Early versus delayed treatment of relapsed ovarian cancer (MRC OV05/EORTC 55955): a randomised trial

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Summary

Background Serum CA125 concentration often rises several months before clinical or symptomatic relapse in women with ovarian cancer. In the MRC OV05/EORTC 55955 collaborative trial, we aimed to establish the benefits of early treatment on the basis of increased CA125 concentrations compared with delayed treatment on the basis of clinical recurrence.

Methods Women with ovarian cancer in complete remission after first-line platinum-based chemotherapy and a normal CA125 concentration were registered for this randomised controlled trial. Clinical examination and CA125 measurement were done every 3 months. Patients and investigators were masked to CA125 results, which were monitored by coordinating centres. If CA125 concentration exceeded twice the upper limit of normal, patients were randomly assigned (1:1) by minimisation to early or delayed chemotherapy. Patients and clinical sites were informed of allocation to early treatment, and treatment was started as soon as possible within 28 days of the increased CA125 measurement. Patients assigned to delayed treatment continued masked CA125 measurements, with treatment commencing at clinical or symptomatic relapse. All patients were treated according to standard local practice. The primary outcome was overall survival. Analysis was by intention to treat. This study is registered, ISRCTN87786644.

Findings 1442 patients were registered for the trial, of whom 529 were randomly assigned to treatment groups and were included in our analysis (265 early, 264 delayed). With a median follow-up of 56·9 months (IQR 37·4–81·8) from randomisation and 370 deaths (186 early, 184 delayed), there was no evidence of a difference in overall survival between early and delayed treatment (HR 0·98, 95% CI 0·80–1·20, p=0·85). Median survival from randomisation was 25·7 months (95% CI 23·0–27·9) for patients on early treatment and 27·1 months (22·8–30·9) for those on delayed treatment.

Interpretation Our findings showed no evidence of a survival benefit with early treatment of relapse on the basis of a raised CA125 concentration alone, and therefore the value of routine measurement of CA125 in the follow-up of patients with ovarian cancer who attain a complete response after first-line treatment is not proven.

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Introduction

Early detection and treatment of cancer is commonly believed to improve outcomes for patients. This idea is the main rationale for regular follow-up after completion of cancer treatment. However, data from the few randomised studies that have investigated timing of therapy[1–5] are conflicting with respect to early treatment for patients presenting with metastatic disease, and no randomised trials have adequately addressed timing of treatment for recurrent cancer.[6,7]

The serum tumour marker CA125 is used for initial diagnosis and monitoring of response to chemotherapy for epithelial ovarian cancer. Regular measurement during follow-up is one of the best examples in oncology of a test that can detect recurrence of cancer months before symptoms or signs occur.[8–12] Although most women can expect a good response and improved survival after chemotherapy for their first recurrence,[13] this treatment is rarely curative and has side-effects. Concerns about CA125 testing and the implications of raised CA125 concentration are major sources of anxiety.

A woman with a rising CA125 concentration, who remains well, without symptoms or signs of recurrent disease, presents a major management dilemma.[14] Because of this issue, practice varies widely in terms of whether or not regular CA125 measurements are done and in the timing of initiation of second-line chemotherapy. We therefore undertook a randomised trial with the aim of establishing the benefits of early treatment on the basis of increased serum CA125 concentrations compared with delayed treatment on the basis of clinical recurrence.

Methods

Trial design and patients

The British Medical Research Council (MRC) OV05 and European Organisation for Research and Treatment of Cancer (EORTC) 55955 trials were collaborative trials undertaken with a joint trial management group and monitored by a single independent data monitoring committee. All statistical analyses were done at the MRC Clinical Trials Unit. Ethics approval for MRC OV05 was obtained from the London multicentre research ethics

committee and at each site. EORTC 55955 received local ethics approval at each site.

Women with histologically confirmed epithelial ovarian, fallopian tube, or serous primary peritoneal cancer (based on local pathology) in complete clinical remission after completion of first-line platinum-based chemotherapy with a normal CA125 concentration were eligible for trial registration. Written informed consent was obtained.

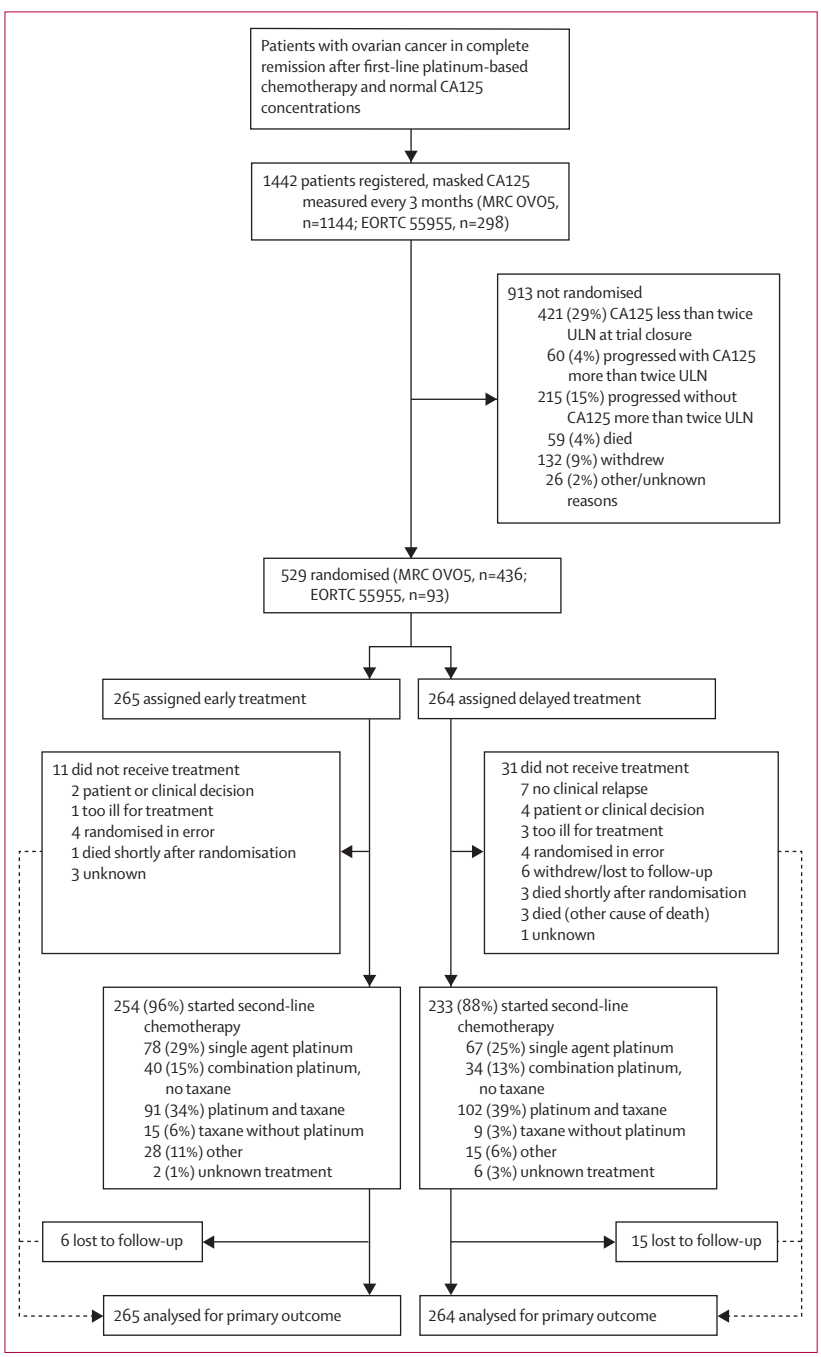

Figure 1: **Trial profile**
ULN=upper limit of normal.

Procedures

After registration, trial visits occurred every 3 months and included physical and gynaecological examinations, ultrasound and radiological examinations according to local practice, quality of life assessment, and a CA125 blood test. CA125 testing was done in local laboratories that agreed to mask results to clinicians and patients, participate in local quality assurance schemes, and send results to coordinating centres. If CA125 concentration increased to twice the site upper limit of normal, patients were randomly assigned to early treatment, with the clinical site notified of the randomisation, or to delayed treatment. Patients were informed of allocation to early treatment, and treatment was started as soon as possible within 28 days after an unmasked confirmatory CA125 concentration twice the upper limit of normal. If a woman was assigned to delayed treatment, the site was not notified, and masked follow-up continued until clinical recurrence was detected and delayed treatment started. Quality of life was assessed before each chemotherapy cycle until the end of third-line treatment with the EORTC QLQ-C30 questionnaire.[15] Choice of chemotherapy was according to standard local practice.

Randomisation and masking

Randomisation to early or delayed treatment groups (1:1 ratio) was done independently by each coordinating centre. The method of minimisation was used with the stratification factors: International Federation of Gynecology and Obstetrics (FIGO) stage (I *vs* II *vs* III *vs* IV); first-line chemotherapy (single agent platinum *vs* platinum combination without taxane *vs* platinum-taxane combination *vs* other); time from completion of first-line chemotherapy to raised CA125 concentration (<6 *vs* 6–11 *vs* 12–24 *vs* >24 months); age (MRC OV05 at randomisation, EORTC 55955 at registration; <30 *vs* 30–55 *vs* 56–65 *vs* >65 years); and site. CA125 results were masked to sites and patients until randomisation to early treatment or until clinical recurrence for those in the delayed treatment group.

Statistical analysis

The primary outcome measure was overall survival calculated from date of randomisation to date of last follow-up or death from any cause. At the time of analysis, survivors were censored at the date they were last known to be alive. Secondary outcomes were: time to second-line chemotherapy (calculated from date of randomisation to date of initiation of second-line chemotherapy, women who did not receive second-line chemotherapy were censored at the date of last contact); time to third-line treatment or death (calculated from date of randomisation to date of starting third-line treatment or death, whichever occurred first, survivors without treatment censored at the last contact); quality of life with duration of good quality of life in the global health score (defined as improved or no more than a 10% decrease from

prerandomisation score); and time of first global health-related deterioration (defined as more than 10% decrease from prerandomisation score or death).

The trial was initially designed to detect a 10% improvement in 2-year overall survival from 5% delayed treatment to 15% early treatment. However, in 2002 (with 191 women randomly assigned to treatment groups) the 2-year overall survival of women assigned to delayed treatment was estimated to be closer to 40%. The independent data monitoring committee (without reference to outcome data from the early treatment group) recommended that sample-size estimations were revised to give a range of registrations and randomisations required to give sufficient power. Revised estimates (continuing to target a 10–15% absolute improvement), which included a range of 2-year survival estimates in the delayed treatment group from 40% to 50%, required 530–1400 registrations and 350–650 randomisations and were included in a protocol amendment. After the trial closed to registrations in August, 2005, with 1442 registered women, the randomisation rate fell. In February, 2007, when the study had been open for longer than 10 years and 510 patients had been randomly assigned to treatment groups, the trial management group carefully considered trial closure options. At this time the estimated 2-year overall survival in the delayed-treatment group was 54%. To detect a 10% absolute improvement with 5% significance level and 85% power, 345 events were needed. This target was assessed as achievable and was agreed by the trial management group as the target number of events for the primary analysis. All women were followed up until randomisation or an event that precluded randomisation and for survival. Clinical follow-up with masked CA125 measurements continued for 6 months after close of randomisation.

Stata (version 10.1) was used for all analyses. The primary analysis was the log-rank test, stratified by MRC versus EORTC, applied to compare the Kaplan-Meier survival curves for all time-to-event outcome measures. Cox model sensitivity analyses estimating the treatment effect and adjusting for stratification and prognostic factors were done for overall survival. All women were included in the analysis, which was by intention to treat. All p values are two-sided. To adjust for imbalances in follow-up between the two groups, curtailing was used for main analyses of time-to-event outcome measures, by censoring data at 5 years from randomisation for MRC OV05 and 3 years for EORTC 55955. Additional sensitivity analyses were done for uncurtailed data.

This study is registered, ISRCTN87786644.

Role of the funding source

The MRC and EORTC reviewed and approved the study design. The study sponsors, the MRC for OV05 and EORTC for 55955, had no role in the conduct of the study or in writing of this report. The writing committee had full access to all study data and had responsibility for the decision to submit for publication.

Results

MRC OV05 started in May, 1996, and EORTC 55955 in May, 1999, closing to registrations on Aug 31, 2005, with

	Early treatment (n=265)	Delayed treatment (n=264)
Age		
<30 years	0	0
30–55 years	81 (31%)	89 (34%)
56–65 years	110 (42%)	93 (35%)
>65 years	74 (28%)	82 (31%)
Median (years)	60 (53–66)	61 (53–68)
FIGO stage		
IA	5 (2%)	0
IB	1 (<1%)	2 (1%)
IC	15 (6%)	18 (7%)
II	30 (11%)	28 (11%)
III	181 (68%)	182 (69%)
IV	33 (12%)	34 (13%)
Histology		
Serous	172 (65%)	154 (58%)
Endometrioid	30 (11%)	31 (12%)
Mucinous	9 (3%)	8 (3%)
Clear cell	11 (4%)	9 (3%)
Undifferentiated	22 (8%)	16 (6%)
Adenocarcinoma, not otherwise specified	14 (5%)	39 (15%)
Other	3 (1%)	3 (1%)
Unknown/missing	4 (2%)	4 (2%)
WHO performance status		
0	182 (69%)	198 (75%)
1	78 (29%)	65 (25%)
2	4 (2%)	1 (<1%)
3	1 (<1%)	0
First-line chemotherapy		
Single agent platinum	104 (39%)	105 (39%)
Combination platinum (no taxane)	16 (6%)	16 (6%)
Platinum and taxane based	143 (54%)	143 (54%)
Other	2 (1%)	0
Time to registration after completion of first-line chemotherapy		
<3 months	211 (80%)	205 (78%)
4 months	19 (7%)	17 (6%)
5 months	5 (2%)	18 (7%)
6 months	7 (3%)	5 (2%)
>6 months	23 (9%)	19 (7%)
Time to doubling of CA125 concentration after completion of first-line chemotherapy		
<6 months	53 (20%)	51 (19%)
6–11 months	87 (33%)	89 (34%)
12–24 months	69 (26%)	67 (25%)
>24 months	52 (20%)	52 (20%)
Unknown	4 (2%)	5 (2%)

Data are number (%) or median (IQR). FIGO=International Federation of Gynecology and Obstetrics.

Table 1: **Characteristics at registration of all patients randomly assigned to treatment groups**

See Online for webappendix

1442 women registered (1144 MRC, 298 EORTC; figure 1). Women were registered from 59 centres across the UK, Spain, Norway, the Netherlands, France, Russia, Belgium, Ireland, Austria, and South Africa. Baseline characteristics of registered women are shown in the webappendix. All women had confirmation of remission (normal CA125 concentration and no evidence of disease after surgery and first-line chemotherapy, radiologically confirmed in all but two patients), 94% (1362 women) within 3 months before registration. Median time from completion of first-line chemotherapy to registration was 1·7 months (IQR 1·0–3·2), with 1066 (74%) women registered within 3 months. 492 registered women had an event during follow-up that excluded them from randomisation (figure 1). When randomisation closed (March 31, 2008), 421 (29%) registered women were still in clinical remission with a normal CA125 concentration and were eligible for randomisation. Median survival from end of first-line chemotherapy to last follow-up or death for all women registered in the trial was 70·8 months (95% CI 64·1–78·0).

Between Feb 26, 1997, and March 31, 2008, 529 women were randomly assigned to treatment groups (37% of those registered; 265 to early and 264 to delayed chemotherapy). The randomised treatment groups were well balanced for baseline characteristics at registration (table 1). The median time from registration to randomisation was 9·1 months (IQR 5·5–18·2). Time from completion of first-line chemotherapy to increase of CA125 concentration to twice the upper limit of normal was well balanced between the groups; 104 (20%) women had a rise within 6 months after first-line chemotherapy, 176 (33%) between 6 and 12 months, and 240 (45%) after 12 or more months. Randomisation was within 28 days of the date of the CA125 concentration rising to twice the upper limit of normal for 483 (91%) participants (webappendix).

When data were locked for the primary analysis on Feb 16, 2009, with a median follow-up of 56·9 months (IQR 37·4–81·8) from randomisation, 370 (70%) women assigned to treatment groups had died (186 early, 184 delayed treatment). Almost all deaths were disease related (97% early, 96% delayed; table 2). There was no evidence of a difference in overall survival (figure 2; hazard ratio [HR] 0·98, 95% CI 0·80–1·20; p=0·85; HR <1 in favour of delayed treatment group; table 3). Median survival from randomisation was 25·7 months (95% CI 23·0–27·9) in patients receiving early treatment and 27·1 months (22·8–30·9) in those receiving delayed. 2-year survival was 53·7% in patients allocated early treatment and 54·7% in those receiving delayed treatment—a difference (delayed minus early) at 2 years of 0·7% (95% CI for difference –5·8 to 7·6). Cox models adjusted for stratification and prognostic factors (table 3) did not change the overall result, showing the unadjusted results to be robust. Censored and uncensored analyses also gave the same result (table 3).

Women assigned to early treatment started chemotherapy 4·8 months (95% CI 3·6–5·3) earlier than those allocated delayed treatment (figure 2), 179 (68%) within 1 month from randomisation, and 241 (91%) within 3 months. Type of second-line chemotherapy regimen was well balanced—a platinum-taxane combination was administered to 91 (34%) women assigned to early treatment and 102 (39%) of those assigned delayed (a difference of 11 women), and single agent platinum to 78 (29%) of those receiving early treatment and 67 (25%) of those allocated delayed (figure 1). A higher proportion of women in the early treatment group (169, 64%) received six or more chemotherapy cycles than in the delayed treatment group (134, 51%). 21 women assigned early treatment and 14 delayed treatment underwent secondary surgery. More women assigned to delayed treatment (31, 12%) had no second-line chemotherapy (compared with only 11 [4%] in the early treatment group), in seven (3%) patients because they had not clinically relapsed at the time of data locking. Details of other reasons why second-line chemotherapy was not received are shown in figure 1.

After second-line chemotherapy, 177 women (67%) assigned to early and 142 women (54%) to delayed treatment started third-line treatment (table 2)—a difference of 13% (95% CI for difference 4·7–21·3). The median time from randomisation to third-line treatment or death was 12·5 months (95% CI 11·4–13·3) in the early-treatment group and 17·1 months (15·6–19·1) in the delayed-treatment group, showing that women assigned to early treatment needed further treatment for clinical progression on average 4·6 months (95% CI 4·2–5·8) earlier than those assigned to delayed (figure 2, table 3; HR 0·69, 95% CI 0·57–0·83; p=0·0001).

	Early treatment (n=265)	Delayed treatment (n=264)	All (n=529)
Overall survival			
Alive	79 (30%)	80 (30%)	159 (30%)
Dead	186 (70%)	184 (70%)	370 (70%)
Cause of death			
Disease related	180	177	357
Disease and treatment related	0	2	2
Treatment related	1	0	1
Other*	4	5	9
Unknown	1	0	1
Median survival	25·7 (23·0–27·9)	27·1 (22·8–30·9)	25·9 (23·5–28·3)
Third-line treatment or death			
Alive, no third-line treatment	30 (11%)	35 (13%)	65 (12%)
Alive, received third-line treatment	39 (15%)	35 (13%)	74 (14%)
Died, received third-line treatment	138 (52%)	107 (41%)	245 (46%)
Died, no third-line treatment	58 (22%)	87 (33%)	145 (27%)

Data are number (%) or median (95% CI). *Other causes of death were: bronchopneumonia, pulmonary embolism, cardiac arrest and pulmonary embolism, cerebral vascular accident, bronchopneumonia and ischaemic heart disease, renal failure, chronic obstructive pulmonary disease, and two patients with no details specified but classified as other cause of death.

Table 2: **Summary of events**

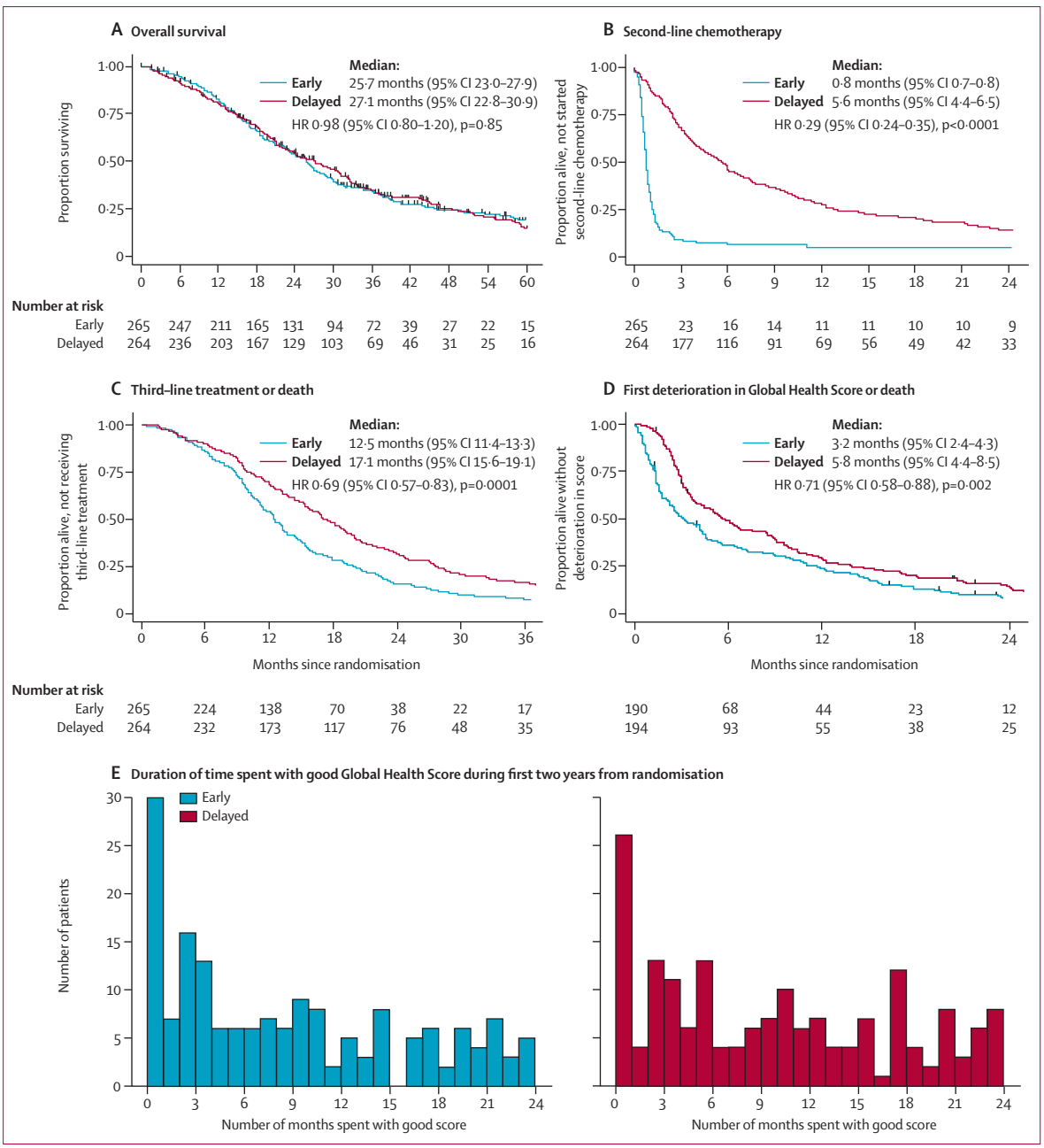

Figure 2: **Main outcome measures**
Kaplan-Meier plots for (A) overall survival, (B) second-line chemotherapy, (C) third-line treatment or death, and (D) first deterioration in Global Health Score or death. (E) Duration of time spent with good Global Health Score during the first 2 years from randomisation. HR=hazard ratio.

There was no evidence of treatment interactions in exploratory analyses to establish whether the effect of early compared with delayed treatment varied in subgroups of women defined by type of first-line chemotherapy (single agent platinum *vs* platinum-taxane combination; p value for interaction=0·07), age (30–55 *vs* 56–65 *vs* >65 years; p=0·65), FIGO stage (p=0·20), and WHO performance status (0 *vs* 1; p=0·51; figure 3). There was no detectable difference in treatment effect before and after June, 2003, after the shift to platinum-taxane combinations as second-line chemotherapy (p=0·90). The effect of early compared with delayed treatment did not differ between women who were randomly assigned to treatment groups soon after completion of first-line treatment compared with later (<6 *vs* 6–11 *vs* 12–24 *vs* >24 months from completion of first-line treatment to randomisation; p=0·34). All treatment interaction analyses were prespecified in the statistical analysis plan,

	Hazard ratio (95% CI)	Log-rank p value
Unadjusted	0·98 (0·80–1·20)	0·85
Adjusted		
For stratification factors*	0·99 (0·80–1·22)	..
For prognostic factors†	0·98 (0·79–1·21)	..
For stratification and prognostic factors	1·01 (0·82–1·25)	..
Sensitivity analyses‡	1·01 (0·82–1·23)	0·96

*Age, International Federation of Gynecology and Obstetrics stage, first-line chemotherapy, time from completion of first-line chemotherapy to doubling of CA125 concentration, and country. †Histology, WHO performance status, and time from doubling of CA125 concentration to randomisation. ‡Sensitivity analyses of non-curtailed data (all follow-up data received, not curtailed at 5 years for MRC OV05 and 3 years for EORTC 55955).

Table 3: **Hazard ratios for overall survival**

	Delayed treatment	Early treatment	O-E	Variance	HR (95% CI)
Age					
30–55 years	59/89	58/81	−2·75	28·86	0·91 (0·63–1·31)
56–65 years	65/93	75/110	3·41	34·29	1·10 (0·79–1·54)
>65 years	60/82	53/74	−3·00	27·69	0·90 (0·62–1·30)
FIGO stage					
I	13/20	13/21	0·84	6·42	1·14 (0·53–2·47)
II	17/28	14/30	3·33	7·50	1·56 (0·76–3·19)
III	130/182	134/181	−1·31	65·77	0·98 (0·77–1·25)
IV	24/34	25/33	−5·94	11·20	0·59 (0·33–1·06)
First-line chemotherapy					
Single agent platinum	74/105	81/104	−10·78	37·80	0·75 (0·55–1·03)
Platinum and taxane	95/143	93/143	5·11	46·80	1·12 (0·84–1·49)
WHO performance status					
0	134/198	120/182	1·85	62·97	1·03 (0·80–1·32)
1	49/65	61/78	−3·32	27·21	0·89 (0·61–1·29)
Timing of second-line chemotherapy					
Pre-ICON4	98/112	118/139	−0·74	53·30	0·99 (0·75–1·29)
Post-ICON4	70/117	64/115	−1·40	32·64	0·96 (0·68–1·35)
End of first-line treatment to randomisation					
<6 months	40/46	44/48	3·65	19·90	1·20 (0·77–1·86)
6–11 months	79/93	72/88	−1·92	37·16	0·95 (0·69–1·31)
12–24 months	42/72	51/75	−6·29	23·07	0·76 (0·51–1·15)
>24 months	23/53	19/54	3·08	10·28	1·35 (0·73–2·49)

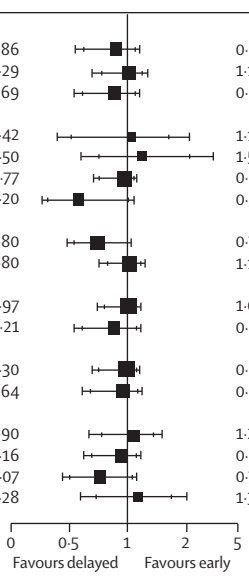

Figure 3: **Treatment interactions**

Data are number of events/number of patients, observed (O) minus expected (E) events, variance, and hazard ratio (HR; 95% CI).

with the exception of timing of second-line treatment and time from first-line treatment to randomisation, which were ad hoc.

Median time spent with good global health score was 7·2 months (95% CI 5·3–9·3) for women assigned to early and 9·2 months (6·4–10·5) for those assigned to delayed treatment (figure 2). Time from randomisation to first deterioration in global health score or death (figure 2) was shorter (median 3·2 months, 95% CI 2·4–4·3) in the early group compared with delayed (5·8 months, 4·4–8·5; HR 0·71, 95% CI 0·58–0·88; p=0·002). Subgroup analyses of individual components of the QLQ-C30 subscales showed deterioration in score sooner in the early group than in the delayed group for almost all subscales, and there was evidence of significant disadvantages for role, emotional, social, and fatigue subscales (table 4) with early treatment. Since the QLQ-C30 questionnaire asks about symptoms only in the previous week, and the forms were completed just before each course of chemotherapy, this method could underestimate any reduction in quality of life due to chemotherapy.

Discussion

Our results challenge the widespread belief that earlier treatment for recurrent cancer must be better, particularly for cancers for which recurrent disease is disseminated and curative options few. They provide no evidence that early initiation of chemotherapy because of a rising CA125 concentration improves survival or quality of life compared with delaying of chemotherapy until signs or symptoms of recurrence for women with complete radiological and biochemical remission after first-line chemotherapy for ovarian cancer. There are no other randomised controlled trials addressing this question (see panel). With such a large amount of information, 70% of patients having died, a late effect of treatment is very unlikely. One explanation for our findings could be that the lead time between CA125 rise and clinical recurrence, particularly for rapidly growing, possibly more chemosensitive tumours, might be too short for early introduction of chemotherapy to have a beneficial effect. However, we found no evidence that early chemotherapy had greater effect in those with a short time from end of first-line chemotherapy to randomisation (figure 3).

The median lead time between randomisation with CA125 rise and second-line chemotherapy for clinical recurrence was 4·8 months. If more recently proposed criteria of an early signal of CA125 recurrence were used[19] the proportion of patients with a rise in CA125 might have been higher, more patients might have been randomised, with those starting chemotherapy in the early-treatment group having a greater lead time. The lead time might also have been greater if CA125 had been measured more frequently. If we had seen any benefit from earlier treatment, one could anticipate that a longer lead time could give greater benefits. However, since there was no evidence that earlier chemotherapy resulted in survival or quality of life benefit, increasing of the lead time would result in more women living with the anxiety associated with an increased CA125 concentration for longer.

First-line chemotherapy had to be platinum-based, but because the type of chemotherapy might vary according to timing of relapse and previous experience with different treatments (eg, neuropathy), choice of second-line regimen was left to the treating clinician. There was a small difference in chemotherapy regimens given for relapse; 34% of those in the early-treatment group received platinum-taxane combination therapy at relapse, compared with 39% of those receiving delayed treatment. This small difference (11 patients), which could favour delayed treatment, might have arisen as a result of the

change to combination therapy due to the positive results of the ICON4/OVAR trial,[13] with oncologists wishing to treat symptomatic patients more aggressively. However, this small difference is unlikely to account for the absence of benefit from early treatment, and there was no difference in the effect of treatment before and after 2003, when ICON4/OVAR was published and clinical practice changed.[13] There were other differences in chemotherapy administered that might favour early treatment, including more second-line chemotherapy, more second-line chemotherapy cycles, and more third-line treatments.

We have not presented adverse events from individual chemotherapy drugs and regimens, since specific chemotherapy regimens were not mandated. Thus, toxic effects were not included as a secondary outcome measure. However, the safety of individual participants in the trial was monitored. Serious adverse events and adverse events of all regimens and cause of death were reviewed by the independent data monitoring committee at each of their meetings, and no safety concerns were identified.

The extent of initial surgery was not recorded and was not used as a stratification factor. We were aware of the importance of residual disease as a prognostic factor for outcome after first-line therapy, but felt that accurate surgical data would be difficult to obtain for all patients. We assumed that, since women who entered this trial were in clinical and radiological remission with a normal CA125 concentration, a good prognostic group had been selected and other prognostic factors derived from earlier in patients' cancer histories would be less important. Furthermore, with randomisation of a large number of patients, important prognostic factors (both known and currently unknown) should be equally distributed between the randomised groups. Recent analysis of a trial in which extent of residual disease was an inclusion criterion has however shown that this factor remains significant after first-line therapy.[20] We are unable to exclude an imbalance in the randomised groups with respect to extent of residual disease as an explanation for our findings, but suggest that this effect is unlikely.

There was no evidence for a benefit of early treatment in the small group of women presenting with recurrent FIGO stage I or II ovarian cancer after adjuvant chemotherapy. This result is perhaps not surprising, since outcomes after recurrence are similar for women with early and advanced initial disease.[20] For other cancers, cure is sometimes achieved with surgery alone or combined with adjuvant therapy, but isolated recurrence is rare with ovarian cancer.[16,21,22] Patients who have complete resection of recurrent ovarian cancer have been shown in observational studies to have better survival than those with incomplete resection.[21,22]

Early detection of relapse by CA125 monitoring could be said to lead to more patients being diagnosed at relapse with completely resectable disease and having successful surgery, and thus longer survival. However, the ability to completely resect recurrent tumour could be dependent on the biology of the tumour, and not time of detection. Contrary to expectations, we have shown that earlier chemotherapy had no survival benefit. Therefore, randomised trials showing a benefit from surgery for relapsed disease are essential before CA125 follow-up is routinely recommended to trigger radiological detection of relapse amenable to surgical treatment.

For the first time women can be given evidence-based advice and can make informed choices about follow-up. Women should be informed that there is no evidence of

	Median time to deterioration (months)		Hazard ratio (95% CI)	p value
	Early treatment (n=174)	Delayed treatment (n=178)		
Functional				
Physical	8·7	8·6	1·01 (0·75–1·35)	0·94
Role	3·5	6·0	0·74 (0·55–0·98)	0·006
Emotional	4·2	7·5	0·77 (0·58–1·02)	0·02
Cognitive	8·3	10·0	1·01 (0·75–1·36)	0·93
Social	4·1	8·6	0·72 (0·54–0·96)	0·003
Symptom				
Fatigue	2·6	6·1	0·64 (0·48–0·85)	<0·0001
Nausea and vomiting	5·5	9·2	0·89 (0·66–1·20)	0·31
Pain	5·9	6·3	1·00 (0·75–1·34)	0·97
Dyspnoea	5·2	8·6	0·81 (0·61–1·09)	0·07
Insomnia	4·1	7·9	0·82 (0·62–1·10)	0·08
Appetite loss	7·1	8·2	0·96 (0·72–1·28)	0·69
Constipation	5·8	7·8	0·85 (0·63–1·14)	0·14
Diarrhoea	10·5	11·0	0·99 (0·74–1·32)	0·94
Financial difficulties	18·6	18·1	0·96 (0·71–1·29)	0·70

EORTC=European Organisation for Research and Treatment of Cancer.

Table 4: **Time to first deterioration in quality of life score or death for subscales of EORTC QLQ-C30 questionnaire**

Panel: **Research in context**

Systematic review

A Cochrane systematic review protocol[16] evaluating follow-up strategies in ovarian cancer after first-line treatment was assessed as up to date as of July, 2008. We therefore did systematic searches repeating the search strategies[16] for randomised controlled trials from January, 2008, to date using Embase,[17] Medline, and The Cochrane Central Register of Controlled Trials[18] including search terms for ovarian cancer, follow-up, and CA125. Searches returned 134 potentially relevant articles; however, no randomised controlled trials addressing a similar question to MRC OV05/EORTC 55955 were found.

Interpretation

MRC OV05/EORTC 55955 is the only randomised controlled trial designed to investigate the timing of relapsed treatment for ovarian cancer on the basis of CA125 concentration.

a benefit from early treatment on the basis of rising CA125 concentration, and no deterioration in quality of life by delaying chemotherapy. If CA125 concentration rises during follow-up, chemotherapy can be safely delayed until symptoms or signs of tumour recurrence develop. Regular CA125 monitoring might remain a requirement in clinical trials, but women might wish not to be told their results. Some women, despite these trial results, might choose to continue regular CA125 monitoring as an aid to planning their life. However, the results of this trial suggest that they can opt to forgo routine CA125 monitoring if their disease is in complete remission after first-line treatment, and be reassured that if they are worried or develop any signs suspicious of tumour relapse they will have rapid access to CA125 measurement.

Contributors

Trial design was developed by GJSR, MKBP, MELVDB, CC, DG, GCJ, and AMS. Patient recruitment was carried out by GJSR, MELVDB, DG, AL, GCJ, GK, CM, and all MRC OV05 and EORTC 55955 collaborators. Data analysis was done by CLG, WQ, MKBP, and CC. Data interpretation was done by GJSR, AMS, WQ, CLG, MKBP, MELVDB, CC, DG, and GCJ. The first draft of the report was written by GJSR, AMS, MELVBD, CLG, WQ, CC, and MKBP. All of the writing committee commented on the report.

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Conflicts of interest

We declare that we have no conflicts of interest.

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