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DOI:

[10.1016/S1470-2045\(18\)30566-7](https://doi.org/10.1016/S1470-2045(18)30566-7)

Document Version

Accepted author manuscript

[Link to publication record in Manchester Research Explorer](#)

Citation for published version (APA):

Jayson, G. (2018). Neoadjuvant chemotherapy versus debulking surgery in advanced tubo-ovarian cancers: pooled analysis of individual patient data from the EORTC 55971 and CHORUS trials. *Lancet Oncology*, 19(12), 1680-1687. [https://doi.org/10.1016/S1470-2045\(18\)30566-7](https://doi.org/10.1016/S1470-2045(18)30566-7)

Published in:

Lancet Oncology

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Neoadjuvant chemotherapy versus upfront debulking surgery in advanced tubo-ovarian cancers: meta-analysis of individual patient data from the EORTC and CHORUS trials

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Summary

Background Individual patient data from two randomised trials comparing neoadjuvant chemotherapy with upfront debulking surgery in advanced tubo-ovarian cancer were analysed to examine long-term outcomes for patients and to identify any preferable therapeutic approaches for subgroup populations.

Methods We did a preplanned meta-analysis of individual patient data from the European Organisation for Research and Treatment of Cancer (EORTC) 55971 trial (NCT00003636) and the Medical Research Council Chemotherapy Or Upfront Surgery (CHORUS) trial (ISRCTN74802813). In the EORTC trial, eligible women had biopsy-proven International Federation of Gynecology and Obstetrics (FIGO) stage IIIC or IV invasive epithelial tubo-ovarian carcinoma. In the CHORUS trial, inclusion criteria were similar to those of the EORTC trial, and women with apparent FIGO stage IIIA and IIIB disease were also eligible. The main aim of the meta-analysis was to show non-inferiority in overall survival with neoadjuvant chemotherapy compared with upfront debulking surgery, using the reverse Kaplan-Meier method. Tests for heterogeneity were based on Cochran's Q heterogeneity statistic.

Findings Data for 1220 women were included in the meta-analysis, 670 from the EORTC trial and 550 from the CHORUS trial. 612 women were randomly allocated to receive upfront debulking surgery and 608 to receive neoadjuvant chemotherapy. Median follow-up was 7.6 years (IQR 6.0–9.6; EORTC, 9.2 years [IQR 7.3–10.4]; CHORUS, 5.9 years [IQR 4.3–7.4]). Median age was 63 years (IQR 56–71, range 25–88) and median size of the largest metastatic tumour at diagnosis was 8 cm (IQR 4.8–13.0, range 0–50). 55 (5%) women had FIGO stage II–IIIB disease, 831 (68%) had stage IIIC disease, and 338 (28%) had stage IV disease, with staging data missing for 104 (9%) women. [A: please check numbers of women a] In the entire population, no difference in median overall survival was noted between patients who underwent neoadjuvant chemotherapy and upfront debulking surgery (27.6 months [IQR 14.1–51.3] and 26.9 months [12.7–50.1], respectively; hazard ratio [HR] 0.97, 95% CI 0.86–1.09, p=0.586). [A: data in Results were different (I think you had added those for PFS), I've amended to match Results; please check carefully] Median overall survival for EORTC and CHORUS patients was significantly different at 30.2 months (IQR 15.7–53.7) and 23.6 months (10.5–46.0), respectively (HR 1.20, 95% CI 1.06–1.36; p=0.004), but was not heterogeneous (Cochran's Q, p=0.17). Variable outcomes were noted in some cohorts.

Interpretation Long-term follow-up data substantiate previous results showing [A: OK change for "confirm"] that neoadjuvant chemotherapy and upfront debulking surgery result in similar overall survival in advanced tubo-ovarian cancer, with preferential outcomes [A: can you be specific?] in some [A: which?] patients. This meta-analysis, with long-term follow-up, shows that neoadjuvant chemotherapy is a valuable treatment option for patients with stage IIIC–IV tubo-ovarian cancer, particularly in patients with a high tumour burden at presentation or poor performance status.

Funding National Cancer Institute, Vlaamse Liga tegen kanker (Flemish League against Cancer), Cancer Research UK, Royal College of Obstetricians and Gynaecologists, Medical Research Council (MRC) Clinical Trials Unit, and MRC. [A: please check]

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Introduction

[A: we have edited your Article to achieve consistency with Lancet style, avoid repetition, enhance readability, and reduce length. We minimise use of abbreviations] More than 70% of women with carcinoma of the ovary,

fallopian tube, or peritoneum (hereafter referred to as tubo-ovarian cancer) present with advanced disease and usually have a very poor prognosis.¹ Since Griffiths² reported in 1975 the association between low residual tumour load and improved survival after debulking

Lancet Oncol 2018

Published Online
October 30, 2018
[http://dx.doi.org/10.1016/S1470-2045\(18\)30566-7](http://dx.doi.org/10.1016/S1470-2045(18)30566-7)

See Online/Comment
[http://dx.doi.org/10.1016/S1470-2045\(18\)30566-7](http://dx.doi.org/10.1016/S1470-2045(18)30566-7)
PII

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[A: please ask all authors to check their affiliation is correct and provide their department name (if not already done so)]

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Research in context

Evidence before this study

Before the start of this analysis on June 6, 2015, and before submission of this Article on March 11, 2018, we searched PubMed with no language restrictions using the keywords ["ovarian cancer"] AND ["randomized" OR "randomised" do you mean "[randomized" OR "randomised"] or vice versa"?] AND ["clinical trial"] AND ["neoadjuvant chemotherapy" OR "primary chemotherapy"] to identify publications that analysed the role of neoadjuvant chemotherapy followed by interval debulking in comparison with upfront debulking surgery followed by chemotherapy in patients with advanced ovarian cancer. We found that survival data from randomised studies had been published for only two trials: the European Organisation for Research and Treatment of Cancer (EORTC) 55971 trial, and the Medical Research Council Chemotherapy or Upfront Surgery (CHORUS) trial. Both trials concluded that neoadjuvant chemotherapy followed by interval debulking surgery was not inferior to primary debulking surgery followed by chemotherapy in patients with International Federation of Gynecology and Obstetrics (FIGO) stage IIIC or IV ovarian carcinoma. In both studies, no subgroup analyses showed a difference in survival between the two treatment groups. In addition to these two trials, the SCORPION and JCOG0602 randomised trials concluded that perioperative morbidity was better with interval debulking after neoadjuvant chemotherapy than after primary debulking surgery.

Added value of this study

We report a preplanned individual patient data meta-analysis of the EORTC and CHORUS randomised trials, to examine the long-term outcomes in patients with advanced ovarian cancer treated with neoadjuvant chemotherapy followed by interval debulking versus upfront debulking surgery followed by chemotherapy. We also did subgroup analyses on the basis of stratification factors that were common to both trials—ie,

randomising centre, largest tumour size (excluding ovaries) before surgery (<5 cm, ≥5 to ≤10 cm, >10 cm to ≤20 cm, or >20 cm), and clinical FIGO stage. Our analysis shows that, with longer median follow-up, both neoadjuvant chemotherapy followed by interval debulking surgery and upfront debulking surgery followed by chemotherapy are associated with similar overall survival and progression-free survival. We also show that neoadjuvant chemotherapy is associated with better progression-free survival and overall survival in women presenting with FIGO stage IV disease, and patients with FIGO stage IIIC disease with extrapelvic metastases smaller than 5 cm have better progression-free survival after upfront debulking.

Implications of all the available incidence

[A: can you add a sentence to put your findings in the context of all the available evidence? This section should not simply restate your conclusion. We have reworded some sections. Please check carefully] The findings of this analysis should be applied in the context of each patient's clinical picture. Participants in this study had FIGO stage IIIC or IV tubo-ovarian cancer with metastatic disease with a high tumour burden at presentation, and many had a poor performance status. This individual patient data meta-analysis suggests that neoadjuvant chemotherapy should be the standard of care for most patients with stage IV tubo-ovarian cancer and that primary surgery should only be undertaken in exceptional circumstances in patients with FIGO stage IV disease on an individual basis. However, women with FIGO stage IIIC disease with extrapelvic metastases smaller than 5 cm had a significantly better progression-free survival with upfront surgery than with neoadjuvant chemotherapy, so these patients should first be considered for primary debulking surgery. For patients with FIGO stage IIIB or lower disease, there is no evidence to support the use of neoadjuvant chemotherapy instead of primary surgery.

surgery, primary surgery has been an essential, or even mandatory, therapeutic strategy in clinical practice.³ [A: please check reference numbering, you had referenced Griffiths as number 2 but it was originally 3 in the list] However, to date, no randomised controlled trials have shown that primary debulking surgery improves the prognosis of patients with advanced tubo-ovarian cancer.

An alternative approach to primary debulking surgery is neoadjuvant chemotherapy, administered before attempting cytoreductive surgery. In 2010, the European Organisation for Research and Treatment of Cancer (EORTC) published the first findings from a trial comparing neoadjuvant chemotherapy followed by interval debulking surgery with upfront debulking surgery (EORTC 55971).⁴ This study showed both treatment strategies had similar overall survival and progression-free survival in women with International Federation of Gynecology and Obstetrics (FIGO) stage IIIC or IV tubo-ovarian cancer, and operative and

postoperative morbidity was lower with neoadjuvant chemotherapy. These results were later substantiated in the randomised Medical Research Council (MRC) Chemotherapy Or Upfront Surgery (CHORUS) trial,⁵ leading to the acceptance of neoadjuvant chemotherapy followed by interval debulking surgery as an alternative to upfront debulking surgery in women with stage IIIC and IV tubo-ovarian cancer.⁶ However, the selection of women with advanced ovarian cancer for neoadjuvant chemotherapy or upfront debulking surgery remains controversial.⁷

In 2003, while accrual for the EORTC study was ongoing but before the start of the CHORUS trial, the EORTC and MRC planned the current analysis with the aim of analysing long-term follow-up of both trials and identifying any subgroups of women that might benefit from neoadjuvant chemotherapy compared with upfront debulking surgery. Herein, we report the results of this analysis.

Methods

Study design and data collection

We did a preplanned meta-analysis of individual patient data from the EORTC 55971 trial⁴ and the MRC CHORUS trial,⁵ according to PRISMA guidelines (figure 1, appendix pp 117–120).⁸ Eligibility criteria for these trials and their study designs have been reported elsewhere.^{4,5} The appendix includes the protocols of the EORTC (pp 11–69) and CHORUS (pp 70–116) trials. A list of recruiting sites and investigators is also in the appendix (pp 121–123).

Briefly, in the EORTC trial,⁴ women were eligible if they had had biopsy-proven FIGO stage IIIC or IV invasive epithelial ovarian, primary peritoneal, or fallopian tube carcinoma. If a biopsy specimen was not available, fine-needle aspiration showing an adenocarcinoma was acceptable under the following conditions: presence of a pelvic adnexal mass, presence of extrapelvic metastases of 2 cm or larger (measured during diagnostic laparoscopy or laparotomy, or if laparoscopy or laparotomy was not done, on the basis on CT findings), and a ratio of cancer antigen 125 (CA125) to carcino-embryonic antigen (CEA) greater than 25; biopsy findings were mandatory for inclusion in the trial if any of these three criteria was not present. If the CA125:CEA ratio was less than 25, investigations to exclude a gastrointestinal carcinoma were necessary before entry. In the CHORUS trial,⁵ inclusion criteria were similar to those in the EORTC trial, and women with apparent FIGO stage IIIA and IIIB were also eligible. The size of the largest metastasis was estimated on the basis of CT imaging only in the CHORUS trial.

In both trials, participants were randomly allocated to receive either upfront debulking surgery followed by at least six courses of platinum-based chemotherapy, or three courses of neoadjuvant platinum-based chemotherapy followed by interval debulking surgery followed by at least three additional courses of platinum-based chemotherapy.^{4,5} In women allocated to receive upfront debulking surgery whose surgery was completed without optimum cytoreduction, interval debulking surgery was permitted, and these patients were included for analyses in the upfront debulking surgery group. In the EORTC trial, [A: addition correct?] randomisation used a minimisation technique and was stratified by the following factors: institution, method of biopsy (image-guided, laparoscopy, laparotomy, or fine-needle aspiration), FIGO stage IIIC or IV disease, and largest tumour size (excluding ovaries) before surgery (<5 cm, ≥5 to <10 cm, >10 to ≤20 cm, or >20 cm). In the CHORUS trial, [A: addition correct?] randomisation used a minimisation method with a random element, which stratified patients according to randomising centre, largest radiological tumour size, clinical FIGO stage, and prespecified chemotherapy regimen [A: this sentence seems like repetition, unless the first sentence is about the EORTC trial and this sentence is about CHORUS (as I have edited, by assumption)]. Can you please

Figure 1: PRISMA flow diagram

EORTC=European Organisation for Research and Treatment of Cancer 55971 trial. CHORUS=Medical Research Council Chemotherapy Or Upfront Surgery trial.

	EORTC (n=670)	CHORUS (n=550)	Total (n=1220)
Age (years)	62 (54–69)	65 (58–72)	63 (56–71)
Range	25–86	26–88	25–88
Largest metastatic tumour size (mm)	80 (42–140)	80 (50–120)	80 (48–130)
Range			0–500
CA125 at entry (kU/L)	116 (41–171)	10 (1–100)	1089 (431–2599)
Range	15–41 456	26–39 323	15–41 456

Data are median (IQR), unless otherwise indicated. CA125=cancer antigen 125. CHORUS=Medical Research Council Chemotherapy Or Upfront Surgery trial. EORTC=European Organisation for Research and Treatment of Cancer 55971 trial. [A1: please provide IQRs with the median]

Table 1: Baseline characteristics, by study

double-check the wording?]. For details on size of residual tumour, residual tumour per country, type of surgery, number of cycles and type of chemotherapy, and time to (re)initiation of chemotherapy, we refer to the original reports.^{4,5}

Procedures

Our analysis was designed in 2003 by the chief investigators of the EORTC and CHORUS trials (IV and SK) and members of the EORTC and MRC trial managing committees. Trial databases were set up to ensure appropriate comparable information was gathered in both trials to allow the planned individual patient data meta-analysis. Women were followed up until database lock. Data from CHORUS were transferred to EORTC headquarters [A: please add address] and

	Upfront debulking surgery (n=612)	Neoadjuvant chemotherapy (n=608)	Total (n=1220)
Age (years)	63 (55–71)	64 (57–70)	63 (56–71)
Range	25–87	33–88	25–88
Largest metastatic tumour size (mm)	80 (49–130)	80 (47–125)	80 (48–130)
Range	0–430	0–500	0–500
CA125 at entry (kU/L)	1039 (409–2548)	1137 (446–2606)	1089 (431–2599)
Range	16–39 323	15–41 456	15–41 456

Data are median (IQR), unless otherwise indicated. CA125=cancer antigen 125.

Table 2: Baseline characteristics, by allocated treatment

Figure 2: Overall survival and progression-free survival, by treatment

[A: please provide HR and 95% CI for each plot; numbers at risk at 10 years are missing, please add]

analysed by us [A: who?] in cooperation with the EORTC statistician (CC). We derived median follow-up with the EORTC standard method, which uses the reverse

1 Kaplan-Meier method and calculates time-to-events for all patients; in the original CHORUS paper, however, only the median duration of follow-up for surviving patients was calculated. [A: Ok as edited?]

5 The primary outcome of our meta-analysis was overall survival, and the prespecified secondary endpoint was progression-free survival. Prespecified subgroup analyses were done on the basis of stratification factors that were common to both trials: randomising centre, 10 largest tumour size (excluding ovaries) before surgery (<5 cm, ≥5 to ≤10 cm, >10 to ≤20 cm, or >20 cm), and clinical FIGO stage. Definitions for overall survival and progression-free survival have been published elsewhere.⁴

Statistical analysis

At the planning stage, we estimated that the pooled dataset would contain between 800 and 900 events (deaths). Assuming a median overall survival of 3 years, 20 this number of events allowed assessment of non-inferiority,^{9,10} with a one-sided type I error of 0.05 and a power of 80%, with inferiority regarded as an increase of more than 18–19% in hazard. Similarly, the estimated number of events would allow 90% power in detecting a 25 hazard increase of 22–23%. [A: text in red added to explain “it” and “this”] Applying a two-sided test of superiority at 5%, the dataset would allow detection of an 18% increase in hazard with 80% power.

The principal analysis was done on an intention-to-treat basis. Median overall survival and progression-free survival were estimated by the Kaplan-Meier method and compared via the log-rank test. Hazard ratio (HR) estimates and their 95% CIs were obtained from a Cox proportional hazards model. In those subgroups for 35 which the proportional hazards assumption was violated, restricted mean survival times were calculated to provide a more useful [A: more useful than what?] general measure to report the average survival times between the two treatment arms.¹¹ Multivariable time-to-event analyses were done using a Cox proportional hazards model, with univariate screening followed by a multivariable stepwise selection procedure.¹² All baseline characteristics and results were checked for homogeneity between the two studies and stratified per trial when 45 possible. Tests for heterogeneity in progression-free survival or overall survival were based on Cochran’s Q heterogeneity statistic. All analyses were done with SAS, version 9.4.

Role of funding source

The funders of the studies had no role in study design, data collection, data analysis, data interpretation, or writing of the report. CC, MN, and MKBP had full access to MRC CHORUS raw data. CC had full access to EORTC 55971 raw data. The corresponding author had full access to all data in the study and had final responsibility for the decision to submit for publication.

Results

Patients' data from both trials were updated and merged into one database (database lock for EORTC was on June 6, 2015; for CHORUS, June 3, 2014), which contained 1220 patients with tubo-ovarian cancer who had been randomly allocated to receive either upfront debulking surgery (n=612) or neoadjuvant chemotherapy (n=608). Total combined recruitment lasted almost 12 years (in EORTC, 670 patients from Oct 12, 1998 to Nov 29, 2006; in CHORUS, 550 patients from March 5, 2004, to Aug 26, 2010). Median follow-up was 7.6 years (IQR 6.0–9.6 years; EORTC, 9.2 years [IQR 7.3–10.4]; CHORUS, 5.9 years [IQR 4.3–7.4]). Characteristics of patients by study and study group are summarised in tables 1 and 2, respectively. Pretreatment characteristics were well balanced between both treatment groups. Median age was 63 years (IQR 56–71, range 25–88) and median size of the largest metastatic tumour at diagnosis was 8 cm (IQR 4.8–13.0, range 0–50). 55 (5%) women had FIGO stage II–IIIB disease, 831 (68%) had stage IIIC disease, and 230 (19%) had stage IV disease, with staging data missing for 104 (9%) women. [A: I've added these data from the Summary, to ensure the Results contain all data in the Summary]

Overall survival and progression-free survival for the entire population were similar with neoadjuvant chemotherapy and upfront debulking surgery, with median overall survival of 27.6 months (IQR 14.1–51.3) and 26.9 months (12.7–50.1), respectively (HR 0.97, 95% CI 0.86–1.09; p=0.568). [A: you had written in the next sentence (now deleted) 0.87; please check] and progression-free survival of 11.6 months (IQR 7.9–17.7) and 11.1 months (6.4–17.5), respectively (HR 0.89–xx; p=0.688; figure 2). [A: please add HR and 95% CI] The lower one-sided 95% CIs for overall survival and progression-free survival excluded the 18% non-inferiority margin.

Overall survival was significantly better in the EORTC trial as compared with the CHORUS trial (median 30.2 months [IQR 15.7–53.7] vs 23.6 months [10.5–46.9]; HR 1.20, 95% CI 1.06–1.36; p=0.004; figure 3), but progression-free survival was similar in the two trials (median 11.5 months [IQR 8.0–17.0] vs 10.9 months [6.1–18.1]; HR 0.96, 95% CI 0.86–1.08; p=0.531; appendix p 1). [A: I've deleted first page of your appendix because we add a title page later; please check p values in appendix, log-rank is p=0.530] Overall survival and progression-free survival according to trial and treatment groups are presented in the appendix (pp 2, 3). [A: please check p values in appendix, log-rank p differs in plot and table below plot] Cochran's Q for heterogeneity was not significant for either overall survival (p=0.17) or progression-free survival (p=0.32).

Median overall survival was significantly different for women with FIGO stage IV disease compared with those with stage III and II cancer (median 23.3 months [IQR 12.4–40.8] vs 30.0 months [15.6–55.7] and

Figure 3: Overall survival, by study

EORTC=European Organisation for Research and Treatment of Cancer 55 al. CHORUS=Medical Research Council Chemotherapy Or Upfront Surgery trial. [A: please provide HR and 95% CI; numbers at risk at 10 years are missing, please add]

Figure 4: Overall survival in patients with FIGO stage IV disease, by treatment

FIGO=International Federation of Gynecology and Obstetrics. [A: numbers at risk at 10 years are missing, please add]

45.4 months [31.6–recorded], respectively; for stage IV vs stage II, HR 2.75, 95% CI 1.49–5.08; for stage III vs stage II, 1.92, 95% CI 1.05–3.49; p<0.0001 for trend [A: OK? Is the p value across all groups?]; appendix p 4). [A: please check edits in red are correct; data match appendix, but original text was the other way around] Overall survival was similar with neoadjuvant chemotherapy and upfront debulking surgery in patients with stage IIIC disease (respectively, median 30.8 months [IQR 16.5–51.3] and

Figure 5: Progression-free survival and overall survival in patients with FIGO stage IIIC disease and a largest metastatic tumour size less than 5 cm at entry, by treatment
FIGO=International Federation of Gynecology and Obstetrics. [A: numbers at risk at 10 years are missing, please add]

	Restricted mean survival time (months)	95% CI
Overall survival		
Upfront debulking surgery	47.3	40.4–54.1
Neoadjuvant chemotherapy	39.3	33.9–44.8
Progression free survival		
Upfront debulking surgery	27.5	21.2–33.8
Neoadjuvant chemotherapy	17.0	13.8–20.2

FIGO=International Federation of Gynecology and Obstetrics.

Table 3: Estimates of restricted mean survival time in patients with FIGO stage IIIC disease and largest metastatic tumour size less than 5 cm at study entry

28.4 months [14.1–55.7]; HR 1.04, 95% CI 0.90–1.21; $p=0.569$; appendix p 5). Progression-free survival was also similar with neoadjuvant chemotherapy and upfront debulking surgery in patients with stage IIIC disease (median 12.2 months [IQR 8.4–18.3] and 11.7 months [7.5–19.5], respectively; HR 1.06, 95% CI 0.92–1.22; $p=0.429$; appendix p 6). [A: please check p values in appendix, log-rank is $p=0.428$] However, in patients with stage IV tubo-ovarian cancer, neoadjuvant chemotherapy was associated with significantly better overall survival than was upfront debulking surgery (median 24.3 months [IQR 14.1–47.6] vs 21.2 months [10.0–36.4]; HR 0.76, 95% CI 0.58–1.00; $p=0.048$; figure 4). [A: since you do not mention figure 4B in the Results, I've deleted it] Forest plots for overall survival according to FIGO stage are in the appendix [A: if you want to include figure 4B, please add it to the appendix]. Progression-free survival was also significantly better in stage IV disease with neoadjuvant chemotherapy than with upfront debulking surgery (median 10.6 months [IQR 7.9–15.0] vs 9.7 months [5.2–13.2], respectively; HR 0.77, 95% CI 0.59–1.00; $p=0.048$; appendix p 7). [A: please check p values in appendix, $p=0.049$ on plot]

Patients with extrapelvic metastases smaller than 5 cm at the time of randomisation had the best overall survival of all participants (appendix p 8). In patients with FIGO stage IIIC disease and a largest metastatic tumour size less than 5 cm, progression-free survival was better with upfront debulking surgery than with neoadjuvant chemotherapy (median 12.2 months [IQR 8.5–23.3] vs 11.7 months [8.3–16.4]; HR 1.36, 95% CI 1.06–1.75; $p=0.017$; figure 5A) Forest plots according to largest metastatic tumour size are in the appendix (p 9). Overall survival did not differ between upfront debulking surgery and neoadjuvant chemotherapy (median 33.0 months [IQR 13.5–78.7] and 30.2 months [16.5–51.3], respectively; HR 1.26, 95% CI 0.96–1.65; $p=0.092$; figure 5B). Because of deviation from the proportional hazards assumption in this subgroup, restricted mean survival times are presented in table 3. Age and performance status were not predictive for treatment effect on survival (appendix p 10)

Discussion

This preplanned analysis of updated data from the EORTC and CHORUS trials assessing neoadjuvant chemotherapy versus upfront debulking surgery in advanced tubo-ovarian cancer (stage IIIC and IV) shows that, with long-term follow-up, neoadjuvant chemotherapy results in non-inferior overall survival and progression-free survival as compared with upfront debulking surgery. The planned non-inferiority margin—an increase in Δ of more than 18–19%—was well outside the lower bounds of the 95% CIs [11% and 13%] [A: check against Results, I queried 95% CIs] for progression-free survival and overall survival, respectively). Hence, this meta-analysis with long-term

follow-up substantiated previous findings showing that both upfront debulking surgery and neoadjuvant chemotherapy are potential treatment options for patients with FIGO stage IIIC or IV tubo-ovarian cancer. The analysis also showed that patients diagnosed with stage IV disease had significantly better progression-free survival and overall survival with neoadjuvant chemotherapy as compared with upfront debulking surgery, whereas women with stage IIIC disease with extrapelvic metastases smaller than 5 cm had significantly better progression-free survival with upfront debulking surgery as compared with neoadjuvant chemotherapy. For women with stage III disease and larger metastases (≥ 5 cm), either approach resulted in the same overall survival. Our analyses showed that in women with stage IIIC disease and extrapelvic metastases at diagnosis smaller than 5 cm, survival curves for both progression-free survival and overall survival cross in both treatment groups [A: OK change for "both progression-free survival and overall survival curves have crossing treatment arms" to avoid use of "arms" which is not Lancet style?], indicating deviation from the proportional hazards assumptions. Therefore, restricted mean survival times give a better indication of the treatment effect than do median times.¹¹ These findings indicate that when deciding on a treatment strategy, one should account not only for the risk of perioperative morbidity⁶ and the possibility of debulking the patient's disease to zero residual tumour⁷ but also for FIGO stage and the extent of metastatic disease at presentation.

Although both the EORTC and CHORUS trials permitted cytological diagnosis of malignant disease, the evolution in knowledge regarding subtypes of tubo-ovarian cancer disease means that only histology can reliably distinguish between high-grade and low-grade serous carcinomas at the time of writing.¹³ This reliance on histological diagnosis [A: OK addition to clarify meaning of "this"?] is important because low grade serous carcinomas are much less sensitive to chemotherapeutic regimens [A: OK addition to clarify meaning of "this"?] than other treatment strategies? Please add comparator] and primary surgery is an important and much preferred intervention in this group [A: preferable to what? Please add comparator] [A: How does this management preference relate to reliance on histological diagnosis (if that is what you meant by "this"? Please clarify meaning of this sentence).¹⁴ Therefore, to facilitate optimum decision making, tissue should be obtained for histological diagnosis in all cases of tubo-ovarian cancer [A: correct addition:] and assessed in combination with extensive radiological imaging. Obtaining tissue for histological examination is usually possible by use of image-guided biopsy (usually of the omental cake), although a laparoscopic approach is necessary in some cases and provides additional information on disease distribution, which can be included in the decision-making process.^{15–17}

Both the EORTC and CHORUS trials investigated the timing of surgery in advanced tubo-ovarian cancer; these trials have been criticised [A: can you reference this criticism?] for inclusion of low proportions of patients with no macroscopic disease (R0) and for poor survival [A: OK as edited, since Lancet style is to avoid use of "rates" where there is no time component?]. However, at the time the patients in these trials were enrolled [A: OK change for "randomised"?], neoadjuvant chemotherapy was not accepted as an alternative to upfront debulking surgery, and furthermore most patients recruited to these trials had extensive FIGO stage IIIC or IV disease that was visible on CT. Moreover, the SCORPIO¹⁵ and JCOG0602¹⁸ randomised trials [A: what was the date of these trials? What interventions were they testing, in what population?] concluded that interval debulking after neoadjuvant chemotherapy was associated with improved perioperative morbidity as compared with primary debulking surgery. A randomised trial of neoadjuvant chemotherapy versus primary debulking surgery in advanced tubo-ovarian cancer (the TRUST trial; NCT001/ISRCTNxxx) [A: can you reference or provide an NCT id or other registry id?], has recruited up to 50% of patients with maximal cytoreduction (R0) [A: OK change for "patients from selected centres have been recruited with R0 of 50% or more"?]. The results of this trial are awaited.

One limitation of our meta-analysis is that only patients with FIGO stage IIIC and IV disease were included in the EORTC trial, whereas in the CHORUS trial only a few patients with stage IIIA and B were included. Furthermore, the number of patients with stage IIIC–IV disease without residual tumour after upfront debulking surgery was lower in the CHORUS trial than in the EORTC trial.

Application of the findings of this analysis to the care of women with FIGO stage IIIC or IV tubo-ovarian cancer should be assessed in the context of each patient's clinical picture. Women in the EORTC and CHORUS studies that contributed data to this analysis had metastatic disease with a high tumour burden at presentation, and many had a poor performance status.¹⁹ This clinical scenario is not uncommon, and improving outcomes for this population is as important—if not more so—than for patients with better prognostic factors. The results of this analysis are derived from one of the largest cohorts of women with FIGO stage IV disease in phase 3 studies. Although some patients with stage IV disease have a better prognosis and present with less spread and more easily resectable disease¹⁴ than other patients with stage IV disease [A: this seems rather obvious; can you explain what you mean by inclusion of this sentence?], our data suggest that neoadjuvant chemotherapy should be the standard of care for most patients with FIGO stage IV tubo-ovarian cancer, and primary surgery should only be undertaken in exceptional circumstances in women selected on an individual basis.

Contributors

All authors contributed to study design and study implementation. IV and SK wrote the draft of the report, and all authors were involved in writing and approval of the report. All authors have seen and approved the final version and, after consultation with the collaborators, agreed to submit for publication.

Declaration of interests

MN reports grants from the Medical Research Council Clinical Trials Unit and Cancer Research UK, during the conduct of the study. NJ reports that the Royal United Hospital (his employing institution) received support [A: from EORTC?] for a clinical trials nurse, who obtained and [A: verified?] data from some participants in one of the trials reported here [A: which?]. CM reports personal fees and [A: travel?] expenses from Roche Farma España, outside the submitted work; [A: travel?] expenses from AstraZeneca, outside the submitted work; and other [A: please say what "other" was] from Pharmamar, outside the submitted work. TP reports personal fees and non-financial support from AstraZeneca, outside the submitted work; non-financial support from Roche and IGEA Medical, outside the submitted work; and is co-chief investigator for the ICON7 trial of bevacizumab in first-line treatment of patients with advanced ovarian cancer. IV, CC, GBK, MKBP, TE, GCJ, AMS, RV, WGMCC, BBP, GK, AC, GS, NSR, and SK declare no competing interests.

Acknowledgments

This study was supported by grants (2U10 CA11488-28 through 2U10 CA011488-36) from the National Cancer Institute; and by a donation from the Vlaamse Liga tegen kanker (Flemish League against Cancer) to the EORTC Charitable Trust. Funding was also provided by Cancer Research UK. Funding for a pilot phase of the trial was provided by the Royal College of Obstetricians and Gynaecologists and was supported by core Medical Research Council (MRC) Clinical Trials Unit (CTU) funding. The MRC was the trial sponsor, and the trial was undertaken and analysed at the MRC CTU. [A: can you please be clearer about which organisations sponsored which trial(s)? ie, EORTC, CHORUS, and this meta-analysis?]

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