A Systematic Meta-Analysis of Randomized Controlled Trials of Adjuvant Chemotherapy for Localized Resectable Soft-Tissue Sarcoma

Nabeel Pervaiz[1]
Nigel Colterjohn, MD[2†]
Forough Farrokhyar, MPhil, PhD[2]
Richard Tozer, MD, PhD[3]
Alvaro Figueredo, MD[3]
Michelle Ghert, MD[2]

[1] University of Waterloo, Waterloo, Ontario, Canada.

[2] Department of Surgery, McMaster University and Hamilton Health Sciences, Juravinski Cancer Center, Hamilton, Ontario, Canada.

[3] Department of Medicine, McMaster University and Hamilton Health Sciences, Juravinski Cancer Center, Hamilton, Ontario, Canada.

[†] Deceased.

The authors recognize the EORTC 62931 trial, which is now closed, representing data from a further randomized 351 patients. Published data from this trial will be a valuable addition to the current meta-analysis.

Address for reprints: Michelle Ghert, MD, 699 Concession St., Hamilton, Ontario, Canada L8V 5C2; Fax: (905) 575-6343; E-mail: michelle.ghert@jcc.hhsc.ca

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BACKGROUND. The use of adjuvant chemotherapy to treat adults with localized resectable soft-tissue sarcoma remains controversial. The objective of this systematic review was to update the 1997 meta-analysis of randomized controlled trials (RCTs) to reassess the efficacy of doxorubicin-based chemotherapy with respect to recurrence and survival.

METHODS. A comprehensive literature search was performed to identify RCTs of adjuvant chemotherapy for adult patients diagnosed with localized resectable soft-tissue sarcoma. Two reviewers independently assessed eligibility and quality of the studies using a modified version of the Detsky Quality Scale. The outcome measures were local, distant, and overall recurrence and survival calculated through the fixed effect or random effect model.

RESULTS. Four new eligible trials were identified allowing for a total of 18 trials representing 1953 patients to be included in the analysis. The odds ratios (OR) for local recurrence was 0.73 (95% confidence interval [CI] 0.56-0.94; $P = .02$) in favor of chemotherapy. For distant and overall recurrence the OR was 0.67 (95% CI 0.56-0.82; $P = .0001$) in favor of chemotherapy. In terms of survival, doxorubicin alone had an OR of 0.84 (95% CI, 0.68-1.03; $P = .09$), which as not statistically significant. However, the OR for doxorubicin combined with ifosfamide was 0.56 (95% CI, 0.36-0.85; $P = .01$) in favor of chemotherapy.

CONCLUSIONS. This updated meta-analysis confirms the marginal efficacy of chemotherapy in localized resectable soft-tissue sarcoma with respect to local recurrence, distant recurrence, overall recurrence, and overall survival. These benefits are further improved with the addition of ifosfamide to doxorubicin-based regimens, but must be weighed against associated toxicities. ***Cancer* 2008;113:573–81.** © *2008 American Cancer Society.*

KEYWORDS: chemotherapy, soft tissue, sarcoma, adjuvant, meta-analysis, randomized controlled trial, localized, resectable.

Sarcomas of the soft tissue are a heterogeneous group of malignant tumors of mesenchymal origin that originate in connective tissue. Local control with wide surgical resection with or without adjuvant radiation has a success rate of close to 90%.[1-4] However, approximately 40% to 50% of patients with a large (>5 cm), deep, high-grade soft-tissue sarcoma eventually develop distant metastases, primarily in the lung.[5,6] In these instances the potential for cure drastically decreases and the 5-year survival ranges from 25% to 30% in spite of aggressive surgical management of metastases.[7-9]

The role of adjuvant therapy, in the form of doxorubicin-based chemotherapy, remains controversial in the setting of localized resectable soft-tissue sarcoma. Randomized controlled trials (RCTs)

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over the past 3 decades have been limited by sample size and varied chemotherapy regimens with discrepant results.[10-17]

A 1997 meta-analysis of all known randomized clinical trials was performed based on the intention-to-treat method combining the individual trial results (the Sarcoma Meta-analysis Collaboration, SMAC 1997).[17] The outcomes of this multicenter meta-analysis indicated that doxorubicin-based chemotherapy served to significantly improve time to local and distant recurrence, as well as overall recurrence-free survival. Overall survival approached, but did not reach, statistical significance with wide confidence intervals. As such, few facilities have accepted the treatment as a standardized procedure, and instead opt to administer adjuvant chemotherapy on a case-by-case basis.

Within the last decade further randomized controlled trials have been published to further evaluate the efficacy of systemic chemotherapy.[18-21] In addition, the dosages of doxorubicin have been intensified and the addition of ifosfamide to the treatment regimens has become common practice.[18-21] The objective of the current analysis was to perform a systematic review and update the 1997 meta-analysis with evidence from recent randomized clinical trials to reassess the impact of chemotherapy on the survival and local, distant, and overall recurrence of adult patients with localized resectable soft-tissue sarcoma.

MATERIALS AND METHODS

Literature Search

A literature review was performed on all randomized controlled trials that assessed the impact of adjuvant chemotherapy on soft-tissue sarcoma in adults. Searches through the Medline and EMBASE electronic databases were conducted through April 2007, identifying RCTs published between 1997 and April 2007. RCTs before 1997 were identified using the SMAC meta-analysis published in that year. The reason for this was that the analysis to be performed utilized the same inclusion and exclusion criteria and thus the SMAC publication was deemed to be inclusive of relevant past RCTs. Keywords employed in the search process included: soft tissue, sarcoma, neoplasm, chemotherapy, adjuvant, connective tissue, tumor, and cancer. These were arranged using varying combinations of the Boolean operators "AND," "NOT," and "OR," and the results were limited to RCTs. The literature search was further limited to articles published in English or those that had been translated to English—all other languages were restricted.

Inclusion and Exclusion Criteria

Only RCTs in which adult patients diagnosed with localized, resectable soft-tissue sarcoma randomized to a treatment group that received adjuvant chemotherapy or to a control group without chemotherapy were included in the analysis. There was no date limitation as all RCTs published up to the search date were eligible for review. All trials that did not follow such a methodology were excluded. Other exclusion criteria were studies on bone sarcomas, pediatric populations, and patients with advanced or metastatic disease.

All studies considered were assessed by 2 independent reviewers for eligibility and quality according to the criteria of a modified version of the Detsky Quality Scale for Randomized Controlled Trials.[22] The studies included in the SMAC study were not individually assessed by the Detsky Quality Scale because they had met similar inclusion criteria to be included in the previous meta-analysis. There was a high level of agreement between the reviewers (intraclass correlation coefficient 0.94; $P = .022$). The reviewers resolved disagreements by discussion to achieve consensus.

Outcome Measures

The 4 outcomes that were targeted for analysis were local recurrence, distant recurrence, overall recurrence, and overall survival. Those patients that experienced a local recurrence were not censored in the distant recurrence analysis or vice versa because it was not inferred that 1 type of recurrence would rule out the other. Overall recurrence was thus identified as the number of patients in each trial that experienced a local recurrence, distant recurrence, or both. Overall survival was taken to refer to the number of deaths that occurred in each trial versus the number of patients that survived. Time-dependent survival was not calculated due to the unavailability of individual data points.

Evaluation of Heterogeneity

Before analyzing the data we developed hypotheses regarding potential sources of heterogeneity in recurrence rates, ie, differences in study quality, whether studies were published or unpublished, and whether randomization was concealed or not. The tests of heterogeneity using the Cochran Q statistic were applied to evaluate the extent of variability in results

between trials. This method tests the null hypothesis that all of the apparent variability is due to chance.

Statistical Methods

The analysis was conducted on an intention-to-treat basis. A meta-analysis of pooled odds ratios (ORs) using random effect or fixed effect model was performed using Comprehensive Meta-Analysis v. 2 software (Biostat, Englewood, NJ). A random effect model was applied when the *P*-value for the test of heterogeneity was less than .10. A subgroup analysis was done to assess the role of different chemotherapy regimen on recurrence or death. ORs, absolute risk reduction (ARR), and hazard ratios (HRs) with 95% confidence intervals (CIs) are reported. In addition, the number of patients needed to treat (NNT) was calculated for each outcome to estimate the number of patients that would need to receive treatment before reducing the risk in 1. An alpha of 0.05 as was considered a criterion for significance level.

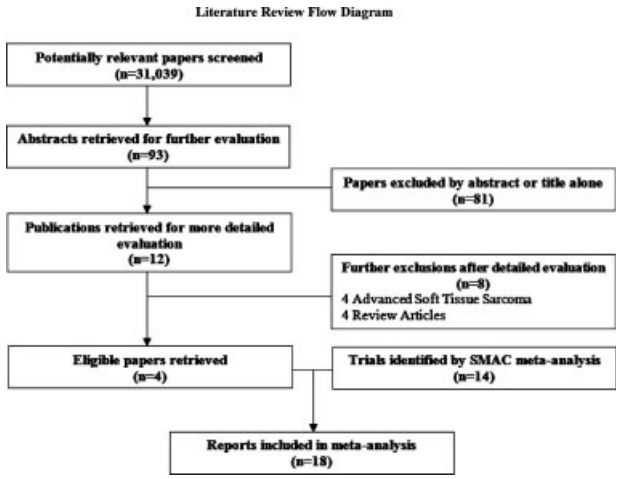

FIGURE 1. Literature review flow diagram. This flow diagram outlines the literature search and indicates reasons for article exclusions. There were 4 eligible articles retrieved, which led to a total of 18 trials being included in this meta-analysis when combined with those identified by the SMAC 1997 publication.

RESULTS

Literature Search

The screening of 31,039 possible articles yielded 93 abstracts for additional review. These abstracts were narrowed down to 12 publications obtained in full for a more thorough appraisal. Four studies were excluded as the samples consisted of advanced, rather than localized, soft-tissue sarcoma patients. Another 4 studies were review articles and thus were ineligible for analysis. Overall, 4 RCTs found in 4 different publications met the inclusion criteria. Combining the results of these trials with the 14 RCTs identified by the SMAC publication allowed for a total of 18 RCTs to be incorporated into the meta-analysis (Fig. 1).

Study Characteristics

All 18 RCTs were performed on adult patients diagnosed with soft-tissue sarcoma of varying subtypes. All of the tumors, however, were predetermined to be localized and resectable before patients were included in the trials. Of the 18 RCTs, 13 used a treatment regimen consisting of doxorubicin alone or combined with other chemotherapy drugs. Doxorubicin dosage in these trials ranged from 50 to 70 mg/m^2 per cycle. The remaining 5 RCTs utilized only doxorubicin combined with ifosfamide. In these trials the doxorubicin dosage ranged from 50 to 90 mg/m^2 per cycle and ifosfamide dosage ranged from 1500 to 5000 mg/m^2 per cycle (Table 1). All of the trials compared treatment between patients assigned to local treatment (surgery with or without radiotherapy) with neo/adjuvant chemotherapy and patients assigned to local treatment alone.

Local Recurrence

Data from 17 trials including 1700 patients and 296 local recurrences were analyzed. Adjuvant doxorubicin-based chemotherapy did not significantly lower local recurrences with an OR of 0.75 (95% CI, 0.56-1.01; $P = .055$) (Fig. 2). Adjuvant doxorubicin-based chemotherapy in conjunction with ifosfamide was found to have an OR of 0.66 (95% CI, 0.39-1.12; $P = .12$), which was also not statistically significant with the numbers available. However, with all studies included in the analysis there was a significant decrease in local recurrence and the OR was 0.73 (95% CI, 0.56-0.94; $P = .02$). The test of heterogeneity was not significant for the above analysis ($P = .46$). The ARR in local recurrence was 3% (95% CI, 1%-7%; $P = .13$) for doxorubicin-based chemotherapy alone and 4% (95% CI, 0%-7%; $P = .04$) for all studies. For doxorubicin-based chemotherapy combined with ifosfamide, the ARR for local recurrence was 5% (95% CI, 1%-12%; $P = .12$). The number of patients needed to obtain such a benefit (NNT) for all studies was 25.

Distant Recurrence

This analysis was conducted on data from 17 trials including 1700 patients and 553 distant recurrences. With all studies included in the analysis there was a significant decrease in distant recurrence, with an OR of 0.67 (95% CI, 0.56-0.82; $P = .0001$). Test of het-

TABLE 1
General Characteristics of Included Randomized Controlled Trials

Study	Methods	No. of patients	Intervention		Dosage of treatment	Outcome measures
			Treatment	Control		
Bergonie 1981[17]	RCT, 1981-1988	65	LT plus doxorubicin-based combination chemotherapy	LT alone	50mg/m^2 per cycle, 400-500mg/m^2 total	Local recurrence, distant recurrence, survival
DFCI/MGH 1978[17]	RCT, 1978-1983	46	LT plus doxorubicin chemotherapy	LT alone	60mg/m^2 per cycle, 450mg/m^2 total	Local recurrence, distant recurrence, survival
ECOG 1978[17]	RCT, 1978-1972	47	LT plus doxorubicin chemotherapy	LT alone	70mg/m^2 per cycle, 490mg/m^2 total	Overall recurrence, survival
EORTC 1977[17]	RCT, 1977-1978	468	LT plus doxorubicin-based combination therapy	LT alone	50mg/m^2 per cycle, 400mg/m^2 total	Local recurrence, distant recurrence, survival
GOG 1973[17]	RCT, 1973-1982	225	LT plus doxorubicin chemotherapy	LT alone	60mg/m^2 per cycle, 480mg/m^2 total	Local recurrence, distant recurrence, survival
IGSC 1983[17]	RCT, 1983-1986	92	LT plus doxorubicin chemotherapy	LT alone	70mg/m^2 per cycle, 420mg/m^2 total	Local recurrence, distant recurrence, survival
MDA 1973[17]	RCT, 1973-1976	59	LT plus doxorubicin-based combination chemotherapy	LT alone	60mg/m^2 per cycle, 420 mg/m^2 total	Local recurrence, distant recurrence, survival
Mayo 1975[17]	RCT, 1975-1981	76	LT plus plus doxorubicin-based combination chemotherapy	LT alone	50mg/m^2 per cycle, 200 mg/m^2 total	Local recurrence, distant recurrence, survival
NCI4 1977[17]	RCT, 1977-1981	26	LT plus doxorubicin-based combination chemotherapy	LT alone	50-70mg/m^2 per cycle, 500-550mg/m^2 total	Local recurrence, distant recurrence, survival
NCI5 1977[17]	RCT, 1977-1981	80	LT plus doxorubicin-based combination chemotherapy	LT alone	50-70mg/m^2 per cycle, 500-550mg/m^2 total	Local recurrence, distant recurrence, survival
NCI6 1977[17]	RCT, 1977-1981	41	LT plus doxorubicin-based combination chemotherapy	LT alone	50-70mg/m^2 per cycle, 500-550mg/m^2 total	Local recurrence, distant recurrence, survival
Rizzoli 1981[17]	RCT, 1981-1986	77	LT plus doxorubicin chemotherapy	LT alone	75mg/m^2 per cycle, 450mg/m^2 total	Local recurrence, distant recurrence, survival
SSG 1981[17]	RCT, 1981-1986	240	LT plus doxorubicin chemotherapy	LT alone	60mg/m^2 per cycle, 540mg/m^2 total	Local recurrence, distant recurrence, survival
Brodowicz 2000[18]	RCT, Start: 1992	59	LT plus doxorubicin, ifosfamide, and DTIC chemotherapy	LT alone	Doxorubicin: 50mg/m^2 per cycle Ifosfamide: 1500mg/m^2 per cycle DTIC: 200mg/m^2 per cycle	Local recurrence, distant recurrence, survival
Gortzak 2001[20]	RCT	134	LT plus doxorubicin and ifosfamide chemotherapy	LT alone	Doxorubicin: 50mg/m^2 per cycle Ifosfamide: 5000g/m^2 per cycle	Local recurrence, distant recurrence, survival
Petrioli 2002[21]	RCT, 1985-1996	88	LT plus epirubicin and ifosfamide chemotherapy	LT alone	Epirubicin: 75mg/m^2 per cycle Ifosfamide: 1500mg/m^2 per cycle	Local recurrence, distant recurrence, survival
Frustaci 2001[19]	RCT, 1992-1996	104	LT plus epidoxorubicin and ifosfamide chemotherapy	LT alone	Epidoxorubicin: 60mg/m^2 per cycle Ifosfamide: 1800mg/m^2 per cycle	Local recurrence, distant recurrence, survival
SAKK 1987[17]	RCT, 1987-1990	29	LT plus doxorubicin and ifosfamide chemotherapy	LT alone	50-90mg/m^2 per cycle 550mg/m^2 total	Local recurrence, distant recurrence, survival

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

TABLE 2
Relative Risks and 95% Confidence Intervals for Local Recurrence, Distant Recurrence, Overall Recurrence, and Survival

	Local recurrence		Distant recurrence		Overall recurrence		Survival	
Treatment	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI
Doxorubicin	0.75	0.56-1.01	0.69	0.56-0.86	0.69	0.56-0.86	0.84	0.68-1.03
Doxorubicin with ifosfamide	0.66	0.39-1.12	0.61	0.41-0.92	0.61	0.41-0.92	0.56	0.36-0.85
Combined	0.73	0.56-0.94	0.67	0.56-0.82	0.67	0.56-0.82	0.77	0.64-0.93

RR indicates relative risk, 95% CI, 95% confidence interval.

TABLE 3
Absolute Risk Reductions and 95% Confidence Intervals for Local Recurrence, Distant Recurrence, Overall Recurrence, and Survival

	Local recurrence		Distant recurrence		Overall recurrence		Survival	
Treatment	ARR	95% CI	ARR	95% CI	ARR	95% CI	ARR	95% CI
Doxorubicin	3%	1%-7%	9%	4%-14%	9%	4%-14%	5%	6%-21%
Doxorubicin with ifosfamide	5%	1%-12%	10%	1%-19%	12%	3%-21%	11%	3%-19%
Combined	4%	0%-7%	9%	5%-14%	10%	5%-15%	6%	2%-11%

ARR indicates absolute risk reduction, 95% CI, 95% confidence interval.

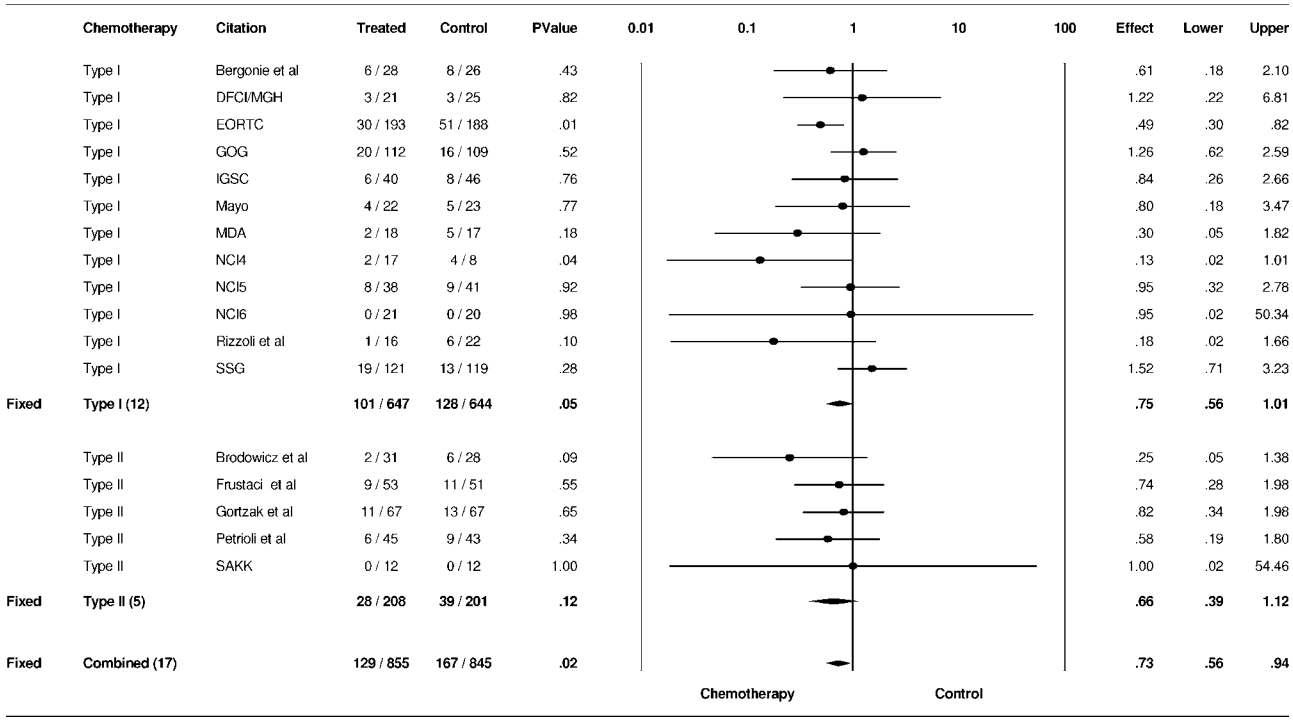

FIGURE 2. Odds ratios of local recurrence by type of chemotherapy regimen. Forest plot for odds ratios risk of local recurrence by type of chemotherapy regimen. Type I indicates adjuvant doxorubicin-based chemotherapy. Type II indicates adjuvant doxorubicin-based chemotherapy in combination with ifosfamide. Combined results are also provided.

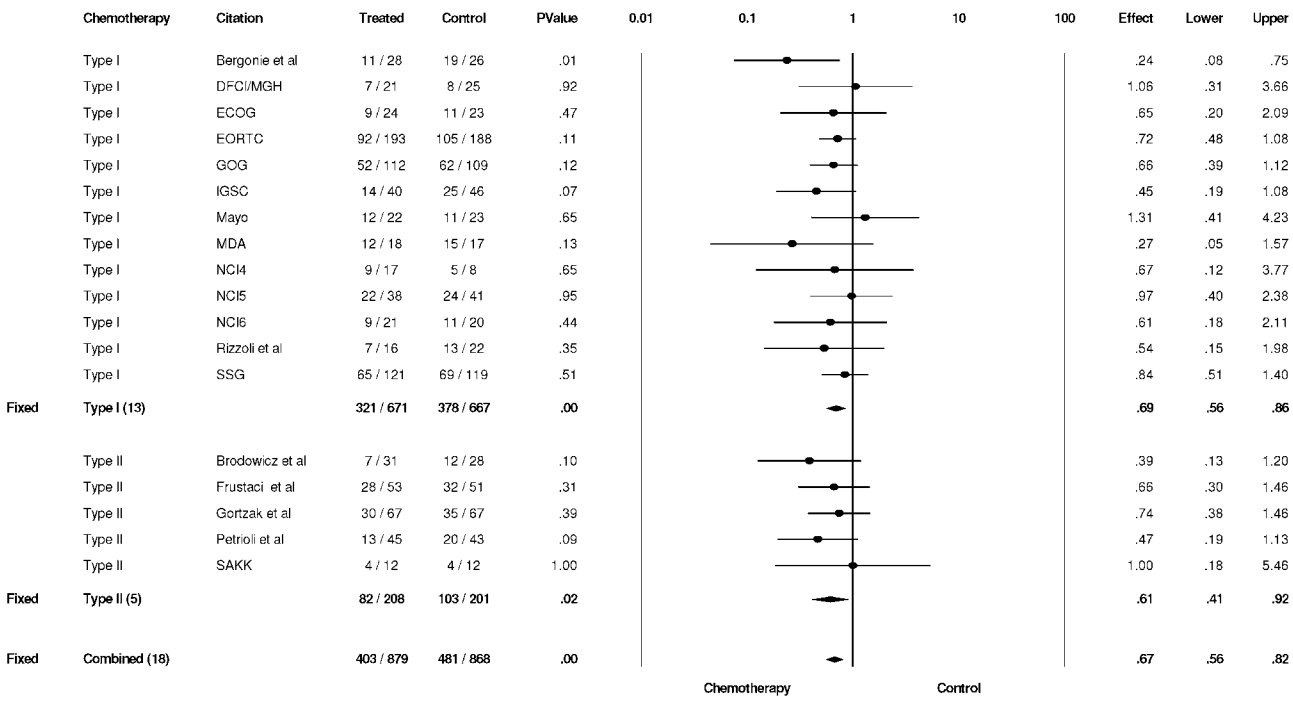

FIGURE 3. Odds ratios of distant recurrence by type of chemotherapy regimen. Forest plot for odds ratios of distant recurrence by type of chemotherapy regimen. Type I indicates adjuvant doxorubicin-based chemotherapy. Type II indicates adjuvant doxorubicin-based chemotherapy in combination with ifosfamide. Combined results are also provided.

erogeneity was not significant ($P = .80$). A significant reduction in distant recurrences was also found with both adjuvant doxorubicin-based chemotherapy, with an OR of 0.69 (95% CI, 0.56-0.86; $P = .001$), and with adjuvant doxorubicin-based chemotherapy combined with ifosfamide, with an OR of 0.61 (95% CI, 0.41-0.92; $P = .02$) (Fig. 3). The ARR in distant recurrence with adjuvant doxorubicin-based chemotherapy was 9% (95% CI, 4%-14%; $P = .0003$), and 9% (95% CI, 5%-14%; $P = .000$) for all studies. The ARR was 10% with adjuvant doxorubicin-based chemotherapy in combination with ifosfamide (95% CI, 1%-19%; $P = .03$). With all studies considered the NNT for distant recurrence was 12.

Overall Recurrence

Data from all 18 eligible trials on 1747 patients and 884 total recurrences were included in this analysis. With combined data from all studies the risk reduction in overall recurrence was significant, with an OR of 0.67 (95% CI, 0.56-0.82; $P = .0001$) (Fig. 4). The test of heterogeneity was not significant ($P = .76$). Adjuvant doxorubicin-based chemotherapy was found to significantly reduce overall recurrence, with an OR of 0.69 (95% CI, 0.56-0.86; $P = .0008$). A significant reduction also occurred with adjuvant doxorubicin-based chemotherapy combined with ifosfamide, with an OR of 0.61 (95% CI, 0.41-0.92; $P = .02$). Adjuvant doxorubicin alone yielded a significant ARR of 9% (95% CI, 4%-15%; $P = .0005$). Studies using doxorubicin and ifosfamide had a significant ARR of 12% (95% CI, 3%-21%; $P = .01$). Data from all studies yielded an ARR of 10% (95% CI, 5%-15%; $P \leq .001$). The NNT for overall recurrence for all studies was 10.

Survival

This analysis was conducted on 18 trials including 1953 patients and 829 deaths. Data from all trials showed that adjuvant chemotherapy significantly reduced the risk of death with an HR of 0.77 (95% CI, 0.64-0.93; $P = .01$) (Fig. 5). The test of heterogeneity was not significant ($P = .80$). Adjuvant doxorubicin-based treatment resulted in a reduction in mortality that was not significant, with an HR of 0.84 (95% CI, 0.68-1.03; $P = .09$). The studies involving doxorubicin combined with ifosfamide, however, showed significantly reduced mortality, with an HR of 0.56 (95% CI, 0.36-0.85; $P = .01$). The risk difference analysis showed an ARR of 5% with adjuvant doxorubicin alone (95% CI, 6%-21%; $P = .07$), which was not significant. With data from all trials, how-

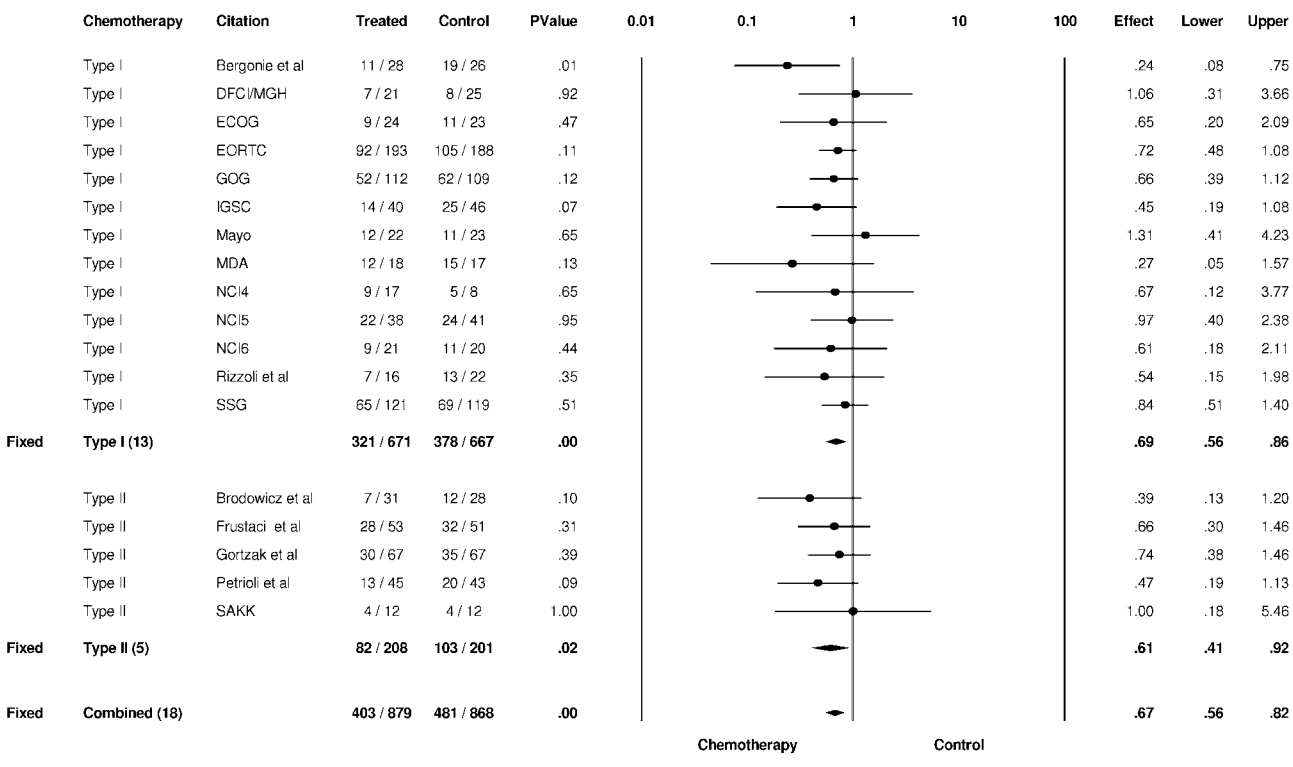

FIGURE 4. Odds ratios of overall recurrence by type of chemotherapy regimen. Forest plot for odds ratios of overall recurrence by type of chemotherapy regimen. Type I indicates adjuvant doxorubicin-based chemotherapy. Type II indicates adjuvant doxorubicin-based chemotherapy in combination with ifosfamide. Combined results are also provided.

ever, there was an ARR of 6% (95% CI, 2%-11%; $P = .003$), or a 40% versus 46% risk of death, which was statistically significant. Doxorubicin in combination with ifosfamide analyzed alone also had a significant ARR of 11% (95% CI, 3%-19%; $P = .01$), or a 30% versus 41% risk of death. Data from all trials showed an NNT of 17 to prevent 1 death.

DISCUSSION

This updated meta-analysis represents the largest study to date of pooled data from randomized controlled trials for adjuvant chemotherapy for localized resectable soft-tissue sarcoma. Our results concur with those of the 1997 meta-analysis in that we found a small but definite risk reduction in local recurrence, distant recurrence, and overall recurrence with the use of adjuvant chemotherapy (Tables 2 and 3). However, whereas the SMAC study suggested a trend toward improved overall survival with chemotherapy, the current meta-analysis reached statistical significance for overall survival with adjuvant chemotherapy. This new finding may be attributed to either the larger sample size, resulting in narrower confidence intervals, or to the evolution in the administration of chemotherapeutic regimens involving dose intensification and the addition of ifosfamide to doxorubicin-based protocols.

The majority of trials in the SMAC study were closed before it became apparent that the addition of ifosfamide to doxorubicin-based regimens may have a somewhat higher antitumor activity on patients with advanced or metastatic soft-tissue sarcoma.[23-25] As a result, only 1 of the trials in the SMAC study involved ifosfamide in the chemotherapy arm.[17] In contrast, all 4 additional studies in the current meta-analysis included an arm with ifosfamide in addition to doxorubicin.[18-21] In a subgroup analysis for overall survival, we found that data pooled from all studies with only doxorubicin-based protocols did not show a statistically significant risk reduction in overall survival, whereas data pooled from all studies did show improvement in overall survival, with an NNT of 17 and a risk reduction of death from 46% to 40%. Doxorubicin in combination with ifosfamide resulted in a risk reduction in death from 41% to 30%. Although these risk reductions are statistically significant, the decision as to whether they are clinically significant

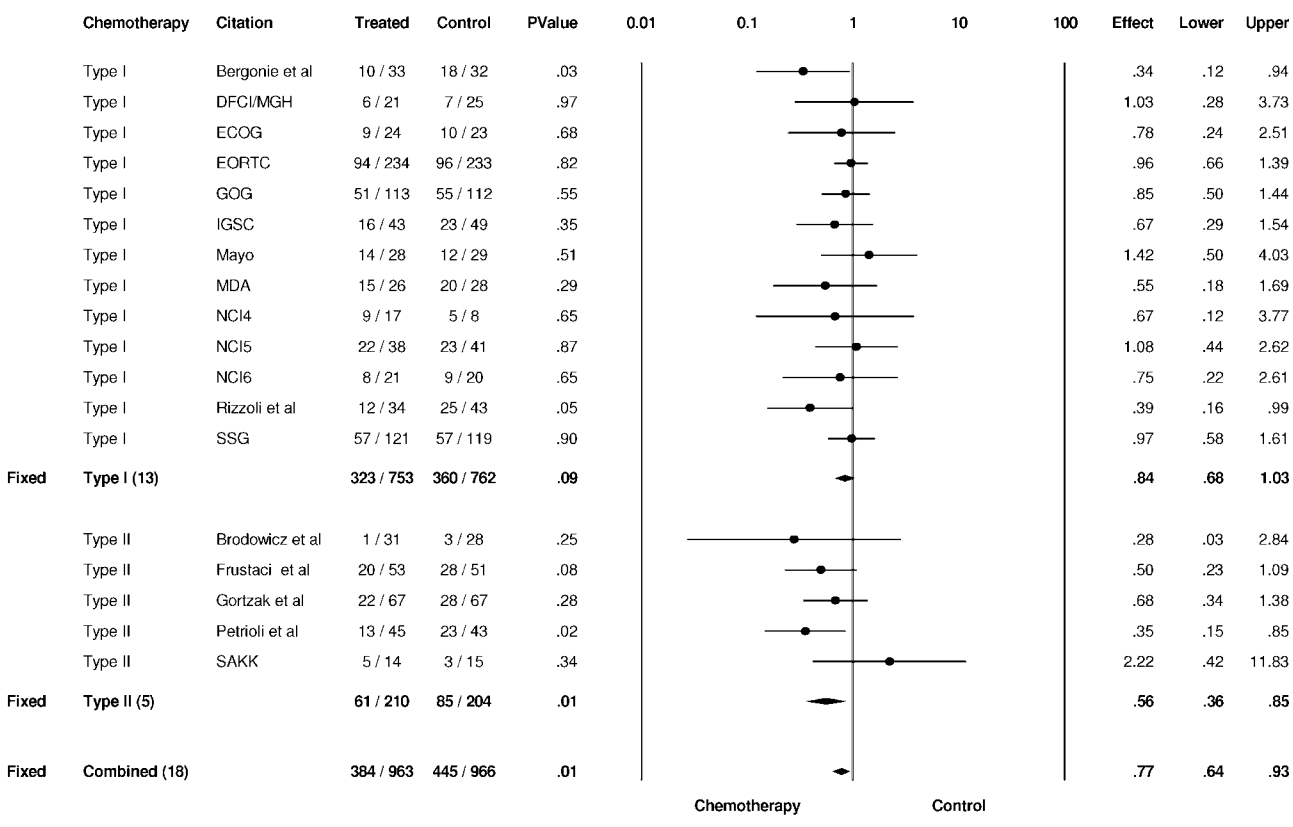

FIGURE 5. Hazard ratios of survival by type of chemotherapy regimen. Forest plot for hazard ratios of survival by type of chemotherapy regimen. Type I indicates adjuvant doxorubicin-based chemotherapy. Type II indicates adjuvant doxorubicin-based chemotherapy in combination with ifosfamide. Combined results are also provided.

depends on individual patient factors and chemotherapeutic risks.

The patient populations across the various studies were heterogeneous with respect to specific soft-tissue sarcoma pathologic subtype as well as tumor location. Patient randomization normally controls for this, but can be an issue in meta-analyses, particularly in rare disease states such as soft-tissue sarcoma. We performed tests for heterogeneity between studies for all endpoints and did not find significant heterogeneity for any of the analyses, indicating the appropriateness of data pooling for these studies.[26]

The SMAC study included subgroup analyses and concluded that the effects of chemotherapy in reducing the risk of recurrence and death were most significant in extremity sarcomas. The current study did not include these analyses, as individual data points were not available. However, subgroup analyses are currently not recommended in meta-analyses unless the subgroup stratification was part of the original study design for all studies included. In addition, subgroup analysis in the current study would lead to small subgroups and increase the risk of flawed conclusions generated by chance alone.

There is accumulating evidence from retrospective studies and trials involving advanced disease that synovial sarcoma may have better clinical response to systemic therapies than other soft-tissue sarcoma subtypes.[24,27,28] Whether this is related to tumor biology, location, or younger peak incidence and better compliance with chemotherapeutic regimens is unknown. The current study could not assess the efficacy of chemotherapy in this subgroup given the absence of individual data points, whereas the subgroup analysis of 155 synovial sarcomas in the SMAC study did not show a statistical improvement in survival with adjuvant chemotherapy (OR 0.85, 95% CI 0.53, 1.35). It is possible that with the addition of ifosfamide in the recent trials greater efficacy could be identified.

The ability of the current study to build on the results of the SMAC study and narrow the confidence intervals would enable physicians to fully appreciate

the potential benefit of systemic therapy in this patient population. In rare diseases we continue to be challenged by the heterogeneity of tissue types seen in soft-tissue sarcoma, and currently limited evidence regarding their respective individual clinical responses to doxorubicin- and ifosfamide-based therapy. Meeting this challenge will be paramount as we move forward in delineating further strategies in the management of soft-tissue sarcoma, and possibly individualized multimodality therapy to specific tissue type.

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