Original Article

Improved Survival from Ovarian Cancer in Patients Treated in Phase III Trial Active Cancer Centres in the UK

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Abstract

Aims: Ovarian cancer is the principal cause of gynaecological cancer death in developed countries, yet overall survival in the UK has been reported as being inferior to that in some Western countries. As there is a range of survival across the UK we hypothesised that in major regional centres, outcomes are equivalent to the best internationally.
Materials and methods: Data from patients treated in multicentre international and UK-based trials were obtained from three regional cancer centres in the UK; Manchester, University College London and Leeds (MUL). The median progression-free survival (PFS) and overall survival were calculated for each trial and compared with the published trial data. Normalised median survival values and the respective 95% confidence intervals (ratio of pooled MUL data to trial median survival) were calculated to allow inter-trial survival comparisons. This strategy then allowed a comparison of median survival across the UK, in three regional UK centres and in international centres.
Results: The analysis showed that the trial-reported PFS was the same in the UK, in the MUL centres and in international centres for each of the trials included in the study. Overall survival was, however, 45% better in major regional centre-treated patients (95% confidence interval 9–73%) than the median overall survival reported in UK trials, whereas the median overall survival in MUL centres equated with that achieved in international centres.
Conclusion: The data suggest that international survival statistics are achieved in UK regional cancer centres.
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Key words: Cancer centre; clinical trial; ovarian cancer; prognosis; survival outcomes; UK

Introduction

Ovarian carcinoma is responsible for over 4000 deaths each year in the UK; more than all other gynaecological cancers combined. The standard treatment in the first-line setting is debulking surgery followed by cytotoxic chemotherapy with carboplatin and paclitaxel. Strategies to improve outcomes include the use of preoperative chemotherapy [1,2], dose-dense chemotherapy [3,4] or the addition of anti-angiogenic agents to standard doublet therapy [5–8].

In keeping with these advances, survival outcomes for ovarian cancer have improved worldwide, including in the UK. However, survival in the UK has been consistently reported to be worse than that in some other European countries, North America and Australia [9,10]. Within the UK there is evidence of variation in outcomes between

cancer networks and regions [11,12]. This may be less related to socio-economic status [13] than to other prognostic factors at presentation. One critical issue is the quality of care, particularly after initial relapse, and to address this we collected ovarian cancer survival data from three UK cancer centres, which participated in five recent randomised trials in ovarian carcinoma. Our aim was to compare the progression-free survival (PFS) and overall survival statistics of women treated in regional cancer centres in the UK with those of women treated across the UK and internationally. We aimed to test the hypothesis that UK, major regional cancer centre-associated survival was superior to other UK centres.

Materials and Methods

Selection of Clinical Trials for Evaluation

Trials were selected if recently completed, overall survival statistics were available and the MUL centres had recruited sufficient numbers of patients to allow meaningful analysis. Five clinical trials met these criteria. The design and statistical plan for each trial have been described in the primary publications. Three trials involved patients receiving first-line treatment for ovarian cancer: CHORUS [2], GOG-0182-ICON5 [14] and ICON7 [6,7]. Two were in recurrent disease: ICON6 [8] and SaPPrOC [15], which recruited patients with platinum-sensitive and platinum-resistant disease, respectively.

The numbers of UK women recruited to each of the trials is presented as the numerator and the total number in the trial as the denominator: ICON5 363/4312 (8.4%); ICON7 375/1528 (24.5%); ICON6 379/486 (78%); SAPPROC 107/107 (100%); CHORUS 539/552 (97.6%). Trials were categorised as having been predominantly UK based (ICON6, CHORUS and SAPPROC) or international (ICON5 and ICON7). Thus, of the international group of trials, the UK contribution was 12.6% and in the UK-centric group of trials the contribution was 89.5% of patients.

Comparison of Specialist Centres and Overall Study Populations

Data were extracted from clinical trial databases and supplemented with clinical records for patients treated in three major regional cancer centres in the UK with expertise in the management of women with gynaecological cancers and in clinical trials (The Christie NHS Foundation Trust, Manchester; University College London Hospitals NHS Foundation Trust, London; and the St James's Institute of Oncology, Leeds: MUL).

Pre-treatment characteristics including FIGO stage, surgical outcomes and post-progression therapy were compared with those of the relevant overall trial populations. No distinction was made between the arms to which the patients were randomised and thus survival data across trial arms were summated for comparative purposes. Kaplan—Meier analysis, calculated from the date of study

entry to the last available follow-up censored in September 2014, was used to calculate the median PFS and overall survival for MUL patients. MUL median survival values were then compared with those in the overall trial populations, taken from published data.

The median PFS and overall survival data were summarised further by calculating the ratio between the MUL median PFS or overall survival value and the trial median PFS or overall survival value for each study, where the trial median PFS or overall survival for the UK-centric studies was defined as 1. In the first part of the analysis we compared MUL survival with the median survival for UK-centred studies. We then compared the MUL survival statistics with the median survival in international trials, enabling a comparison between the three groups. The 95% confidence interval ratios for the MUL subset median values were similarly calculated.

When summating ratios from trials together to allow a comparison between MUL, UK and international data, the numbers of MUL patients recruited to each trial were used to weight the calculated overall survival ratio so that trials where MUL centres recruited more patients had a greater effect on the overall calculated survival ratio. Thus, the summated mean overall survival ratio (Figure 1) was calculated as: the sum of the products of the MUL survival ratio for each trial and the number of patients recruited from MUL centres to that trial, divided by the total number of MUL patients.

The effect of post-progression (off-trial) treatment was assessed using a post-progression survival ratio, calculated from the difference between median PFS and overall survival between MUL and overall trial populations.
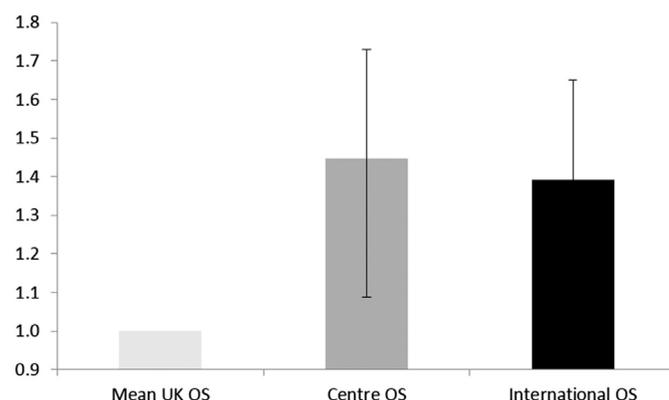
Fig 1. Overall survival in specialist cancer centres, international centres and the UK average survival. The data show the relative overall survival for patients treated in UK-centric trials, defined as unity and labelled as Mean UK OS. The Manchester, UCL and Leeds (MUL) centre overall survival is labelled as Centre OS, showing a 45% increase in overall survival in centre-treated patients, when compared with Mean UK OS. This is compared with the overall survival achieved by the MUL group in international clinical trials (the International OS bar). The International OS bar reflects the relative survival of MUL patients to the median overall survival of the international trial set compared with the UK OS, which is defined as 1. The MUL centre overall survival statistic is presented as ± 95% confidence intervals.

For each trial, the ratio of MUL overall survival/trial median overall survival was calculated and the data analysed according to two defined groups: UK-centric trials (ICON6, CHORUS and SAPPROC) or international trials (ICON5 and ICON7). This strategy allowed us to compare the effect of centre-based treatment with the overall results for the UK and with international trial statistics.

Results

The primary results of the trials have been published. In brief, CHORUS [2], GOG-0182-ICON5 [14] and SaPPrOC [15] showed no significant difference in PFS between control and investigational regimens, whereas ICON6 [8] and ICON7 [6,7] reported significantly improved PFS with the addition of concurrent and maintenance anti-angiogenic therapy to chemotherapy.

The MUL subset comprised ≤8% of the overall study populations within the CHORUS, GOG-0182-ICON5 and ICON7 trials and a larger proportion of patients in ICON6 (27%) and SaPPrOC (29%) (Table 1). Within the MUL data set, the proportion of patients randomised to the investigational arm resembled that in the overall study population (Table 1) and the patient characteristics with respect to FIGO stage and surgical outcome were also similar to the overall patient population for each trial (Table 1). The only exception was that in ICON7 fewer MUL patients had <1 cm disease after debulking surgery.

Survival Outcome Comparisons between MUL and Overall Trial Populations

The survival data are summarised in Table 2, which also shows that the median duration of follow-up for MUL and ITT populations were comparable. The median PFS in the MUL subset was similar to that of the specific trial populations for both UK-centric and international trials. The 95% confidence interval for the MUL subset largely encompassed the median value for the overall trial populations. In CHORUS, however, the median PFS and corresponding 95% confidence interval were greater than the median value for the overall study population; 15.4 months (95% confidence interval 11.5−17.2, $P < 0.05$) in the MUL group and 11.3 months in the overall trial. In ICON7 the median PFS in the MUL subset was shorter (16.8 months) than the overall trial population (18.7 months) but the 95% confidence interval for the MUL subset included this value, indicating that the difference was not statistically significant.

In UK-based trials, the median overall survival ratios in the MUL subset were for the SaPPrOC trial 1.59 (95% confidence interval 0.65−2.01), for CHORUS 1.57 (95% confidence interval 1.11−2.10) and for ICON6 1.37 (95% confidence interval 1.19−1.65). For international studies, the MUL subset median overall survival was equivalent to that of ICON5 but in ICON7 the median MUL overall survival ratio was slightly lower than in the overall trial population, but this was not statistically significant (0.89, 95% confidence interval 0.66−1.26; not significant). Table 2 summarises PFS and overall survival outcomes in the overall trial populations and in the MUL subset of patients. The median durations of follow-up for MUL and ITT populations were comparable (Table 2).

The overall survival result from the MUL ICON7 patients led us to explore the data further. In ICON7, a pre-specified subgroup, consisting of high-risk patients [6], seemed to benefit from bevacizumab and cytotoxic chemotherapy. The overall population, however, which included patients with FIGO stage IC–IV disease, derived only modestly improved PFS. We therefore also examined the overall survival of patients in this high-risk group. Of the MUL ICON7 patients, 28 of 62 patients (45%) were defined as high risk compared with only 30% in the ITT population. Thus, the MUL subset seemed to represent a relatively poorer prognostic group. Nevertheless, this high-risk subgroup achieved the same median overall survival in the MUL centres as that seen in the high-risk subgroup within the overall trial population (overall survival ratio 1.01, 95% confidence interval 0.83−1.4; not significant).

Table 1
Summary of patient populations; Manchester, UCL and Leeds (MUL) compared with trial populations as a whole

	CHORUS [2]		SaPPrOC [15]		ICON6 [8]		GOG-0182-ICON5 [14]		ICON7 [6,7]	
Recruitment period	2004−2010		2011−2012		2007−2011		2001−2004		2006−2009	
	MUL	ITT	MUL	ITT	MUL	ITT	MUL	ITT	MUL	ITT
No. patients	45	550	31	107	124	456	47	4312	62	1528
Percentage in investigational arm	49	50	double blinded	66	69	74	79	80	47	50
FIGO stage (%)										
III	76	75					79	84−87	76	68
IV	24	25					21	13−16	11	13
Residual disease (%)										
≤1 cm	47	56					45	69	52	73
>1 cm	27	44					51	31	42	25

ITT, Intention to Treat.
ICON6 and SaPPrOC are trials for recurrent disease and therefore the initial FIGO stage and residual disease statistics were not available from the primary publications.

Table 2
Median survival statistics in Manchester, UCL and Leeds (MUL) and overall trial data

	CHORUS [2]	SaPPrOC [15]	ICON6 [8]	ICON5 [14]	ICON7 [6,7]	ICON7 high-risk subgroup
Median duration of follow-up, years						
MUL subset	3	1.1	2.5	4.5	4	3
ITT population	3	NR	NR	3.7	4	NR
Median PFS, months (95% confidence interval)						
MUL subset	15.4 (11.5–17.2)	5.0 (3.7–7.6)	10.1 (9.5–11.0)	20.6 (15.7–27.7)	16.8 (13.8–18.9)	13.0 (1.0–55.0)
ITT population	11	4.7	10	15.9	18.7	13.2
Median overall survival, months (95% confidence interval)						
MUL subset	37.7 (26.7–50.3)	19.1 (7.8–24.2)	31.4 (27.3–37.9)	53.9 (41–113)	51.6 (38–73)	35.5 (29.2–49.1)
ITT population	24	12	23	44	58	35
Survival ratios MUL compared with ITT trial populations						
PFS	1.4	1.08	1.0	1.3	0.90	
Overall survival	1.57	1.59	1.37	1.23	0.89	1.01
Post-progression survival ratio	1.7	1.91	1.78	1.18	0.87	

MUL, Manchester, UCL, Leeds; ITT, Intention to Treat; PFS, progression-free survival.

Comparison of Median Overall Survival between Manchester, UCL and Leeds (MUL) and Trial ITT Data

We normalised the MUL survival statistics for the two groups of trials against the median overall survival achieved in UK-based trials. In the UK-based trials, the analyses showed that the overall survival ratios were relatively higher in the MUL subset of patients for all three trials. The combined weighted mean, which takes into account the numbers of patients recruited to a particular trial, for all three trials was 1.45 (95% confidence interval 1.09–1.80), implying that MUL centres achieved statistically significantly better overall survival than UK centres overall, while matching the survival statistics achieved in international centres (Figure 1).

For the international trials, the calculated overall survival ratio was 1.23 (95% confidence interval 0.93–2.57) in ICON5 and 0.89 (95% confidence interval 0.66–1.26) in the total ITT ICON7 populations, reflecting the case mix of patients recruited to ICON7 in the MUL centres. The weighted mean overall survival ratio for both of these trials was 1.04 and the 95% confidence interval indicated no significant difference in outcome between the MUL centres and the international participating centres.

Optimum Debulking and Post-progression Treatment at MUL Centres

Two potential explanations for superior outcomes at MUL centres include superior cytoreductive surgery at MUL centres and greater use of post-progression therapy and, in particular, dose-dense cytotoxic regimens at these centres. Looking at the MUL CHORUS patients who underwent primary surgery, 21 of 33 patients (64%) had optimum debulking surgery, whereas the overall trial statistic described 41% of such patients achieving this degree of cytoreductive surgery. With respect to post-progression statistics, the ICON6 data set was the largest, including data from 125 MUL-treated patients. This data set showed

that the MUL centres provided a median of two post-progression regimens, with a range of up to six. Patients received a median of one dose-dense regimen, where cytotoxic therapy is given on a weekly basis, with a range of up to three such regimens.

Discussion

Our analyses suggest that survival outcomes in regional referral centres in the UK treating high numbers of women with ovarian cancer are similar to those observed internationally and are significantly better than the average survival in the UK, resulting in a 45% improvement in overall survival when compared with the national average.

One hypothesis to explain the improved survival might be that there is an element of selection bias, which favoured treatment in the MUL centres. However, this is unlikely to be the case as Table 1 shows that the demographic characteristics of MUL patients closely resemble those of the overall trial populations. Furthermore, if one accepts that these demographic characteristics are similar, then protocol-defined treatments should result in the same PFS, whether patients are treated in a regional cancer centre or not; the data that we present here support this hypothesis. Thus, the equality of patients' demographic characteristics and PFS suggest that case selection bias does not explain the improved outcome in large regional cancer centres. Rather, the data suggest that the differences in survival probably arise because of care provided after the patient leaves the clinical trial protocol-defined regimen, which is usually at the point of developing progressive disease. In other words, MUL centres may provide more effective post-relapse therapy.

The explanation for the improved survival cannot be precisely and reliably determined from this analysis, as post-progression therapy details were not available from the primary publications. However, it is noteworthy that in the Oceans [16,17] trial, a recent international

randomised trial of anti-angiogenic therapy in recurrent ovarian cancer, a third of patients received at least seven lines of therapy. The median overall survival for both arms of the Oceans trial was 33 months, which equates with the median overall survival of MUL patients participating in ICON6.

Our analysis is retrospective and is therefore subject to confounding factors. For example, the median PFS and overall survival statistics in the MUL subsets were calculated from the pooled groups of patients, irrespective of the arms to which the patients were randomly assigned. For studies that showed no significant difference between treatment arms this is not a concern, but for ICON6 and ICON7, where the investigational arms were superior, this approach might incur unforeseen bias. On the other hand, we chose this approach because the randomisation of demographically balanced groups of patients should have adjusted for this potential issue and because post-progression treatment, reflecting overall quality of care, would apply to the entire trial cohort. The proportions of women included in each treatment arm were in fact similar between the MUL and the ITT populations.

The trials that were included in this study were selected on the basis that the overall survival statistics of participating patients were available. As some trials started 10 years ago it is possible that the overall management of the disease in the UK is now more uniform, e.g. higher rates of complete cytoreduction, which might reduce the magnitude of differences identified here. However, the Calman-Hine report was published in 1995 and therefore when these trials were initiated the effect of centralisation should already have been well established.

Another confounding factor is that MUL outcomes were compared with those of the entire trial population without excluding MUL participants. It is possible therefore that with respect to the UK-centred trials, the superior outcomes in MUL treated women may have been diluted. Nevertheless, it is important to note that our data do not suggest that the MUL centres offer superior treatment to that available in other large UK regional cancer centres. The MUL centres were selected because they were considered representative of major research-active UK centres. The high level of recruitment activity to key randomised trials at these centres provided us with enough patients and data to allow a meaningful analysis to be carried out. It is probable that other large regional centres in the UK would have similar survival statistics.

The use of the median to estimate the magnitude of treatment effect could be questioned. In both ICON6 and ICON7, non-proportional hazards were observed and therefore the restricted mean was considered a more appropriate estimate of treatment effect. To enable a comparison between all the studies we therefore used the median survival statistic, which seemed reasonable given the similarity in median follow-up interval between the MUL and overall trial populations.

The results of this study suggest that the superior overall survival achieved in large regional cancer centres in the UK, compared with centres overall, resulted from longer post-progression survival. We believe that the most likely explanation lies in a more determined approach to control disease in the platinum-sensitive and platinum-resistant disease settings. Although some women in the UK may be less prepared to undergo repeated lines of chemotherapy, than for example in the USA, this would not account for within UK differences. Whereas 'standard of care' chemotherapy can be readily administered in all designated cancer centres in the UK, post-progression treatment can be more toxic and less well tolerated, requiring a stronger clinical infrastructure, which is available in large centres. Although quality of life issues remain to be determined, this study provides a basis for re-thinking the optimum framework for managing recurrent ovarian cancer in the UK, which might require further centralisation of care to highly specialised multidisciplinary teams that could offer access to, for example, dose-dense therapy, secondary cytoreductive surgery and/or the broad portfolio of new agents available in phase I–III clinical trials at such centres.

Conclusions

It is reassuring that MUL centres achieve international outcome standards. However, the overall survival statistics across the UK remain inferior to many other Western nations [18] and further work should identify the underlying explanations for the differences.

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