Primary chemotherapy versus primary surgery for newly diagnosed advanced ovarian cancer (CHORUS): an open-label, randomised, controlled, non-inferiority trial

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Summary

Background The international standard of care for women with suspected advanced ovarian cancer is surgical debulking followed by platinum-based chemotherapy. We aimed to establish whether use of platinum-based primary chemotherapy followed by delayed surgery was an effective and safe alternative treatment regimen.

Methods In this phase 3, non-inferiority, randomised, controlled trial (CHORUS) undertaken in 87 hospitals in the UK and New Zealand, we enrolled women with suspected stage III or IV ovarian cancer. We randomly assigned women (1:1) either to undergo primary surgery followed by six cycles of chemotherapy, or to three cycles of primary chemotherapy, then surgery, followed by three more cycles of completion chemotherapy. Each 3-week cycle consisted of carboplatin AUC5 or AUC6 plus paclitaxel 175 mg/m², or an alternative carboplatin combination regimen, or carboplatin monotherapy. We did the random assignment by use of a minimisation method with a random element, and stratified participants according to the randomising centre, largest radiological tumour size, clinical stage, and prespecified chemotherapy regimen. Patients and investigators were not masked to group assignment. The primary outcome measure was overall survival. Primary analyses were done in the intention-to-treat population. To establish non-inferiority, the upper bound of a one-sided 90% CI for the hazard ratio (HR) had to be less than 1·18. This trial is registered, number ISRCTN74802813, and is closed to new participants.

Findings Between March 1, 2004, and Aug 30, 2010, we randomly assigned 552 women to treatment. Of the 550 women who were eligible, 276 were assigned to primary surgery and 274 to primary chemotherapy. All were included in the intention-to-treat analysis; 251 assigned to primary surgery and 253 to primary chemotherapy were included in the per-protocol analysis. As of May 31, 2014, 451 deaths had occurred: 231 in the primary-surgery group versus 220 in the primary-chemotherapy group. Median overall survival was 22·6 months in the primary-surgery group versus 24·1 months in primary chemotherapy. The HR for death was 0·87 in favour of primary chemotherapy, with the upper bound of the one-sided 90% CI 0·98 (95% CI 0·72–1·05). Grade 3 or 4 postoperative adverse events and deaths within 28 days after surgery were more common in the primary-surgery group than in the primary-chemotherapy group (60 [24%] of 252 women *vs* 30 [14%] of 209, p=0·0007, and 14 women [6%] *vs* 1 woman [<1%], p=0·001). The most common grade 3 or 4 postoperative adverse event was haemorrhage in both groups (8 women [3%] in the primary-surgery group *vs* 14 [6%] in the primary-chemotherapy group). 110 (49%) of 225 women receiving primary surgery and 102 (40%) of 253 receiving primary chemotherapy had a grade 3 or 4 chemotherapy related toxic effect (p=0·0654), mostly uncomplicated neutropenia (20% and 16%, respectively). One fatal toxic effect, neutropenic sepsis, occurred in the primary-chemotherapy group.

Interpretation In women with stage III or IV ovarian cancer, survival with primary chemotherapy is non-inferior to primary surgery. In this study population, giving primary chemotherapy before surgery is an acceptable standard of care for women with advanced ovarian cancer.

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Introduction

Ovarian cancer is the leading cause of death from gynaecological cancer in developed countries.[1] More than 75% of women have advanced disease (International Federation of Gynecology and Obstetrics [FIGO] stage IIIC or IV) at diagnosis, of whom a substantial proportion are unwell and unfit and have a 5-year survival rate of less than 25%.[1] Primary cytoreductive surgery followed by platinum-based chemotherapy is the mainstay of treatment for advanced disease. Although no randomised trials of primary surgery exist, observational studies consistently report that a lower postoperative tumour residuum is associated with longer survival.[2–8] Achievement of optimum debulking (defined in the study period as disease <1 cm in maximum diameter at completion of surgery) can need complex and widespread surgery, and is more likely to be achieved when done by specialist gynaecological

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oncologists.[9–11] Even so, many women treated in specialist centres will have bulky residual tumour after surgery.

An alternative treatment strategy using primary chemotherapy with delayed surgery has been developed. This strategy is based on the high response rate to platinum-based chemotherapy and many women have had rapid symptomatic improvement and reduction in tumour burden with it. The primary-chemotherapy strategy seemed to increase optimum debulking rates and reduce surgery related complications in observational studies,[12,13] but two meta-analyses of non-randomised studies produced conflicting results on the effect of delaying surgery on survival.[14,15]

We designed the CHORUS trial to test the hypothesis that giving primary chemotherapy with delayed surgery could result in survival similar to primary surgery, with reduced surgical morbidity. A non-inferiority design was chosen because we judged that a reduction in surgery related morbidity without detriment to survival would justify the use of this treatment strategy in clinical practice.

Methods

Study design and participants

We designed this trial as an investigator-designed and led multicentre, randomised phase 3 trial that took place in the UK and New Zealand (appendix). We obtained national ethical and regulatory approvals in both countries and local approvals at each centre. Trial conduct and progress were monitored by an independent data monitoring committee and overseen by the UK Medical Research Council Clinical Trials

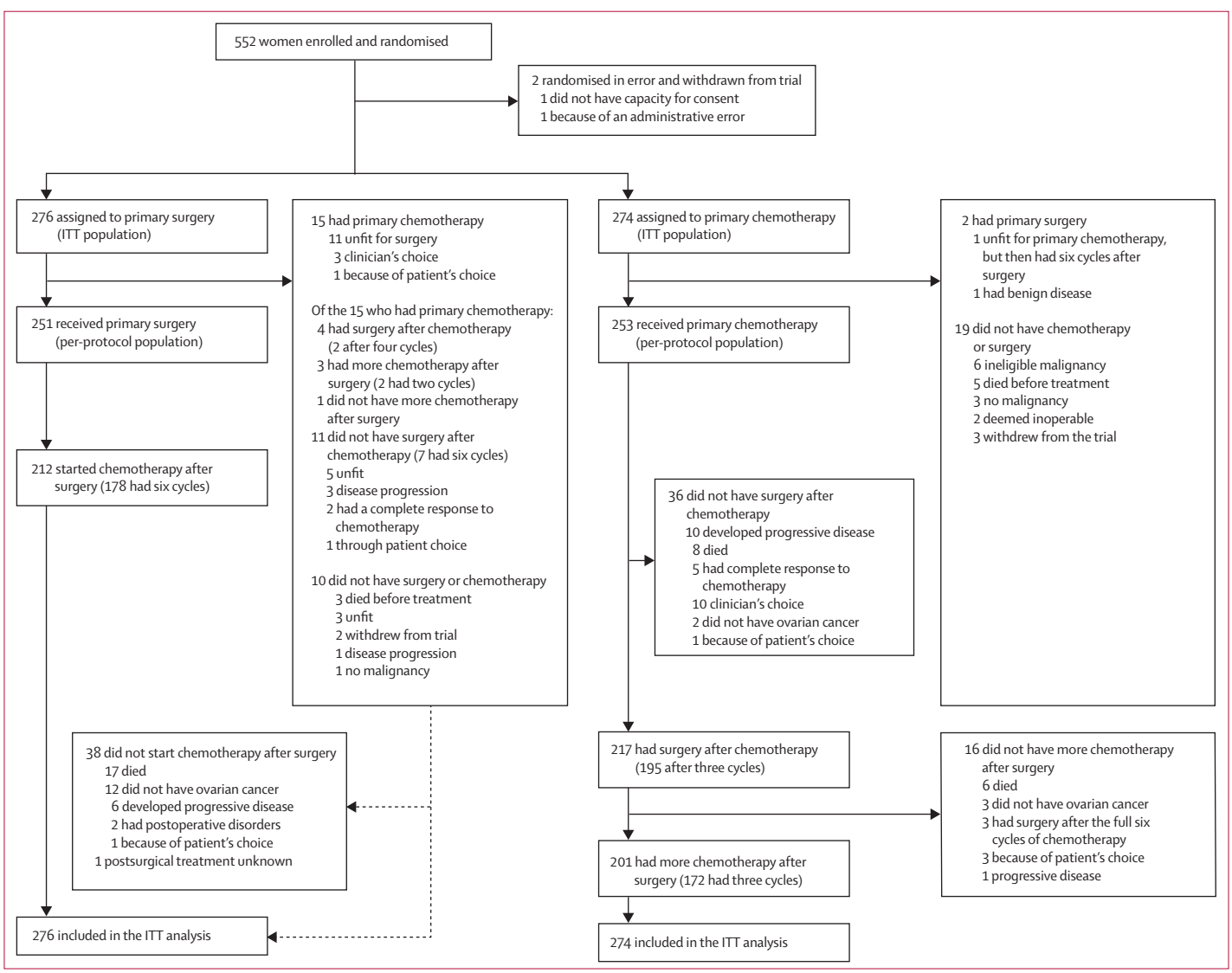

Figure 1: **Trial profile**
ITT=intention to treat.

Unit (MRC CTU) Gynaecological Cancer Trial Steering Committee. All participating centres were public hospitals that regularly undertook treatment of ovarian cancer with multidisciplinary teams that included specialist surgeons, oncologists, and pathologists.

The planned population was women with clinical or imaging evidence of a pelvic mass with extrapelvic disease compatible with FIGO 1988 stage III or IV ovarian, fallopian tube, or primary peritoneal cancer,[16] who were fit for surgery and chemotherapy. Their ratio of serum cancer antigen 125 (CA125) to carcinoembryonic antigen (CEA) had to be greater than 25;[17] if less, investigations to exclude a gastrointestinal carcinoma were necessary before entry. Histological or cytological confirmation of diagnosis was not needed before random assignment. All women provided written informed consent.

Randomisation and masking

Enrolled women were randomly assigned (1:1) to undergo either debulking primary surgery followed by chemotherapy, or to primary chemotherapy with delayed surgery afterwards. We did the random assignment centrally at the MRC CTU by telephone using a minimisation method with a random element, and stratified the women according to randomising centre, largest radiological tumour size, clinical FIGO stage, and prespecified chemotherapy regimen. Patients and investigators were not masked to group assignment.

Procedures

At screening, all women had a clinical assessment, an imaging test (a CT or MRI scan of the abdomen and pelvis, and a radiograph of the chest), and concentrations of serum tumour markers measured (CA125 and CEA).

We then assigned the women to undergo either debulking primary surgery followed by six cycles of chemotherapy, or to three cycles of primary chemotherapy, then surgery, followed by three more cycles of completion chemotherapy. Women assigned to primary chemotherapy had either histological or cytological confirmation of their diagnosis before starting chemotherapy, either through laparoscopic or image-biopsy samples, or fine-needle aspiration of a tumour site or effusion, according to local practice. The chemotherapy used was six cycles of carboplatin AUC5 or carboplatin AUC6, plus paclitaxel 175 mg/m² every 3 weeks; an alternative carboplatin combination regimen; or carboplatin AUC5 or AUC6 monotherapy. The intended regimen was established on an individual basis and depended on patient fitness, choice, and usual local practice, and was prespecified before random assignment.

All surgery was done in 64 centres by specialist gynaecological oncologists who have been accredited by the Royal College of Obstetricians and Gynaecologists (RCOG). Such surgeons operate on at least 15 patients with ovarian cancer each year and their work is regularly peer reviewed. In a further 23 registered centres, only non-surgical management was provided. The intent of surgery was tumour debulking to no macroscopic residual disease. The recommended surgical procedures were: a midline incision; sampling of free fluid or peritoneal washings for cytology; a thorough inspection of the abdomen and pelvis including upper abdominal viscera, diaphragm, and retroperitoneal spaces; and hysterectomy, bilateral oophorectomy, and omentectomy. Pelvic and para-aortic nodes were to be sampled for women who were thought to have FIGO stage IIIB disease or less. Ultraradical procedures included several resections of large or small bowel, diaphragmatic stripping, splenectomy, partial cystectomy, and complete para-aortic or pelvic lymphadenectomy. These procedures were recommended only if they would help with cytoreduction for optimum debulking. The volume of disease was assessed by the surgeon at the start and end of the debulking operation, and was recorded systematically as the largest diameter of disease in 13 abdominal or pelvic areas: diaphragm, liver surface, paracolic gutters, omentum, intestines, peritoneal surface, pelvis, adnexa, pelvic and para-aortic lymph

	Primary surgery (n=276)	Primary chemotherapy (n=274)	Total (n=550)
Median age (years)	66 (26–87, 57–72)	65 (34–88, 59–71)	65 (26–88, 58–72)
Median tumour size (cm)	8 (0·7–30, 5–12)	8 (0·9–28, 5–12)	8 (0·7–30, 5–12)
≤2 cm	13 (5%)	13 (5%)	26 (5%)
≤5 cm	59 (21%)	60 (22%)	119 (22%)
≤10 cm	111 (40%)	110 (40%)	221 (40%)
≤20 cm	79 (29%)	79 (29%)	158 (29%)
>20 cm	7 (3%)	7 (3%)	14 (3%)
Unmeasurable disease	7 (3%)	5 (2%)	12 (2%)
Clinical FIGO stage			
III	206 (75%)	206 (75%)	412 (75%)
IV	70 (25%)	68 (25%)	138 (25%)
CA125/CEA ratio			
>25	272 (99%)	268 (98%)	540 (98%)
≤25	4 (1%)	6 (2%)	10 (2%)
WHO performance status			
0	83 (30%)	88 (32%)	171 (31%)
1	138 (50%)	133 (49%)	271 (49%)
2	53 (19%)	49 (18%)	102 (19%)
3	1 (<1%)	4 (1%)	5 (1%)
Missing data	1	0	1
Prespecified chemotherapy regimen			
Single agent carboplatin	66 (24%)	63 (23%)	129 (23%)
Carboplatin plus paclitaxel	207 (75%)	210 (77%)	417 (76%)
Carboplatin plus other chemotherapy agent	3 (1%)	1 (<1%)	4 (1%)

Data are median (range, IQR) or n (%; percentages calculated for patients with non-missing data). FIGO=International Federation of Gynaecology and Obstetrics. CA125=cancer antigen 125. CEA=carcinoembryonic antigen.

Table 1: **Baseline characteristics**

nodes, spleen, and liver. Neither intraoperative photographs or postoperative imaging were obtained.

Women needed to start their assigned treatment within 4 weeks after assignment. In the primary-surgery group, interval debulking surgery (ie, a second operation after three cycles of chemotherapy) was allowed in women with more than 1 cm residual disease after primary surgery. Women randomly assigned to primary chemotherapy were scheduled for surgery after cycle 3 of chemotherapy. In both groups, postoperative chemotherapy was started within 6 weeks after surgery. During chemotherapy, assessments at every cycle included clinical review and measurement of CA125 concentrations. Women were followed up and monitored by clinical review and CA125 measurements done monthly for 9 months, then every 3 months for 2 years, every 6 months for 3 years, then annually until death, they withdrew from the study, or the study finished. Imaging was done after three cycles of chemotherapy and at completion of all planned treatment. During follow-up, the need for imaging was triggered by clinical symptoms or a rise in CA125 concentrations. Disease progression during the study was defined according to WHO criteria,[18] but during follow-up, progression could also be defined by a rise in CA125 concentrations according to Gynaecologic Cancer Inter Group (GCIG) criteria.[19]

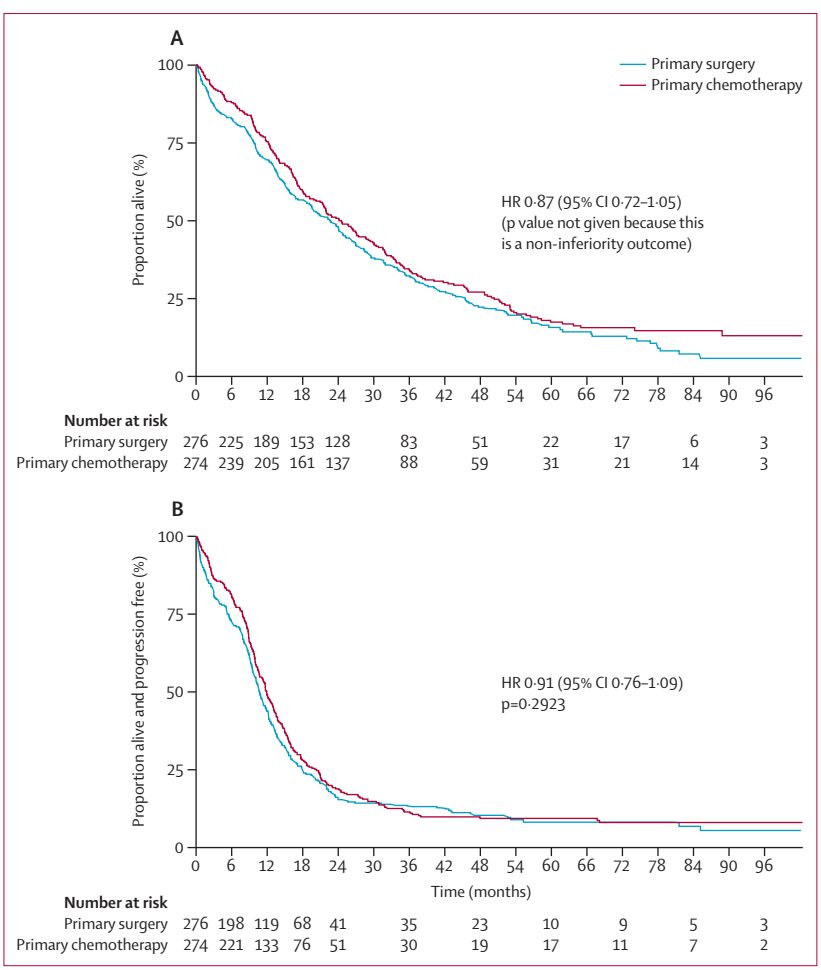

Figure 2: **Kaplan-Meier curves for overall survival (A) and progression-free survival (B)**
Data are unadjusted survival curves in the intention-to-treat population. HR=hazard ratio.

We measured quality of life with the EORTC quality of life questionnaire core-36 (QLQC-30) and the ovarian cancer-specific quality of life questionnaire (QLQ-Ov28).[20] These were completed at study entry before the woman knew her allotted treatment, repeated after cycles 3 and 6 of chemotherapy, and at 6 and 12 months after treatment assignment.

Outcomes

The primary outcome measure was overall survival. Secondary efficacy outcomes were progression-free survival and quality of life. We recorded adverse events, graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 3.0, at each chemotherapy cycle and after.

Statistical analysis

The expected 3 year survival rate was 50% with primary surgery. We defined the non-inferiority boundary, selected after consideration of the size of differences noted in similar trials and clinical consensus, to exclude a detriment of more than 6% with primary chemotherapy, with a 10% (one-sided) level of significance. Therefore, to show non-inferiority, the upper bound of the one-sided 90% CI for the hazard ratio (HR) had to be less than 1·18. Our trial (CHORUS) was designed in accordance with the EORTC 55971 trial,[21] with the intention of combining the results of the two separate trials in a later meta-analysis. The combined sample size was calculated to give a total of 1250 women between EORTC and CHORUS with 90% power; CHORUS had 65% power for comparison between the two treatment groups. The predefined trigger for analysis was the final assigned patient completing at least 2 years' follow-up in the trial. The primary analysis was done in January, 2013, presented at the 2013 American Society of Clinical Oncology annual meeting,[22] and updated for this publication after additional data resolution.

We did all primary analyses on an intention-to-treat basis. Because CHORUS was a non-inferiority trial, we did a sensitivity analysis of overall survival in the per-protocol population that comprised all women who began their assigned treatment. All estimates in this analysis are presented with a one-sided 90% CI, in accordance with the trial design, accompanied by two-sided 95% CIs for completeness.

We defined overall survival as the time from randomisation until death, with data for survivors censored at the time they were last known to be alive. Treatment groups were compared by use of a stratified log-rank test, adjusted for variables used to stratify the random assignments, and HRs were calculated from a Cox proportional hazards model that included the same

stratification factors. Proportional hazards assumptions were assessed with the Grambsch-Therneau test.[23]

We defined progression-free survival as the time from randomisation until the date of first progression or death, whichever occurred first. Women who did not die or have disease progression were censored at the date of their last visit. The primary analysis of progression-free survival only included progression events that were confirmed radiologically or clinically. A secondary analysis was done that also included progression events based on the rise in CA125 alone because this was allowed within the trial but was not routinely used, and events that were not clinically or radiologically confirmed.

We assessed global quality of life at 6 and 12 months using analysis of covariance with adjustment for baseline scores. No imputation was undertaken to deal with missing data at any timepoint, and only complete cases were included in the analysis. For comparisons of mean scores, a difference between the treatment groups of ten points was viewed as being clinically meaningful, whereas for comparison of results for an individual patient a change of five points was used.[24,25]

We compared and combined CHORUS and EORTC 55971 with the methods described by Parmar[26] and the HRs from the two trials. We used Stata version 12 or later for all analyses.

This trial is registered with ISRCTN, number ISRCTN74802813.

Role of the funding source

The funder of the study approved the study design but had no role in data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between March 1, 2004, and Aug 30, 2010, 552 women were recruited: 539 from 74 UK trial centres and 13 from two centres in New Zealand. Surgery was done at 64 trial centres. Two women were randomly assigned in error and withdrawn from the trial immediately after; one woman because she was unable to give informed consent to participation and the other because of an administrative error. These women were excluded from all analyses, and 550 women were therefore included in the final analyses (figure 1). 276 women were assigned to primary surgery, and 274 were assigned to primary chemotherapy.

Baseline characteristics were similar in both groups (table 1). In the primary-chemotherapy group, we confirmed epithelial ovarian, fallopian tube, or primary peritoneal cancer by laparoscopy in 45 (16%) of 274 women image-guided biopsy samples in 114 (42%), and cytology in 112 (41%). After disease confirmation, 11 (4%) of 274 women had an alternative diagnosis (appendix).

At the time of data cutoff (May 31, 2014), 451 of 550 women were known to have died: 231 in the primary-surgery group and 220 in the primary-chemotherapy group. The median duration of follow-up for the 99 surviving women was 4·4 years (IQR 3·5–6·1). Most deaths were due to ovarian cancer (399 women [88%]), four (1%) attributed to treatment and 48 (11%) to other causes (appendix).

Survival was similar in both groups although lower than predicted (figure 2). The 3 year survival rate was 32% in the primary-surgery group versus 34% with primary chemotherapy, and median overall survival was 22·6 months and 24·1 months, respectively. The HR for death in the intention-to-treat population was 0·87 in favour of women assigned to primary chemotherapy (upper bound of the one-sided 90% CI 0·98 [95% CI 0·72–1·05]), excluding the predefined non-inferiority boundary of 1·18.

	Primary surgery (n=255)	Primary chemotherapy (n=219)	Total (n=474)
FIGO stage			
IIA	2 (1%)	0 (0%)	2 (<1%)
IIB	5 (2%)	0 (0%)	5 (1%)
IIC	5 (2%)	7 (3%)	12 (3%)
IIIA	7 (3%)	7 (3%)	14 (3%)
IIIB	8 (3%)	13 (6%)	21 (5%)
IIIC	175 (72%)	145 (71%)	320 (72%)
IV	41 (17%)	31 (15%)	72 (16%)
Missing or unobtainable data	12	16	28
Histology			
High-grade serous	184 (74%)	150 (71%)	334 (73%)
Low-grade serous	10 (4%)	9 (4%)	19 (4%)
Serous not specified*	25 (10%)	26 (12%)	51 (11%)
Mucinous	2 (1%)	4 (2%)	6 (1%)
Endometrioid	11 (4%)	5 (2%)	16 (3%)
Clear cell	4 (2%)	13 (6%)	17 (4%)
Mixed	2 (1%)	0 (0%)	2 (<1%)
Other†	12 (5%)	3 (1%)	15 (3%)
Missing or unobtainable data	5	9	14
Differentiation			
Poor	165 (75%)	149 (79%)	314 (77%)
Intermediate	43 (19%)	27 (14%)	70 (17%)
Well	13 (6%)	12 (6%)	25 (6%)
Missing data	34	31	65

Data are n (%). This table includes only women who had surgery. Exclusions are, from the primary surgery group: 10 who had no treatment, and 11 who had no surgery after chemotherapy; from the primary chemotherapy group: 19 who had treatment for other disorders or withdrew from the study, and 36 who had no surgery after chemotherapy. FIGO=International Federation of Gynaecology and Obstetrics. *Tumour grade was not reported in these cases (nsp=not specified). Pathology was reported by local pathologists and not centrally reviewed. On the basis of the typical frequency of histological subtypes, most of these cases were probably high-grade serous. †Other types of tumour were diagnosed. In the primary surgery group there were five gastrointestinal cancers, two borderline ovarian tumours, one germ-cell tumour, one Krukenberg tumour, one carcinoid tumour, and one endometrioid ovarian cancer with a synchronous stage IIIA endometrioid endometrial cancer. One woman had no evidence of malignancy. In the primary chemotherapy group, there was one borderline ovarian tumour, one fibrothecoma, and one moderately differentiated adenocarcinoma consistent with primary peritoneal or ovarian origin.

Table 2: **Postsurgery FIGO stage and histological diagnosis**

	Primary surgery (n=255)	Primary chemotherapy (n=219)	Total (n=474)
Median length of operation (min)	120 (12–450, 80–161)	120 (30–330, 90–155)	120 (12–450, 89–160)
Missing data	27	32	58
Residual disease (all patients)			
0 cm	39 (17%)	79 (39%)	118 (27%)
≤1 cm	57 (24%)	68 (34%)	125 (29%)
>1 cm	137 (59%)	54 (27%)	191 (44%)
Missing data	22	18	40
Residual disease (stage III patients)			
0 cm	29 (16%)	64 (43%)	93 (28%)
≤1 cm	44 (25%)	49 (33%)	93 (28%)
>1 cm	105 (59%)	36 (24%)	141 (43%)
Missing	15	13	28
Residual disease (stage IV patients)			
0 cm	10 (18%)	15 (29%)	25 (23%)
≤1 cm	13 (24%)	19 (37%)	32 (30%)
>1 cm	32 (58%)	18 (35%)	50 (47%)
Missing data	7	5	12

Data are median (range, IQR) or n (%).This table includes only women who had surgery; patients with missing data are excluded.

Table 3: **Surgery details**

	Primary surgery (n=255)	Primary chemotherapy (n=219)	Total (n=474)
Any grade 3 or 4 adverse event	60 (24%)	30 (14%)*	90 (20%)
Haemorrhage	8 (3%)	14 (7%)	22 (5%)
Venous thromboembolism	5 (2%)	0 (0%)	5 (1%)
Dysrhythmia	3 (1%)	0 (0%)	3 (1%)
Hypotension	6 (2%)	2 (1%)	8 (2%)
Fever (no infection)	0 (0%)	0 (0%)	0 (0%)
Diarrhoea	4 (2%)	2 (1%)	6 (1%)
Intestinal or rectal fistula	2 (1%)	1 (<1%)	3 (1%)
Nausea	12 (5%)	1 (<1%)	13 (3%)
Vomiting	12 (5%)	1 (<1%)	13 (3%)
Bowel obstruction	2 (1%)	1 (<1%)	3 (1%)
Gastrointestinal pain	4 (2%)	2 (1%)	6 (1%)
Vaginal or vesicovaginal fistula	1 (<1%)	1 (<1%)	2 (<1%)
Urethral obstruction	1 (<1%)	0 (0%)	1 (<1%)
Weight loss	0 (0%)	0 (0%)	0 (0%)
Infection	16 (6%)	6 (3%)	22 (5%)
Missing data	3	10	13
Death within 28 days after surgery	14 (6%)	1 (<1%)	15 (3%)
Disease progression	5 (2%)	..	..
Pulmonary emboli	2 (<1%)	1 (<1%)	..
Sepsis	3 (1%)	..	..
Problems related to fluid balance or renal failure	2 (<1%)	..	..
Coagulopathy or disseminated intravascular coagulation	1 (<1%)	..	..
Respiratory failure	1 (<1%)	..	..

Data are n (%). This table includes only women who had surgery. *Fisher's exact p value, comparing overall grade 3 or 4 events between groups=0·007.

Table 4: **Postoperative grade 3 or 4 adverse events and mortality**

Statistics for progression-free survival were similarly in favour of the primary chemotherapy group with medians of 12·0 months versus 10·7 months for the primary-surgery group. The HR for progression-free survival was 0·91 (95% CI 0·76–1·09). Results of the secondary analysis for progression-free survival that included measurements of CA125 only, and unconfirmed progression events, were similar (appendix). The CI for progression-free survival allowed us to rule out a detriment of more than 8% with the primary-chemotherapy group, well within the non-inferiority boundary set for overall survival.

The per-protocol population, comprised of all women who began their allocated treatment:, included 251 women in the group assigned to primary surgery and 253 assigned to primary chemotherapy. Of these women, 209 in the primary-surgery group and 203 in the primary-chemotherapy group were known to have died at the time of data freeze. Median survival was 23·7 months in the primary-surgery group versus 25·8 months (HR 0·89 in favour of primary chemotherapy, 95% CI 0·73–1·08). Survival data in the per-protocol population were consistent with data in the intention-to-treat population (appendix). We investigated exploratory subgroups of baseline characteristics (age, stage, tumour size, performance status, and planned chemotherapy) and did not identify good evidence that any subgroups benefited more or less from primary chemotherapy (appendix). The volume of residual disease was prognostic in both the primary-surgery and primary-chemotherapy groups (appendix).

251 (91%) of 276 women assigned to primary surgery started treatment as allocated and 212 (77%) then had postoperative chemotherapy (figure 1). In the

primary-chemotherapy group, 253 (92%) of 274 women started their allocated treatment and 217 (79%) then underwent delayed surgery. The median duration of treatment was 22 weeks in both groups (primary surgery IQR 17–24 weeks, primary chemotherapy IQR 19–24 weeks; appendix).

Definitive stage and histological diagnosis were obtained after surgery (table 2). 392 of 446 women (88%) had FIGO stage IIIC or IV disease.

The median operation time was 120 min in both groups. Data for residual disease were available for 232 of the 255 women who had surgery in the primary-surgery group and 201 of the 219 women who had surgery in the primary-chemotherapy group. Debulking to less than 1 cm residual disease was achieved in 96 women (41%) in the primary-surgery group versus 147 women (73%) in the primary-chemotherapy group, p=0·0001; and to no macroscopic disease in 39 women (17%) who had primary surgery versus 79 women (39%) who had primary chemotherapy (p=0·0001; table 3).

Baseline global quality of life scores were available for 230 patients assigned to primary surgery and 227 assigned to primary chemotherapy. At baseline, primary-surgery patients had a mean score of 48·4 (SD 26·23), and primary-chemotherapy patients had a mean of 52·3 (25·70). At 6 months, the mean score had improved to 61·5 (SD 23·63, 103 patients) for primary-surgery patients and 69·1 (18·71, 114 patients) for primary-chemotherapy patients; at 12 months the mean scores were 61·8 (SD 24·16, 64 patients) for primary surgery and 67·5 (22·38, 69 patients) for primary chemotherapy. Analysis of variance, adjusted for baseline scores, showed that the primary-chemotherapy group had slightly higher scores than the primary-surgery group at 6 months (means difference –7·6 [95% CI –13·3 to –1·9], p=0·0438) and 12 months (means difference –5·7 [95% CI –13·6 to 2·3], p=0·0515). More patients who received primary chemotherapy showed improvement in global quality of life of at least 5 points than patients who received primary surgery, at 6 months (64/102, 63% *vs* 52/95, 55%, p=0·311) and 12 months (37/61, 61% *vs* 25/57, 44%, p=0·097), although neither difference was significant.

Postoperative adverse event data were available for 252 of 255 women in the primary-surgery group and 209 of 219 women in the primary-chemotherapy group. The primary-surgery group had more grade 3 or 4 adverse events (60 [24%]) than the primary-chemotherapy group (30 [14%], p=0·007; table 4). The most common grade 3 or 4 adverse event was haemorrhage in both groups (8 women [3%] in the primary-surgery group *vs* 14 [6%] in primary chemotherapy). Additionally, fewer women were discharged from hospital within 14 days after surgery in the primary-surgery group compared with primary chemotherapy (198/249, 80% *vs* 197/211, 93%, p<0·0001), and there were more postoperative deaths in the primary-surgery group within 28 days than in the primary-chemotherapy group (14 of 255 women [6%] *vs* one of 219 women [<1%], p=0·001, table 4).

	Primary surgery (n=228)	Primary chemotherapy (n=254)	Total (n=482)
Chemotherapy regimen (first cycle)			
Carboplatin monotherapy	89 (39%)	75 (30%)	164 (34%)
Carboplatin plus paclitaxel	138 (61%)	178 (70%)	316 (66%)
Carboplatin plus other chemotherapy drug	0 (0%)	1 (<1%)	1 (<1%)
No carboplatin (other cytotoxic drugs used)	1 (<1%)	0 (0%)	1 (<1%)
Number of cycles of carboplatin received			
0	1 (<1%)	0 (0%)	1 (<1%)
1	8 (4%)	7 (3%)	15 (3%)
2	10 (4%)	7 (3%)	17 (4%)
3	6 (3%)	22 (9%)	28 (6%)
4	4 (2%)	5 (2%)	9 (2%)
5	11 (5%)	12 (5%)	23 (5%)
6	188 (82%)	201 (79%)	389 (81%)
>10% change to carboplatin dose			
Only one cycle	8 (4%)	7 (3%)	15 (3%)
Dose modified	87 (38%)	100 (39%)	187 (39%)
Dose not modified	132 (58%)	147 (58%)	279 (58%)
>10% change to paclitaxel dose			
Only one cycle	5 (4%)	4 (2%)	9 (3%)
Dose modified	36 (26%)	49 (28%)	85 (127%)
Dose not modified	97 (70%)	125 (70%)	222 (70%)
Did not receive paclitaxel	90	76	166
Delays to chemotherapy*			
No	143 (63%)	182 (72%)	325 (68%)
Yes	84 (37%)	71 (28%)	155 (32%)
Missing data	0	1	1

Data are n (%). This table includes only women who had chemotherapy. 36 women had no surgery after chemotherapy. *Delay defined as cycle starting more than 28 days after the previous cycle, more than 28 days after randomisation, or more than 56 days after surgery.

Table 5: **Chemotherapy received**

Chemotherapy data were available for 228 women in the primary-surgery group and 254 in the primary-chemotherapy group (table 5); most women received carboplatin plus paclitaxel. One patient had a yolk sac tumour at surgery and went on to receive chemotherapy with bleomycin, etoposide, and cisplatin. Most women who started chemotherapy received six cycles and did not need a dose modification. Toxic effects were as expected for carboplatin-based chemotherapy: 110 of 225 women (49%) in the primary-surgery group and 102 of 253 women (40%) in the primary-chemotherapy group had a grade 3 or 4 toxic effect from chemotherapy (p=0·0654), mostly uncomplicated neutropenia (20% and 16%, respectively) (appendix). One fatal toxic effect, neutropenic sepsis, occurred in the primary-chemotherapy group.

Discussion

Our study (CHORUS) showed that for women with stage III or IV ovarian cancer with a high tumour burden, survival after receiving primary chemotherapy followed by surgery was not inferior compared with receiving primary surgery, and surgical morbidity and mortality were significantly reduced (panel).

The median survival of 22–24 months was less than expected, but was similar in both groups. The explanation for the less-than-expected overall survival might be attributed to the older median age of recruited patients (65 years), that 77% of tumours were poorly differentiated, and a substantial proportion of women had poor performance status of 2 or 3 (19%). Compared with first-line phase 3 trials in women with advanced ovarian cancer, such as the MITO 7-ENGOT-Ov-10 study[27] (median age 59 years), ICON7[28] (median age 57 years) and surgical trials targeting advanced ovarian cancer such as EORTC 55971[21] (median age 62 years), and the interval debulking studies Gynaecological Oncology Group study[29] (median age 57 years), and EORTC[6] (median age 59 years), the patients recruited to CHORUS had a higher average age. Equally, the proportion of women with poor performance status was greater than other similar trials. Thus, CHORUS assessed the timing of surgery in a group of patients with more adverse prognostic features than in other clinical trials.

In view of the widely recognised association between the volume of postoperative disease, which is usually expressed as a diameter of residual tumour nodules, and prognostic outlook, careful intraoperative assessment was done at 13 sites in the abdominal cavity. The proportion of patients whose disease was cytoreduced to 1 cm or less in the primary-surgery and primary-chemotherapy groups were 41% and 73%, respectively, similar to data from the EORTC trial[6] in which the equivalent statistics were 41·6% and 80·6%, respectively. Similar results pertain to the rates of complete cytoreduction. Despite differences in recorded operating times, the effectiveness of debulking surgery in these two trials was the same. Because no randomised trials have yet compared standard surgery with aggressive or radical surgery, whether the CHORUS patients would have benefited from longer and more aggressive attempts at debulking surgery is unclear.[30]

The postsurgical mortality in the primary-chemotherapy group was less than 1%, whereas 6% of patients in the primary-surgery group died within 28 days of surgery. This result was higher than expected, although it still lies within the range reported from reviews[31,32] that describe the surgical management of elderly women with advanced ovarian cancer. These figures can probably be attributed to the poor performance status of the women recruited to the trial and the improvement in their general condition associated with primary chemotherapy. Had there been difficulties with patient care, patients who had received preoperative chemotherapy might also have incurred greater postsurgical morbidity and mortality, but this was not the case. Indeed, CHORUS shows that primary chemotherapy given before delayed surgery is associated with significantly fewer grade 3 and 4 postsurgical morbidities, p<0·007. Additionally, in the primary-chemotherapy group, 93% of patients were discharged within 14 days from operation, compared with only 80% in the primary-surgery group, which is clearly important in an era when treatment costs are of increasing concern.

The chemotherapeutic regimen given most often was carboplatin plus paclitaxel. The decision to use combination or monotherapy was at the discretion of the attending medical oncologist and in accordance with national guidance, which states that the addition of paclitaxel to treatment is not mandatory after the findings of the ICON3 trial.[33] The findings from this trial were that monotherapy with carboplatin and chemotherapy with cyclophosphamide, adriamycin, and cisplatin were as effective as paclitaxel plus carboplatin as first-line treatment for women needing chemotherapy for ovarian cancer, and that the favourable toxicity profile for carboplatin monotherapy suggests that it is a reasonable option as first-line chemotherapy for this cancer type. The use of combination chemotherapy also emphasises the effect of performance status on clinical decision making; ie, in the first cycle of

Panel: Research in context

Systematic review

We searched PubMed and the abstracts of major conferences (American Society of Clinical Oncology, International Gynaecological Cancer Society, and the European Society of Gynaecological Oncology), and manually searched reference lists for relevant English-language articles published between Jan 1, 1980, to Oct 30, 2014. PubMed search terms used were "ovarian cancer", "surgery", "neoadjuvant chemotherapy", and "primary chemotherapy". We found only one relevant randomised trial,[21] about primary surgery or neoadjuvant chemotherapy in advanced ovarian cancer, which resulted in similar survival patterns.

Interpretation

CHORUS is the second trial to investigate timing of surgery in the first-line treatment of advanced ovarian cancer. We recruited a population with a poor outlook; patients were older and had a worse performance status than patients in other trials where patients were recruited after surgery. Our findings were consistent with the results of the EORTC 55971 trial (figure 3).[21] These two trials confirm that primary chemotherapy before delayed surgery is an alternative clinical management strategy to primary surgery, which could reduce morbidity in many women with advanced ovarian cancer.

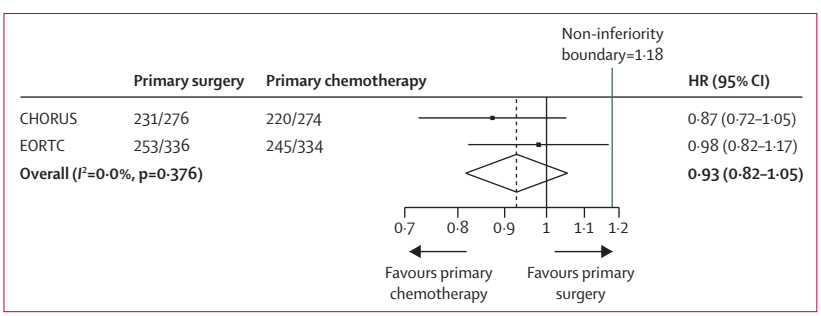

Figure 3: **Forest plot of overall survival in CHORUS and EORTC 55971**
HR=hazard ratio.

chemotherapy only 56% of women with a WHO score of 2 or 3 were given combination therapy, compared with 72% of women with a score of 0 or 1.

In summary, CHORUS shows that for patients with advanced ovarian cancer and a poor performance status profile, primary chemotherapy followed by delayed surgery are associated with similar overall survival as patients given primary surgery. The associated reduction in treatment-associated morbidity and mortality, combined with a trend towards better quality of life suggests that primary chemotherapy is a valid option for treating these patients.

Contributors

SK and AMS were the chief investigators in this trial. SK, GCJ, A-MS, and MP designed the trial and wrote the protocol. SK, A-MS, GCJ, HK, TL, DL, TP, SB, MM, MN, JHo, and MP were trial management group members. SK, GCJ, HK, TL, DL, TP, SD, SE, JT, and JHe recruited and treated participants within the trial. GM provided pathology input and review. SB and MM coordinated the trial at the MRC. MN and MP were the trial statisticians. SK, JHo, and MN wrote the report, and MN analysed the data and constructed the figures. All authors were involved in data interpretation, manuscript review, and approval of the final manuscript.

Declaration of interests

JHo, MN, SB, MM, and MP are employed by the Medical Research Council. The other authors declare no competing interests.

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