Articles

Adjuvant chemotherapy for localised resectable soft-tissue sarcoma of adults: meta-analysis of individual data

*Sarcoma Meta-analysis Collaboration**

Summary

Background Individually, randomised trials have not shown conclusively whether adjuvant chemotherapy benefits adult patients with localised resectable soft-tissue sarcoma.

Methods A quantitative meta-analysis of updated data from individual patients from all available randomised trials was carried out to assess whether adjuvant chemotherapy improves overall survival, recurrence-free survival, and local and distant recurrence-free intervals (RFI) and whether chemotherapy is differentially effective in patients defined by age, sex, disease status at randomisation, disease site, histology, grade, tumour size, extent of resection, and use of radiotherapy.

Findings 1568 patients from 14 trials of doxorubicin-based adjuvant chemotherapy were included (median follow-up 9·4 years). Hazard ratios of 0·73 (95% CI 0·56–0·94, p=0·016) for local RFI, 0·70 (0·57–0·85, p=0·0003) for distant RFI, and 0·75 (0·64–0·87, p=0·0001) for overall recurrence-free survival, correspond to absolute benefits from adjuvant chemotherapy of 6% (95% CI 1–10), 10% (5–15), and 10% (5–15), respectively, at 10 years. For overall survival, the hazard ratio of 0·89 (0·76–1·03) was not significant (p=0·12), but represents an absolute benefit of 4% (1–9) at 10 years. These results were not affected by prespecified changes in the groups of patients analysed. There was no consistent evidence that the relative effect of adjuvant chemotherapy differed for any subgroup of patients for any endpoint. However, the best evidence of an effect of adjuvant chemotherapy for survival was seen in patients with sarcomas of the extremities.

Interpretation The meta-analysis provides evidence that adjuvant doxorubicin-based chemotherapy significantly improves the time to local and distant recurrence and overall recurrence-free survival. There is a trend towards improved overall survival.

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*Writing committee, participating investigators, institutions, and secretariat listed at end of paper

Correspondence to: Dr J F Tierney, MRC Cancer Trials Office, 5 Shaftesbury Road, Cambridge CB2 2BW, UK (e-mail: jt@mrc-cto.cam.ac.uk)

Introduction

Soft-tissue sarcomas are rare and complex tumours of mesenchymal origin. Although most patients present with apparently localised disease, which allows good local control, about 50% die from subsequent metastases.[1] The reported activity of doxorubicin in this disorder[2–4] has led to much research on the use of doxorubucin-based adjuvant chemotherapy. However, because of difficulties in accruing patients, few trials have been large enough to detect moderate treatment effects reliably, and most have had equivocal results. Many qualitative reviews of trial publications (eg, McGrath et al,[5] Mertens et al[6]) have failed to synthesise these results reliably. Three meta-analyses of published reports, one of which was restricted to sarcomas of the extremities,[7] have suggested that adjuvant chemotherapy may prolong the local recurrence-free interval (local RFI) and distant recurrence-free interval (distant RFI),[8] recurrence-free survival,[7,8] and overall survival.[7–9] However, such analyses, based on results extracted from published reports, are subject to several potential biases, such as exclusion of unpublished trials, variable follow-up, postrandomisation exclusions, and differing definitions of endpoints.[9]

The most reliable way to assess the available evidence and establish the size of any effect of adjuvant chemotherapy is to collect individual data for all patients randomised in all eligible trials, and to combine the results of these trials in an appropriate intention-to-treat analysis. This approach is the best for time-to-event analyses. Follow-up can be brought up to date and more flexible and detailed analyses, including subgroup analyses, are possible. Such a meta-analysis was therefore initiated by the UK Medical Research Council Cancer Trials Office, Cambridge, in collaboration with University College London Medical School (London), Institut Curie (Paris), Hamilton Regional Cancer Centre (Ontario), and the European Organisation for Research and Treatment of Cancer (EORTC; Brussels). Primarily, this meta-analysis aimed to assess whether adjuvant chemotherapy improves survival of patients with localised soft-tissue sarcoma and to quantify any effect of chemotherapy on the appearance of local and distant disease. It aimed also to investigate whether certain groups of patients benefit more, or less, from chemotherapy.

Patients and methods

The methods used were prespecified in a protocol (available from the corresponding author on request).

Study	Accrual period	Drugs given in addition to doxorubicin	Doxorubicin dose (mg/m²)		Disease sites	Number of patients
			Total	Per cycle		
GOG[21]	1973–82	None	480	60	Uterus	225
DFCI/MGH[22]	1978–83	None	450	90	Extremities, trunk, head, neck, retroperitoneum	46
ECOG[23]	1978–82	None	490	70	Extremities, trunk, head, neck, retroperitoneum	47
SSG[24]	1981–86	None	540	60	Extremities, trunk, head, neck, breast, thorax, abdomen	240
Rizzoli[25,26]	1981–86	None	450	75	Extremities	77
IGSC[27,28]	1983–86	None	420	70	Extremities, trunk, head, neck, retroperitoneum	92
MDA[29]	1973–76	Cyclophosphamide, dactinomycin, vincristine	420	60	Extremities, trunk	59*
Mayo[30,31]	1975–81	Vincristine, cyclophosphamide, dactinomycin, dacarbazine	200	50	Extremities, trunk	76
NCI 4[32,33]†	1977–81	Cyclophosphamide, methotrexate	500–550	50–70	Extremities	26
NCI 5[34,35]†	1977–89	Cyclophosphamide, methotrexate	500–550	50–70	Trunk, head, neck, breast, retroperitoneum	80
NCI 6[32,33]†‡	1977–81	Cyclophosphamide, methotrexate	500–550	50–70	Extremities	41
EORTC[36]	1977–88	Cyclophosphamide, vincristine, dacarbazine	400	50	Extremities, trunk, head, neck	468
Bergonie[37]	1981–88	Cyclophosphamide, vincristine, dacarbazine	400–500	50	Extremities, trunk, head, neck, retroperitoneum, pelvis	65
Sakk (57/87) (unpublished)	1987–90	Ifosfamide	550	50–90	Extremities, trunk	29

GOG=Gynecologic Oncology Group; DFCI/MGH=Dana-Farber Cancer Institute/Massachusetts General Hospital; ECOG=Eastern Cooperative Oncology Group; SSG=Scandinavian Sarcoma Group; Rizzoli=Istituti Ortepedici Rizzoli; IGSC=Intergroup Sarcoma Committee; MDA=M D Anderson Cancer Center; Mayo=Mayo Clinic; NCI=National Cancer Institute; EORTC=European Organisation for Research and Treatment of Cancer; Bergonie=Institut Bergonie; SAKK=Swiss Group for Clinical Cancer Research.
*Data not available for 3 patients. †Time to event taken from date of definitive surgery rather than randomisation date. ‡Differed from NCI 4 in the way surgery was selected.

Table 1: **Characteristics of trials included**

Data were sought for all patients randomised in all eligible randomised trials (published or unpublished) and updated follow-up requested. The criteria for inclusion of trials were that they randomly assigned patients with localised resectable soft-tissue sarcoma adjuvant chemotherapy or no chemotherapy after local treatment; that the randomisation method precluded previous knowledge of the treatment assignment; and that accrual was completed by December, 1992. Within trials, patients were excluded from the main analyses if, at randomisation, they were known to be younger than 15 years, had metastatic disease, or had received induction chemotherapy. Furthermore, patients with locally recurrent disease at randomisation were excluded from the analyses of RFIs and recurrence-free survival.

Trials were identified by searches of MEDLINE and CANCERLIT, with the optimum search strategy developed by the Cochrane Collaboration[10] and EMBASE, and also by examination of the reference lists of trial publications, review articles, and books. Trial investigators collaborating in the meta-analysis and trial registers (UK Committee on Cancer Research Register of Clinical Trials and Physicians Data Query Clinical Protocols) were also consulted to help identify unpublished trials.

The updated data requested were: date of birth or age, sex, disease status at randomisation, disease site, histology, grade, tumour size, primary treatment, allocated treatment, extent of resection, date of randomisation, survival status, cause of death, date of death or last follow-up, local-recurrence status, date of local recurrence, distant-recurrence status, and date of distant recurrence. All data received were checked thoroughly to ensure both the accuracy of the meta-analysis database and the quality of randomisation and follow-up. Any queries were resolved and the final database entries verified by the responsible trial investigator or statistician.

Local RFI and distant RFI were defined as the time from randomisation until first local or distant recurrence. Patients without recurrence by the time of last follow-up were censored on that date, and patients who died without recurrence were censored on the date of death. Patients who had a local recurrence were not censored in the analysis of distant recurrence or vice versa (except for two trials in which only the first recurrence was recorded), because local recurrence did not seem to preclude the possibility of later distant recurrence and vice versa. Recurrence-free survival was taken as the time from randomisation until any recurrence or death (by any cause), whichever happened first. Patients alive without recurrence were censored on the date of last follow-up. Overall survival was defined as the time from randomisation until death (by any cause). Surviving patients and those lost to follow-up were censored on the date of last follow-up. In each case, unless otherwise specified by the investigators, the date of last follow-up was taken to refer to both disease status and survival status.

Survival analyses were stratified by trial, and the log-rank-expected number of events and variance were used to calculate the hazard ratios for individual trials and combined across all trials by the fixed-effects model.[11] Thus, the time-to-event for individual patients was used within trials to calculate hazard ratios, representing the overall risk of death or recurrence on adjuvant chemotherapy compared with control. Within prespecified subgroups of patients, similar stratified analyses were done for all endpoints except local RFI, for which there were too few events for any meaningful analyses to be done. As defined above, some patients were excluded from the main analyses. All other randomised patients were included in the main analyses, which were carried out by intention to treat. The effect of exclusions of patients was explored by sensitivity analyses. Simple (non-stratified) Kaplan-Meier curves were generated.[12] Control-group baseline probabilities for each endpoint, derived from these curves at 10 years, together with overall hazard ratios, were used to calculate the absolute effects of treatment.[13]

χ^2 tests were used to test for gross statistical heterogeneity over all trials (χ^2 tests for heterogeneity) and the consistency of effect across different subsets of trials and across different subgroups of patients (χ^2 tests for interaction). These tests were aimed primarily at detecting quantitative differences (differences in size rather than direction), because there was no a-priori reason to expect qualitative differences. When subgroups had a natural order, the χ^2 test for trend was used. In all tests of significance the two-sided p value is given.

Results

Of 23 potentially eligible trials, six were excluded—four because they were not adjuvant studies;[14–17] one because all patients received preoperative intra-arterial induction chemotherapy before randomisation;[18] and one because the tumours were deemed non-resectable (EST-3782, unpublished). Three further trials were not eligible: two because they are still accruing patients (NCI-92-C-0210, EORTC 62931); and one because it closed in December, 1996 (Italian Cooperative Group). Data could not be obtained for two published studies[19,20] and one unpublished study (SWOG-8791), accounting for a total of 31 patients. The meta-analysis is therefore based

Characteristic	Number of patients
Age (years)	
<15	8 (1%)
15–30	312 (20%)
31–60	850 (54%)
>60	364 (23%)
Not available	34 (2%)
Sex	
Male	686 (44%)
Female	847 (54%)
Not available	35 (2%)
Disease status	
Primary	1155 (74%)
Recurrent	179 (11%)
Metastatic	16 (1%)
Re-excision	21 (1%)
Not available	197 (13%)
Disease site	
Extremity	904 (58%)
Trunk	185 (12%)
Uterus	264 (17%)
Other	163 (10%)
Not available	52 (3%)
Histology	
Leiomyosarcoma	183 (12%)
Liposarcoma	140 (9%)
Malignant fibrous histiocytoma	309 (20%)
Synovial	165 (10%)
Other (no AIDS-related tumours)	492 (31%)
Not available	279 (18%)
Grade*	
Low	86 (5%)
High	1048 (67%)
Not available	434 (28%)
Tumour size (cm)	
<5	280 (18%)
5–10	452 (29%)
>10	258 (16%)
Not available	578 (37%)
Extent of resection	
Clear	1189 (76%)
Marginal/involved	231 (15%)
Not available	148 (9%)
Radiotherapy	
No	792 (51%)
Yes	744 (47%)
Not available	32 (2%)

*Low=American Joint Cancer Committee (AJC) grade 1, Federation Nationale des Centre de Lutte Contre le Cancer (FNLCC) grade 1, and Broder's grades 1 and 2. High=AJC grades 2 and 3, FNLCC grades 2 and 3, and Broder's grades 3 and 4.

Table 2: **Characteristics of all patients (1568) in included trials**

on 14 trials (table 1; 13 published,[21–37] one unpublished) including 1568 patients. This total represents 98% of patients from known, eligible, and completed randomised trials. Follow-up for most trials was updated, giving a median of 9·4 years (medians for individual trials 4·9–17·6 years).

All identified trials used chemotherapy with doxorubicin alone or in combination with other drugs. Total planned doses ranged from 200 mg/m^2 to 550 mg/m^2 with a dose per cycle of 50–90 mg/m^2. The patients reflect the eligibility criteria of the individual trials (table 2), although we emphasise that some were excluded from the main analyses (table 3).

All treatment comparisons were between patients assigned local treatment plus adjuvant chemotherapy and patients assigned local treatment only (controls). Local treatment was surgery with or without radiotherapy.

Effects of adjuvant chemotherapy

Local RFI—Data from 13 trials on 1315 patients and 229 local recurrences were included in this analysis. One trial (ECOG[23]) recorded recurrence but did not distinguish between local and distant recurrence; it could not, therefore, be included in analyses of local and distant RFI. The results for individual trials had wide CIs and were inconclusive (figure 1), but for the results combined, the overall hazard ratio was significantly in favour of chemotherapy (χ^2 [1 df] 5·78, p=0·016). There was no clear evidence of heterogeneity in the effect of chemotherapy between trials (χ^2 [10 df] 14·06, p=0·17). The overall hazard ratio of 0·73 (95% CI 0·56–0·94) represents a 27% reduction in the risk of local recurrence and corresponds to an absolute benefit of 6% (95% CI 1–10) at 10 years, with the local RFI improved from 75% to 81%. Most local recurrences occurred during the first 4 years after randomisation (figure 2).

Distant RFI—Data from 13 trials on 1315 patients, and 413 distant recurrences were included in this analysis. All individual trial estimates favoured chemotherapy (figure 1), but the CIs were wide. Three reached conventional levels of significance (p<0·05), but none was significant at p<0·01. The combined results gave a highly significant overall benefit of adjuvant chemotherapy (χ^2 [1 df] 13·23, p=0·0003) with little evidence of statistical heterogeneity (χ^2 [12 df] 7·00, p=0·86). The overall hazard ratio of 0·70 (95% CI 0·57–0·85) or 30% reduction in the risk of metastases, suggests an absolute benefit of 10% (95% CI 5–15) at 10 years, with the distant RFI improved from 60% to 70% (figure 2).

Overall recurrence-free survival—Data were available for all 14 trials; 1366 patients and 707 recurrences or deaths were included in this analysis. The overall hazard ratio of 0·75 (95% CI 0·64–0·87) was strongly in favour of adjuvant chemotherapy (figure 1; χ^2 [1 df] 14·59, p=0·0001) with little evidence of statistical heterogeneity between trials (χ^2 [13 df] 9·26, p=0·75), equivalent to a 25% reduction in the risk of recurrence or death. The absolute improvement is 10% at 10 years (95% CI 5–15), such that overall recurrence-free survival would be improved from 45% to 55% (figure 2).

Overall survival—For the primary endpoint of overall survival, data were available for all 14 trials, and 1544 patients and 691 deaths were included (table 3). The

Patients excluded	Local RFI		Distant RFI		Overall recurrence-free survival		Overall survival	
	Hazard ratio (95% CI)	Events/ patients	Hazard ratio (95% CI)	Events/ patients	Hazard ratio (95% CI)	Events/ patients	Hazard ratio (95% CI)	Events/ patients
Local recurrence, <15 years old, metastases, or received induction chemotherapy	0·73 (0·56–0·94)	229/1315	0·70 (0·57–0·85)	413/1315	0·75 (0·64–0·87)	707/1366	0·91 (0·78–1·07)	597/1366
<15 years old, metastases, or received induction chemotherapy	0·73 (0·57–0·92)	268/1493	0·68 (0·57–0·82)	493/1493	0·74 (0·65–0·85)	821/1544	0·89 (0·76–1·03)	691/1544
None	0·72 (0·57–0·92)	270/1517	0·68 (0·57–0·81)	498/1517	0·75 (0·65–0·85)	840/1568	0·90 (0·77–1·04)	709/1568

Table 3: **Sensitivity of main results to exclusion of patients**

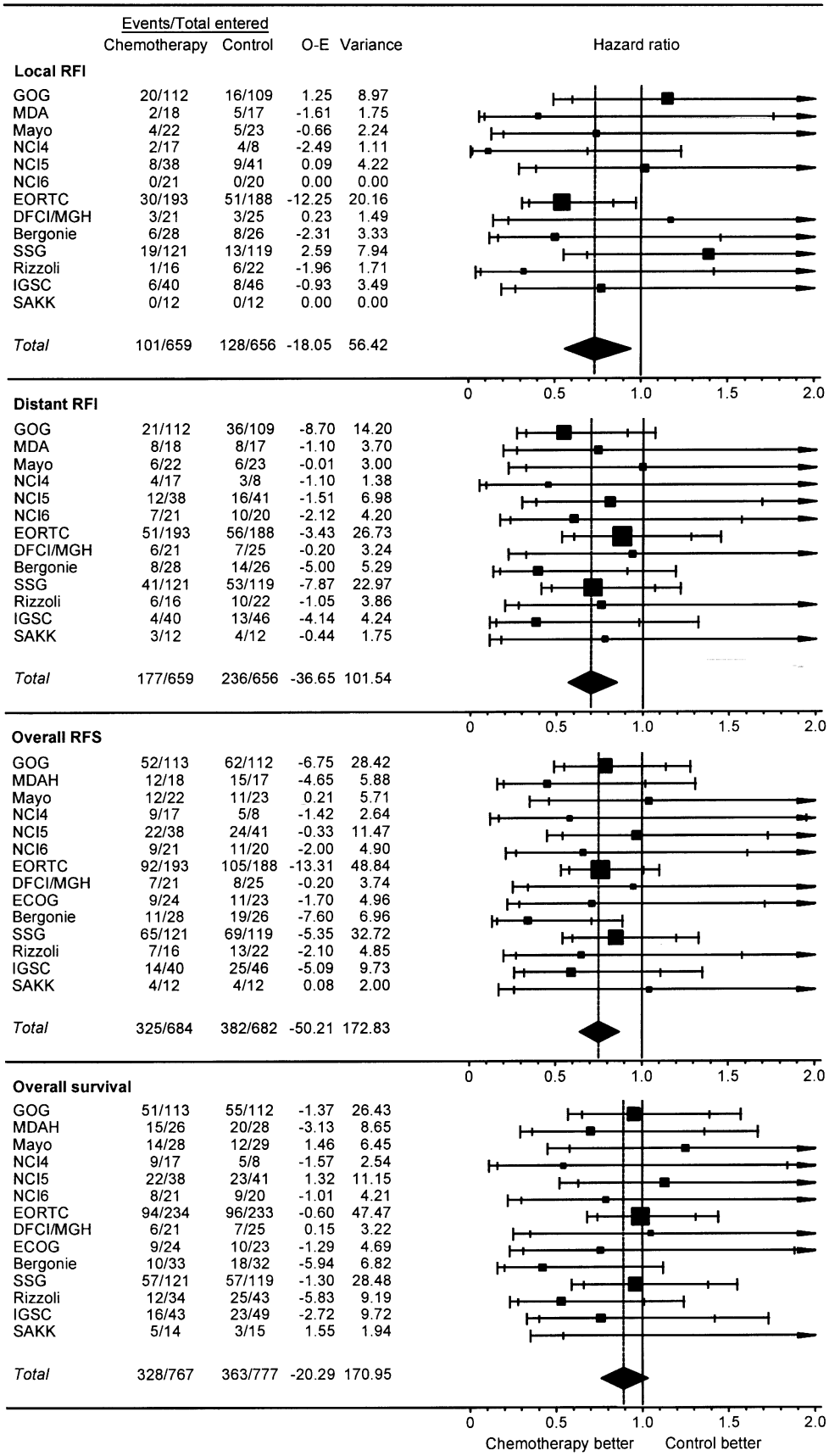

Figure 1: **Meta-analysis of effects of adjuvant chemotherapy versus control**

Squares represent hazard ratios; area is proportional to amount of information available in trial; bars=95% CI (inner limit) and 99% CI (outer limit). Diamonds=overall hazard ratios for results of all trials combined; extremes of diamond give 95% CI. Trial group abbreviations as in table 1. O–E=observed–expected. RFS=recurrence-free survival

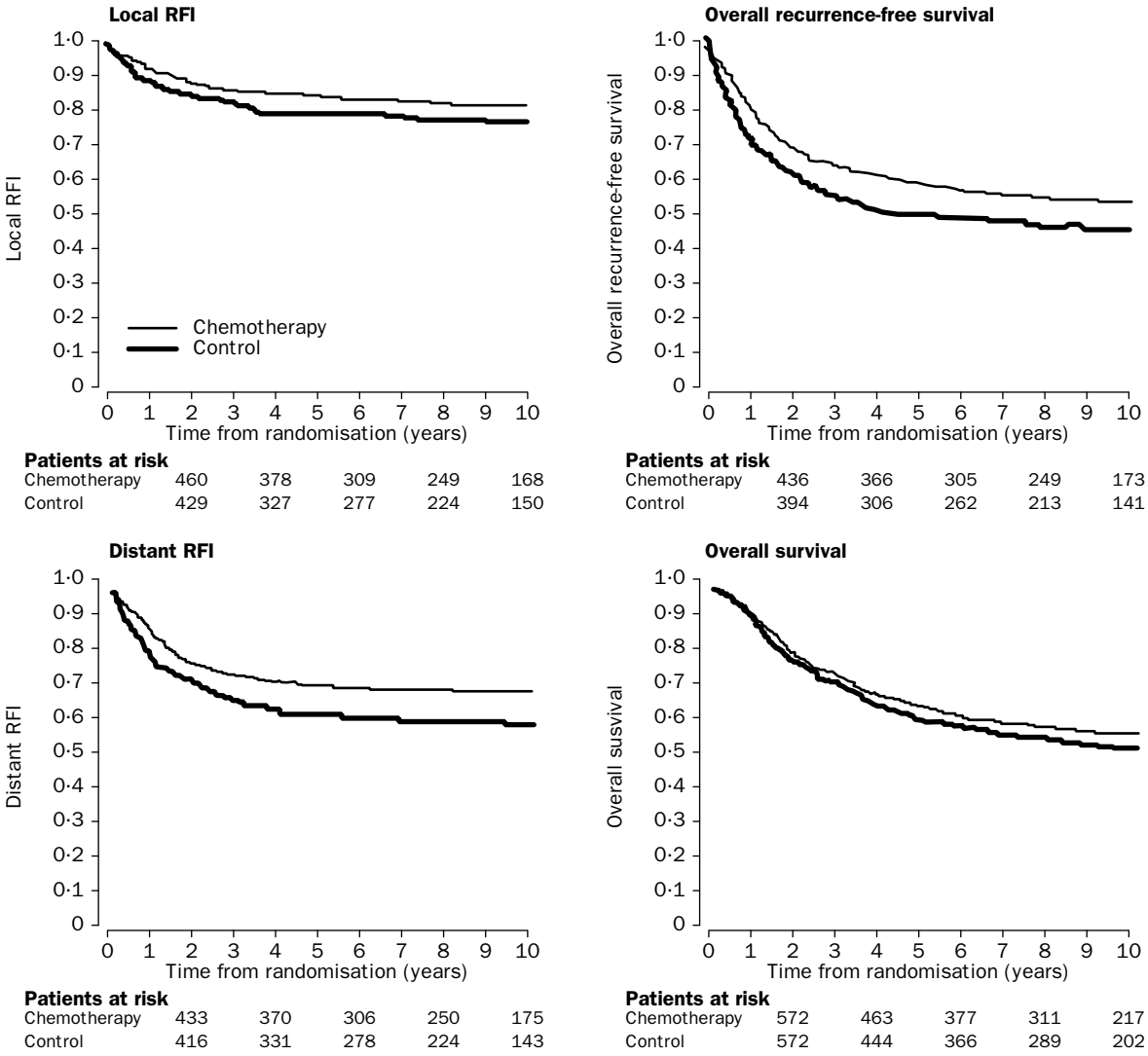

Figure 2: **Kaplan-Meier curves of local RFI, distant RFI, overall recurrence-free survival, and overall survival for adjuvant chemotherapy versus control**

trend for overall survival was in favour of chemotherapy (figure 1) with a hazard ratio of 0·89 (95% CI 0·76–1·03) but it was not significant (χ^2 [1 df] 2·41, p=0·12). There was no evidence of statistical heterogeneity across trials (χ^2 [13 df] 11·8, p=0·54), nor any evidence that the result was influenced by whether the trials used doxorubicin alone or in combination with other drugs (interaction χ^2 [1 df] 0·17, p=0·68). The results were similar in an analysis of death from soft-tissue sarcoma only for the ten trials that gave cause of death (hazard ratio 0·88 [95% CI 0·73–1·06]; χ^2 [1 df] 1·72, p=0·19). The potential absolute benefit was 4% (95% CI 1–9) at 10 years, representing a possible survival improvement from 50% to 54% (figure 2).

Table 3 shows that for local RFI, distant RFI, overall recurrence-free survival and overall survival, the results were not affected by the inclusion or exclusion of various groups of patients, despite some large changes in numbers of events.

Subgroup analyses

Although data for most variables were available for more than 90% of patients, fewer data were available for histology (82%, of which 59% had undergone review), grade (72%, of which 25% had undergone review), and tumour size (63%).

For overall survival, there was no clear evidence to suggest that any subgroup benefited more or less from adjuvant chemotherapy (figure 3). There was some suggestion that men benefited more than women from chemotherapy.

Among patients with lesions of the extremities (376 deaths, 886 patients), the hazard ratio was 0·80 (p=0·029), equivalent to a 7% absolute benefit at 10 years. This group had the clearest evidence of a treatment effect on survival. The wide CIs for the other sites reflect the small numbers, and there was no clear evidence that the results differed from those for extremity sarcomas (p=0·58).

The effect of chemotherapy was greater for both distant RFI and overall recurrence-free survival than for overall survival and so there may be a greater possibility of detecting differences between subgroups; there was, however, no evidence of a differential effect of chemotherapy on these endpoints in any of the subgroups defined above.

Owing to clinical interest, additional subgroup analyses were specified a posteriori to examine whether

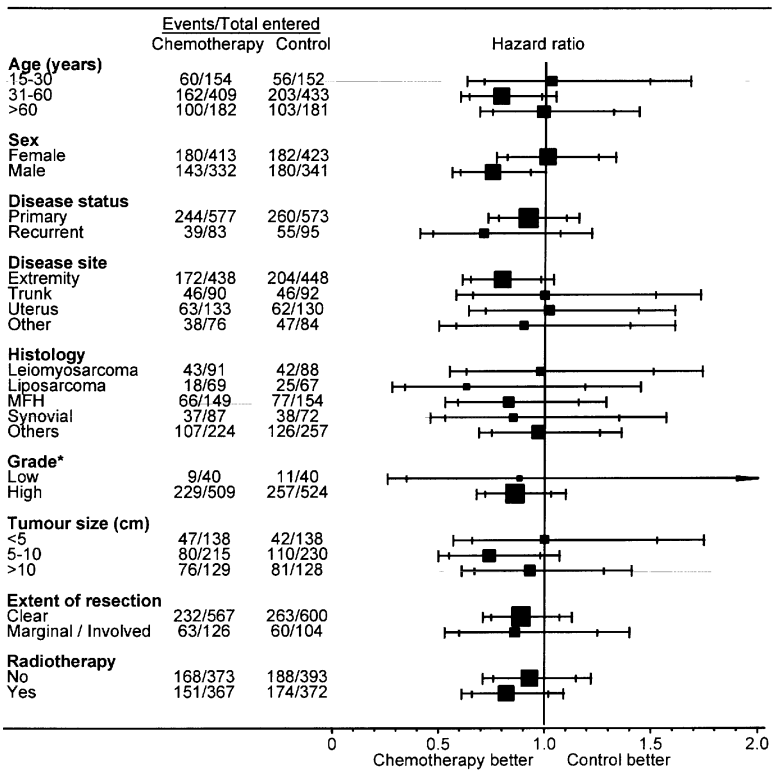

Figure 3: **Effect of adjuvant chemotherapy on overall survival by subgroup**
Format as figure 1; squares represent overall hazard ratio for each subgroup when results of all trials are combined.
Age class (interaction χ^2 [2 df] 2·32, p=0·31; trend χ^2 [1 df] 0·02, p=0·88), sex (interaction χ^2 [1 df] 3·86, p=0·049), disease status at randomisation (interaction χ^2 [1 df] 1·36, p=0·24), disease site (interaction χ^2 [3 df] 1·96, p=0·58), histology (interaction χ^2 [4 df] 1·91, p=0·75), grade (interaction χ^2 [1 df] 0·001, p=0·97), tumour size class (interaction χ^2 [2 df] 1·81, p=0·40; trend χ^2 [1 df] 0·002, p=0·96), extent of resection (interaction χ^2 [1 df] 0·02, p=0·88), and use of radiotherapy (interaction χ^2 [1 df] 0·71, p=0·40).
MFH=malignant fibrous histiocytoma.

there was a differential effect of adjuvant chemotherapy in patients with large, high-grade tumours of the extremity compared with others and also across patients defined by tumour size greater or less than 8 cm. However, fewer data were available for these definitions (60% and 56%, respectively), and for both overall survival and overall recurrence-free survival the relative effect of chemotherapy was similar. (Figures and results not shown are available from the corresponding author on request.)

Discussion

This meta-analysis provides the most reliable, up-to-date, and comprehensive summary of the average effect of adjuvant chemotherapy for localised soft-tissue sarcoma.

We found good evidence that adjuvant doxorubicin-based chemotherapy improves the time to local and distant recurrence and overall recurrence-free survival with a trend towards improved overall survival. In each case, estimates of the effect of adjuvant chemotherapy were not affected by the exclusion of quite large numbers of patients. Furthermore, the effect of adjuvant chemotherapy on overall survival was not affected by whether doxorubicin was given alone or in combination with other drugs or by whether deaths from all causes or only soft-tissue sarcoma deaths were considered.

Several hypotheses could explain why the impact of adjuvant chemotherapy appears less for overall survival than for other endpoints. On relapse, patients may receive effective salvage therapy that improves survival. When relapse is treated by local therapy, in particular thoracotomy for lung metastases, differences in rates of recurrence between treatment and control groups could affect our estimates. When this is modelled on the assumption that thoracotomy is offered equally and is effective on both groups, the impact on estimates of survival is negligible (details available on request). By contrast, the use of chemotherapy on relapse is probably more common and perhaps more effective in the control group (since tumours previously exposed to adjuvant chemotherapy may be drug resistant), and survival for relapsed patients would therefore be proportionately greater. Therefore, as for many adjuvant trials, the comparison becomes one of immediate versus deferred chemotherapy. Another possibility is that adjuvant chemotherapy genuinely has no effect on overall survival (either as adjuvant or second-line treatment), but does have an effect on recurrence of local and distant disease. Alternatively, adverse effects of adjuvant chemotherapy on overall survival could mask underlying survival benefits. However, when only sarcoma deaths were analysed, thus excluding serious late and early toxic effects of doxorubicin, the estimate of the treatment effect was similar to the main results, suggesting that this hypothesis is not correct.

The analyses did not provide consistent evidence that

the relative effect of adjuvant chemotherapy was smaller or larger for any particular type of patient. There was some suggestion that men might benefit more than women. Also, the clearest evidence and the largest observed effect was in patients with lesions of the extremities. This result does not necessarily mean that chemotherapy is less effective in other sites, for which there were substantially fewer patients. However, the results of subgroup analyses must always be interpreted cautiously,[38] especially when multiple analyses have been done and the overall result shows no significant difference, or data are limited, as in these analyses. Nevertheless, the prognoses for different tumour types vary substantially, and the same relative effect of chemotherapy can have a different absolute effect and perhaps a different clinical interpretation. At 10 years, baseline survival ranged from 35% to 80% and baseline recurrence-free survival from 35% to 75% across the various subgroups. Thus, the hazard ratios of 0·89 for survival and 0·75 for recurrence-free survival are equivalent to absolute potential benefits from adjuvant chemotherapy of between 2% and 4% and 6% and 11%, respectively.

Although this meta-analysis can provide only average estimates of the effect of adjuvant chemotherapy for localised resectable soft-tissue sarcoma, it is probably the best evidence on which to base treatment policy. Overall, the analyses suggest that immediate doxorubicin-based chemotherapy can lengthen the time alive without recurrence, and there is a trend toward improved survival. However, the analyses cannot provide any guidance on particular drug regimens or doses. Although the trials included in the meta-analysis did not collect data on patient-reported quality-of-life measures, doxorubicin toxicity was reported. Common acute effects were leucopenia, alopecia, nausea, and vomiting, sometimes leading to lack of compliance or reduction in doxorubicin dose. Serious cardiac complications associated with doxorubicin were observed in some trials, but cardiotoxic death was uncommon. Furthermore, such deaths will have been accounted for in our analyses, which included deaths by all causes.

There was little evidence that certain types of patients benefited more or less from adjuvant chemotherapy. However, soft-tissue sarcomas are a heterogeneous group, affecting a broad range of patients, and their underlying prognoses will assist both clinicians and patients in assessing whether the net benefit of treatment is clinically worthwhile, particularly in the light of doxorubicin toxicity.

Further follow-up, particularly of the later trials and inclusion of current randomised trials of adjuvant chemotherapy, will add to the evidence in future updates of this meta-analysis.

The rarity and complexity of soft-tissue sarcomas has meant that accrual of sufficient numbers of patients into trials has been, and continues to be, difficult. Our results may convince some researchers that future trials should contain a doxorubicin-based chemotherapy control arm. Others may consider that an overall survival advantage of doxorubicin-based chemotherapy is still questionable (except perhaps for extremity sarcomas). In either case, future randomised trials must be larger than those undertaken previously if they are reliably to detect treatment effects of moderate size—generally the best that can be expected from new treatments. For example, to detect differences of around 10% in overall survival or recurrence-free survival would require around 900 patients. This total is clearly not possible without large-scale collaboration between research groups and preferential entry of patients into sarcoma trials.

Sarcoma Meta-analysis Collaboration

Writing Committee—J F Tierney, L A Stewart, M K B Parmar.
Secretariat—C D M Fletcher, G Jones, V Mosseri, M K B Parmar, M Patel, M C Ruiz de Elvira, R L Souhami, L A Stewart, R Sylvester, J F Tierney, T Tursz.
Institutions—Jubileum Institute, Lund University Hospital (T A Alvegård, H Sigurdsson; Scandinavian Sarcoma Group); Columbia-Presbyterian Medical Center, Columbia University, New York (K Antman; Dana-Faber Cancer Institute/Massachusetts General Hospital); SIAK Coordinating Center, Bern (M Bacchi); Comprehensive Cancer Center, University of Michigan (L H Baker; Intergroup Sarcoma Committee); M D Anderson Cancer Center, University of Texas (R S Benjamin); Gynecologic Oncology Group Statistical Office, Roswell Park Cancer Institute, Buffalo (M F Brady); Christie Hospital, Manchester (V Bramwell; EORTC); Institut Bergonie, Bordeaux (B N Bui); Mayo Clinic, Rochester, Minnesota (J H Edmonson); Brigham and Women's Hospital, Boston (C D M Fletcher); Istituti Ortopedici Rizzoli, Bologna (F Gherlinzoni); Hamilton Regional Cancer Center, Ontario (G Jones, M Patel); University Hospital, Lausanne (S Leyvraz; Swiss Group for Clinical Cancer Research); Department of Biostatistics, Institut Curie, Paris (V Mosseri); University of Alabama at Birmingham (G A Omura; Gynecologic Oncology Group); Medical Research Council Cancer Trials Office, Cambridge (M K B Parmar, L A Stewart, J F Tierney); Centre René Huguenin, St Cloud (J Rouëssé; EORTC); European Group for Blood and Marrow Transplantation, University College London, London (M C Ruiz de Elvira); Eastern Cooperative Oncology Group Statistical Office, Dana-Farber Cancer Institute, Boston (L Ryan); Department of Oncology, University College London Medical School, London (R L Souhami); Meta-analysis Unit, EORTC Data Center, Brussels (R Sylvester); Institute Gustave-Roussy, Villejuif (T Tursz; EORTC); Department of Oncology, Universitaire Ziekenhuizen, Leuven (A T van Oosterom; EORTC); Surgery Branch, National Cancer Institute, Bethesda (J C Yang).

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References

1 Delaney TF, Yang JC, Glatstein E. Adjuvant therapy for adult patients with soft tissue sarcomas. *Oncology* 1991; **5:** 105–18.
2 Blum R, Carter S. A new anticancer drug with significant clinical activity. *Ann Intern Med* 1974; **80:** 249–59.
3 Benjamin R, Wiernik P, Bachur N. Adriamycin: a new effective agent in the therapy of disseminated sarcomas. *Med Pediatr Oncol* 1975; **1:** 63–76.
4 Gottlieb JA, Baker LH, O'Bryan RM, et al. Adriamycin (NSC-123127) used alone and in combination for soft tissue and bony sarcomas. *Cancer Chemother Rep* 1975; **6:** 271–82.
5 McGrath PC, Sloan DA, Kenady DE. Adjuvant therapy of soft-tissue sarcomas. *Clin Plast Surg* 1995; **1:** 21–29.
6 Mertens WC, Bramwell VHC. Adjuvant chemotherapy for soft tissue sarcomas. *Hematol Oncol Clin North Am* 1995; **9:** 801–15.
7 Zalupski MM, Ryan JR, Hussein ME, et al. Defining the role of adjuvant chemotherapy for patients with soft tissue sarcoma of the extremities. In Salmon SE, ed. Adjuvant therapy of cancer VII. Philadelphia: JB Lippincott, 1993: 385–92.
8 Jones GW, Chouinard M, Patel M. A systematic overview and quantitative meta-analysis. *Clin Invest Med* 1991; **14** (suppl 19): A772.
9 Tierney JF, Mosseri V, Stewart LA, Souhami RL, Parmar MKB. Adjuvant chemotherapy for soft-tissue sarcoma: review and meta-analysis of the published results of randomised clinical trials. *Br J Cancer* 1995; **72:** 469–75.
10 Dickersin K, Scherer R, Lefebvre C. Identifying relevant studies for

systematic reviews. In: Chalmers I, Altman DG, eds. Systematic reviews. London: BMJ Publishing Group, 1995: 17–36.
11 Yusuf F, Peto R, Lewis J, Collins R, Sleight T. Beta blockade during and after myocardial infarction: an overview of randomised clinical trials. *Prog Cardiovasc Dis* 1985; **27:** 335–71.
12 Kaplan EL, Meier P. Nonparametric estimation from incomplete observation. *J Am Stat Assoc* 1958; **53:** 457–81.
13 Freedman LS. Tables of the number of patients required in clinical trials using the logrank test. *Stat Med* 1982; **1:** 121–29.
14 Schoenfeld DA, Rosenbaum C, Horton J, Wolter JM, Falkson G, Deconti RC. A comparison of adriamycin versus vincristine and adriamycin, and cyclophosphamide versus vincristine, actinomycin-D, and cyclophosphamide for advanced sarcoma. *Cancer* 1982; **50:** 2757–62.
15 Pinedo HM, Verweij J. The treatment of soft tissue sarcomas with focus on chemotherapy: a review. *Radiother Oncol* 1986; **5:** 193–205.
16 Baker LH, Frank J, Fine G, et al. Combination chemotherapy using adriamycin, DTIC, cyclophosphamide, and actinomycin D for advanced soft tissue sarcomas: a randomized comparative trial—a phase III Southwest Oncology Group study (7631). *J Clin Oncol* 1987; **5:** 851–61.
17 Borden EC, Mato DA, Edmonson JH, Ritch PS, Masanori S. Randomized comparison of doxorubicin and vindesine to doxorubicin for patients with metastatic soft-tissue sarcomas. *Cancer* 1990; **66:** 862–67.
18 Eilber FR, Giuliano AE, Huth JF, Morton DL. A randomized prospective trial using postoperative adjuvant chemotherapy (adriamycin) in high-grade extremity soft tissue sarcoma. *Am J Clin Oncol* 1988; **11:** 39–45.
19 Kinsella T, Sindelar W, Lack E, Glatstein E, Rosenberg SA. Preliminary results of a randomized study of adjuvant radiation therapy in resectable adult retroperintoneal soft tissue sarcomas. *J Clin Oncol* 1988; **6:** 18–25.
20 Piver MS, Shashikant BL, Marchetti DL, Emrich LJ. Effect of adjuvant chemotherapy on time to recurrence and survival of stage I uterine sarcomas. *J Surg Oncol* 1988; **38:** 233–39.
21 Omura GA, Blessing JA, Major F, et al. A randomised trial of adjuvant adriamycin in uterine sarcomas: a Gynecologic Oncology Group study. *J Clin Oncol* 1985; **3:** 1240–45.
22 Antman K, Suit H, Amato D, et al. Preliminary results of a randomized trial of adjuvant doxorubicin for sarcomas: lack of apparent difference between treatment groups. *J Clin Oncol* 1984; **2:** 601–08.
23 Lerner HJ, Amato DA, Savlov E, et al. Eastern Cooperative Oncology Group: a comparison of adjuvant doxorubicin and observation for patients with localized soft tissue sarcoma. *J Clin Oncol* 1987; **5:** 613–17.
24 Alvegård TA, Sigurdsson H, Mouridsen H, et al. Adjuvant chemotherapy with doxorubicin in high grade soft tissue sarcoma: a randomized trial of the Scandinavian Sarcoma Group. *J Clin Oncol* 1989; **7:** 1504–13.
25 Gherlinzoni F, Bacci G, Picci P, et al. A randomized trial for treatment of high grade soft tissue sarcoma of the extremities: preliminary results. *J Clin Oncol* 1986; **4:** 552–58.
26 Picci P, Bacci G, Gherlinozi F, et al. Results of randomized trial for the treatment of localised soft tissue tumors (STS) of the extremities in adult patients. In: Ryan JR, Baker LH, eds. Recent concepts in sarcoma treatment. Dordrecht: Kluwer Academic Publishers, 1988: 144–48.
27 Baker LH. Adjuvant therapy for soft tissue sarcomas. In: Ryan JR, Baker LH, eds. Recent concepts in sarcoma treatment. Dordrecht: Kluwer Academic Publishers, 1988: 130–35.
28 Antman K, Ryan L, Borden E, et al. Pooled results from three randomized adjuvant studies of doxoru bicin versus observation in soft tissue sarcoma: 10 year results and review of the literature. In: Salmon SE, ed. Adjuvant therapy of cancer VI. Philadelphia: WB Saunders, 1990: 529–43.
29 Benjamin RS, Terjanian TO, Fenoglio CJ, et al. The importance of combination chemotherapy for adjuvant treatment of high-risk patients with soft-tissue sarcomas of the extremities. In: Salmon SE, ed. Adjuvant therapy of cancer V. Orlando: Grune and Stratton, 1987: 735–44.
30 Edmonson JH, Fleming TR, Ivins JC, et al. Randomized study of systemic chemotherapy following complete excision of nonoesseous sarcomas. *J Clin Oncol* 1984; **2:** 1390–96.
31 Edmonson JH. Systemic chemotherapy following complete excision of nonosseous sarcomas: Mayo Clinic experience. *Cancer Treat Symp* 1985; **3:** 89–97.
32 Rosenberg SA, Tepper J, Glatstein E, et al. Prospective randomized evaluation of adjuvant chemotherapy in adults with soft tissue sarcoma of the extremities. *Cancer* 1983; **52:** 424–34.
33 Chang AE, Kinsella T, Glatstein E, et al. Adjuvant chemotherapy for patients with high-grade soft-tissue sarcomas of the extremity. *J Clin Oncol* 1988; **6:** 1491–500.
34 Glenn J, Kinsella T, Glatstein E, et al. A randomized, prospective trial of adjuvant chemotherapy in adults with soft tissue sarcomas of the head and neck, breast, and trunk. *Cancer* 1985; **55:** 1206–14.
35 Glenn J, Sindelar W, Kinsella T, et al. Results of multimodality therapy of resectable soft-tissue sarcomas of the retroperitoneum. *Surgery* 1985; **97:** 316–25.
36 Bramwell V, Rouesse J, Steward W, et al. Adjuvant CYVADIC chemotherapy for adult soft tissue sarcoma—reduced local recurrence but no improvement in survival: a study of the European Organization for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group. *J Clin Oncol* 1994; **12:** 1137–49.
37 Ravaud A, Bui NB, Coindre JM, et al. Adjuvant chemotherapy with cyvadic in high risk soft tissue sarcoma: a randomized prospective trial. In: Salmon SE, ed. Adjuvant therapy of cancer VI. Philadelphia: WB Saunders, 1990: 556–66.
38 Collins R, Gray R, Godwin J, Peto R. Avoidance of large biases and large random errors in the assessment of moderate treatment effects: the need for systematic overviews. *Stat Med* 1987; **6:** 245–50.