Adjuvant chemotherapy for localised resectable soft tissue sarcoma in adults (Review)

Sarcoma Meta-analysis Collaboration (SMAC) - see acknowledgement section for list of authors

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[Intervention Review]

Adjuvant chemotherapy for localised resectable soft tissue sarcoma in adults

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ABSTRACT

Background

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

Objectives

Adjuvant chemotherapy aims to lessen the recurrence of cancer after surgery with or without radiotherapy. The objective of this review was to assess the effects of adjuvant chemotherapy in adults with resectable soft tissue sarcoma after such local treatment.

Search methods

We searched the Cochrane Controlled Trials Register, UKCCCR Register of Cancer Trials, Physicians Data Query, EMBASE, MEDLINE and CancerLit.

Selection criteria

Randomised trials of adjuvant chemotherapy after local treatment in adults with localised resectable soft tissue sarcoma were included. Only trials in which accrual was completed by December 1992 were included.

Data collection and analysis

Individual patient data were obtained. Accuracy of data and quality of randomisation and follow-up of trials was assessed.

Main results

Fourteen trials of doxorubicin-based adjuvant chemotherapy involving 1568 patients were included. Median follow-up was 9.4 years. For local recurrence-free interval the hazard ratio (HR) with chemotherapy was 0.73 (95% Confidence Interval (CI) 0.56 to 0.94). For distant recurrence-free interval it was 0.70 (95% CI 0.57 to 0.85). For overall recurrence-free survival it was 0.75 (95% CI 0.64 to 0.87). These correspond to significant absolute benefits of 6 to 10% at 10 years. For overall survival (OS) the HR of 0.89 (95% CI 0.76 to 1.03) was not significant but potentially represents an absolute benefit of 4% (95% CI 1 to 9) at 10 years. There was no consistent evidence of a difference in effect according to age, sex, stage, site, grade, histology, extent of resection, tumour size or exposure to radiotherapy. However, the strongest evidence of a beneficial effect on survival was shown in patients with sarcoma of the extremities.

Authors' conclusions

Doxorubicin-based adjuvant chemotherapy appears to significantly improve time to local and distant recurrence and overall recurrence-free survival in adults with localised resectable soft tissue sarcoma. There is some evidence of a trend towards improved overall survival.

PLAIN LANGUAGE SUMMARY

Doxorubicin after initial treatment for sarcoma reduces risk of recurrence

Usually at diagnosis sarcoma shows no sign of having spread outside the original site and treatment is surgery (with/without radiotherapy). In about half the patients the cancer recurs. There is evidence that doxorubicin-based chemotherapy after initial treatment reduces recurrence, either at the original site or elsewhere in the body. Chemotherapy also seems to increase the length of time patients live, but this is less certain.Greater benefit was seen in men and those whose tumour originated in a limb, but these results may have occurred by chance.

BACKGROUND

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 (Delaney 1991). The reported activity of doxorubicin in this disorder (Blum 1974, Benjamin 1975, Gottlieb 1975) has led to much research on the use of doxorubicin-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 (e.g., recently McGrath 1995, Mertens 1995) have failed to synthesise these results reliably. Three meta-analyses of the published literature, one of which was restricted to sarcomas of the extremities (Zalupski 1993), have suggested that adjuvant chemotherapy may prolong the local recurrence-free interval (local RFI) and distant recurrence-free interval (distant RFI) (Jones 1994), recurrence-free survival (Zalupski 1993, Jones 1994) and overall survival (Zalupski 1993, Jones 1994, Tierney 1995). However, such analyses, based on results extracted from the published reports are subject to several potential biases such as exclusion of unpublished trials, variable follow-up, post-randomisation exclusions and differing definitions of endpoints (Tierney 1995).

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 the University College London Medical School (London), the Institut Curie (Paris), the Hamilton Regional Cancer Centre (Ontario), and the European Organisation for Research and Treatment of Cancer (EORTC; Brussels). This meta-analysis was conducted on behalf of the Sarcoma Meta-analysis Collaboration (SMAC). Data was collated, checked and analysed by the MRC CTO. The collaborative group met in December 1995 to discuss preliminary results. This review was first published by SMAC in the Lancet (SMAC 1997) and is reproduced with their permission.

OBJECTIVES

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 patient groups benefit more, or less, from chemotherapy.

METHODS

Criteria for considering studies for this review

Types of studies

Trials (published and unpublished) were eligible for inclusion provided they randomised patients with localised resectable soft tissue sarcoma to receive either adjuvant chemotherapy or no chemotherapy following local treatment. The randomisation method should have precluded prior knowledge of the treatment assignment and accrual should have been completed by December 1992.

Types of participants

Adult patients with localised resectable soft tissue sarcoma. Individual data from all randomised patients were included in the meta-analysis. Where possible data were obtained for individuals who had been excluded from the original trial analyses. These individuals were included in the meta-analysis.

Types of interventions

Trials that compared either adjuvant chemotherapy or no chemotherapy following local treatment.

Types of outcome measures

Survival, local and distant recurrence-free intervals and recurrence-free survival.

Search methods for identification of studies

Trials were identified by searches of MEDLINE and CancerLit, with the optimal search strategy developed by the Cochrane Collaboration (Dickersin 1995) 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 (United Kingdom Committee on Cancer Research Register of Clinical Trials and Physicians Data Query Clinical Protocols) were also consulted to help identify unpublished trials. Searches were updated to October 1999 to identify new trials and the status of ongoing trials.

Data collection and analysis

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

Data was sought for all patients randomised in all eligible randomised trials (published or unpublished) and updated follow-up requested. 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 recurrence-free and distant recurrence-free intervals 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 where 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 (Yusuf 1985). 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 as compared to control. Within pre-specified subgroups of patients, similar stratified analyses were done for all endpoints except local recurrence-free interval, 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 on intention to treat. The impact of patient exclusions were explored by sensitivity analyses. Simple (non-stratified) Kaplan-Meier curves were generated (Kaplan 1958). These are not currently reproducible in the Cochrane Library but can be found in the meta-analysis publication. 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 (Freedman 1982).

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

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of ongoing studies.

Of 23 potentially eligible trials, four were excluded because they were not adjuvant studies (Schoenfeld 1982, Pinedo 1988, Baker 1987), one because all patients received preoperative intra-arterial induction chemotherapy before randomisation (Eilber 1988) and one because the patients were deemed non-resectable (EST-3782). Three further trials were not eligible: one because it is still accruing patients (EORTC 62931); and two because they closed after the December, 1992 cut-off for inclusion in first cycle of analyses (Frustaci 1987, NCI-92-C-0210). It is unlikely at this stage that inclusion of the relatively immature results of the Italian trial (Frustaci 1987) and the small number of patients from the American trial (NCI-92-C-0210) will impact on the results and conclusions of the review and so an update of the analysis is not planned until the EORTC study has closed (EORTC 62931). Data could not be obtained for two published studies (Kinsella 1988, Piver 1988) and one unpublished study (SWOG-8791) accounting for a total of 31 patients. The meta-analysis is therefore based on 14 trials (13 published, one unpublished) including 1568 patients (Table of included studies). 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 (median for individual trials of 4.9 to 17.6 years).

All identified trials used chemotherapy with doxorubicin alone or in combination with other drugs. Total planned doses ranged from 200mg/m2 to 550mg/m2 with a dose per cycle of 50 to 90mg/m2. The patients reflect the eligibility criteria of these individual trials, although it should be noted that some were excluded from the main analyses.

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.

Risk of bias in included studies

Only properly randomised trials were included, where the randomisation method precluded prior knowledge of the treatment assignment and accrual was completed by December 1992. 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.

Effects of interventions

Effects of adjuvant chemotherapy

Local recurrence-free interval

Data from 13 trials on 1315 patients and 229 local recurrences were included in this analysis. One trial (ECOG 1978) 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 confidence intervals and were inconclusive but, for the results combined, the overall hazard ratio was significantly in favour of chemotherapy (chi-square = 5.78, df = 1, p = 0.016). There was no clear evidence of heterogeneity in the effect of chemotherapy between trials (chi-square = 14.06, df = 10, p = 0.17). The overall hazard ratio of 0.73 (95% Confidence IntervaI 0.56-0.94) represents a 27% reduction in the risk of local recurrence and translates into an absolute benefit of 6% (95% CI 1-10) at 10 years, with the local recurrence-free interval improved from 75% to 81%. Most local recurrences took place in the first four years after randomisation.

Distant recurrence-free interval

Data from 13 trials on 1315 patients and 413 distant recurrences were included in this analysis. All individual trial estimates favoured chemotherapy, but 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 (chi-square = 13.23, df = 1, p = 0.0003) with little evidence of statistical heterogeneity (chi-square = 7.00, df = 12, 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 distant recurrence-free interval improved from 60% to 70%.

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 (chi-square = 14.59, df = 1, p = 0.0001) with little evidence of statistical heterogeneity between trials (chi-square = 9.26, df = 13, 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 45-55%.

Overall survival

For the primary endpoint of overall survival, data were available for all 14 trials, and 1544 patients and 691 deaths were included. The trend for overall survival was in favour of chemotherapy with a hazard ratio of 0.89 (95% CI 0.76-1.03), but it was not significant

(chi-square = 2.41, df = 1, p = 0.12). There was no evidence of statistical heterogeneity across trials (chi-square = 11.8, df = 13, p = 0.54), nor any evidence that the result was influenced by whether the trials used doxorubicin singly or in combination with other drugs (interaction chi-square = 0.17, df = 1, p = 0.68). The results were similar in an analysis of death from soft tissue sarcoma only for the 10 trials that gave cause of death (hazard ratio = 0.88, chi-square = 1.72, df = 1, p = 0.19). The potential absolute benefit was 4% (95% CI -1 to 9%) at 10 years, representing a possible survival improvement from 50% to 54%.

For local recurrence-free interval, distant recurrence-free interval, overall recurrence-free survival and survival, the results were not affected by the inclusion or exclusion of various groups of patients, despite some large changes in the number 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 (Age class:interaction chi-square=2.32, df = 2, p = 0.31; trend chi-square = 0.02, df = 2, p = 0.88; disease status at randomisation: interaction chi-square = 1.36, df = 1, p = 0.24; disease site: interaction chi-square = 1.96, df = 3, p = 0.58; histology: interaction chi-square = 1.91, df = 4, p = 0.75; grade: interaction chi-square = 0.001, df = 1, p = 0.97, tumour size class: interaction chi-square = 1.81, df = 2, p = 0.40, trend chi-square = 0.002, df = 1, p = 0.96; extent of resection: interaction chi-square = 0.02, df = 1, p = 0.88 and radiotherapy: interaction chi-square = 0.71, df = 1, p = 0.40). There was some suggestion that men benefited more than women from chemotherapy (interaction chi-square = 3.86, df = 1, p = 0.049).

Among patients with lesions of the extremities (376 deaths and 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 confidence intervals for the other sites reflects the small numbers, and there was no clear evidence that the results are different from those for extremity sarcomas (p = 0.58).

The effect of chemotherapy was greater for both distant recurrence-free interval 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 in any of the subgroups defined above.

Owing to clinical interest, additional subgroup analyses were specified a posteriori to examine whether there was a differential effect of adjuvant chemotherapy in patients with large, high grade tumours of the extremity compared to others and also across patients defined by tumour size greater or less than 8cm. However, less 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 toward improved overall survival. In each case, estimates of the effect of adjuvant chemotherapy were not affected by the exclusion of sometimes 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. Where relapse is treated by local therapy, in particular thoracotomy for lung metastases, differences in rates of recurrence on treatment and control could affect our estimates. When this is modelled on the assumption that thoracotomy is offered equally and is effective on both groups, then the impact on estimates of survival are minimal (details available on request). By contrast, the use of chemotherapy on relapse is probably more common and perhaps more effective in the control arm (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 associated with doxorubicin, the estimate of 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 extremity lesions. This does not necessarily mean it is less effective in other sites, for which there were substantially fewer patients. However, the results of subgroup analyses must always be interpreted cautiously (Collins 1987), especially when multiple analyses have been done and the overall result shows no significant difference, or data is limited, as in these analyses. Nevertheless, the prognoses for different tumour types varies considerably, such that 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.

AUTHORS' CONCLUSIONS

Implications for practice

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 with respect to particular drug regimens and 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 relatively 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 patient population 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.

Implications for research

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 in question (except perhaps for extremity sarcomas). In either case, future randomised trials must be larger than those undertaken previously, if they are to reliably 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 is clearly not possible without large-scale collaboration between research groups and preferential entry of patients into sarcoma trials.

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sub1. 15-30 *{published and unpublished data}*

sub1. 31-60 *{published and unpublished data}*

sub1. >60 *{published and unpublished data}*

sub2. Female *{published and unpublished data}*

sub2. Male *{published and unpublished data}*

sub3. Primary *{published and unpublished data}*

sub3. Recurrent *{published and unpublished data}*

sub4. Extremity *{published and unpublished data}*

sub4. Others *{published and unpublished data}*

sub4. Trunk *{published and unpublished data}*

sub4. Uterus *{published and unpublished data}*

sub5. Leiomyosarcoma *{published and unpublished data}*

sub5. Liposarcoma *{published and unpublished data}*

sub5. MFH *{published and unpublished data}*

sub5. Others *{published and unpublished data}*

sub5. Synovial *{published and unpublished data}*

sub6. High *{published and unpublished data}*

sub6. Low *{published and unpublished data}*

sub7. <5cm *{published and unpublished data}*

sub7. =5-10cm *{published and unpublished data}*

sub7. >10cm *{published and unpublished data}*

sub8. Clear *{published and unpublished data}*

sub8. Not clear *{published and unpublished data}*

sub9. No *{published and unpublished data}*

sub9. Yes *{published and unpublished data}*

References to studies excluded from this review

Baker 1987 *{published data only}*
Baker LH, Franks J, Fine G, Balcerzak SP, Stephens RL, Stuckey WJ, et al.Combination chemotherapy using Adriamycin, DTIC, cyclophosphamide, and actinomycin D for advanced soft tissue sarcomas: a randomised comparative trial, A phase III, Southwest Oncology Group Study. *Journal of Clinical Oncology* 1987;**5**(6):851–61.

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Eilber FR, Giuliano AE, Huth JF, Morton DL. A randomised prospective trial using postoperative adjuvant chemotherapy (Adriamycin) in high-grade extremity soft-tissue sarcoma. *American Journal of Clinical Oncology* 1988; **11**(1):39–45.

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NCI-92-C-0210 *{unpublished data only}*
NCI. Phase III randomized trial of adjuvant DOX/IFF vs no adjuvant chemotherapy following complete resection of adult high-grade soft tissue sarcoma confined to an extremity. Data on file Unpublished.

Pinedo 1988 *{published data only}*
Pinedo HM, Verweij J. The treatment of soft tissue sarcomas with focus on chemotherapy: a review. *Radiotherapeutic Oncology* 1986;**5**:193–205.

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Piver MS, Lele SB, Marchetti DL, Emrich LJ. Effect of adjuvant chemotherapy on time to recurrence and survival of stage I uterine sarcomas. *Journal of Surgical Oncology* 1988;**38**:233–9.

Schoenfeld 1982 *{published data only}*

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SWOG-8791 *{unpublished data only}*

SWOG. Phase III randomized study of adjuvant chemotherapy with ADR/DTIC/IPP vs no adjuvant therapy following resection with or without irradiation of adult grage III soft tissue sarcomas. Data on file Unpublished.

References to ongoing studies

EORTC 62931 *{published data only}*

Phase II randomized study of adjuvant high-dose DOX/IFF with G-CSFvs no adjuvant chemotherapy for high-grade soft tissue sarcoma. Ongoing study Starting date of trial not provided. Contact author for more information.

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Benjamin 1975

Benjamin R, Weirnick P, Bachur N. Adriamycin: a new effective agent in the therapy of disseminated sarcomas. *Medical and Pediatric Oncology* 1975;**1**:63–76.

Blum 1974

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Collins R, Gray R, Godwin J, Peto R. Avoidance of large biases and large random errors in the assessment of moderate effects of treatment effects: the need for systematic overviews. *Statistics in Medicine* 1987;**6**:245–50.

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Freedman 1982

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Yusuf S, Peto R, Lewis J, Collins R, Sleight P. Beta-blockade during and after myocardial infarction: An overview of the randomised trials. *Progress in Cardiovascular Diseases* 1985; **27**(5):335–71.

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References to other published versions of this review

SMAC 1997

Sarcoma Meta-analysis Collaboration. Adjuvant chemotherapy for localised resectable soft-tissue sarcoma of adults: meta-analysis of individual data. *The Lancet* 1997; **350**:1647–54.

* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Bergonie 1981

Methods	RCT, 1981-88	
Participants	65 adults with sarcoma of the extremities, trunk, head, neck, retroperitoneum or pelvis	
Interventions	Local treatment (surgery with or without radiotherapy) plus doxorubicin*-based combination (cyclophosphamide, vincristine, dacarbazine) chemotherapy vs local treatment alone *50 mg/m2 per cycle, 400-500 mg/m2 total	
Outcomes	Local recurrence, distant recurrence, survival	
Notes		
Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	A - Adequate

DFCI/MGH 1978

Methods	RCT, 1978-83	
Participants	46 adults with sarcoma of the extremities, trunk, head, neck, or retroperitoneum	
Interventions	Local treatment (surgery with or without radiotherapy) plus doxorubicin* chemotherapy vs local treatment alone *60 mg/m2 per cycle, 450 mg/m2 total	
Outcomes	Local recurrence, distant recurrence, survival	
Notes		
Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

ECOG 1978

Methods	RCT, 1978-82
Participants	47 adults with sarcoma of the extremities, trunk, head, neck or retroperitoneum
Interventions	Local treatment (surgery with or without radiotherapy) plus doxorubicin* chemotherapy vs local treatment alone *70mg/m2 per cylcle, 490mg/m2 total
Outcomes	Any recurrence, survival
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

EORTC 1977

Methods	RCT, 1977-88
Participants	468 adults with sarcoma of the extremities, trunk, head, neck
Interventions	Local treatment (surgery with or without radiotherapy) plus doxorubicin*-based combination (cyclophosphamide, vincristine, dacarbazine) chemotherapy vs local treatment alone *50 mg/m2 per cycle, 400 mg/m2 total
Outcomes	Local recurrence, distant recurrence, survival
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

GOG 1973

Methods	RCT, 1973-82
Participants	225 adults with sarcoma of the uterus
Interventions	Local treatment (surgery with or without radiotherapy) plus doxorubicin* chemotherapy vs local treatment alone *60 mg/m2 per cycle, 480 mg/m2 total

GOG 1973 (*Continued*)

Outcomes	Local recurrence, distant recurrence, survival	
Notes		
Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	A - Adequate

IGSC 1983

Methods	RCT, 1983-86	
Participants	92 adults with sarcoma of the extremities, trunk, head, neck or retroperitoneum	
Interventions	Local treatment (surgery with or without radiotherapy) plus doxorubicin* chemotherapy vs local treatment alone *70 mg/m2 per cycle, 420 mg/m2 total	
Outcomes	Local recurrence, distant recurrence, survival	
Notes		
Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	A - Adequate

Mayo 1975

Methods	RCT, 1975-81	
Participants	76 adults with sarcoma of the extremities or trunk	
Interventions	Local treatment (surgery) plus doxorubicin*-based combination (vincristine, cyclophosphamide, dactinomycin, dacarbazine) chemotherapy vs local treatment alone *50 mg/m2 per cycle, 200 mg/m2 total	
Outcomes	Local recurrence, distant recurrence, survival	
Notes		
Risk of bias		
Item	**Authors' judgement**	**Description**

Mayo 1975 (*Continued*)

Allocation concealment?	Unclear	B - Unclear

MDA 1973

Methods	RCT, 1973-76
Participants	59 adults with sarcoma of the extremities or trunk
Interventions	Local treatment (surgery with or without radiotherapy) plus doxorubicin*-based combination (cyclophosphamide, dactinomycin, vincristine) chemotherapy vs local treatment alone *60 mg/m2 per cycle, 420 mg/m2 total
Outcomes	Local recurrence, distant recurrence, survival
Notes	Data not available for 3 patients

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

NCI4 1977

Methods	RCT, 1977-81
Participants	26 adults with sarcoma of the extremities
Interventions	Local treatment (surgery with or without radiotherapy) plus doxorubicin*-based combination (cyclophosphamide, methotrexate) chemotherapy vs local treatment alone *50-70 mg/m2 per cycle, 500-550 mg/m2 total
Outcomes	Local recurrence, distant recurrence, survival
Notes	Time to event taken from the time of definitive surgery rather than the date of randomisation

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

NCI5 1977

Methods	RCT, 1977-81
Participants	80 adults with sarcomas of the trunk, head, neck, breast or retroperitoneum
Interventions	Local treatment (surgery with or without radiotherapy) plus doxorubicin*-based combination (cyclophosphamide, methotrexate) chemotherapy vs local treatment alone *50-70 mg/m2 per cycle, 500-550 mg/m2 total
Outcomes	Local recurrence, distant recurrence, survival
Notes	Time to event taken from date of definitive surgery rather than date of randomisation

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

NCI6 1977

Methods	RCT, 1977-81
Participants	41 adults with sarcoma of the extremities
Interventions	Local treatment (surgery with or without radiotherapy) plus doxorubicin*-based combination (cyclophosphamide, methotrexate) chemotherapy vs local treatment alone *50-70 mg/m2 per cycle, 500-550 mg/m2 total
Outcomes	Local recurrence, distant recurrence, survival
Notes	Time to event taken from the date of definitive surgery rather than the date of randomisation

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Rizzoli 1981

Methods	RCT, 1981-86
Participants	77 adults with sarcoma of the extremities
Interventions	Local treatment (surgery with or without radiotherapy) plus doxorubicin* chemotherapy vs local treatment alone *75mg/m2 per cycle, 450mg/m2 total

Rizzoli 1981 (*Continued*)

Outcomes	Local recurrence, distant recurrence, survival	
Notes		
Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

SAKK 57/87

Methods	RCT, 1987-90	
Participants	29 adults with sarcoma of the extremities or trunk	
Interventions	Local treatment (surgery with or without radiotherapy) plus doxorubicin*-based combination (ifosfamide) chemotherapy vs local treatment alone *50-90 mg/m2 per cycle, 550 mg/m2 total	
Outcomes	Local recurrence, distant recurrence, survival	
Notes	Unpublished	
Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

SSG 1981

Methods	RCT, 1981-86	
Participants	240 adults with sarcoma of the extremities, trunk, head, neck, breast, thorax, abdomen	
Interventions	Local treatment (surgery with or without radiotherapy) plus doxorubicin* chemotherapy vs local treatment alone *60 mg/m2 per cycle, 540 mg/m2 total	
Outcomes	Local recurrence, distant recurrence, recurrence-free survival, survival	
Notes		
Risk of bias		
Item	**Authors' judgement**	**Description**

Allocation concealment?	Yes	A - Adequate

sub1. 15-30

Methods	Subgroup analysis by age (stratified by trial)
Participants	
Interventions	
Outcomes	
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	D - Not used

sub1. 31-60

Methods	Subgroup analysis by age (stratified by trial)
Participants	
Interventions	
Outcomes	
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	D - Not used

sub1. >60

Methods	Subgroup analysis by age (stratified by trial)
Participants	
Interventions	
Outcomes	

sub1. >60 (*Continued*)

Notes		
Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	D - Not used

sub2. Female

Methods	Subgroup analysis by sex (stratified by trial)	
Participants		
Interventions		
Outcomes		
Notes		
Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	D - Not used

sub2. Male

Methods	Subgroup analysis by sex (stratified by trial)	
Participants		
Interventions		
Outcomes		
Notes		
Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	D - Not used

sub3. Primary

Methods	Subgroup analysis by disease status at randomisation (stratified by trial)	
Participants		
Interventions		
Outcomes		
Notes		
Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	D - Not used

sub3. Recurrent

Methods	Subgroup analysis by disease status at randomisation (stratified by trial)	
Participants		
Interventions		
Outcomes		
Notes		
Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	D - Not used

sub4. Extremity

Methods	Subgroup analysis by disease site (stratified by trial)
Participants	
Interventions	
Outcomes	
Notes	
Risk of bias	

sub4. Extremity (*Continued*)

Item	Authors' judgement	Description
Allocation concealment?	Unclear	D - Not used

sub4. Others

Methods	Subgroup analysis by disease site (stratified by trial)
Participants	
Interventions	
Outcomes	
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	D - Not used

sub4. Trunk

Methods	Subgroup analysis by disease site (stratified by trial)
Participants	
Interventions	
Outcomes	
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	D - Not used

sub4. Uterus

Methods	Subgroup analysis by disease site (stratified by trial)
Participants	
Interventions	
Outcomes	
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	D - Not used

sub5. Leiomyosarcoma

Methods	Subgroup analysis by histology (stratified by trial)
Participants	
Interventions	
Outcomes	
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	D - Not used

sub5. Liposarcoma

Methods	Subgroup analysis by histology (stratified by trial)
Participants	
Interventions	
Outcomes	
Notes	

Risk of bias

sub5. Liposarcoma (*Continued*)

Item	Authors' judgement	Description
Allocation concealment?	Unclear	D - Not used

sub5. MFH

Methods	Subgroup analysis by histology (stratified by trial)
Participants	
Interventions	
Outcomes	
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	D - Not used

sub5. Others

Methods	Subgroup analysis by histology (stratified by trial)
Participants	
Interventions	
Outcomes	
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	D - Not used

sub5. Synovial

Methods	Subgroup analysis by histology (stratified by trial)	
Participants		
Interventions		
Outcomes		
Notes		
Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	D - Not used

sub6. High

Methods	Subgroup analysis by grade (stratified by trial)	
Participants		
Interventions		
Outcomes		
Notes	High grade: AJC grades 2 and 3, FNLCC grades 2 and 3 and Broder's grades 3 and 4	
Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	D - Not used

sub6. Low

Methods	Subgroup analysis by grade (stratified by trial)
Participants	
Interventions	
Outcomes	
Notes	Low grade: American Joint Cancer Committee (AJC) grade 1, Federation Nationale des Centre de Lutte Contre le Cancer (FNLCC) grade 1 and Broder's (B) grades 1 and 2
Risk of bias	

sub6. Low (*Continued*)

Item	Authors' judgement	Description
Allocation concealment?	Unclear	D - Not used

sub7. <5cm

Methods	Subgroup analysis by tumour size (stratified by trial)
Participants	
Interventions	
Outcomes	
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	D - Not used

sub7. =5-10cm

Methods	Subgroup analysis by tumour size (stratified by trial)
Participants	
Interventions	
Outcomes	
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	D - Not used

sub7. >10cm

Methods	Subgroup analysis by tumour size (stratified by trial)
Participants	
Interventions	
Outcomes	
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	D - Not used

sub8. Clear

Methods	Subgroup analysis by extent of resection (stratified by trial)
Participants	
Interventions	
Outcomes	
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	D - Not used

sub8. Not clear

Methods	Subgroup analysis by extent of resection (stratified by trial)
Participants	
Interventions	
Outcomes	
Notes	

Risk of bias

sub8. Not clear (*Continued*)

Item	Authors' judgement	Description
Allocation concealment?	Unclear	D - Not used

sub9. No

Methods	Subgroup analysis by radiotherapy (stratified by trial)
Participants	
Interventions	
Outcomes	
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	D - Not used

sub9. Yes

Methods	Subgroup analysis by radiotherapy (stratified by trial)
Participants	
Interventions	
Outcomes	
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	D - Not used

GOG: Gynecologic Oncology Group; DFCI/MGH: Dana-Farber Cancer Institute / Massachusetts General Hospital; ECOG: Eastern Cooperative Oncology Group; SSG: Scandinavian Sarcoma Group; Rizzoli: Istituti Ortopedici Rizzoli; IGSC: Intergroup Sarcoma Committee; MDA: M.D. Anderson Cancer Center; Mayo: Mayo Clinic; NCI: National Cancer Institute, EORTC: European Organization for Research and Treatment of Cancer; Bergonie: Institut Bergonie, SAKK: Swiss Group for Clinical Cancer Research.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Baker 1987	Ineligible: Not an adjuvant study, but a chemotherapy comparison in advanced disease
Borden 1990	Ineligible: Not an adjuvant study, but a chemotherapy comparison in advanced disease
Eilber 1988	Ineligible: All patients received intra-arterial induction chemotherapy before randomisation
EST-3782	Ineligible: Only patients with inoperable, unresectable, or incompletely resected pimaries included
Frustaci 1987	Ineligible: Trial closed after the cut-off date described in inclusion criteria, but is eligible for inclusion in an update
Kinsella 1988	Eligible: Data could not be obtained
NCI-92-C-0210	Ineligible: Trial closed after the cut-off date described in inclusion criteria, but is eligible for inclusion in an update
Pinedo 1988	Ineligible: Not a RCT, but a review of chemotherapy
Piver 1988	Eligible: Data could not be obtained
Schoenfeld 1982	Ineligible: Not an adjuvant study, but a chemotherapy comparsion in advanced disease
SWOG-8791	Eligible: Data could not be obtained

Characteristics of ongoing studies *[ordered by study ID]*

EORTC 62931

Trial name or title	Phase II randomized study of adjuvant high-dose DOX/IFF with G-CSFvs no adjuvant chemotherapy for high-grade soft tissue sarcoma
Methods	
Participants	Patients with high-grade sarcoma following definitive surgery

EORTC 62931 (*Continued*)

Interventions	High-dose doxorubicin* + ifosfamide + G-CSF chemotherapy vs *75 mg/m2 per cycle, 375 mg/m2 total
Outcomes	Local recurrence, recurrence-free survival, survival, toxicity, morbidity
Starting date	
Contact information	EORTC
Notes	

DATA AND ANALYSES

Comparison 1. Effects of adjuvant chemotherapy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Local Recurrence-free Interval	13	1315	Peto Odds Ratio (95% CI)	0.73 [0.56, 0.94]
2 Distant Recurrence-free Interval	13	1315	Peto Odds Ratio (95% CI)	0.70 [0.57, 0.85]
3 Overall Recurrence-free Survival	14	1366	Peto Odds Ratio (95% CI)	0.75 [0.64, 0.87]
4 Overall Survival	14	1544	Peto Odds Ratio (95% CI)	0.89 [0.76, 1.03]

Comparison 2. Subgroup analysis

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Overall Survival	24		Peto Odds Ratio (95% CI)	Totals not selected
1.1 Age	3		Peto Odds Ratio (95% CI)	Not estimable
1.2 Sex	2		Peto Odds Ratio (95% CI)	Not estimable
1.3 Disease status (at randomisation)	2		Peto Odds Ratio (95% CI)	Not estimable
1.4 Disease site	4		Peto Odds Ratio (95% CI)	Not estimable
1.5 Histology	5		Peto Odds Ratio (95% CI)	Not estimable
1.6 Grade	2		Peto Odds Ratio (95% CI)	Not estimable
1.7 Tumour size	3		Peto Odds Ratio (95% CI)	Not estimable
1.8 Extent of resection	2		Peto Odds Ratio (95% CI)	Not estimable
1.9 Radiotherapy	2		Peto Odds Ratio (95% CI)	Not estimable

Analysis 1.1. Comparison 1 Effects of adjuvant chemotherapy, Outcome 1 Local Recurrence-free Interval.

Review: Adjuvant chemotherapy for localised resectable soft tissue sarcoma in adults

Comparison: 1 Effects of adjuvant chemotherapy

Outcome: 1 Local Recurrence-free Interval

Study or subgroup	Chemo n/N	No Chemo n/N	Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI	Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI
GOG 1973	20/112	16/109		1.15 [0.60, 2.21]
MDA 1973	2/18	5/17		0.40 [0.09, 1.75]
Mayo 1975	4/22	5/23		0.74 [0.20, 2.76]
NCI4 1977	2/17	4/8		0.11 [0.02, 0.68]
NCI5 1977	8/38	9/41		1.02 [0.39, 2.65]
NCI6 1977	0/21	0/20		0.0 [0.0, 0.0]
EORTC 1977	30/193	51/188		0.54 [0.35, 0.84]
DFCI/MGH 1978	3/21	3/25		1.17 [0.23, 5.81]
Bergonie 1981	6/28	8/26		0.50 [0.17, 1.46]
SSG 1981	19/121	13/119		1.39 [0.69, 2.78]
Rizzoli 1981	1/16	6/22		0.32 [0.07, 1.42]
IGSC 1983	6/40	8/46		0.77 [0.27, 2.19]
SAKK 57/87	0/12	0/12		0.0 [0.0, 0.0]
Total (95% CI)				**0.73 [0.56, 0.94]**

Heterogeneity: Chi^2 = 14.08, df = 10 (P = 0.17); I^2 =29%

Test for overall effect: Z = 2.40 (P = 0.016)

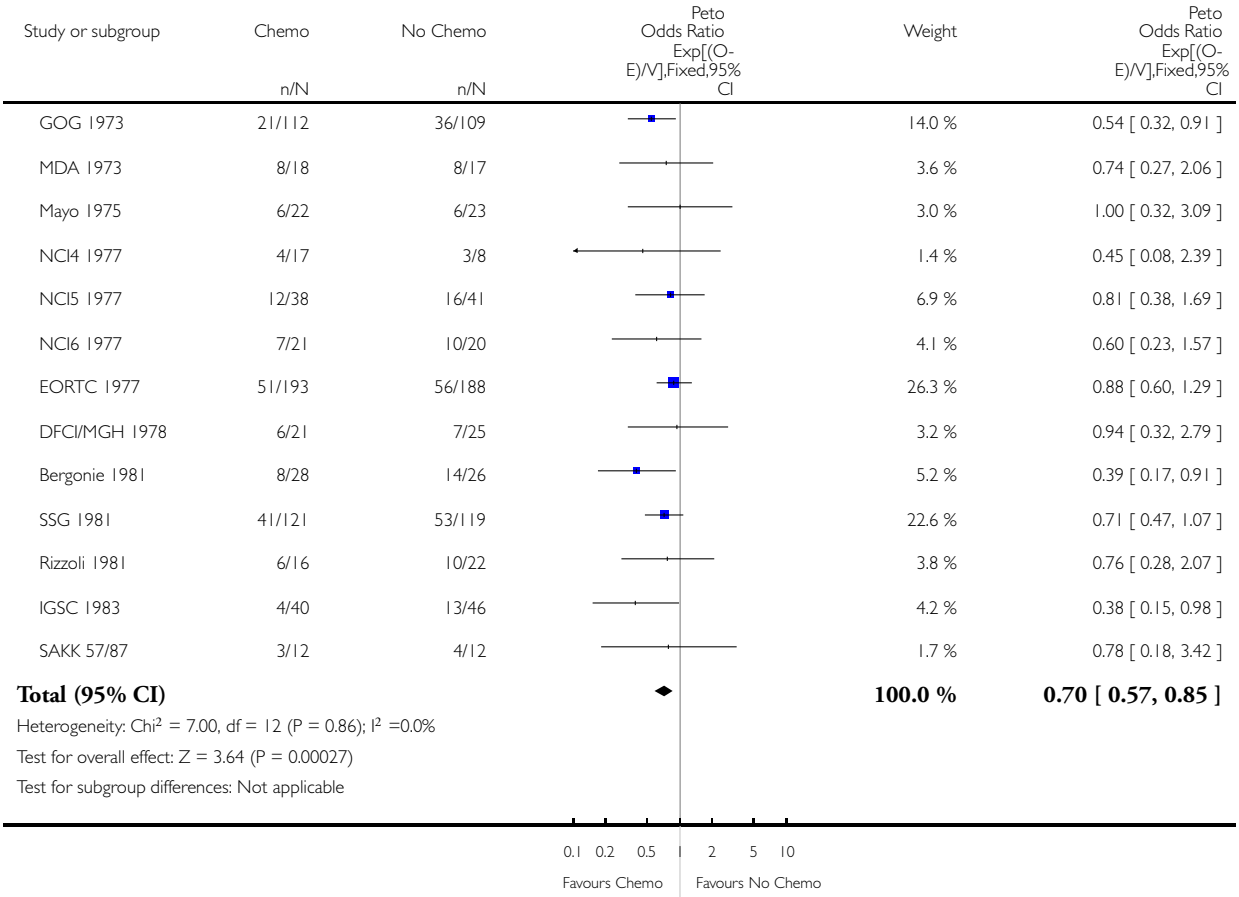
Test for subgroup differences: Not applicable

Analysis 1.2. Comparison 1 Effects of adjuvant chemotherapy, Outcome 2 Distant Recurrence-free Interval.

Review: Adjuvant chemotherapy for localised resectable soft tissue sarcoma in adults

Comparison: 1 Effects of adjuvant chemotherapy

Outcome: 2 Distant Recurrence-free Interval



Heterogeneity: $Chi^2 = 7.00$, df = 12 (P = 0.86); $I^2 = 0.0\%$

Test for overall effect: Z = 3.64 (P = 0.00027)

Test for subgroup differences: Not applicable

Analysis 1.3. Comparison 1 Effects of adjuvant chemotherapy, Outcome 3 Overall Recurrence-free Survival.

Review: Adjuvant chemotherapy for localised resectable soft tissue sarcoma in adults

Comparison: 1 Effects of adjuvant chemotherapy

Outcome: 3 Overall Recurrence-free Survival

Study or subgroup	Chemo n/N	No Chemo n/N	Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI	Weight	Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI
GOG 1973	52/113	62/112		16.4 %	0.79 [0.55, 1.14]
MDA 1973	12/18	15/17		3.4 %	0.45 [0.20, 1.02]
Mayo 1975	12/22	11/23		3.3 %	1.04 [0.46, 2.36]
NCI4 1977	9/17	5/8		1.5 %	0.58 [0.17, 1.95]
NCI5 1977	22/38	24/41		6.6 %	0.97 [0.54, 1.73]
NCI6 1977	9/21	11/20		2.8 %	0.66 [0.27, 1.61]
EORTC 1977	92/193	105/188		28.3 %	0.76 [0.58, 1.01]
DFCI/MGH 1978	7/21	8/25		2.2 %	0.95 [0.34, 2.61]
ECOG 1978	9/24	11/23		2.9 %	0.71 [0.29, 1.71]
Bergonie 1981	11/28	19/26		4.0 %	0.34 [0.16, 0.71]
SSG 1981	65/121	69/119		18.9 %	0.85 [0.60, 1.20]
Rizzoli 1981	7/16	13/22		2.8 %	0.65 [0.27, 1.58]
IGSC 1983	14/40	25/46		5.6 %	0.59 [0.32, 1.11]
SAKK 57/87	4/12	4/12		1.2 %	1.04 [0.26, 4.16]
Total (95% CI)				**100.0 %**	**0.75 [0.64, 0.87]**

Heterogeneity: Chi² = 9.26, df = 13 (P = 0.75); I² =0.0%

Test for overall effect: Z = 3.82 (P = 0.00013)

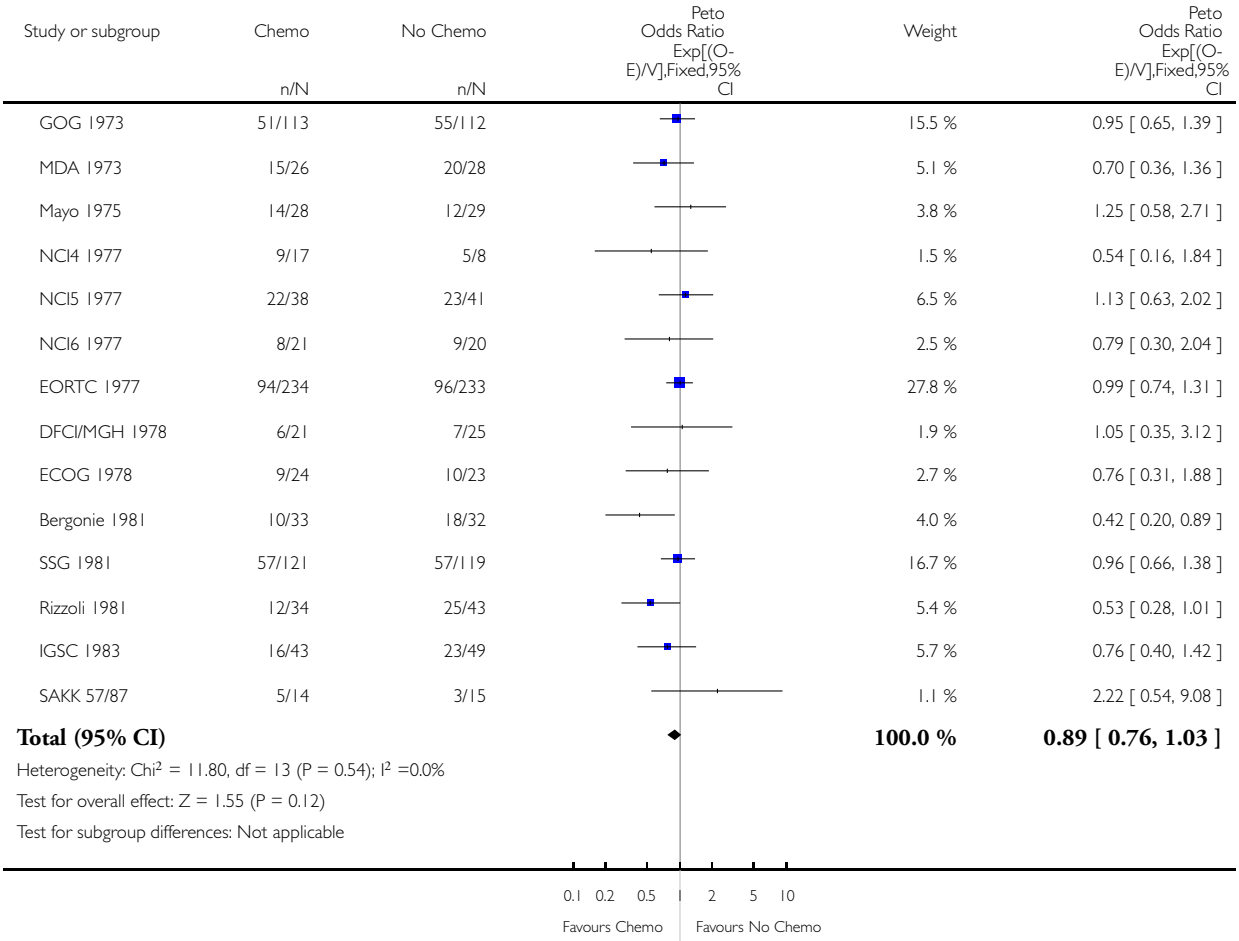
Test for subgroup differences: Not applicable

Analysis 1.4. Comparison 1 Effects of adjuvant chemotherapy, Outcome 4 Overall Survival.

Review: Adjuvant chemotherapy for localised resectable soft tissue sarcoma in adults

Comparison: 1 Effects of adjuvant chemotherapy

Outcome: 4 Overall Survival



Analysis 2.1. Comparison 2 Subgroup analysis, Outcome 1 Overall Survival.

Review: Adjuvant chemotherapy for localised resectable soft tissue sarcoma in adults

Comparison: 2 Subgroup analysis

Outcome: 1 Overall Survival

Study or subgroup	Chemo n/N	No Chemo n/N	Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI	Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI
1 Age				
sub1. 15-30	60/154	56/152		1.03 [0.71, 1.49]
sub1. 31-60	162/409	203/433		0.79 [0.64, 0.98]
sub1. >60	100/182	103/181		0.99 [0.75, 1.32]
2 Sex				
sub2. Female	180/413	182/423		1.01 [0.82, 1.25]
sub2. Male	142/332	180/241		0.75 [0.60, 0.93]
3 Disease status (at randomisation)				
sub3. Primary	244/577	260/573		0.92 [0.78, 1.10]
sub2. Male	39/83	55/95		0.71 [0.47, 1.07]
4 Disease site				
sub4. Extremity	172/738	204/448		0.80 [0.65, 0.98]
sub4. Trunk	46/90	46/92		1.00 [0.66, 1.52]
sub4. Uterus	63/133	62/130		1.02 [0.72, 1.44]
sub4. Others	38/76	47/84		0.90 [0.58, 1.40]
5 Histology				
sub5. Leiomyosarcoma	43/91	42/88		0.98 [0.63, 1.51]
sub5. Liposarcoma	18/69	25/67		0.63 [0.34, 1.19]
sub5. MFH	66/149	77/154		0.83 [0.59, 1.16]
sub5. Synovial	37/87	38/72		0.85 [0.53, 1.35]
sub5. Others	107/224	126/257		0.97 [0.75, 1.26]
6 Grade				
sub6. Low	9/40	11/40		0.88 [0.35, 2.21]
sub6. High	229/509	257/524		0.86 [0.72, 1.03]
7 Tumour size				
sub7. <5cm	47/138	42/138		1.00 [0.66, 1.53]
sub7. =5-10cm	80/215	110/230		0.74 [0.55, 0.98]

(*Continued* . . .)

(. . . *Continued*)

Study or subgroup	Chemo n/N	No Chemo n/N	Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI	Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI
sub7. >10cm	76/129	81/128		0.93 [0.67, 1.28]
8 Extent of resection				
sub8. Clear	232/567	263/600		0.89 [0.75, 1.07]
sub8. Not clear	63/126	60/104		0.86 [0.60, 1.25]
9 Radiotherapy				
sub9. No	168/373	188/393		0.93 [0.76, 1.15]
sub9. Yes	151/367	174/372		0.82 [0.66, 1.02]

WHAT'S NEW

Last assessed as up-to-date: 2 July 2000.

Date	Event	Description
22 February 2011	Review declared as stable	IPD data

HISTORY

Review first published: Issue 1, 1999

Date	Event	Description
19 August 2008	Amended	Converted to new review format.
3 July 2000	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

All reviewers participated in the design, execution, and analysis of the review and reviewed twice commented on the overall intellectual content.

DECLARATIONS OF INTEREST

There is no known conflict of interest.

SOURCES OF SUPPORT

Internal sources

- Medical Research Council, UK.

External sources

- No sources of support supplied

NOTES

This review was converted from an Individual Patient Data review originally intended for paper publication. It will, therefore, be updated as per the schedule of the IPD reviewers, rather than according to Cochrane guidelines.

It is unlikely at this stage that inclusion of the relatively immature results of the Italian trial (Frustaci 1987) and the small number of patients from the American trial (NCI-92-C-0210) will impact on the results and conclusions of the review and so an update of the analysis is not planned until the EORTC study has closed (EORTC 62931). This is not expected until at least 2003. - 24/05/02

INDEX TERMS

Medical Subject Headings (MeSH)

Antineoplastic Agents [*therapeutic use]; Antineoplastic Combined Chemotherapy Protocols [therapeutic use]; Chemotherapy, Adjuvant; Doxorubicin [therapeutic use]; Meta-Analysis as Topic; Randomized Controlled Trials as Topic; Sarcoma [*drug therapy; surgery]

MeSH check words

Adult; Humans