Secondary cytoreduction followed by chemotherapy versus chemotherapy alone in platinum-sensitive relapsed ovarian cancer (SOC-1): a multicentre, open-label, randomised, phase 3 trial

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Summary

Background The benefits of secondary cytoreduction for platinum-sensitive relapsed ovarian cancer are still widely debated. We aimed to assess the efficacy of secondary cytoreduction plus chemotherapy versus chemotherapy alone in this patient population.

Methods This multicentre, open-label, randomised, controlled, phase 3 trial (SOC-1), was done in four primarily academic centres in China (two in Shanghai, one in Hangzhou, and one in Guangzhou). Eligible patients were women aged 18 years and older with platinum-sensitive relapsed epithelial ovarian cancer with a platinum-free interval of at least 6 months after the end of first-line platinum-based chemotherapy and were predicted to have potentially resectable disease according to the international model (iMODEL) score and PET-CT imaging. iMODEL score was calculated using six variables: International Federation of Gynecology and Obstetrics stage, residual disease after primary surgery, platinum-free interval, Eastern Cooperative Oncology Group performance status, serum level of cancer antigen 125 at recurrence, and presence of ascites at recurrence. An iMODEL score of 4·7 or lower predicted a potentially complete resection. As per a protocol amendment, patients with an iMODEL score of more than 4·7 could only be included if the serum level of cancer antigen 125 was more than 105 U/mL, but the principal investigators assessed the disease to be resectable by PET-CT. Eligible participants were randomly assigned (1:1) via a permuted block design (block size of six) and stratified by study centre, iMODEL score, residual disease at primary surgery, and enrolment in the Shanghai Gynecologic Oncology Group SUNNY trial, to undergo secondary cytoreductive surgery followed by intravenous chemotherapy (six 3-weekly cycles of intravenous paclitaxel [175 mg/m²] or docetaxel [75 mg/m²] combined with intravenous carboplatin [area under the curve of 5 mg/mL per min]; surgery group) or intravenous chemotherapy alone (no surgery group). Primary endpoints were progression-free survival and overall survival, analysed in all participants randomly assigned to treatment, regardless of treatment received (intention-to-treat [ITT] population). Here, we report the final analysis of progression-free survival and the prespecified interim analysis of overall survival. Safety was assessed in all participants who received their assigned treatment and had available adverse event data. This study is registered with ClinicalTrials.gov, NCT01611766, and is ongoing but closed to accrual.

Findings Between July 19, 2012, and June 3, 2019, 357 patients were recruited and randomly assigned to the surgery group (182) or the no surgery group (175; ITT population). Median follow-up was 36·0 months (IQR 18·1–58·3). In the no surgery group, 11 (6%) of 175 participants had secondary cytoreduction during second-line therapy while 48 (37%) of 130 participants who had disease progression crossed-over and had surgery at a subsequent recurrence. Median progression-free survival was 17·4 months (95% CI 15·0–19·8) in the surgery group and 11·9 months (10·0–13·8) in the no surgery group (hazard ratio [HR] 0·58; 95% CI 0·45–0·74; p<0·0001). At the interim overall survival analysis, median overall survival was 58·1 months (95% CI not estimable to not estimable) in the surgery group and 53·9 months (42·2–65·5) in the no surgery group (HR 0·82, 95% CI 0·57–1·19). In the safety population, nine (5%) of 172 patients in the surgery group had grade 3–4 surgical morbidity at 30 days, and no patients in either group had died at 60 days after receiving assigned treatment. The most common grade 3–4 adverse events during chemotherapy were neutropenia (29 [17%] of 166 patients in the surgery group *vs* 19 [12%] of 156 patients in the no surgery group), leucopenia (14 [8%] *vs* eight [5%]), and anaemia (ten [6%] *vs* nine [6%]). Four serious adverse events occurred, all in the surgery group. No treatment-related deaths occurred in either group.

Interpretation Secondary cytoreduction followed by chemotherapy was associated with significantly longer progression-free survival than was chemotherapy alone in patients with platinum-sensitive relapsed ovarian cancer, and patients should be counselled about the option of secondary cytoreduction in specialised centres. Long-term survival outcomes will be assessed using mature data on overall survival.

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For the Chinese translation of the abstract see Online for appendix 1

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Introduction

Approximately 80% of patients with advanced ovarian cancer will relapse after first-line chemotherapy and targeted maintenance therapy.[1] Secondary cytoreduction is a widely practiced, but controversial, option for patients with platinum-sensitive relapse. The rationale for its use in the management of ovarian cancer is similar to that for primary debulking surgery, because the success of the treatment depends on the completeness of the resection.[1,2] By removing ischaemic or hypoxic areas of tumour lesions through debulking surgery, residual tumour cells can be reperfused, reoxygenated, and proliferate, becoming more sensitive to chemotherapy. Previous retrospective cohort studies have suggested that improved survival is observed in patients with relapsed ovarian cancer who had a complete resection.[3,4] However, the survival benefit of secondary cytoreduction has not been validated in randomised controlled trials, and not all patients who have a relapse are suitable for the procedure.[3–7] Three randomised phase 3 trials on secondary cytoreduction have been initiated in Germany (AGO DESKTOP III), the USA (GOG-0213), and China (SGOG SOC-1).[8] DESKTOP III showed both a progression-free survival and overall survival benefit of cytoreductive surgery for relapsed ovarian cancer.[6,9] By comparison, the GOG-0213 study did not show a survival benefit of surgery,[7] and worldwide debate continues.

See Online for appendix 2

Using the international model (iMODEL) score for predicting the feasibility of complete resection,[10] SGOG initiated the randomised controlled SOC-1 trial in China. In view of the increasing evidence showing the sensitivity and specificity of ^{18}F-fluorodeoxyglucose (^{18}F-FDG) PET-CT in predicting complete resection in relapsed ovarian cancer,[11,12] we combined iMODEL score and PET-CT imaging to select appropriate patients who might benefit from complete resection with the aim of determining the efficacy of secondary cytoreduction in relapsed ovarian cancer. Here we report the final results of progression-free survival and the prespecified interim analysis of overall survival in the SOC-1 trial.

Methods

Study design and participants

The SOC-1 study is a multicentre, open-label, randomised, controlled, phase 3 trial done at four primarily academic sites in China (Zhongshan Hospital, Fudan University, Shanghai; Zhejiang Cancer Hospital, Hangzhou; Fudan University Cancer Hospital, Shanghai; and Sun Yat-sen University Cancer Centre, Guangzhou; appendix 2 p 3), which included the major national cancer centres, with the number of surgeries for ovarian cancer per year at each site ranging 200–800.

Eligible patients were women aged 18 years and older with platinum-sensitive, relapsed epithelial ovarian cancer,

Research in context

Evidence before this study

We searched PubMed, with no language restrictions, between Jan 1, 1983, and Oct 8, 2020, for publications that assessed the efficacy of secondary cytoreduction in platinum-sensitive, relapsed ovarian cancer using the terms ["relapsed ovarian cancer" OR "recurrent ovarian cancer"] AND ["secondary cytoreduction" OR "secondary cytoreductive surgery"] AND ["clinical trial"]. We further assessed the identified publications for efficacy or safety of secondary cytoreduction. At the time when this study was designed, no randomised phase 3 trial had reported on the efficacy of secondary cytoreduction. In 2003, we did a retrospective study and found that survival of patients with suboptimal resection (residual disease >1 cm) was worse than that with chemotherapy alone. In 2017, results from DESKTOP III showed a progression-free survival benefit in the surgery compared with the no surgery group, and then an overall survival benefit was reported in 2020. In the Gynecologic Oncology Group-0213 study, enrolled patients were selected on the basis of investigator discretion, without use of an objective tool, and the investigators did not find any survival benefit of surgery in first relapsed ovarian cancer. By comparison, DESKTOP III required specific criteria for entry (Eastern Cooperative Oncology Group performance status of 0, ascites volume of 500 mL or less, and complete resection in the initial surgery).

Added value of this study

Using the international model (iMODEL) score to predict the possibility of complete resection, the SOC-1 trial showed a progression-free survival benefit in patients who had secondary cytoreduction followed by chemotherapy versus chemotherapy alone in patients with relapsed ovarian cancer. The results of this trial support the efficacy of secondary cytoreduction in patients with relapsed ovarian cancer selected using iMODEL scores and PET-CT imaging.

Implications of all the available evidence

Similar to results from the DESKTOP III study, secondary cytoreduction followed by chemotherapy was associated with significantly improved progression-free survival than was chemotherapy alone in patients with platinum-sensitive relapsed ovarian cancer, and could be recommended as a standard of care in specialised centres and selected patients based on the iMODEL and PET-CT imaging, but it should be confirmed with mature overall survival data.

defined as a platinum-free interval of at least 6 months between the end of first-line platinum-based chemotherapy and disease progression, with progression defined by Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1. Before study entry, patients were assessed as to whether they were likely to have a complete resection using the iMODEL combined with PET-CT imaging. The iMODEL score was calculated by summing scores allocated to six variables: International Federation of Gynecology and Obstetrics (FIGO) stage (with stage I or II allocated a score of 0, and stage III or IV a score of 0·8), residual disease after primary surgery (complete resection with no gross residual disease given a score of 0 and any gross residual disease [residual disease of ≥0·1 cm in diameter] given a score of 1·5), platinum-free interval (with ≥16 months given a score of 0 and <16 months given a score of 2·4), Eastern Cooperative Oncology Group (ECOG) performance status (with status of 0–1 given a score of 0 and status of 2–3 given a score of 2·4), serum level of cancer antigen 125 (CA125) at recurrence (with ≤105 U/mL given a score of 0 and >105 U/mL given a score of 1·8), and ascites at recurrence (with absence of ascites given a score of 0 and presence of ascites given a score of 3·0). Each variable was assigned a risk score on the basis of the beta coefficient obtained from the logistic regression model. In total, an iMODEL score of 4·7 or less out of 11·9 indicated a high probability of complete resection.[10] A PET-CT scan was obtained at screening at each local site. For the PET-CT scan, patients were scanned from the head to the proximal thigh about 1 h after intravenous injection of ^{18}F-FDG. Helical CT scans were first done without contrast enhancement. PET image datasets were iteratively reconstructed by applying CT data for attenuation correction, and the coregistered images were displayed on a workstation. Recurrent lesions and tumour resectability were assessed according to the lesion's morphological and metabolic characteristics on the basis of comprehensive reviewing of CT, PET, and fused PET-CT images. All PET-CT images were assessed by two experienced, independent, nuclear medicine clinicians who were blinded to treatment assignment. Disagreements were solved via discussion between the two clinicians. An assessment of the efficiency of PET-CT scanning in detecting relapses was done when the first 100 patients enrolled. Patients were excluded if it was deemed impossible to achieve complete resection according to their iMODEL score and PET-CT scan, this was the second or later relapse, they previously had more than one line of chemotherapy, or they had any comorbidity which was a contraindication for surgery or chemotherapy. A full list of inclusion and exclusion criteria are in the appendix 2 (pp 1–2).

Since study commencement, the protocol (appendix 2) has been amended as follows. First, an inclusion criterion was added that if the principal investigators reached a consensus that the recurrent disease detected by PET-CT imaging could be completely resected in patients with an iMODEL score of more than 4·7 and a serum level of CA125 of more than 105 U/mL, the index of CA125 in the iMODEL could be scored as 0 (amended as of Oct 30, 2013).[10] Second, two amendments were made to the randomisation step. The initial allocation of 2:1 (surgery *vs* no surgery) was amended to 1:1 with three stratification factors on Oct 30, 2013. A fourth stratification factor was added (whether enrolled in the SGOG SUNNY trial[13] [a study of upfront surgery or neoadjuvant chemotherapy followed by interval debulking surgery in first-line therapy; NCT02859038]) on Sept 25, 2017. Third, we made one amendment to the primary endpoint to add progression-free survival on Nov 21, 2019, because of an unexpectedly high rates of one-way treatment switching from no surgery to surgery.

The two trials (SOC-1 and SUNNY) have independent clinical research coordinators and harmonisation managers. Each trial assessed the patients according to their protocol. If the two visiting schedules were very close (within 2 weeks), considering the compliance of patients, the objective testing results could be shared between the two trials.

The trial protocol was written by investigators and is compliant with Good Clinical Practice guidelines and the Declaration of Helsinki, and was approved by independent ethics committees at each site. Each patient provided written, informed consent.

Randomisation and masking

Eligible patients were randomly assigned centrally (1:1) to receive either secondary cytoreduction followed by chemotherapy (surgery group) or chemotherapy alone (no surgery group), stratified by study centre, iMODEL score (<4·7 or ≥4·7), residual disease at primary surgery (complete or incomplete resection), and enrolment in the SGOG SUNNY trial[13] (none, upfront surgery group, or neoadjuvant chemotherapy group). The randomisation code was generated by an independent statistician and randomisation was done using permuted block randomisation (block size of six) and at the SGOG office with patient data checked by the principal investigator (RZ). This trial was open label, so patients and investigators were not masked to treatment assignment.

All the processes of assessment of disease progression and medical judgement recorded were masked in the SOC-1 and SUNNY trials. The masked database for SOC-1 was audited by a third-party contract clinical research associate.

Procedures

Patients in the surgery group were assigned to receive surgery within 4 weeks after randomisation. An en bloc resection was recommended for those with carcinomatosis. Patients whose tumour sites were ablated were not considered for a complete resection, unless the treating surgeon ablated all tumour sites and explored the normal tissue. Chemotherapy would be

given as soon as possible, usually 10–14 days after surgery, but not until the patient had recovery from surgery, with no time limit. Patients in the no surgery group were given chemotherapy within 4 weeks after randomisation. For both treatment groups, recommended chemotherapy was a platinum-based regimen, with six 3-weekly cycles of intravenous paclitaxel (175 mg/m²) or docetaxel (75 mg/m²) combined with intravenous carboplatin (area under the curve [AUC] of 5 mg/mL per min). An additional 2–3 cycles were allowed for patients who had a partial response at investigator discretion. Targeted maintenance therapy was allowed in this trial (bevacizumab or poly (ADP-ribose) polymerases [PARP] inhibitor), and surgery was allowed at subsequent recurrence. Patients with available germline *BRCA* (*gBRCA*) status were analysed.

Serum concentrations of CA125 were assessed every cycle during chemotherapy. At the end of randomised treatment, physical examination, CA125 assessment, and radiological imaging (usually ultrasound) were done during a routine follow-up visit. Radiological images were assessed by an independent radiologist in each centre who was masked to treatment assignment and if they suspected progression of disease, subsequent CT, MRI, or PET-CT imaging was done. Each patient was followed-up once every 3 months from randomisation in the first 5 years, and then, every 6 months thereafter. Disease progression was assessed according to RECIST version 1.1,[14] and each progression event was confirmed by masked investigators (XC and YF), but primary endpoints were not centrally reviewed.

Postoperative complications up to 30 days after surgery were graded using the Memorial Sloan-Kettering Cancer Center complication severity grading method[15] in the surgery group in all patients who initiated their assigned treatment. Mortality rates 60 days after the start of assigned treatment were assessed in both groups. Adverse events were assessed at each cycle of chemotherapy until 30 days after the last cycle of chemotherapy according to the National Cancer Institute Common Terminology Criteria for adverse events (CTCAE) version 4.03. Adverse events were reported according to the Medical Dictionary for Regulatory Activities (version 2.0) and summarised by preferred system and organ class and treatment received. If a patient had a grade 4 event of neutropenia with a temperature of more than 38·5°C, a grade 4 event of neutropenia persisting for 7 days or longer, or a grade 4 event of thrombocytopenia, the dose of paclitaxel or docetaxel could be reduced by 25% and carboplatin reduced to an AUC of 4 mg/mL per min. One dose level reduction each was permitted for the second-line chemotherapy. Major protocol violations included, but were not limited to, deviation from the inclusion and exclusion criteria and refusal to participate with the randomised treatment.

Patient-reported quality of life was assessed using the European Organisation for Research and Treatment of Cancer (EORTC) 30-item core quality of life questionnaire (QLQ-C30; global health status with scores of 0–100) and Trial Outcome Index of the Functional Assessment of Cancer Therapy-Ovary (FACT-O TOI; ranging from 0 to 100, with higher scores indicating a better quality of life) at baseline and at 6, 12, 24, and 60 months after randomisation.

Outcomes

Progression-free survival and overall survival were the two primary endpoints. Progression-free survival was defined as the time from the date of randomisation to disease progression or death due to any cause, whichever occurred first. Overall survival was defined as the interval between the date of randomisation and date of death due to any cause.

The secondary endpoints were accumulating treatment-free survival, overall survival after adjustment of one-way treatment switching (ie, from the no surgery group to the surgery group), safety, quality of life, validation of the predictive and prognostic value of the iMODEL score, patient compliance, and time to first and second subsequent anticancer therapy.

Accumulating treatment-free survival was defined as overall survival minus each treatment period after randomisation including the time of surgery (from randomisation or next surgery to the first cycle of chemotherapy) and chemotherapy, without subtracting the time on targeted maintenance therapy. Treatment-free survival was used as a novel endpoint in a 2019 immunotherapeutic trial to characterise the time free of systemic anticancer therapy that could be obtained with specific treatment.[16] Time to first and second subsequent anticancer therapy were defined as the time from the date of randomisation until the starting date of the first and second subsequent anticancer therapy (after the second and the third relapse) or death, whichever occurred first, or the date of last follow-up. For patients without progression or death at the time of analysis, progression-free survival was censored at the time of last follow-up. For patients who were alive at the time of analysis, overall survival was censored at the time of last follow-up. Patients who died before receiving a subsequent line of treatment were censored at the date of death. Adjusted overall survival, predictive and prognostic value of the iMODEL score, and patient compliance will be reported separately because analysis is not yet complete.

Statistical analysis

The statistical analysis plan for the primary analysis and assessment of the patient-reported outcomes is available in appendix 2. We analysed efficacy endpoints in the intention-to-treat population (ie, all patients randomly assigned to treatment, regardless of treatment received) and we analysed safety in the per-protocol population (ie, all patients who received their assigned study treatment and had available adverse event data). We

	Surgery group (n=182)	No surgery group (n=175)
Age, years	55·2 (50·4–63·9)	53·1 (47·7–59·4)
ECOG performance status		
0	134 (74%)	144 (82%)
1–2	48 (26%)	31 (18%)
ASA score*		
1	126 (69%)	159 (91%)
2	56 (31%)	16 (9%)
Patients' preference		
Surgery	83 (46%)	72 (41%)
No surgery	31 (17%)	30 (17%)
No specific preference	45 (25%)	52 (30%)
Missing	23 (13%)	21 (12%)
Histology		
Serous grade 2–3	158 (87%)	145 (83%)
Other	24 (13%)	30 (17%)
FIGO stage		
I/II	34 (19%)	29 (17%)
III	128 (70%)	121 (69%)
IV	20 (11%)	25 (14%)
Residual disease		
No gross residual disease	83 (46%)	77 (44%)
Gross residual disease	99 (54%)	98 (56%)
Adjuvant chemotherapy		
Yes	182 (100%)	173 (99%)
No	0	2 (1%)
Intraperitoneal chemotherapy		
Yes	22 (12%)	11 (6%)
No	160 (88%)	164 (94%)
Neoadjuvant chemotherapy		
Yes	24 (13%)	41 (23%)
No	158 (87%)	134 (77%)
iMODEL score		
<4·7	123 (68%)	110 (63%)
4·7	39 (21%)	36 (21%)
>4·7	20 (11%)	29 (17%)
(Table 1 continues in next column)		
(Continued from previous column)		
CA125 concentration at recurrence, U/mL		
≤105	128 (70%)	115 (66%)
>105	54 (30%)	59 (34%)
Platinum-free interval before first recurrence, months		
<16	79 (43%)	86 (49%)
≥16	103 (57%)	89 (51%)
Imaging type		
PET-CT	173 (95%)	157 (90%)
Other	9 (5%)	18 (10%)
Number of recurrent lesions by imaging		
1–3	59 (32%)	47 (27%)
4–19	43 (24%)	57 (33%)
≥20	80 (44%)	71 (41%)
Ascites at recurrence		
Absent	181 (99%)	173 (99%)
Present	1 (1%)	2 (1%)
Extra-abdominal lesions		
Yes	46 (25%)	36 (21%)
No	136 (75%)	139 (79%)
gBRCA mutation†		
Yes	8 (4%)	9 (5%)
No	31 (17%)	27 (15%)
Missing	143 (79%)	139 (79%)

Data are median (IQR) or n (%). Gross residual disease was defined as residual disease of 0·1 cm or larger in diameter. ASA=American Society of Anaesthesiologists. CA125=Cancer antigen 125. ECOG=Eastern Cooperative Oncology Group. FIGO=International Federation of Gynaecology and Obstetrics. iMODEL=international model. *Assessed by investigators. †Germline *BRCA1* or *BRCA2* pathogenic or likely pathogenic mutation.

Table 1: **Baseline characteristics**

determined that approximately 129 events of progression or death would provide at least 80% power to detect an anticipated 18% increase (from 22% to 40%) of the 2-year progression-free survival in favour of the surgery group at a two-sided α level of 5%, with a hazard ratio (HR) of 0·61. 209 deaths had to be observed for the final analysis of overall survival with a 78% power, and HR of 0·68 (corresponding to an increase from 60% to 70·5% at 3-year overall survival). To do the first analysis within a reasonable timeframe, 356 patients would be enrolled over 10 years with a minimum follow-up of 3 years.

To maintain an overall significance level at 0·05, we used a hierarchical statistical test strategy to test this hypothesis. Specifically, we first tested the difference in progression-free survival at a two-sided α level of 0·05. Overall survival could only be tested when progression-free survival was significant. No interim analysis was planned for progression-free survival. The trial would be terminated if there was no significant difference in progression-free survival. Two analyses for overall survival would be done: an interim analysis when 105 deaths had occurred and a final analysis when 209 deaths had occurred. We used the Haybittle-Peto interim monitoring boundary stopping rule in the interim analysis for overall survival and a p value of less than 0·001 would be considered to be significant. We used the Kaplan-Meier method to estimate progression-free and overall survival, and other time-to-event endpoints, with differences tested by log-rank test using a stratified Cox proportional hazards model to estimate HR and 95% CIs after adjustment for stratification factors. We also did a visual inspection of log-negative-log plots (plots of the logarithm of the negative survival probability against the logarithm of the event time in two treatment groups) to check the proportional hazards assumption for progression-free survival and overall

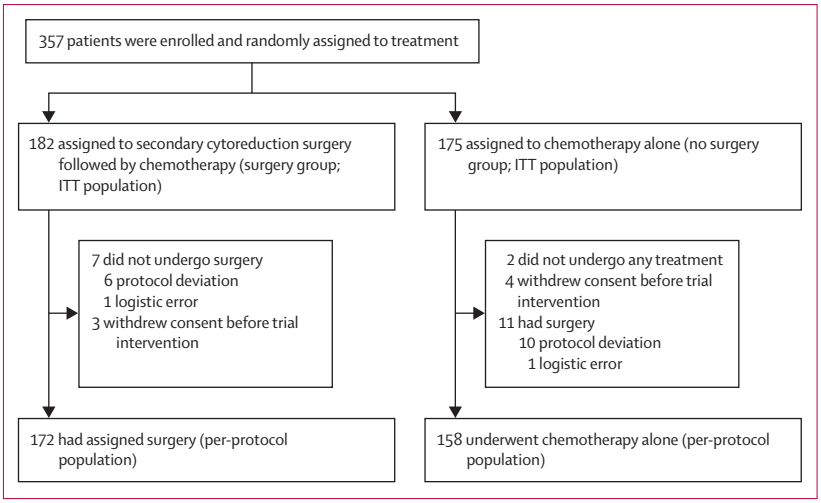

Figure 1: **Trial profile**
ITT=intention-to-treat.

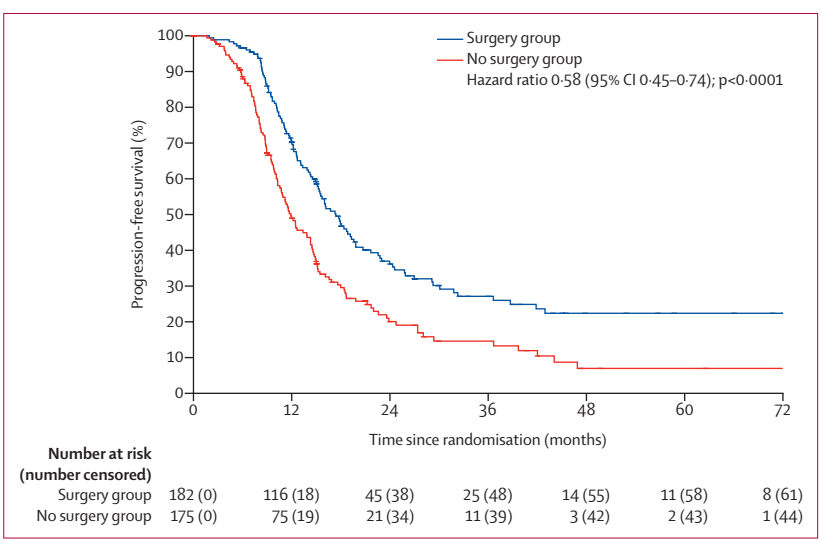

Figure 2: **Progression-free survival in the intention-to-treat population**

survival. We did a prespecified analysis of restricted mean survival time to assess the mean accumulating treatment-free survival time.

Sensitivity analyses were planned for overall survival excluding the centre with the highest proportion of treatment switches; however, due to immaturity of the overall survival data, this will be reported elsewhere. We did subgroup analyses of progression-free survival by different variables. Covariate categories including age, ECOG performance status, patient's preference before randomisation, centre, iMODEL score, residual disease at primary surgery, histology, number of tumour lesions detected by imaging were prespecified, while FIGO stage, neoadjuvant chemotherapy, and extra-abdominal lesions were post hoc. We also did post-hoc subgroup analyses of progression-free and interim overall survival by surgical outcome. Subgroup analyses were done within subgroups, with a test of interactions of subgroups with treatment. Estimated HRs and CIs were presented as a forest plot with $p_{interaction}$ values for each subgroup analysis. A post-hoc comparison of recurrent lesions by surgical outcomes was done using the χ^2 test. Post-hoc American Society of Anaesthesiologist (ASA) assessments done by the investigators and anaesthesiologists were compared in the surgery group because of unexpected higher proportion of ASA score of 1 as assessed by the investigators. We included all available data in the analysis without any imputation of missing data, which was applicable to the analyses of quality-of-life data. We analysed quality-of-life scores using a mixed-effects model for repeated measures restricted to patients who had a baseline assessment and at least one subsequent assessment, such that patients with missing baseline or post-baseline assessments were excluded from the analysis.

An independent data monitoring committee monitored the safety of patients and the progress of the trial periodically. We did all statistical analyses using SPSS (version 25.0) and R (version 3.6.1). This study is registered with ClinicalTrials.gov, number NCT01611766.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between July 19, 2012, and June 3, 2019, 357 patients were recruited and randomly assigned to the surgery group (182) or no surgery group (175; intention-to-treat population). Baseline characteristics are shown in table 1. Of 182 patients assigned to the surgery group, 172 (95%) had secondary cytoreduction surgery, and 158 (90%) of 175 assigned to the no surgery group had their assigned treatment (per-protocol population). Three (2%) patients in the surgery group and four (2%) patients in the no surgery group withdrew consent before any trial intervention started (figure 1). Seven (4%) patients in the surgery group did not have surgery as planned, and 11 (6%) patients in the no surgery group had surgery. At the time of the database lock (Dec 17, 2019), 130 patients in the no surgery group had a subsequent relapse, of whom 48 (37%) crossed-over and had cytoreductive surgery. The association bewteen cross-over rate and patients' preference in the no surgery group is described in appendix 2 (p 7).

Median follow-up was 36·0 months (IQR 18·1–58·3; 36·0 months [18·0–60·6] for the surgery group and 33·9 months [18·1–52·1] for the no surgery group), at which point 243 patients had disease progression (113 in the surgery group and 130 in the no surgery group), and 111 patients had died (55 in the surgery group and 56 in the no surgery group). Median progression-free survival

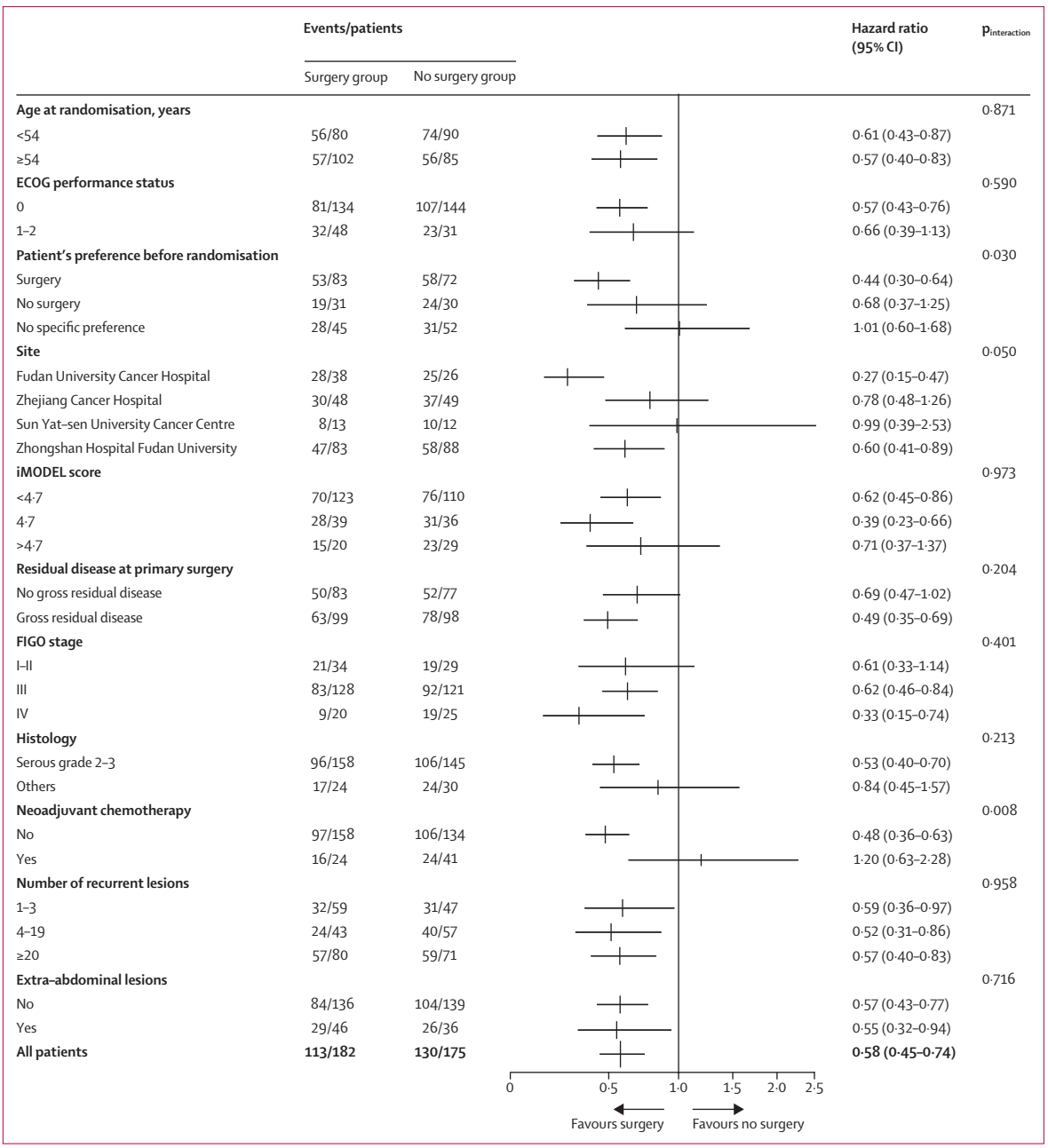

Figure 3: **Prespecified and post-hoc subgroup analyses of progression-free survival in the intention-to-treat population**
ECOG=Eastern Cooperative Oncology Group. FIGO=International Federation of Gynecology and Obstetrics.

was 17·4 months (95% CI 15·0–19·8) in the surgery group and 11·9 months (10·0–13·8) in the no surgery group (HR 0·58, 95% CI 0·45–0·74; p<0·0001; figure 2). The stratified Cox proportional hazards model showed a similar result (HR 0·56, 95% CI 0·43–0·72; p<0·0001). Visual inspection of survival curves indicated that the proportional hazards assumption was met (appendix 2 p 10). 2-year progression-free survival was 38% (95% CI 30–46) in the surgery group and 22% (16–28) in the no surgery group. Prespecified and post-hoc subgroup analyses of progression-free survival are shown in figure 3 and in appendix 2 (p 9).

At the time of the database lock (Dec 17, 2019), 105 (95%) of 111 patients who died had died from ovarian cancer. In the surgery group, one patient died due to secondary gallbladder cancer and one patient died by suicide. In the no surgery group, one patient died due to leukaemia, one due to cardiopulmonary arrest, one due to paraneoplastic syndrome encephalitis, and one due to road traffic injury. At the interim

	Grade 1–2	Grade 3	Grade 4
Pleural effusion	1 (1%)	3 (2%)	0
Pulmonary embolism	0	0	0
Deep-vein thrombosis	0	1 (1%)	0
Cerebral infarction	0	0	0
Bowel obstruction	9 (5%)	0	0
Wound infection	2 (1%)	2 (1%)	0
Abdominal infections	10 (6%)	1 (1%)	0
Pneumonia	2 (1%)	0	0
Urinary tract infection	1 (1%)	0	0
Gastroenteritis	0	0	0
Arrhythmia	4 (2%)	0	0
Relaparotomy for haemorrhage	0	0	0
Blood transfusion for haemorrhage	0	0	0
Intestinal fistula	0	0	0
Lymphocyst	1 (1%)	0	0
Anastomotic bleeding	0	1 (1%)	0
Renal impairment	0	1 (1%)*	0
Repeat laparotomy	0	0	0

Data are n (%). Adverse events are reported according to the Memorial Sloan-Kettering Cancer Center complication severity grading criteria. Patients who had an event more than one time are counted only once for that particular MedDRA term. For such patients, the worst intensity and causality to trial treatment or surgery for every term has been used. MedDRA=Medical Dictionary for Regulatory Activities. *One patient had a serious adverse event and received haemodialysis treatment.

Table 2: **Postoperative 30-day complications in the per-protocol surgery group (n=172)**

	Surgery group (n=166)*			No surgery group (n=156)†		
	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4
Leucopenia	60 (36%)	8 (5%)	6 (4%)	62 (40%)	7 (5%)	1 (1%)
Neutropenia	40 (24%)	17 (10%)	12 (7%)‡	50 (32%)	14 (9%)	5 (3%)
Thrombocytopenia	32 (19%)	3 (2%)	2 (1%)	73 (47%)	4 (3%)	1 (1%)
Anaemia	74 (45%)	8 (5%)	2 (1%)	89 (57%)	9 (6%)	0
Gastrointestinal	5 (3%)	0	0	5 (3%)	1 (1%)	0
Hepatic	15 (9%)	0	0	28 (18%)	0	1 (1%)
Increased blood creatinine	1 (1%)	0	1 (1%)§	1 (1%)	0	0
Infection	1 (1%)	1 (1%)	0	0	0	0
Peripheral sensory neuropathy	2 (1%)	0	0	1 (1%)	0	0
Pulmonary event	0	1 (1%)	0	0	0	0

Data are n (%). Patients who had an event more than one time are counted only once for that particular MedDRA term. For such patients, the worst intensity and causality to trial treatment or surgery for every term has been used. MedDRA=Medical Dictionary for Regulatory Activities. *Of 182 patients (intention-to-treat population), six did not receive chemotherapy, and ten who received chemotherapy had unavailable data of adverse events. †Of 175 patients (intention-to-treat population), seven did not receive chemotherapy, and 12 who received chemotherapy had unavailable data of adverse events. ‡Three patients had serious adverse events and all resolved without sequelae. §One patient had a serious adverse event that did not resolve, and haemodialysis treatment was performed.

Table 3: **Adverse events during chemotherapy**

analysis (after 105 deaths were recorded), median overall survival was 58·1 months (95% CI not estimable to not estimable) in the surgery group and 53·9 months (42·2–65·5) in the no surgery group (HR 0·82, 95% CI 0·57–1·19; appendix 2 p 12). Post-hoc analysis of overall survival by surgical outcome is shown in appendix 2 (p 12).

Median time to first subsequent anticancer therapy was 18·1 months (95% CI 15·5–20·8) in the surgery group versus 13·6 months (12·3–14·9) in the no surgery group (HR 0·59, 95% CI 0·46–0·76) and median time to second subsequent anticancer therapy was 33·5 months (29·2–37·7) in the surgery group versus 28·1 months (23·5–32·8) in the no surgery group (HR 0·69, 0·51–0·94; appendix 2 p 11). The stratified Cox proportional hazards model showed consistent results (appendix 2 p 8).

The restricted mean survival time (0–72 months) for accumulating treatment-free survival was 46·8 months (95% CI 41·7–51·8) in the surgery group and 42·4 months (36·7–48·0) in the no surgery group (appendix 2 p 13).

The rate of complete resection was 132 (77%) of 172 in patients who were assigned to the surgery group and who had the procedure. In patients with an iMODEL score of more than 4·7 who were assigned to surgery, 11 (61%) of 18 had a complete resection. In comparison, 121 (79%) of 154 patients with an iMODEL score less than 4·7 who were assigned to surgery had a complete resection. A comparison of recurrent lesions by surgical outcomes is shown in appendix 2 (p 4). The median time between randomisation and secondary cytoreduction was 7 days (IQR 5–8). There was a low incidence of aborted procedures (two [1%] of 172 cases; appendix 2 p 3). None of 38 patients who had anastomosis had an intestinal fistula (table 2; appendix 2 p 3). More than half of patients had extensive upper abdominal and extra-abdominal procedures (appendix 2 p 3). Surgical complications at 30 days with grade 3 or worse adverse events occurred in nine (5%) of 172 patients in the surgery group (table 2). Median length of hospital stay was 15·5 days (IQR 13·0–21·0).

176 (97%) of 182 in the surgery group and 168 (96%) of 175 in the no surgery group received second-line intravenous chemotherapy (appendix 2 p 4). Third-line or later subsequent therapy is shown in appendix 2 (p 6). Numbers of patients and the targeted maintenance therapy they received after their assigned treatment are listed in appendix 2 (p 5). 35 (20%) of 176 patients in the surgery group and 44 (26%) of 168 patients in the no surgery group received less than six cycles of chemotherapy due to disease progression, a decrease in treatment decided on by the patients or their treating clinician, toxicity, or subsequent maintenance therapy as decided by the investigators. The median time between surgery and chemotherapy initiation was 16 days (IQR 13–21) in the surgery group and the median time between randomisation and chemotherapy was 2 days (1–4) in the no surgery group. Among the patients treated with second-line chemotherapy who had available adverse event data, 41 (25%) of 166 patients in the surgery group and 31 (20%) of 156 in the no surgery group had grade 3 or worse adverse events during chemotherapy (table 3), and six (4%) of

166 patients in the surgery group and five (3%) of 156 in the no surgery group required dose reductions. The most common grade 3–4 adverse events during chemotherapy were neutropenia (29 [17%] of 166 patients in the surgery group *vs* 19 [12%] of 156 patients in the no surgery group), leucopenia (14 [8%] *vs* eight [5%]), and anaemia (ten [6%] *vs* nine [6%]; table 3). All grade 1–5 adverse events are shown in appendix 2 (p 8). Four serious adverse events occurred, all in the surgery group: neutropenia (three [2%] of 166 patients) and increased blood creatinine (one [1%]). Two patients in the surgery group discontinued treatment due to chemotherapy-related toxicity. No patients died within 60 days of assigned treatment, and no treatment-related deaths occurred in either group.

The *gBRCA* test was done in 75 patients, showing eight (21%) of 39 patients with pathogenic or likely pathogenic mutations in the surgery group and nine (25%) of 36 patients in the no surgery group. We did a post-hoc analysis of ASA assessments by the investigators versus by the anaesthesiologists in the surgery group (appendix 2 p 7).

We assessed prespecified patient-reported outcomes based on EORTC QLQ-C30 global health status, and FACT-O TOI score, the two groups did not differ (appendix 2 p 14).

Discussion

In this trial, secondary cytoreduction plus chemotherapy improved progression-free survival compared with chemotherapy alone in patients with platinum-sensitive, relapsed ovarian cancer. Although data for overall survival is immature, the prespecified interim analysis of overall survival showed no difference between the surgery group and the no surgery group. Times to first and second subsequent anticancer therapy, which are key endpoints between progression-free survival and overall survival,[17] were also longer in patients in the secondary cytoreduction plus chemotherapy group than in those in the chemotherapy alone. In 2014, a white paper from the Society of Gynecologic Oncology followed three parallel trials on the efficacy of secondary cytoreduction: DESKTOP III, GOG-0213, and SOC-1.[8] The final analysis of DESKTOP III showed that secondary cytoreduction resulted in improved progression-free survival and overall survival compared with chemotherapy alone.[9] Similar to our data, a 5·6 month increase in median progression-free survival was reported in DESKTOP III, with a HR of 0·66 (95% CI 0·52–0·83) in favour of surgery.[6] However, GOG-0213 reported that secondary cytoreduction did not provide a longer overall survival than chemotherapy alone in the ITT population or in a post-hoc subgroup with complete resection.[7]

Several key points about these three studies need to be further discussed. First, the patient populations were different among the three trials. DESKTOP III selected patients using the AGO criteria and SOC-1 selected patients using the iMODEL score combined with PET-CT.[5,10,18] iMODEL score combined with PET-CT in SOC-1 selected more potential candidates than the AGO score in DESKTOP III. By comparison, AGO score was more restrictive and selected recurrent patients with complete resection at primary surgery (appendix 2 p 15). GOG-0213 recruited patients with oligometastatic sites of relapse detected by CT scan, 53% of patients in the surgery group had one or two recurrent sites, of whom 36% were recruited at one site;[7] whereas, in the SOC-1 trial, only 32% of the patients in the surgery group had one, two, or three recurrent sites by PET-CT imaging. Because more than half of patients in the no surgery group in the GOG-0213 trial had one or two sites, the longer median overall survival observed might not have been due to bevacizumab, but rather the different patient populations assessed.[7] Additionally, the enrolled patients in SOC-1 were relatively young compared with those enrolled in DESKTOP III and GOG-0213. Investigators assessed ASA scores for all potential participants at outpatient departments to guarantee the safety of the surgery. In a post-hoc analysis of ASA scores, we found more patients did not have a ASA score of 1. Given the widely used PARP inhibitor maintenance therapy in platinum-sensitive relapsed ovarian cancer, molecular subtypes including *BRCA* status, homologous recombination deficiency, or other genetic markers should be explored to generate a more accurate preoperative algorithm.

Second, quality control on surgery for relapsed disease is important in contributing to a complete resection. Both the current SOC-1 trial and the DESKTOP III[6] trial have found secondary cytoreduction to be superior to chemotherapy alone for improvement in progression-free survival. The final analysis of DESKTOP III found that if a patient has complete resection, overall survival was longer than with chemotherapy alone (61·9 months *vs* 46·0 months).[9] In the current study, although the data are immature, patients with complete resection had increased overall survival than those in the no surgery group, while patients with incomplete resection had the worst median overall survival. These findings are consistent with our report in 2003.[19] By comparison, the GOG-0213 study found that patients with chemotherapy alone had a longer overall survival than those who had surgery, but there was no significant difference between the groups (64·7 months *vs* 56·0 months).[7] However, because of the different selection criteria of the enrolled patients and various subsequent therapies, the survival data among those three trials are not directly comparable.[6,7,9,20,21] Given the safety of secondary cytoreduction in GOG-0213 and the similar proportion of patients who had bevacizumab maintenance therapy in both groups, we hypothesise that quality control of the surgery or delays in chemotherapy administration due to recuperation are possible explanations for the worse overall survival observed in the surgery group in GOG-0213. However, more evidence is needed to explore these theories. The SOC-1 trial was run at four sites in China,

which included the major three cancer centres across the country. The leading principal investigator (RZ) initiated the first phase 2 trial of secondary cytoreduction in 1998 and published the data from this trial in 2004.[4] Surgical outcomes are significantly associated with the procedure volumes of hospitals and surgeons in ovarian cancer.[22,23] Each participating centre of the SOC-1 trial was required to have an annual hospital volume of ovarian cancer patients of more than 200 requiring radical surgery, and all surgeons met the condition of an annual volume of radical surgeries in ovarian cancer of more than 50.

Third, subsequent treatment components might affect the actual efficacy of surgery. Quite a small proportion of patients in our study received bevacizumab and PARP inhibitor maintenance therapy during the second-line therapy. By comparison, most patients in GOG-0213 received bevacizumab maintenance,[7] whereas 23% of patients had bevacizumab therapy and 5% had PARP inhibitor therapy in DESKTOP III.[9] A subgroup analysis of GOG-213 showed a median overall survival of 67·0 months in the no surgery group versus 32·4 months in the surgery group for patients without bevacizumab, and 61·7 months in the no surgery group versus 58·5 months in the surgery group for patients with bevacizumab. Although subsequent maintenance therapy was not a stratification factor in their analyses, the population who were assigned to carboplatin plus paclitaxel had increased survival in favour of the no surgery group (HR 2·3, 95% CI 1·29–4·10); whereas those who were given carboplatin plus paclitaxel and bevacizumab showed no difference between the surgery and no surgery groups (HR 0·95; 95% CI 0·65–1·38).[7] These findings indicated that patients in the surgery group rather than in the no surgery group benefited from bevacizumab.[7] Therefore, the use of bevacizumab might not be the key reason for the difference in overall survival estimates between GOG-0213 and the other two trials. Surgical trials that incorporate targeted maintenance therapy will help to answer this question (NCT03983226;[24] NCT04515602).

In our study, most patients received the subsequent chemotherapy around 16 days after surgery, compared with 40 days in GOG-0213, which suggests that most patients could recover from surgery quicker than observed in GOG-0213. A post-hoc analysis of the GOG-0218 study showed that risk of death increases from 25 days after surgery up to initiation of chemotherapy.[25] Especially for those with complete resection, a period of 20 days between surgery and initiation of chemotherapy had the best survival, compared with 40-day and 60-day periods.[25] In the current trial, during the relatively long-term follow-up period, we did not find any difference in patient-reported quality of life between the surgery and no surgery groups.

The major limitation of the current trial was the 37% of cross-over from the no surgery group to surgery at subsequent relapses, which was decided on by either surgeons or the patients. Such cross-overs might extend the median overall survival in the no surgery group and lead to reduced statistical power to detect a negative result in overall survival. In China, secondary cytoreduction was the standard of care for women with relapsed ovarian cancer in participating centres since the first Chinese prospective trial reported in 2004,[4] and most patients had a preference for surgery over no surgery. The restricted mean survival time analysis showed that patients who had surgery had improved accumulating treatment-free survival. Treatment-free survival has been used as a novel endpoint in an immunotherapeutic trial to characterise the time free of systemic anticancer therapy that could be obtained with specific treatment.[16] One reason why the use of treatment-free survival might be preferable to overall survival as an endpoint might be because of the combination regimens with cessation of therapy after a fixed or maximal duration. In our study, only a few patients used subsequent targeted maintenance therapy, and the targeted maintenance period has not been removed from accumulating treatment-free survival. We aim to use accumulating treatment-free survival to explore the survival benefit affected by a high proportion of cross-over from the no surgery to the surgery group when overall survival data are mature. Hence, mature data for overall survival, adjusted overall survival, and accumulating treatment-free survival will help to answer this question.

In summary, secondary cytoreduction followed by chemotherapy improved progression-free survival with acceptable morbidity compared with chemotherapy alone for patients with platinum-sensitive, relapsed ovarian cancer selected using iMODEL scores and PET-CT imaging. All patients should be counselled about the options of secondary cytoreduction in specialised centres with high volumes of ovarian cancer surgery. Long-term survival outcomes will be assessed using mature data on overall survival and accumulating treatment-free survival.

Contributors

RZ, JZ, and DT contributed to the design of the study. All authors were involved in conduct of the study. All authors had full access to all the data reported in the study and have final responsibility for the decision to submit for publication. TS, SY, RJ, RZ, JZ, JL, PZ, YZ, XC, XH, WT, WG, YF, HY, and YC collected and interpreted the data. TS, HJ, and RJ analysed the data. RZ and TS wrote the first draft of the manuscript. RZ, TS, HJ, and RJ have accessed and verified the data. TS, HJ and RJ had full accessed to the raw data, analysed the data, and wrote the manuscript.

Declaration of interests

We declare no competing interests.

Data sharing

The study protocol and statistical analysis plan are available in appendix 2. Individual participant-level data that underlie the reported results are not available.

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