% CI; 17.5–21.4], $p = 0.002$ and $p = 0.01$, respectively) (Fig. 2.A-B). However, in the group of patients with non-serous histology, low-grade disease had worse PFS (2.8 months [95% CI; 1.4–4.1]) than high-grade disease (7.4 months [95% CI; 6.1–8.6] ($p = 0.046$). In non-serous cancers low-grade and high-grade disease groups had similar OS (20.7 months [95% CI; 11–30.4] vs 18 months [95% CI; 13.7–22.3] $p = 0.9$) (Fig. 2.C-D), and that was also not different from the OS in high-grade serous cancer (19.5 months [95% CI; 17.6 to 21.4], $p = 0.34$) (data not shown).
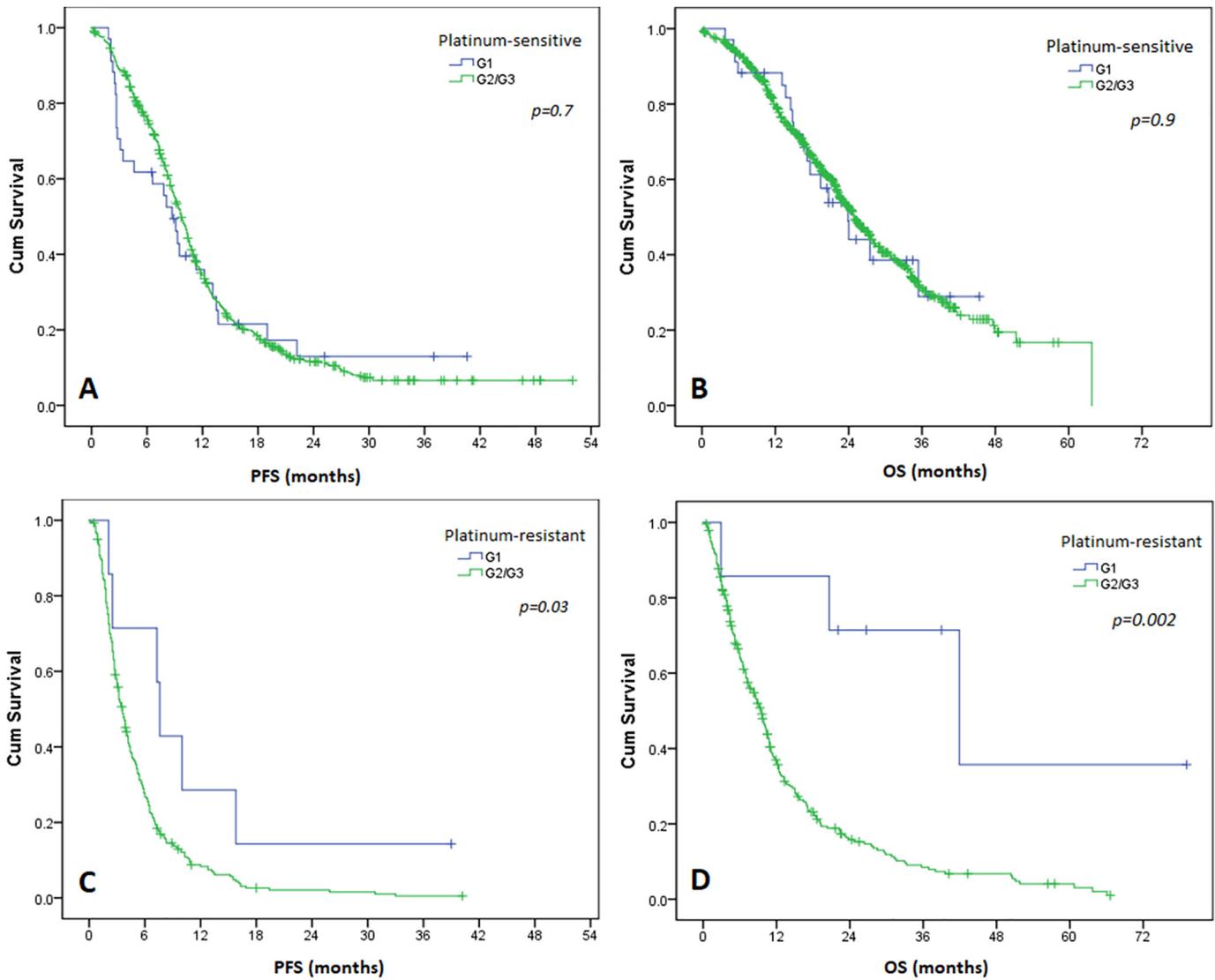
Fig. 1. Progression free survival (PFS) and overall survival (OS) in patients with low-grade and high-grade epithelial ovarian cancer (EOC), according to platinum-sensitive (A, B) and platinum-resistant (C, D) diseases.

3.2.2. Low-grade recurrent EOC; serous vs non-serous histology

In the subgroup of low-grade recurrent EOC, we observed 25(59.5%) serous and 16(40.5%) non-serous histology. Patients with low-grade non-serous cancer had lower PFS (2.8 months [95% CI; 1.4–4.1]) than those with low-grade serous histology (11.3 months [95% CI; 7.6–14.9]) ($p = 0.004$). Similarly, OS tended to be lower in patients with non-serous histology compared to those with serous histology, however we observed a borderline statistical significance (20.7 months, [95% CI; 11.0–30.3] vs 41.9 months [95% CI; 19.5–64.2] $p = 0.059$). (Fig. 3A-B).

3.2.3. Low-grade recurrent EOC; TFI ≤ 6 months vs TFI >6 months

We stratified low-grade EOC patients in to according to treatment-free interval after the first-line platinum chemotherapy. Median PFS in platinum-sensitive (TFI > 6 months) recurrent low-grade EOC was 8.7 months [95% CI; 6.7–10.6], and it was 7.6 months [95% CI; 6.8–8.3] in platinum-resistant (TFI ≤ 6 months) disease ($p = 0.91$) (Fig. 3C). Similarly, there was no significant OS difference between platinum-sensitive (23.9 months [95% CI; 17.5–30.2]) and platinum-resistant recurrences (41.9 months [95% CI; 10.7–73.0]) in low-grade EOC ($p = 0.25$) (data not shown).

As similar with the low-grade EOC group, in the subgroup consisting only the patients with low-grade serous histology, we did not observed any survival difference according to platinum-free interval. In this group, PFS for platinum-sensitive disease was 12.2 months [95% CI; 7–17.3] and it was 7.6 months [95% CI; 4.3–10.8]) for platinum-resistant recurrences ($p = 0.69$) (Fig. 3D). Similarly, OS for platinum-sensitive recurrences (35.4 months [95% CI; 11.6–59.1]) was not different from platinum-resistant recurrences (41.9 months [95% CI; 11.4–72.3]) in patients with low-grade serous histology ($p = 0.1$) (data not shown).

3.3. Univariate and multivariate analysis in the cohort of recurrent low-grade EOC

In the cohort of recurrent low-grade EOC, we investigated the prognostic factors for PFS (Table 2). Based on the results of univariate analysis, tumor histology, presence of ascites, treatment strategy including SCRS when feasible and residual disease after SCRS were the factors associated with PFS. In stepwise multivariate cox regression, ascites, SCRS and any residual disease remained as independent variables for PFS. Presence of ascites at the recurrence resulted in a hazard ratio of 3.92 ([95% CI 1.53–10.01] $p = 0.004$). Any residual disease after completion
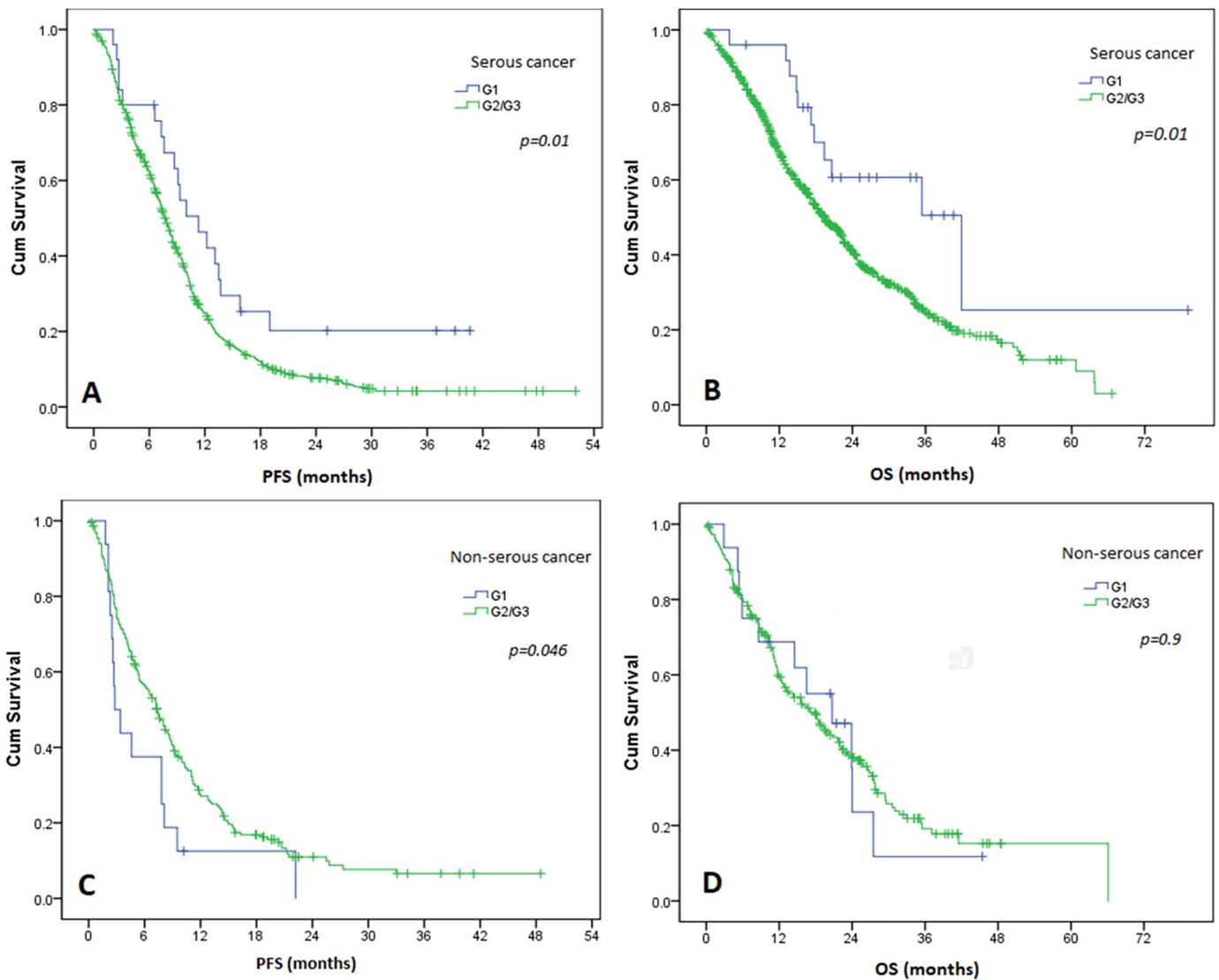
Fig. 2. Progression free survival (PFS) and overall survival (OS) in patients with low-grade and high-grade epithelial ovarian cancer, according to serous (A, B) and non-serous (C, D) histology.

of SCRS was also independently associated with PFS with a hazard ratio of 5.92 ([95% CI 1.17–29.89], $p = 0.03$) and the treatment strategy without SCRS resulted in a hazard ratio of 12.64 ([95% CI 2.69–59.38], $p = 0.001$) with reference to no-residual disease after completion of surgery.

4. Discussion

Low-grade cancers constitute the minority among all epithelial cancers and recurrences are even scarcer in the literature [18]. In our study comprising recurrent epithelial cancers, low-grade cancers constituted 42(4%) of 1050 patients. Our data with recurrent cancer includes low-grade serous, mucinous and low-grade endometrioid cancers with the first recurrence, which are further categorized into serous and non-serous subgroups in order to facilitate a specific subgroup-analysis consisting of recurrent low-grade serous cancer. We observed statistically significant OS difference (24 m vs 18.6 m, $p = 0.02$) between low- and high-grade cancers in the first recurrence, without any difference at PFS. However, OS difference vanished completely in platinum-sensitive disease (23.9 m vs 24.8 m) and was the most pronounced in platinum-resistant recurrences (41.9 m vs 9.5 m). The possible explanation for this observation is that platinum-free interval has prognostic significance at high-grade, but not at low-grade epithelial cancers. Indeed, in low-grade disease we could not show any beneficial impact

of platinum-free interval. In low-grade group, progression-free and overall survival times were not different between early (TFI ≤ 6 months) and late (TFI >6 months) recurrences. Also in a more specific cohort consisting only low-grade serous histology, we did not observed any significant differences at PFS (12.6 m vs 7.6 m, $p = 0.69$) and OS (35.4 m vs 41.9 m, $p = 0.1$) according to platinum-free interval. Similar observation was reported by Gershenson et al., revealing no difference at TTP between platinum-sensitive and -resistant recurrences (8.6 vs 6.6 months) in low-grade serous cancer [12]. Recently, the ESMO-ESGO consensus conference deleted for ovarian cancer the "old" definition of platinum-sensitivity, but the scientific backbone data for this modification is generally the data of patients with high grade ovarian cancer [11]. Current study provides data for low-grade recurrent cancers and strengthens that, previously accepted frame of platinum-free interval when defining the platinum-sensitivity is not applicable, or the concept of "platinum-sensitivity" is not relevant for low-grade epithelial cancers.

The prior analysis of Grabowski et al. has shown that responsiveness of low-grade serous cancer to chemotherapy differs from its high-grade counterpart with an overall response rate of 23% vs 90%, respectively [9]. Similarly, mucinous cancers mostly harboring similar driver genetic mutations as low-grade serous cancers, are inherently less chemoresponsive with a response rate of 26% to platinum-based
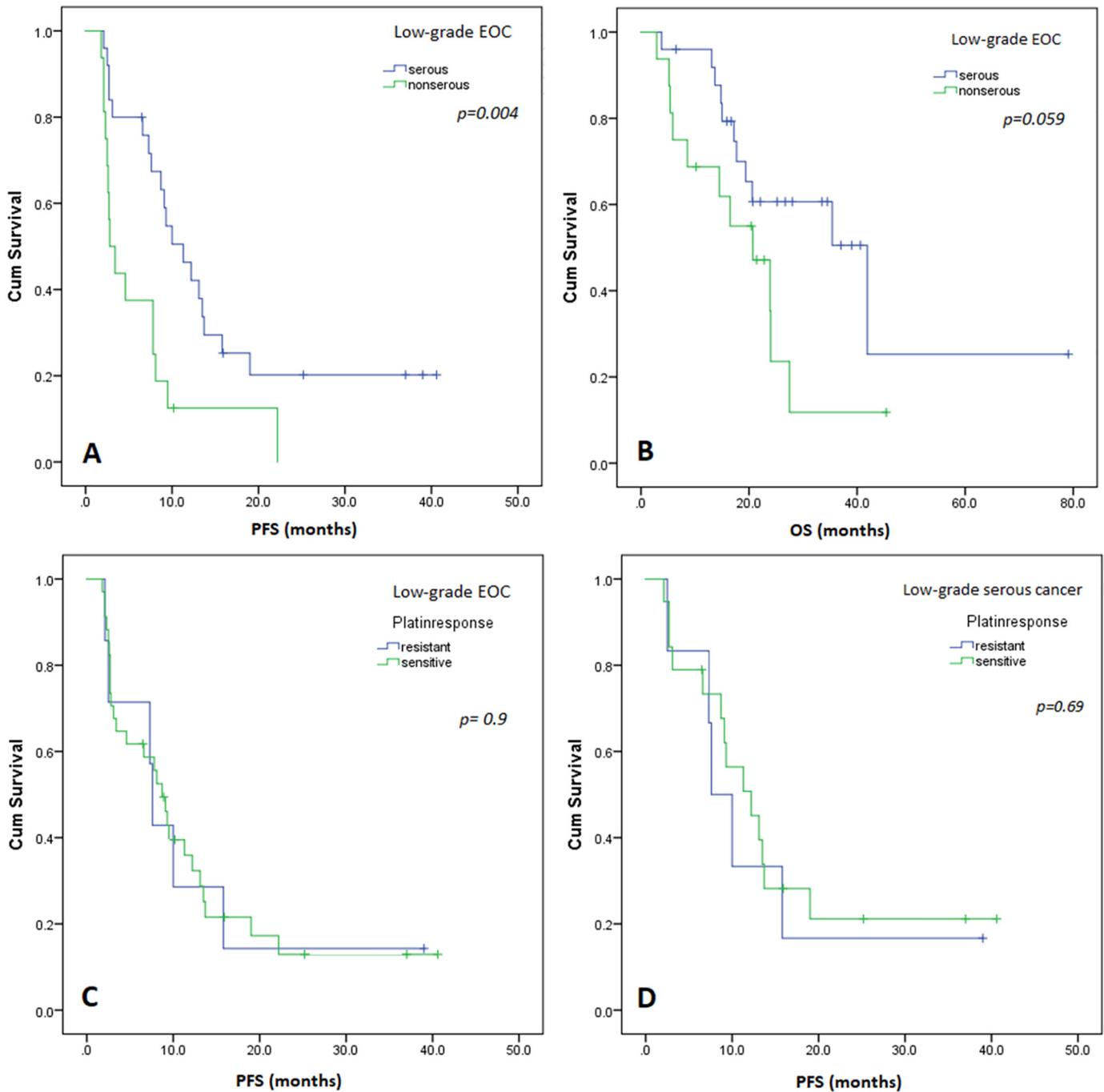
Fig. 3. Progression free survival (PFS) and overall survival (OS) in low-grade epithelial ovarian cancer according to serous and non-serous histology (A, B). PFS in low-grade EOC (C) and low-grade serous histology (D), according to platinum sensitivity.

therapy with compared to 64% response rate in the other subtypes of epithelial cancer [19]. The reported overall response rates in low-grade serous cancer both in neoadjuvant and recurrence setting are ≤4% with a considerably high stabile disease rate of 60–88% [7,12,20]. Compared with platinum-based chemotherapy, low-grade serous cancer can be almost equally responsive to hormonal therapy with a complete response rate of 9% and a stabile disease rate of 62% [21]. Recently, it has been reported by Sehouli et al. that hormone receptor expression is associated with a better PFS without significant impact on OS and ki-67 being a valuable prognostic marker for low-grade serous cancer [22]. Currently there are encouraging results regarding the use of antiangiogenic treatments or MEK and BRAF inhibitors [23]. On the other hand, chemoresistance assays reveal that recurrent low-grade

serous carcinoma shows less likely resistance to etoposide (0%), doxo-rubicin (8%) and topotecan (8%), than carboplatin (50%) and paclitaxel (69%) in vitro analysis [24]. However, given the lack of convincing data for alternative treatments, platinum-based chemotherapy stays as the standard of therapy at the first line and clinically-defined "plati-num-sensitive" recurrences. And complete macroscopic cytoreduction is the mainstay of the treatment that improves PFS and OS in the pri-mary and recurrent diseases [9,25]. Crane et al. showed 45.8 months OS in patients with gross residual disease with compared to 93.6 months for patients with no-gross residual disease after secondary cytoreductive surgery for low-grade serous cancer [25]. Compatible with these results, our study showed that complete cytoreduction to no-gross residual disease is an independent prognostic factor for PFS

Table 2
Univariate and multivariate results for progression-free survival in recurrent low-grade epithelial cancers ($N = 42$).

Variable	N	Univariate HR [95% CI]	p	Multivariate HR [95% CI]	p
Age					
<56 (reference)	21	–			
≥56	21	1.42 [0.72–2.79]	*0.38*		
BMI					
<25 (reference)	18	–			
≥25	24	0.70 [0.35–1.39]	*0.31*		
ECOG score					
0 (reference)	23	–			
1	16	1.30 [0.63–2.67]	*0.46*		
2	2	2.16 [0.48–9.67]	*0.31*		
Histology					
Serous (reference)	25	–			
Non-serous	16	2.65 [1.31–5.36]	***0.006***		
FIGO stage					
I + II (reference)	16	–			
III + IV	24	0.77 [0.38–1.56]	*0.47*		
Platinum Status					
Resistant (reference)	7	–			
Sensitive	34	0.95 [0.39–2.31]	*0.91*	0.41 (0.15–1.16)	*0.09*
Co-medications					
0 (reference)	5	–			
<5 drugs	16	0.95 [0.30–2.96]	*0.93*		
≥5 drugs	21	1.65 [0.55–4.90]	*0.36*		
Ascites					
No (reference)	29	–		–	
Yes	10	3.13 [1.32–7.41]	***0.009***	3.92 [1.53–10.01]	***0.004***
SCRS					
No-residual (reference)	8	–		–	
Any residual	12	5.06 [1.31–19.53]	***0.02***	5.92 [1.17–29.89]	***0.03***
Residual not assessed	1	3.55 [0.35–35.99]	*0.28*	8.79 [0.71–108.92]	*0.09*
SCRS-not performed	21	6.80 [1.91–24.21]	***0.003***	12.64 [2.69–59.38]	***0.001***

Stepwise regression with $p_{in} = 0.10$.
BMI, Body Mass Index; ECOG, Eastern Cooperative Oncology Group; FIGO, International Federation of Gynecology and Obstetrics; SCRS, Secondary Cytoreductive Surgery.

at recurrent low-grade cancers. These finding stands by the retrospective analyses mainly consisting of high-grade recurrent ovarian cancer and revealing secondary cytoreduction to no-gross disease contributes the survival in these patients [26,27]. These metaanalyses suggest particularly the patients with platinum-sensitive disease and single site of recurrence benefit from secondary cytoreduction and only complete cytoreduction has clearly identified benefit on prolongation of OS [26–30]. The interim analysis of DEKSTOP 3 trial showed the 5.6 months PFS benefit in patients with complete cytoreduction and the results of OS is still pending [31]. Our metadata base does not have uniform information regarding the localization of the recurrence, disease burden, selection criteria for SCRS or detailed results of SCRS regarding residual disease and associated survival. However the study reveals that irrespective of platinum-free interval, secondary cytoreduction to no-gross residual disease and ascites are independent predictors for disease progression at recurrent low-grade cancers. Taking in to consideration of low-response rate to systemic treatments, it is reasonable to make the surgical objective as removing all the macroscopic disease at the treatment of these cancers.

Despite low chemotherapy responsiveness, in the subgroup of patients with serous histology, we could demonstrate a survival advantage in low-grade serous cancer in comparison to its high-grade counterpart at the first recurrence. We observed approximately 23 months (41.9 m vs 19.5 m) of OS difference and a less pronounced but statistically significant PFS difference (11.3 m vs 7.7 m) between low-grade and high-grade serous cancers. This result is partially in accordance with the results reported at primary disease, showing longer OS in low-grade

serous cancer than high-grade disease (99 m vs 57 m) but no difference in PFS [20,32]. The pattern of our results represents the indolent behavior of low-grade serous cancers, even at the recurrent disease. However, the question of whether this slow progression is the consequence of slow tumor growing or the consequence of cytotoxic treatments which result with high rates of stabile disease, remains to be answered.

Nevertheless, we did not observe this indolent behavior in low-grade non-serous cancers, which had similar OS with high-grade cancers irrespective of histology. Low-grade non-serous cancers that mainly include mucinous and endometrioid cancers in this cohort, had lower PFS and a tendency to lower OS with compared to low-grade serous cancer and showed worse PFS than high-grade cancers. Despite the better prognosis in early stage, mucinous cancer shows poorer survival than serous cancer in advanced and recurrent diseases, given a lower response rate of standard chemotherapy [3,8,33–35]. In literature it has also been reported mucinous cancers receive less chemotherapy lines at the recurrence, have a lower rate of complete cytoreduction at SCRS and a poorer survival than non-mucinous carcinomas [36,37]. The current study fits well with these analyses and shows that low-grade non-serous cancers has the worst PFS at the recurrence setting and show identical OS with high-grade diseases, which possibly reflects the low-responsiveness to cytotoxic therapy. Similar to low-grade serous cancer, chemoresistance analysis shows that mucinous ovarian cancer cells are more resistant to cisplatin but less resistant to topotecan and doxorubicin, however more clinical data is needed for a modification at the standard of therapy [38].

We have to underline, that our results in this study has several methodological limitations due the design of our analysis based on patients who entered prospective trials with specific inclusion criteria, so generally patients with thrombosis or other severe comorbidities had been excluded. Additionally we had not performed a central pathological review, so we cannot define the rate of inadequate diagnosis what can be crucial for low grade ovarian cancer as reported by Kommoss et al. [39], therefore future trials should implement a central pathological review to prevent this diagnosis. We analyzed patients with low grade ovarian cancer who experienced a relapse, so it can be speculated that this patients are different to patients with primary and chemotherapy-naive patients with low grade ovarian cancer who has no relapse of their disease. Additionally we summarized different histological subtypes what also can limit our interpretations. However, despite the limitations, considering the limited number of patients with recurrent low-grade cancers and hence the limited experience, pooling of these five randomized-controlled trials consisting recurrent epithelial cancers provided us one of the largest series in the literature.

As summary, current study reveals 6 months of platinum-free interval does not have any prognostic value for recurrent low-grade epithelial cancers. This underlines particularly that recently abandoned term of "platinum sensitivity" based on a strict platinum-free interval is not clinically useful for these slow-growing and inherently less-chemoresponsive cancers. However, irrespective of platinum-free interval, low-grade serous cancer shows better prognosis than its high-grade as well as non-serous counterparts. Low-grade non-serous cancers have the worst progression-free survival at the recurrence. And finally, secondary cytoreduction to no-gross residual disease stays as the effective method of therapy and an independent prognostic factor for recurrent low-grade epithelial cancers.

Authorship contribution statement

EC and JPG: Writing-original draft, interpretation of data, Writing-review and editing, conception and design RR: statistical analysis, interpretation of data, writing-review and editing, EIB: critical revision, writing-review and editing, RC: critical revision, writing-review and editing, JS: conception and design, interpretation of data, writing-review and editing.

Declaration of Competing Interest

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