Accepted: 15 May 2023 | Published Online 19 June 2023

DOI: 10.1111/1471-0528.17558

BJOG An International Journal of Obstetrics and Gynaecology

RANDOMISED CONTROLLED TRIAL

Quality of life in patients with advanced ovarian cancer after primary debulking surgery versus neoadjuvant chemotherapy: Results from the randomised SCORPION trial (NCT01461850)

Claudia Marchetti[1,2] | Diana Giannarelli[3] | Giuseppe Vizzielli[1] | GabriellaM. Ferrandina[1,2] | Lucia Tortorella[1] | Francesco Fanfani[1,2] | Barbara Costantini[1] | Tina Pasciuto[4] | Giovanni Scambia[1,2] | Anna Fagotti[1,2]

[1]Division Gynaecologic Oncology, Fondazione Policlinico Universitario A. Gemelli, IRCCS, Rome, Italy

[2]Università Cattolica del Sacro Cuore, Rome, Italy

[3]Biostatistics Unit, Scientific Directorate, IRCCS, Fondazione Policlinico Universitario A. Gemelli, Rome, Italy

[4]Statistical Technology Archiving Research (STAR) Centre, Fondazione Policlinico Universitario A. Gemelli, IRCCS, Rome, Italy

Correspondence
Anna Fagotti, Fondazione Policlinico Universitario A. Gemelli, IRCCS, Università Cattolica del Sacro Cuore, Rome, Italy.
Email: anna.fagotti@unicatt.it

Funding information
Fondazione Policlinico Gemelli IRCCS

Abstract

Objective: To investigate the effect of treatment with neoadjuvant chemotherapy (NACT) followed by interval debulking surgery (IDS), versus primary debulking surgery (PDS), on quality of life (QoL) in patients with advanced epithelial ovarian cancer (EOC).

Design: Randomised trial conducted in a single institution.

Setting: Division of Gynaecologic Oncology, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy.

Sample: Patients with stage-IIIC/IV EOC and high tumour load.

Methods: Patients were randomised (1:1) to undergo either PDS (PDS group) or NACT followed by IDS (NACT/IDS group).

Main outcome measures: Quality-of-life (QoL) data, assessed using the European Organization for Research and Treatment of Cancer core QoL questionnaire (QLQ-C30) and ovarian cancer module (OV28); co-primary outcomes were the QLQ-C30 global health score at 12 months (cross-sectional analysis) and the difference in mean QLQ-C30 global health score over time between treatment groups (longitudinal analysis).

Results: From October 2011 to May 2016, 171 patients were enrolled (PDS = 84; NACT/IDS = 87). We observed no clinical or statistically significant difference between treatment groups in any of the QoL functioning scales at 12 months, including QLQ-C30 global health score (NACT/IDS group vs PDS group, mean difference 4.7, 95% CI −4.99 to 14.4, $p = 0.340$). Over time, we found lower global health scores for those undergoing PDS than for those receiving NACT (difference in mean score 6.27, 95% CI 0.440–12.11, $p = 0.035$), albeit this was not clinically relevant.

Conclusions: We found no difference in global QoL related to treatment approach at 12 months, even though patients in the NACT/IDS group reported better global health scores across the 12-month period compared with the PDS group; these findings further confirm that NACT/IDS might be a feasible option for patients unsuitable for PDS.

KEYWORDS
advanced ovarian cancer, cytoreduction, laparoscopy, quality of life, randomised clinical trial

Linked article: This article is commented on by Jo Morrison, pp. 1589–1590 and Christina Fotopoulou, pp. 1591–1592 in this issue. To view these mini-commentaries visit https://doi.org/10.1111/1471-0528.17627 and https://doi.org/10.1111/1471-0528.17663

Clinical trial registration: ClinicalTrials.gov, NCT01461850.

1 | INTRODUCTION

The majority of patients with ovarian, fallopian and primary peritoneal cancer present with advanced disease;[1] for these patients, no macroscopic residual disease (NMRD) after primary debulking surgery (PDS) is strongly associated with improved survival outcomes.[2] In the last decade, data from four randomised trials have agreed that neoadjuvant chemotherapy and subsequent interval debulking surgery (NACT/IDS) is a valid alternative to PDS.[3] In a recent metanalysis of these studies, little or no difference was found for overall survival (OS) (hazard ratio, HR 0.96, 95% CI 0.86–1.08) or progression-free survival (PFS) (HR 0.98, 95% CI 0.88–1.08); moreover, NACT seems to have lower morbidity.[3]

The decrease in perioperative complications related to NACT is relevant, as patients with advanced epithelial ovarian cancer (EOC) frequently complain of various treatment- and disease-related side effects that may impact their quality of life (QoL). Outcomes from the European Organisation for Research and Treatment of Cancer (EORTC) 55971 trial showed that QoL in patients treated with NACT followed by IDS is similar to that in patients treated with PDS, but the results were biased by the select number of enrolling institutions.[4] Preliminary data from the SCORPION trial have already been presented and suggest similar results.[5] Since then, no other data from randomised trials in advanced EOC have been obtained on this topic, even though patient-reported QoL has been recommended as an end point in clinical trials.[6]

The SCORPION trial, comparing NACT followed by IDS versus PDS in stage-IIIC/IV ovarian cancer with high tumour load according to laparoscopic predictive index (PI),[7] demonstrated that PFS and OS do not appear to be adversely affected by surgical approach.[5] According to the lower perioperative morbidity rates, it might also be hypothesised that QoL should be no worse in the NACT/IDS group. Here, we report the final results on QoL, which was a secondary end point of the SCORPION trial.

2 | METHODS

2.1 | Study design and participants

In the open-label, randomised, phase-III SCORPION trial (NCT01461850), patients with newly diagnosed advanced EOC and high tumour load were randomly assigned to either NACT followed by IDS or PDS.

Patients aged 18–75 years with presumed International Federation of Gynecology and Obstetrics (FIGO) stage-IIIC/IV ovarian cancer, with Eastern Cooperative Oncology Group (ECOG) performance status 0–2 and who had not received any chemotherapy were eligible for inclusion in the study.

The primary end point was superiority of NACT/IDS versus PDS in terms of perioperative morbidity. Subsequently, a second primary end point was added: superiority of NACT/IDS versus PDS in terms of PFS, and the sample size was enlarged accordingly. The superiority design was chosen in response to sub-analysis of the EORTC 55971 trial, showing that NACT improved clinical outcomes compared with PDS in patients with stage-IV disease versus stage-IIIC disease.[4] By contrast, PDS achieved longer survival compared with NACT/IDS in patients with initial abdominal disease (largest size < 5 cm).

Secondary end points included overall survival and QoL.

The local ethical committee approved the trial. It was registered at ClinicalTrials.gov (NCT01461850) and follows the ethical principles of the Declaration of Helsinki. All patients gave written informed consent before starting the study. Data were collected using Research Electronic Data Capture (REDCap) tools hosted at Fondazione Policlinico Universitario A. Gemelli – Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS).[8] Trial management and progress were monitored by an independent data monitoring committee at the Catholic University of the Sacred Heart Clinical Trial Centre. No patients or public involvement were engaged. A computer-driven minimisation procedure randomly assigned patients based on laparoscopic results to the standard arm (PDS group) or experimental arm (NACT/IDS group) in a 1:1 ratio at the Clinical Trial Unit of the Catholic University of the Sacred Heart, Fondazione Policlinico Universitario A. Gemelli – IRCCS, Rome, Italy, were the study was conducted.

Prior to random assignment, a complete history and physical examination, routine haematology and biochemistry, electrocardiogram (ECG), chest X-ray or computed tomography (CT) scan, abdominal CT scan, and QoL questionnaires were required. Eligible patients were triaged for staging laparoscopy to obtain a histological diagnosis and to provide tumour load assessment through the PI score. The intraoperative inclusion criteria were: histological diagnosis of EOC at frozen section; verified diffused intra-abdominal disease (PI score between 8 and 12 or high tumour load); and absence of mesenteric retraction. Patients were randomised at the time of laparoscopy when all inclusion criteria were met. For those randomised in the PDS group, cytoreduction was performed simultaneously. After that, six cycles of carboplatin area under the curve 5 and paclitaxel 175 mg/m^2 were planned (either every 3 weeks or weekly). In the NACT/IDS group, neoadjuvant chemotherapy was given as administered in the PDS group, but only for three or four cycles. Patients with stable or responding disease underwent IDS with the aim of complete debulking after 3 or 4 weeks of rest. Chemotherapy was then continued to complete the planned six cycles, as per the PDS group. Interval debulking surgery was not conducted in women who demonstrated progressive disease during neoadjuvant chemotherapy. In such instances, the chemotherapy regime used was switched to a second-line regime. The progression of disease was assessed by either Response Evaluation Criteria In Solid Tumours (RECIST) or Gynaecological Cancer InterGroup (GCIG) criteria (clinical or serological).

BJOG An International Journal of Obstetrics and Gynaecology

2.2 | QoL assessment

All patients were included in the QoL study and invited to complete the European Organization for Research and Treatment of Cancer QLQ-C30 and QLQ-OV28 questionnaires to provide a subjective measure of their QoL. The QLQ-C30 and QLQ-OV28 questionnaires have undergone extensive psychometric validation and multiple translations and have been shown to be acceptable to patients.[9–11] The QLQ-C30 contains 30 items, including a global health status score, five function scales (physical, role, emotional, cognitive and social) and nine symptom scales or items (fatigue, nausea or vomiting, pain, diarrhoea, insomnia, appetite loss, constipation, diarrhoea and financial difficulties).[9] The QLQ-OV28 contains 28 items relevant to ovarian cancer, including abdominal or gastrointestinal symptoms, peripheral neuropathy, chemotherapy side effects, hormonal or menopausal symptoms, body image, attitude to disease or treatment, and sexual functioning.[11]

Questionnaires were completed at baseline, at the fourth cycle or before IDS (in the PDS and NACT/IDS group, respectively), at the sixth cycle and at 6 months after completion of chemotherapy (12 months from diagnosis) (Figure 1). Questionnaires were given to patients in paper format, and completed without conferring with others, before medical consultations or the administration of treatment.

Within the QoL study of the SCORPION trial, the co-primary outcomes were the QLQ-C30 global health score at 12 months (cross-sectional analysis) and the difference in mean QLQ-C30 global health score averaged over time between treatment groups (longitudinal analysis). Exploratory outcomes were the other EORTC QLQ-C30 dimensional and functional scores and EORTC OV28 scores over time and at 12 months.

2.3 | Statistical analysis

The calculation of sample size for the analysis of the first co-primary end point (major perioperative morbidity) was based on a rate of moderate/severe early perioperative complications of between 23% and 27% in the PDS arm. A sample size of 110 patients was required to provide 80% power for detecting a reduction of 85% in moderate/severe perioperative complications in the NACT arm (overall rate 4%, two-tailed $\alpha = 0.05$, dropout 5%). Sample size calculation for the second co-primary end point (PFS) was performed assuming a median PFS of 12 months in the control arm (PDS) and a 0.60 hazard ratio (HR) with NACT. Considering a type-I error (two-tailed) $\alpha = 0.05$, a type-II error $\beta = 0.2$ (power 80%) and a 10% dropout rate, 166 patients were needed to detect 120 recurrences in the study population (East®; Cytel Software, Waltham, MA, USA).

The QoL secondary end point was not powered and the QoL analysis in the SCORPION study is exploratory; our report is primarily descriptive, and no formal analysis plan was developed a priori.

Quantitative variables are summarised as mean and standard deviation. Qualitative variables are presented with absolute and percentage frequency tables. Descriptive data are presented for all the QLQ-C30 and QLQ-OV28 scales.

The scales and items of the questionnaires were linearly transformed and analysed according to the EORTC QoL group procedures. Higher scores on the functioning scales and the global health status (GHS) scale indicate a higher level of functioning and better QoL. Higher scores on symptoms correspond to worse or more symptoms. Differences of at least ten points were classified as the minimum clinically meaningful change in a QoL parameter.[12]

For cross-sectional comparisons of QoL outcomes at 12 months, we used analysis of covariance adjusted for baseline score, hence omitting data from the chemotherapy period. Longitudinal analyses used all data collected from baseline to 12 months; we estimated scores at scheduled data collection points from a mixed-effects regression model with a time–treatment interaction, unstructured covariance and patient-level random effects. Comparisons between scale scores in different groups and at different time points were conducted using longitudinal analysis of variance (ANOVA) mixed models for repeated measures. Independent variables were time (four levels: baseline; fourth cycle or before IDS (in PDS group and NACT/IDS group, respectively); at the sixth cycle; and at 6 months after the last cycle of chemotherapy (12 months after diagnosis)) and arms (two levels: PDS and NACT/IDS). A positive score in mean differences of functioning scales and the GHS scale indicates improvement, whereas a negative score suggests decline. A positive score in mean differences of symptom scales indicates decline, whereas a negative score suggests improvement.

All analyses were based on intention to treat (ITT). No statistical adjustments to the analysis were made for multiple testing, as a result of the number of scales. We handled missing data according to the National Cancer Institute of Canada Clinical Trials Group QoL framework.[13] Accordingly, we performed a sensitivity analysis to assess the potential effect of missing values with regards to co-primary end point items, based on three scenarios:

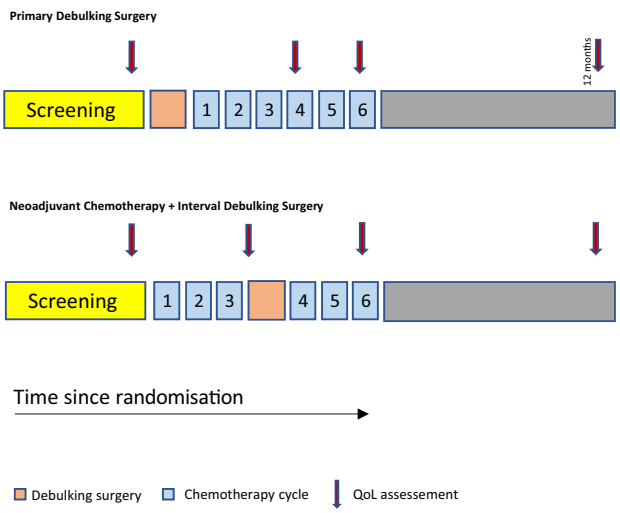

FIGURE 1 Timing of quality-of-life (QoL) questionnaires.

(i) a score of 0 was assigned to deceased patients and the mean score was assigned to patients with missing values who were alive at that time point; (b) a score of 0 was assigned to deceased patients and the mean score minus 10 was assigned to patients with missing values who were alive at that time point; and (iii) a score of 0 was assigned to deceased patients and the mean score minus 20 was assigned to patients with missing values who were alive at that time point.

A p-value smaller than 0.05 has been considered statistically significant. All analyses were performed with SPSS 25.0 (IBM, Armonk, NY, USA).

3 | RESULTS

3.1 | Baseline characteristics

Between October 2011 and May 2016, 171 patients were randomly assigned. Eighty-four patients were assigned to the PDS group and 87 patients were assigned to the NACT/IDS group (Figure 2). QoL information was unavailable for two patients who were lost to follow-up, one for each arm. Of the remaining 169 patients, 26 did not complete treatment (Figure 2). No significant differences were observed between the treatment groups in age, stage and performance status (Table S1). High-grade serous ovarian carcinoma was the most frequent histology (96.4% and 98.9% in PDS and NACT groups, respectively; Table S1). Bowel resection was performed in 71 patients (84.5%) from the PDS group and 14 patients (18.9%) from the NACT group ($p < 0.0001$; Table S2). Carboplatin/paclitaxel, every 3 weeks, was the most common chemotherapy schedule employed (153 of 164 patients receiving chemotherapy, 93.3%).

3.2 | QoL outcomes

Completion rates for each instrument at each time point are shown in Figure 2. The completion rates for the EORTC QoL assessments QLQ-C30 and QLQ-OV28 at randomisation (baseline assessment) were 83.3% (70 of 84 patients) in the PDS group and 82.8% (72 of 87 patients) in the NACT group. After 12 months, 1052 questionnaires were collected (504 in the PDS group and 548 in the NACT group). Overall, 976 forms of QoL were included in the final analysis. No baseline characteristics were identified as being associated with missing QoL forms, suggesting that the non-completion of forms was random (data not shown).

The mean scores and standard deviation of the EORTC QLQ-C30 and QLQ-OV28 scales by treatment arm and assessment time are given in Tables S3 and S4, respectively.

Concerning the EORTC QLQ-C30 subscales, neither clinical nor statistically significant differences between treatment groups were observed in any of the QoL functioning scales at 12 months (cross-sectional analysis), including the QLQ-C30 GHS (NACT/IDS group vs PDS group, mean difference 4.7, 95% CI −4.99 to 14.4, $p = 0.340$; Figure 3; Tables 1 and S5). The only item showing a significant change at 12 months between the study groups was diarrhoea, with a difference in mean score of −8.47, 95% CI −14.87 to −2.07 in the NACT/IDS group versus the PDS group ($p = 0.009$; Table 1); however, the difference was less than ten points, indicating no clinically relevant difference.

The time-averaged difference across the 12-month period (longitudinal analysis) was different among groups and we found lower global health scores for those undergoing PDS than for those receiving NACT, albeit not clinically relevant (NACT/IDS group vs PDS group, difference in mean score 6.27, 95% CI 0.440–12.11, $p = 0.035$; Figure 3; Tables 1 and S5). Similar results for emotional and cognitive functioning were found (Figure 3; Table 1). Notably, over time patients showed a clinically relevant improvement in insomnia (IDS/NACT group vs PDS group, difference in mean score −11.55, 95% CI −19.18 to −3.92, $p = 0.003$) and constipation (IDS/NACT group vs PDS group difference in mean score −10.08, 95% CI −18.88 to −1.27, $p = 0.025$), favouring the NACT group (Figure 3; Table 1). No relevant change of financial difficulties, fatigue, appetite loss or dyspnoea was registered during the QoL assessment. At the same time, nausea and vomiting symptoms worsened over time in both groups (Table 1), without a relevant difference between the two groups.

Concerning QLQ-OV28 subscales, at 12 months, no difference has been highlighted between groups and changes in the scores were generally small and not clinically relevant. However, there were significant differences over time, favouring the IDS/NACT group (Table 2), with regard to peripheral neuropathy scores, other chemotherapy side effects and body image scores (Table 2), with only the last one being clinically relevant (body image scores IDS/NACT group vs PDS group, difference in mean score −10.94, 95% CI −19.49 to −2.4, $p = 0.012$).

4 | DISCUSSION

4.1 | Main findings

This secondary analysis of results from the SCORPION trial showed no difference in global QoL at 12 months between the approaches of PDS and NACT/IDS. Although women undergoing NACT/IDS appear to experience an almost linear improvement in global health, physical, emotional and role functioning with time, for women undergoing PDS, their QoL is initially made worse by treatment before it improves and surpasses the baseline by 12 months. In all of the physical and emotional domains studied, women undergoing NACT/IDS have improved QoL at 12 months compared with women undergoing PDS, although these differences did not reach our predefined threshold of a ten-point difference in QoL score to indicate clinical significance.

BJOG An International Journal of Obstetrics and Gynaecology

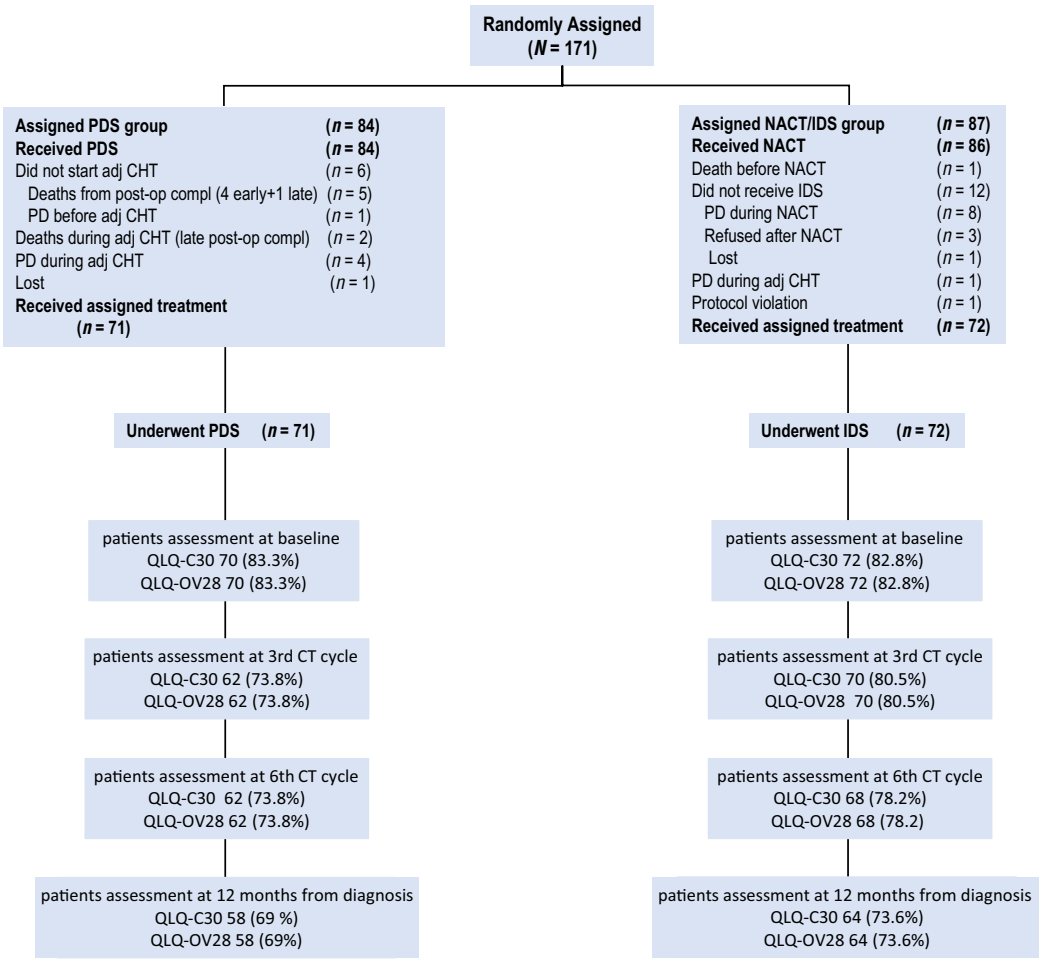

FIGURE 2 CONSORT diagram for data collection (adj CHT, adjuvant chemotherapy; IDS, interval debulking surgery; NACT, neoadjuvant chemotherapy; PDS, primary debulking surgery; post-op, postoperative).

4.2 | Interpretation

Quality-of-life outcomes are often poorly reported in studies of the treatment of advanced ovarian cancer, although it has been proven that they add value to survival data such as OS and PFS, enhance patient-centredness and help guide decision making.[14] The analysis of the randomised EORTC 55971 trial showed that an immediate or delayed surgical approach has no impact on QoL; however, the high rates of missing data in specific centres may have impaired the reliability of the results.[4] More recently, the same topic was addressed in a subgroup analysis of the randomised ICON8 trial, which primarily investigated the effect of weekly versus 3-weekly platinum-based chemotherapy for newly diagnosed advanced EOC.[15] The authors reported that patients who had NACT and IDS had a more remarkable improvement in QoL in the 9 months after randomisation than patients who had PDS. Nonetheless, in the ICON8 trial the choice of upfront or delayed surgery was not randomly assigned and patients with more advanced-stage disease and poorer performance status received NACT, intended to allow chemotherapy downstaging. The uniqueness of the SCORPION population is that all patients are endowed with a verified high tumour load, assessed by laparoscopic PI index, which was an inclusion criterion in itself. Accordingly, as in our preliminary report,[6] the baseline scores appear worse than those reported in previous literature,[4,15] suggesting that high tumour load may justify a worsening of general health status and other QoL items/scales.

A very recent article on changes in QoL according to the extent of surgery found that in patients undergoing extensive surgery there is no deterioration in QoL compared with those receiving surgery of lower complexity.[16] Nonetheless, NACT rates were not presented and most (75%) of the patients undergoing extremely complex surgery were younger than 65 years of age. In comparison, 55% of those in the low complexity group were older than 65 years of age, suggesting some selection bias.[16] Interestingly, the extensive/high-complexity group from Sundar's study experienced a slight worsening in physical, role and emotional function at 6 weeks post-surgery, which resolved by 6–12 months.

Similarly, in the SCORPION trial we found that at the end, at 12 months, patients undergoing PDS (considered as extensive/high-complexity surgery) reach comparable global QoL scores with patients undergoing NACT/IDS,

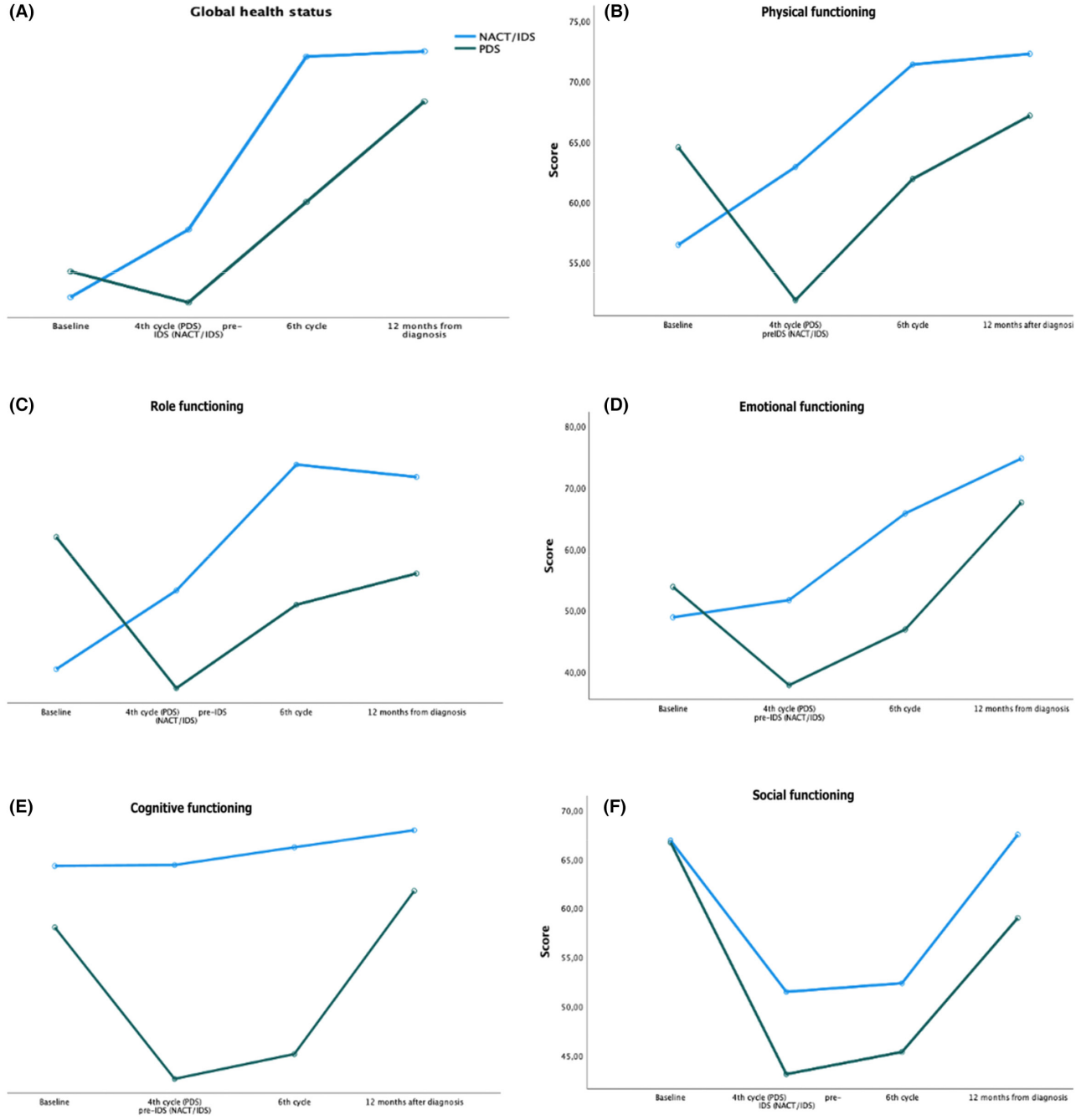

FIGURE 3 Global health and functional scores over time, according to treatment arm: (A) global functioning; (B) physical functioning; (C) role functioning; (D) emotional functioning; (E) cognitive functioning; and (F) social functioning.

but that over a 12-month period, global QoL changes possibly deteriorate in the PDS group, suggesting a slower improvement for these women. This slower recovery is also shown with regards to emotional and cognitive functioning scores.

Concerning symptom subscales, as stated above, we found a trend of a slight deterioration in the PDS group; nonetheless, these outcomes could be partially explained by the substantial difference in complication rates between the groups. In fact, more than 46.4% and 9.5% of PDS patients experienced early and late major postoperative complications, compared with only 11.9% and 1.4%, respectively, in the NACT group (Table S2). Indeed, patients in the PDS group underwent an extremely aggressive surgery that required longer recovery. It should also be underlined that bowel resection and stoma were performed in 84% and 52% of patients in the PDS group (Table S2), respectively, and this might have affected QoL scores related to diarrhoea and body image perception, favouring the NACT/IDS group in which these procedures were definitively less frequent (bowel resection, 18.9%; stoma, 9.5%; Table S2). Conversely, patients undergoing NACT may perceive an improvement in

BJOG An International Journal of Obstetrics and Gynaecology

TABLE 1 QLQ-C30 global health score (GHS) and other significant QLQ-C30 scores.

	PDS group	NACT/IDS group
Global health score		
Patients with GHS data at baseline and 12 months	58	64
Baseline	39.94 (24)	37.29 (20)
12 months	57.53 (27)	62.72 (16)
Difference in 12-month score versus PDS group		+4.7 (95% CI −4.99 to 14.4) $p = 0.34$)
Difference in mean score versus PDS group		+6.27 (95% CI 0.44 to 12.11, $p = 0.035$)
Physical functioning		
Patients with physical functioning score data at baseline and 12 months	58	64
Baseline	64.53 (21)	56.46 (23)
12 months	67.14 (22)	72.27 (26)
Difference in 12-month score versus PDS group		+7.04 (95% CI −1.55 to 15.60, $p = 0.11$)
Difference in mean score versus PDS group		+4.3 (95% CI −1.71 to 10.50, $p = 0.15$)
Role functioning		
Patients with role functioning score data at baseline and 12 months	58	64
Baseline	59.77 (23)	48.69 (27)
12 months	56.71 (28)	64.80 (32)
Difference in 12-month score versus PDS group		+8.31 (95% CI −2.64 to 19.27, $p = 0.14$)
Difference in mean score versus PDS group		+4.23 (95% CI −1.89 to 10.37, $p = 0.17$)
Emotional functioning		
Patients with emotional functioning score data at baseline and 12 months	58	64
Baseline	53.81 (27)	48.86 (26)
12 months	67.57 (30)	74.74 (27)
Difference in 12-month score versus PDS group		+6.31 (95% CI −3.74 to 16.37, $p = 0.22$)
Difference in mean score versus PDS group		+8.75 (95% CI −15.99 to −1.55, $p = 0.01$)
Cognitive functioning		
Patients with cognitive functioning score data at baseline and 12 months	58	64
Baseline	73.60 (24)	80.02 (22)
12 months	77.40 (22)	83.76 (21)
Difference in 12-month score versus PDS group		+4.91 (95% CI −2.62 to 12.46, $p = 0.20$)
Difference in mean score versus PDS group		+14.19 (95% CI −21.56 to −6.81, $p = 0.001$)
Insomnia		
Patients with insomnia score data at baseline and 12 months	58	64
Baseline	45.57 (34)	39.65 (27)
12 months	21.07 (27)	12.67 (22)
Difference in 12-month score versus PDS group		−6.61 (95% CI −14.54 to 2.22, $p = 0.14$)
Difference in mean score versus PDS group		−11.55 (95% CI −19.18 to −3.92, $p = 0.003$)
Constipation		
Patients with constipation score data at baseline and 12 months	58	64
Baseline	34.47 (29)	32.79 (30)
12 months	40.25 (31)	37.03 (32)
Difference in 12-month score versus PDS group		−3.76 (95% CI −15.05 to 7.53, $p = 0.51$)
Difference in mean score versus PDS group		−10.08 (95% CI −18.88 to −1.27, $p = 0.025$)
Diarrhoea		
Patients with diarrhoea score data at baseline and 12 months	58	64
Baseline	10.32 (17)	14.74(21)
12 months	12.68 (23)	4.74(11)
Difference in 12-month score versus PDS group		−8.47 (95% CI −14.87 to −2.07, $p = 0.009$)
Difference in mean score versus PDS group		−1.39 (95% CI −6.23 to 3.44, $p = 0.56$)

Note: Data are *n* (%), mean (SD) or mean (95% CI), unless otherwise indicated.

Abbreviations: IDS, interval debulking surgery; NACT, neoadjuvant chemotherapy; PDS, primary debulking surgery.

TABLE 2 QLQ-OV28 significant scores.

	PDS group	NACT/IDS group
Peripheral neuropathy		
Patients with peripheral neuropathy score data at baseline and 12 months	58	64
Baseline	7.17 (16)	7.05 (13)
12 months	24.52 (15)	24.13 (15)
Difference in 12-month score versus PDS group		−0.76 (95% CI 6.27 to 4.75), $p = 0.79$)
Difference in mean score versus PDS group		−6.86 (95% CI −12.77 to −0.94, $p = 0.023$)
Other chemotherapy side effects		
Patients with other chemotherapy side-effects score data at baseline and 12 months	58	64
Baseline	8.05 (12)	11.04 (14)
12 months	14.29 (16)	10.14 (19)
Difference in 12-month score versus PDS group		−2.55 (95% CI −8.91 to 3.80, $p = 0.43$)
Difference in mean score versus PDS group		−6.10 (95% CI −10.77 to −1.44, $p = 0.01$)
Body image		
Patients with body image score data at baseline and 12 months	58	64
Baseline	41.38 (32)	37.44 (34)
12 months	39.55 (21)	36.73 (27)
Difference in 12-month score versus PDS group		−1.80 (95% CI −9.93 to 6.32, $p = 0.66$)
Difference in mean score versus PDS group		−10.94 (95% CI −19.49 to −2.4, $p = 0.012$)

Note: Data are *n* (%), mean (SD) or mean (95% CI), unless otherwise indicated.

Abbreviations: IDS, interval debulking surgery; NACT, neoadjuvant chemotherapy; PDS, primary debulking surgery.

their clinical condition, with a quicker reduction of insomnia and constipation.

We also found that over time, the PDS group is more impaired by peripheral neurotoxicity and other chemotherapy side effects, albeit this was not clinically relevant. In the ICON8 trial, patients receiving a dose-dense schedule were keener to complain of the same side effect; nonetheless, in our population, there were no differences in this regard, with almost 93% receiving the 3-weekly schedule in the overall population. Therefore, as a possible explanation for this difference, we hypothesised that the NACT/IDS group might have some relief from symptoms resulting from the pause in medical treatment while waiting for IDS.

In the last years, many efforts have been made to develop a possible algorithm to identify preoperatively the best primary approach for advanced ovarian cancer patients.[7,17,18] Although the perfect algorithm has not been found yet, it has become relatively straightforward that it is not just a matter of tumour burden but also of a patient's resilience to recover from aggressive surgery; indeed, frail patients who are unfit for PDS are often those with the most considerable volume of disease. In this context, the choice of NACT could have the double beneficial effect of reducing the disease burden while improving QoL, without affecting survival expectations, according to the results of the SCORPION trial.[5] In this regard, it is also possible that the greater the response to NACT, the better the QoL, further underlining the importance of increasing NACT effectiveness and moving from standard chemotherapy to a more targeted approach.

4.3 | Strengths and limitations

The main strength of our study lies in selecting patients with high tumour load, defined according to a standardised preoperative scoring system (Fagotti score).[7] Although there was a relatively high rate of completion for the QoL questionnaire (at baseline, during treatment and at follow-up), regardless of arm allocation, the study has erratic missing data at each time point, which might have a potential bias in QoL trajectories, because patients with severe comorbidities are less likely to complete questionnaires at more extended time points. However, the compliance rate of questionnaires in both groups did not differ, reducing the risk of biases.

5 | CONCLUSION

In conclusion, no difference between treatment groups was found in global QoL at 12 months. However, patients undergoing NACT report higher mean QoL scores for the functioning scales during treatment. These results further confirm that NACT might be the preferred option for patients not fit for PDS, because of frailty and/or tumour burden. Future research should focus on developing more accurate algorithms and decision aids, to improve decision making for patients and their clinicians, to help make the best choice of treatment. These models should look to optimise the surgical approach for individuals, considering clinical, biological and molecular factors, while maintaining (if not improving) QoL.

AUTHOR CONTRIBUTIONS

The first author wrote the initial draft of the article. All the authors contributed to subsequent revisions of the draft, agreed to submit the article for publication, and vouch for the accuracy and completeness of the data and analyses, and for the fidelity of the trial to the protocol.

ACKNOWLEDGEMENTS

None.

FUNDING INFORMATION

The trial was financially supported by the Fondazione Policlinico Universitario A. Gemelli, IRCCS, Rome, Italy.

CONFLICT OF INTEREST STATEMENT

CM is on the consultant/advisory board for Clovis, Pharmamar, GSK, Astrazeneca and Arquer Diagnostic, and received travel accommodation from Pharmamar and Roche. AF reports commercial interests with AstraZeneca, MSD, Johnson & Johnson and Pharmamar. GS reports research support from MSD and honoraria from Clovis Oncology, and is a consultant for GSK, Tesaro and Johnson & Johnson. All other co-authors have no interests to disclose.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ETHICAL APPROVAL

Ethical approval was obtained (Rome, Catholic University of Sacred Heart, Protocol P/770/CE/2011; Date 27/09/2011). The study follows the ethical principles of the Declaration of Helsinki.

ORCID

Claudia Marchetti https://orcid.org/0000-0001-7098-8956

REFERENCES

1. Lheureux S, Gourley C, Vergote I, Oza AM. Epithelial ovarian cancer. Lancet. 2019;393(10177):1240–53. https://doi.org/10.1016/S0140-6736(18)32552-2
2. Bryant A, Hiu S, Kunonga PT, Gajjar K, Craig D, Vale L, et al. Impact of residual disease as a prognostic factor for survival in women with advanced epithelial ovarian cancer after primary surgery. Cochrane Database Syst Rev. 2022;9(9):CD015048.
3. Coleridge SL, Bryant A, Kehoe S, Morrison J. Neoadjuvant chemotherapy before surgery versus surgery followed by chemotherapy for initial treatment in advanced ovarian epithelial cancer. Cochrane Database Syst Rev. 2021;7(7):CD005343.
4. Greimel E, Kristensen GB, van der Burg ME, Coronado P, Rustin G, del Rio AS, et al. Quality of life of advanced ovarian cancer patients in the randomised phase III study comparing primary debulking surgery versus neo-adjuvant chemotherapy. Gynecol Oncol. 2013;131(2):437–44. https://doi.org/10.1016/j.ygyno.2013.08.014
5. Fagotti A, Ferrandina MG, Vizzielli G, Pasciuto T, Fanfani F, Gallotta V, et al. Randomized trial of primary debulking surgery versus neoadjuvant chemotherapy for advanced epithelial ovarian cancer (SCORPION-NCT01461850). Int J Gynecol Cancer. 2020;30(11):1657–64. https://doi.org/10.1136/ijgc-2020-001640
6. Wilson MK, Pujade-Lauraine E, Aoki D, Mirza MR, Lorusso D, Oza AM, et al. Fifth Ovarian Cancer Consensus Conference of the Gynecologic Cancer intergroup: recurrent disease. Ann Oncol. 2017;28(4):727–32. https://doi.org/10.1093/annonc/mdw663
7. Petrillo M, Vizzielli G, Fanfani F, Gallotta V, Cosentino F, Chiantera V, et al. Definition of a dynamic laparoscopic model for the prediction of incomplete cytoreduction in advanced epithelial ovarian cancer: proof of a concept. Gynecol Oncol. 2015;139(1):5–9. https://doi.org/10.1016/j.ygyno.2015.07.095
8. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform. 2009;42:377–81.
9. Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst. 1993;85:365–76.
10. Dewolf L, Koller M, Velikova G, Johnson C, Scott N, Bottomley A, et al. EORTC quality of life group translation procedure. 3rd ed. Brussels: EORTC Quality of Life Group Publication; 2009.
11. Greimel E, Bottomley A, Cull A, Waldenstrom AC, Arraras J, Chauvenet L, et al. An international field study of the reliability and validity of a disease-specific questionnaire module (the QLQ-OV28) in assessing the quality of life of patients with ovarian cancer. Eur J Cancer. 2003;39(10):1402–8. https://doi.org/10.1016/s0959-8049(03)00307
12. Osoba D, Rodrigues G, Myles J, Zee B, Pater J. Interpreting the significance of changes in health-related quality-of-life scores. J Clin Oncol. 1998;16:139–44.
13. Osoba D, Bezjak A, Brundage M, Zee B, Tu D, Pater J, et al. Analysis and interpretation of health-related quality-of-life data from clinical trials: basic approach of The National Cancer Institute of Canada Clinical Trials Group. Eur J Cancer. 2005;41(2):280–7.
14. Bhat G, Karakasis K, Oza AM. Measuring quality of life in ovarian cancer clinical trials—can we improve objectivity and cross trial comparisons? Cancer. 2020;12:3296.
15. Blagden SP, Cook AD, Poole C, Howells L, McNeish IA, Dean A, et al. Weekly platinum-based chemotherapy versus 3-weekly platinum-based chemotherapy for newly diagnosed ovarian cancer (ICON8): quality-of-life results of a phase 3, randomised, controlled trial. Lancet Oncol. 2020 Jul;21(7):969–77. https://doi.org/10.1016/S1470-2045(20)30218-7
16. Sundar S, Cummins C, Kumar S, Long J, Arora V, Balega J, et al. Quality of life from cytoreductive surgery in advanced ovarian cancer: investigating the association between disease burden and surgical complexity in the international, prospective, SOCQER-2 cohort study. BJOG. 2022;129(7):1122–32. https://doi.org/10.1111/1471-0528.17041
17. Narasimhulu DM, Thannickal A, Kumar A, Weaver AL, McGree ME, Langstraat CL, et al. Appropriate triage allows aggressive primary debulking surgery with rates of morbidity and mortality

comparable to interval surgery after chemotherapy. Gynecol Oncol. 2021;160(3):681–7. https://doi.org/10.1016/j.ygyno.2020.12.026

18. Fleming ND, Nick AM, Coleman RL, Westin SN, Ramirez PT, Soliman PT, et al. Laparoscopic surgical algorithm to triage the timing of tumor reductive surgery in advanced ovarian cancer. Obstet Gynecol. 2018;132(3):545–54. https://doi.org/10.1097/AOG.0000000000002796

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Marchetti C, Giannarelli D, Vizzielli G, Ferrandina G, Tortorella L, Fanfani F, et al. Quality of life in patients with advanced ovarian cancer after primary debulking surgery versus neoadjuvant chemotherapy: results from the randomised SCORPION trial (NCT01461850). BJOG. 2023;130(13):1579–1588. https://doi.org/10.1111/1471-0528.17558