VOLUME 22 · NUMBER 22 · NOVEMBER 15 2004

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Cohort Analysis of Patients With Localized, High-Risk, Extremity Soft Tissue Sarcoma Treated at Two Cancer Centers: Chemotherapy-Associated Outcomes

Janice N. Cormier, Xuelin Huang, Yan Xing, Peter F. Thall, Xuemei Wang, Robert S. Benjamin, Raphael E. Pollock, Cristina R. Antonescu, Robert G. Maki, Murray F. Brennan, and Peter W.T. Pisters

From the Sarcoma Center and Department of Biostatistics, University of Texas M.D. Anderson Cancer Center, Houston, TX; and Department of Surgical Oncology, Department of Medical Oncology, Department of Biostatistics, and Department of Pathology, Memorial Sloan-Kettering Cancer Center, New York, NY.

Submitted February 9, 2004; accepted August 30, 2004.

All investigators contributed to the design of the study and writing of the report. P.W.T. Pisters, M.F. Brennan, R.E. Pollock, R.G. Maki, and R.S. Benjamin provided the conceptual basis for the project. J.N. Cormier and Y. Xing were responsible for the collation of the data set. X. Huang, P.F. Thall, and X. Wang analyzed the data.

Authors' disclosures of potential conflicts of interest are found at the end of this article.

Address reprint requests to Peter W.T. Pisters, MD, Department of Surgical Oncology, Box 444, University of Texas M.D. Anderson Cancer Center, 1515 Holcombe Blvd, Houston, TX 77030-4009; e-mail: ppisters@mdanderson.org.

0732-183X/04/2222-4567/$20.00

DOI: 10.1200/JCO.2004.02.057

ABSTRACT

Purpose
Patients with American Joint Committee on Cancer stage III soft tissue sarcoma (STS) have high risks of distant recurrence and death. The role of chemotherapy for these patients remains controversial despite several randomized trials and a meta-analysis.

Methods
We reviewed the treatments and outcomes of 674 consecutive adult patients presenting with primary stage III extremity STS between 1984 and 1999. Pre- or postoperative doxorubicin-based chemotherapy was used in a nonrandomized fashion in approximately half of this high-risk population. The objective of this review was to evaluate the impact of chemotherapy while accounting for known prognostic variables.

Results
Among 674 patients, 338 (50%) were treated with local therapy only, and 336 (50%) were treated with local therapy plus chemotherapy. The median follow-up for survivors was 6.1 years. Five-year local and distant recurrence-free interval probabilities were 83% and 56%, respectively, for the two groups combined. The 5-year disease-specific survival (DSS) rate was 61%. Cox regression analyses showed a time-varying effect associated with chemotherapy. During the first year, the hazard ratio associated with DSS for patients treated with chemotherapy versus no chemotherapy was 0.37 (95% CI, 0.20 to 0.69; *P* = .002). Thereafter, this hazard ratio was 1.36 (95% CI, 1.02 to 1.81; *P* = .04).

Conclusion
It seems that the clinical benefits associated with doxorubicin-based chemotherapy in patients with high-risk extremity STS are not sustained beyond 1 year. These results suggest that caution should be used in the interpretation of randomized clinical trials of adjuvant chemotherapy that seem to demonstrate clinical benefits with relatively short-term follow-up.

J Clin Oncol 22:4567-4574. © 2004 by American Society of Clinical Oncology

INTRODUCTION

Soft tissue sarcomas (STS) can occur anywhere in the body; the majority (50%) of primary tumors originate in an extremity.[1] Patients with large (> 5 cm), deep, high-grade, extremity STS (American Joint Committee on Cancer [AJCC] stage III[2]) are at significant risk for distant recurrence and subsequent sarcoma-related death.[3-5] As a consequence, patients with stage III disease are often considered for pre- or postoperative anthracycline-based chemotherapy.

The Sarcoma Meta-Analysis Collaboration (SMAC) performed a meta-analysis of all randomized trials comparing adjuvant chemotherapy to no adjuvant therapy for STS arising from extremity, trunk, head and neck, or visceral sites.[6] In this meta-analysis of 14 published trials, doxorubicin-based adjuvant chemotherapy was associated with decreased local and distant recurrence rates, and an increased recurrence-free survival rate, but not an increased overall survival (OS) rate. However, in a subset analysis of the 886 patients with extremity STS, adjuvant chemotherapy was associated with a possible OS benefit, estimated to be 7%.[6] A later randomized prospective trial of 104 patients with high-risk primary and locally recurrent extremity and limb girdle STS showed a significant difference in OS (75 *v* 46 months; $P = .03$) for those treated with surgery plus chemotherapy versus those treated with definitive surgical resection alone.[7] Two additional randomized trials[8,9] (59 and 88 patients, respectively) in patients with primary and locally recurrent STS at heterogeneous anatomic sites also showed improvements in the 5-year OS rate associated with adjuvant chemotherapy, although the differences were not statistically significant. The interpretation of this complex literature is difficult.[10,11]

As a result of the inconclusive body of evidence, there is still considerable variation in regional and international treatment recommendations for patients with high-risk localized STS. We retrospectively analyzed our combined institutional experience to evaluate the effects of adjuvant chemotherapy in a homogeneous population of patients with high-risk (AJCC stage III) extremity STS.

METHODS

Patients

The study population was derived from 8,257 consecutive patients with a diagnosis of STS presenting to Memorial Sloan-Kettering Cancer Center (MSKCC) and the University of Texas M.D. Anderson Cancer Center (MDACC) from January 1, 1984, to June 29, 1999. From this group, 2,135 patients were determined to have nonmetastatic disease arising from an extremity. Patients with stage I and II tumors and locally recurrent disease, as well as patients not treated with definitive surgical resection (ie, patients treated with palliative intent), were excluded. The resulting cohort consisted of 674 patients presenting with primary, high-risk (AJCC [6th edition] stage III[2]) extremity STS treated during this time period. Three hundred eighty-six patients (57%) were identified from the prospective STS database at MSKCC, and the remaining 288 patients (43%) were identified from the MDACC tumor registry and sarcoma database. The medical records of the patients treated at MDACC were reviewed retrospectively. Data that were obtained from the prospective database at MSKCC were confirmed by retrospective review of medical records. This research project was approved by the institutional review boards of both institutions.

The following definitions were used. The tumor was considered to be in the upper extremity if it was distal to the shoulder joint and in the lower extremity if it was distal to the groin. Shoulder, axillary, and iliac fossa tumors were excluded. Tumor size was defined as the maximum dimension obtained with cross-sectional imaging. The size of the resected tumor was used in patients referred after excisional biopsy. All patients had T2b lesions ($>$ 5 cm tumors located beneath the investing fascia of the extremity) that were determined to be high grade (AJCC grade 3 or 4). A microscopically positive surgical margin was defined as tumor present at the inked margin of the specimen.

End Points

Six end points were examined from the time of treatment initiation. Local disease-free survival (DFS) was defined as the time from initial treatment to local disease recurrence or death as a result of STS; distant DFS was the time to distant disease recurrence or death as a result of STS; overall DFS was the time to either local or distant disease recurrence or death as a result of STS; disease-specific survival (DSS) was the time to death as a result of STS. In the analyses of each of these four end points, patients who did not experience the event were censored, and this was assumed to be independent of the event time. Death as a result of causes other than STS was also treated as a censored event. Patients who had a local recurrence were not censored in the analysis of distant recurrence, and vice versa, because one type of recurrence does not preclude the possibility of the other occurring subsequently. In addition, local and distant recurrence-free intervals (RFIs) were calculated as the times to local and distant recurrence, respectively. Patients without recurrence at the time of last follow-up were censored on that date, and patients who died without recurrence were censored on the date of death. Local and distant RFIs were included as end points in the current study to facilitate comparison with the SMAC meta-analysis.[6]

Statistical Methods

Two-sample comparisons were done using *t* tests for quantitative variables and χ^2 tests for discrete variables.[12] Unadjusted probabilities of all outcomes, including local, distant, and overall DFS, local and distant RFI, and DSS, were estimated using the method of Kaplan and Meier (KM).[13] Unadjusted intergroup comparisons based on each outcome were made using the log-rank test.[14] The Cox proportional hazards regression model,[15,16] with the baseline hazard stratified by whether the patient received chemotherapy or not, was used to assess the ability of patient characteristics or treatments to predict each outcome. Goodness-of-fit was assessed by the Grambsch-Therneau test.[16] Hazard functions were estimated using the kernel smoothing method of Simonoff.[17] For each outcome, the estimated hazard functions for patients treated with chemotherapy and for those not treated with chemotherapy crossed, with the chemotherapy group hazard initially lower and then higher. The times at which the hazard functions crossed were estimated by the method of Gilbert et al.[18] Because the curves crossed at approximately 1 year for all outcomes, the effects of chemotherapy versus no chemotherapy during the first year and thereafter were analyzed separately. In these analyses, all patients were included for the first year effects, whereas effects thereafter were based on the subgroup of 591 patients who survived the first year. The comparisons for the subgroup of patients who survived at least 1 year should be interpreted with caution because deaths occurring during the first year may have rendered the treatment groups less comparable after 1 year. All computations were carried out using SAS statistical software version 8.02 (SAS Institute, Cary, NC) on a Compaq EVO 500 computer. A *P* value of less than .05 was regarded as statistically significant.

RESULTS

The median follow-up time for survivors was 6.1 years. Eighty-eight percent of patients underwent limb-sparing surgical resection, and 75% of patients had microscopically negative (R0) surgical margins. Patients with unknown margin status were considered to have microscopically positive surgical margins (R1) in subsequent analyses. Three hundred thirty-six patients (50%) received chemotherapy; 214 (64%) of these received preoperative chemotherapy, whereas 122 (35%) patients were treated with postoperative chemotherapy. Of the 332 patients for whom there is information on the chemotherapy regimen used, 88% received doxorubicin either alone or in combination with other drugs (dacarbazine with or without cyclophosphamide, or ifosfamide with or without dacarbazine and mesna). The distributions of clinicopathologic factors within the subgroups of patients who did and did not receive chemotherapy are listed in Table 1. The use of chemotherapy differed among age cohorts: 62%, 55%, and 38% of patients younger than 40 years, 40 to 60 years, and over 60 years, respectively, were treated with chemotherapy. Reflecting the fact that younger patients were more likely to receive chemotherapy, the median age of chemotherapy patients was 51 *v* 60 years for patients not treated with chemotherapy ($P < .0001$). Patients treated at MDACC were more likely to receive chemotherapy than those treated at MSKCC (57% *v* 43%; $P < .0001$). Table 2 lists the hazard ratios (HRs) from Cox regression analyses of clinicopathologic factors for all of the outcomes. Additional covariates included in the Cox model are treatment site, histopathologic classification, and local treatment with radiation (classified as preoperative, postoperative, or brachytherapy).

Pretreatment Prognostic Factors

Local recurrence end points. One hundred eleven patients (16%) had one or more local recurrences. The median time to first local recurrence among these 111 patients was 1.42 years, whereas the overall median time to first local recurrence has not been reached. The KM

Table 1. Characteristics of 674 Patients With AJCC Stage III Extremity STS

Characteristic	All (N = 674) No. of Patients	All %	Chemotherapy (n = 336) No. of Patients	Chemotherapy %	No Chemotherapy (n = 338) No. of Patients	No Chemotherapy %	*P*
Median age, years*	55.3		50.7		60.3		< .0001
Median tumor size, cm	10		10		9.75		.22
> 5 to < 10	312		143	42	169	50	.15
10 to < 15	212		113	34	99	29	
≥ 15	150		80	24	70	21	
Sex							
Male	379	56	189	56	190	56	.95
Female	295	44	147	44	148	44	
Anatomic site							
Upper extremity	105	16	48	14	57	17	.41
Lower extremity	569	84	288	86	281	83	
Distal extremity	186	28	89	26	97	29	.58
Proximal extremity	488	72	247	74	241	71	
Histopathologic subtype							.07
Malignant fibrous histiocytoma	250	37	129	38	121	36	.54
Liposarcoma	116	17	47	14	69	21	.04
Synovial sarcoma	89	13	47	14	42	12	.63
Unclassified sarcoma	53	8	29	9	24	7	.55
Leiomyosarcoma	42	6	15	4	27	8	.08
Other	124	18	69	21	55	16	.18
Microscopic resection margin status							
R0	503	75	254	76	249	74	.63
R1 or unknown	171	25	82	24	89	26	
Location of treatment*							
MSKCC	386	57	146	43	240	71	< .0001
MDACC	288	43	190	57	98	29	

Abbreviations: AJCC, American Joint Committee on Cancer; R0, microscopically negative surgical margins; R1, microscopically positive surgical margins; MSKCC, Memorial Sloan-Kettering Cancer Center; MDACC, University of Texas M.D. Anderson Cancer Center.
*Significant difference between treatment groups.

Table 2. Hazard Ratio Estimates From Cox Regression Analyses of Clinicopathologic Factors

	Local RFI			Local DFS			Distant RFI			Distant DFS			Overall DFS			DSS		
Factor	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*
Sex																		
Female *v* male	1.03	0.70 to 1.53	NS	0.84	0.67 to 1.05	NS	0.73	0.58 to 0.93	.01	0.73	0.59 to 0.92	.007	0.79	0.64 to 0.99	.04	0.77	0.60 to 0.98	.03
Age, years																		
40-60 *v* < 40	0.92	0.54 to 1.56	NS	1.09	0.80 to 1.49	NS	1.02	0.75 to 1.40	NS	1.04	0.77 to 1.41	NS	1.06	0.79 to 1.41	NS	1.08	0.78 to 1.50	NS
> 60 *v* < 40	1.15	0.67 to 1.99	NS	1.30	0.94 to 1.80	NS	1.07	0.77 to 1.49	NS	1.22	0.89 to 1.67	NS	1.17	0.87 to 1.58	NS	1.38	0.98 to 1.93	NS
Anatomic tumor site																		
Upper *v* lower limb	1.13	0.66 to 1.93	NS	0.86	0.61 to 1.20	NS	0.71	0.49 to 1.03	NS	0.78	0.56 to 1.09	NS	0.85	0.62 to 1.16	NS	0.79	0.55 to 1.14	NS
Proximal *v* distal site	0.77	0.49 to 1.21	NS	1.12	0.85 to 1.48	NS	1.06	0.79 to 1.41	NS	1.01	0.77 to 1.32	NS	0.94	0.73 to 1.22	NS	1.25	0.92 to 1.68	NS
Tumor size, cm																		
10-15 *v* < 10	1.23	0.76 to 1.98	NS	1.26	0.95 to 1.66	NS	1.28	0.97 to 1.71	NS	1.29	0.98 to 1.69	NS	1.29	0.99 to 1.67	NS	1.27	0.95 to 1.71	NS
> 15 *v* < 10	1.34	0.80 to 2.26	NS	1.51	1.12 to 2.04	.007	1.77	1.30 to 2.41	.0003	1.67	1.24 to 2.25	.0007	1.62	1.22 to 2.17	.001	1.56	1.14 to 2.13	.006
Pathologic margins																		
R1 or unknown *v* R0	1.03	0.65 to 1.61	NS	1.23	0.95 to 1.60	NS	1.03	0.78 to 1.36	NS	1.11	0.86 to 1.45	NS	1.11	0.86 to 1.42	NS	1.28	0.97 to 1.69	NS

NOTE. Additional covariates accounted for in the Cox model which are not included in Table 2 include treatment site, histopathologic classification, and local treatment with radiation (classified as preoperative, postoperative, or brachytherapy).
Abbreviations: RFI, recurrence-free interval; DFS, disease-free survival; DSS, disease-specific survival; HR, hazard ratio; NS, not significant ($P > .05$); R0, microscopically negative surgical margins; R1, microscopically negative surgical margins.

estimates of local RFI at 5 and 10 years were 83% (95% CI, 79% to 86%) and 77% (95% CI, 73% to 82%), respectively. The KM estimates of local DFS at 5 and 10 years were 55% (95% CI, 51% to 59%) and 44% (95% CI, 40% to 49%), respectively. In the multivariate analysis, tumor size more than 15 cm was an independent adverse prognostic factor (HR, 1.51; 95% CI, 1.12 to 2.04; $P = .007$) for local DFS (Table 2).

Distant recurrence end points. Three hundred five patients (45%) had distant recurrences. The median time to first distant recurrence among these 305 patients was 1.07 years, whereas the overall median time to distant recurrence was 8.87 years. Two hundred sixty-one patients (39%) had distant metastases as their first site of recurrence. The KM estimates of distant RFI at 5 and 10 years were 56% (95% CI, 52% to 60%) and 49% (95% CI, 45% to 54%), respectively. The distant DFS rates at 5 and 10 years were 53% (95% CI, 49% to 57%) and 46% (95% CI, 42% to 50%), respectively. Patients with tumors more than 15 cm (HR, 1.67; 95% CI, 1.24 to 2.25; $P = .0007$) had a significantly increased risk of distant progression compared with patients with tumors less than 10 cm. Female sex was a favorable prognostic factor for distant DFS (HR, 0.73; 95% CI, 0.59 to 0.92; $P = .007$; Table 2).

Overall DFS. Three hundred sixty-four patients (54%) died or had recurrent disease. The median time to death or recurrence among these 364 patients was 1.06 years, whereas the overall median time to death or recurrence was 3.79 years. The overall DFS rates were 48% (95% CI, 44% to 52%) and 41% (95% CI, 37% to 46%) at 5 and 10 years, respectively. Tumor size more than 15 cm (HR, 1.62; 95% CI, 1.22 to 2.17; $P = .001$) and female sex (HR, 0.79; 95% CI, 0.64 to 0.99; $P = .04$) were the only independent prognostic factors for overall DFS (Table 2).

DSS. Two hundred eighty-seven patients (43%) died as a result of STS, five (0.7%) had treatment-related deaths (surgery-related death, two patients [0.3%]; chemotherapy-related death, three patients [0.4%]), and 74 (11%) died as a result of other causes. The median time to disease-specific death among the 287 patients was 2 years, whereas the overall median time to disease-specific death was 11 years. The DSS rates at 5 and 10 years were 61% (95% CI, 57% to 65%) and 50% (95% CI, 46% to 55%), respectively. Tumor size more than 15 cm (HR, 1.56; 95% CI, 1.14 to 2.13; $P = .006$) and female sex (HR, 0.77; 95% CI, 0.60 to 0.98; $P = .03$) were the only independent prognostic factors for DSS (Table 2).

Effects of Chemotherapy

Of the 336 patients treated with chemotherapy, 147 (44%) were alive at last follow-up, 151 (45%) died as a result of disease, 35 (10%) died as a result of other causes, and three (0.9%) died as a result of treatment-related complications. Of the 338 patients not treated with chemotherapy, 166 (49%) were alive, 131 (39%) died as a result of disease, 39 (12%) died as a result of other causes, and two (0.6%) died as a result of treatment-related complications. A striking feature of the KM survival probability curves for patients treated with chemotherapy and for those who did not receive chemotherapy was that these curves crossed. This pattern persisted for local, distant, and overall DFS and DSS. This violates the proportional hazards assumption underlying the Cox model, and it indicates that effects associated with chemotherapy may vary over time. The estimated times, in years, at which the chemotherapy and no-chemotherapy hazard function curves crossed are 1.19 (95% CI, 0.80 to 1.33) for DSS, 0.72 (95% CI, 0.43 to 0.93) for DFS, 0.81 (95% CI, 0.63 to 1.22) for local DFS, and 0.76 (95% CI, 0.40 to 1.07) for distant DFS. Figure 1 demonstrates this for DSS in terms of the hazard (instantaneous rate) of death, which initially is low in patients treated with chemotherapy but exhibits a sharp increase during the first 2 years. Patients not treated with chemotherapy had an initially higher hazard that steadily declined during 5 years. This indicates that among patients who survived at least 1 year, those who received chemotherapy had a higher risk of death thereafter compared with patients who did not receive chemotherapy. Because the hazard functions associated with chemotherapy and no chemotherapy crossed at times that varied from 0.4 to 1.3 years, depending on the outcome examined, 1 year was chosen as the cut point for describing the time-varying effects of chemotherapy in subsequent analyses. KM survival plots for all end points are presented in Figure 2. Survival plots for chemotherapy and no chemotherapy adjusted for other prognostic factors and patient characteristics also crossed. They are not presented because they were similar to KM estimates.

Local recurrence end points. KM estimates of local RFI for patients treated with chemotherapy versus no chemotherapy were 94% (95% CI, 92% to 97%) *v* 92% (95% CI, 89% to 95%) at 1 year and 83% (95% CI, 78% to 87%) *v* 83% (95% CI 78% to 88%) at 5 years, respectively (Fig 2A). Multivariate analysis indicated that patients treated with local therapy plus chemotherapy experienced no significant difference in local RFI in the first year or beyond the first year compared with those treated with local therapy alone (Fig 3).

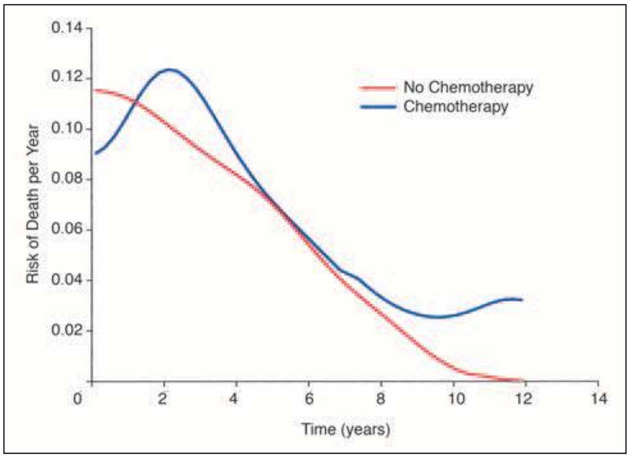

Fig 1. Smoothed instantaneous hazard function curves for disease-specific death of patients who received chemotherapy (n = 336) and those not treated with chemotherapy (n = 338).

KM estimates of local DFS for patients treated with chemotherapy versus no chemotherapy were 89% (95% CI, 86% to 93%) *v* 82% (95% CI, 78% to 86%) at 1 year and 54% (95% CI, 49% to 60%) *v* 56% (95% CI, 50% to 62%) at 5 years, respectively (Fig 2B). A multivariate analysis including treatment with radiation indicated that patients treated with local therapy plus chemotherapy had a significant reduction in local recurrences in the first year after the initiation of treatment (HR, 0.54; 95% CI, 0.35 to 0.85; $P = .008$) compared with patients treated with local therapy alone (Fig 3).

Distant recurrence end points. KM estimates of distant RFI for those treated with chemotherapy versus no chemotherapy were 81% (95% CI, 77% to 85%) *v* 76% (95% CI, 71% to 80%) at 1 year and 55% (95% CI, 50% to 61%) *v* 57% (95% CI, 51% to 63%) at 5 years, respectively (Fig 2C). Multivariate analysis indicated that patients treated with local therapy plus chemotherapy experienced a lower hazard for distant metastasis than patients treated with local therapy alone in the first year (HR, 0.67; 95% CI, 0.46 to 0.96; $P = .03$). Beyond the first year, patients treated with chemotherapy fared worse with respect to distant RFI (HR, 1.54; 95% CI, 1.09 to 2.17; $P = .01$; Fig 3).

KM estimates of distant DFS for patients treated with chemotherapy versus no chemotherapy were 81% (95% CI, 77% to 85%) *v* 75% (95% CI, 70% to 79%) at 1 year and 52% (95% CI, 47% to 58%) *v* 53% (95% CI, 48% to 59%) at 5 years, respectively (Fig 2D). Multivariate analysis indicated that patients treated with local therapy plus chemotherapy fared better with respect to DFS than patients treated with local therapy alone in the first year (HR, 0.64; 95% CI, 0.45 to 0.91; $P = .01$) but fared worse beyond the first year (HR, 1.46; 95% CI, 1.08 to 1.96; $P = .01$; Fig 3).

Overall DFS. KM estimates for overall DFS for patients treated with chemotherapy versus no chemotherapy were 77% (95% CI, 72% to 82%) *v* 71% (95% CI, 66% to 76%) at 1 year and 47% (95% CI, 42% to 53%) *v* 49% (95% CI, 44% to 55%) at 5 years, respectively (Fig 2E). Multivariate analysis indicated that patients treated with local therapy plus chemotherapy fared better with respect to overall DFS than patients treated with local therapy alone in the first year (HR, 0.67; 95% CI, 0.48 to 0.93; $P = .02$) but fared worse, although not statistically significantly so, beyond the first year (HR, 1.33; 95% CI, 0.97 to 1.81; $P = .08$; Fig 3).

DSS. KM estimates of DSS for patients treated with chemotherapy versus no chemotherapy were 95% (95% CI, 93% to 98%) *v* 87% (95% CI, 84% to 91%) at 1 year and 60% (95% CI, 55% to 65%) *v* 62% (95% CI, 56% to 67%) at 5 years, respectively (Fig 2F). Among all end points evaluated, DSS exhibited the largest change in hazard for chemotherapy versus no chemotherapy, with an HR for disease-specific death of 0.37 (95% CI, 0.20 to 0.69; $P = .002$) in the first year and 1.36 (95% CI, 1.02 to 1.81; $P = .04$) after the first year (Fig 3).

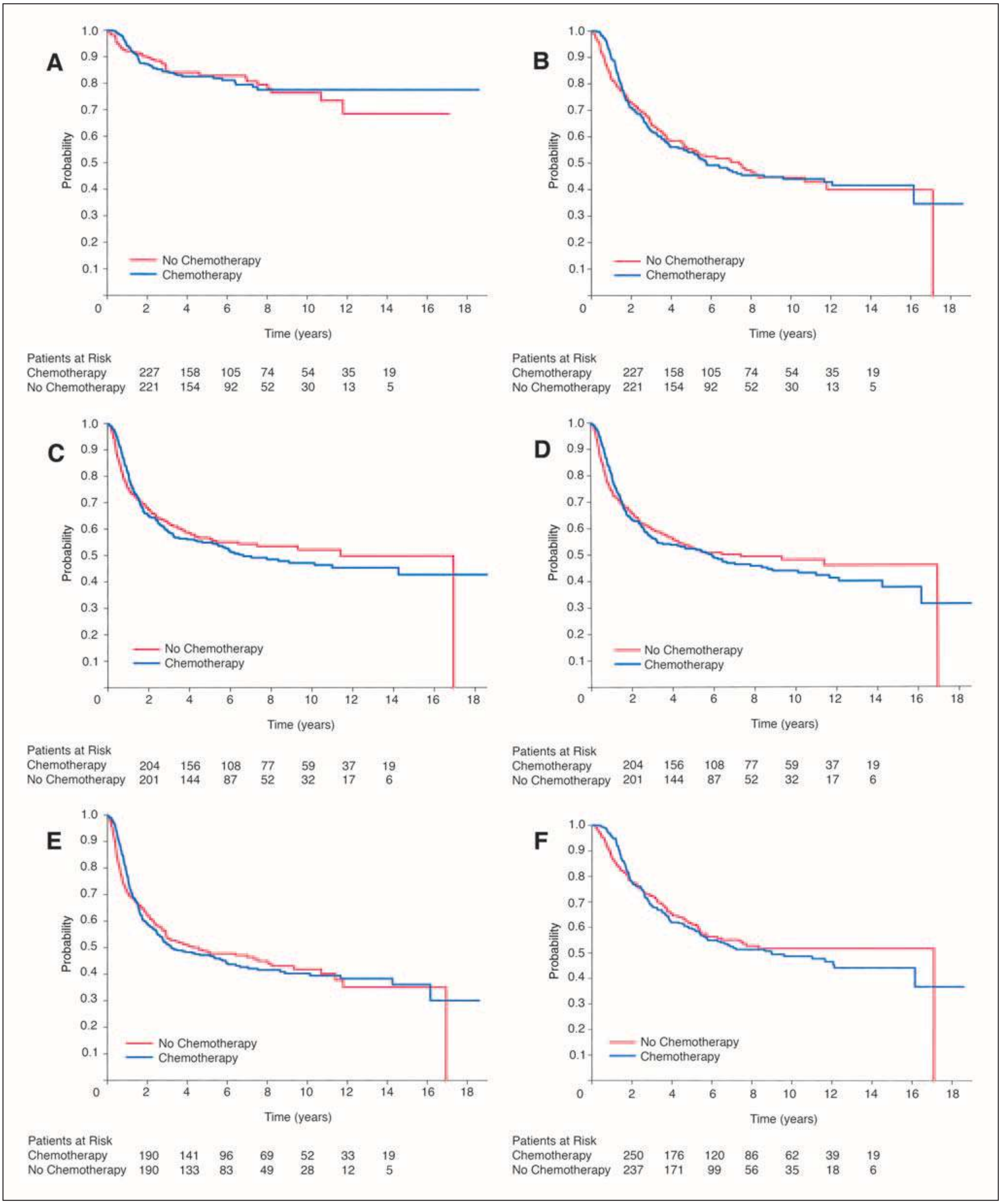

Fig 2. Kaplan-Meier curves of local recurrence-free interval (A), local disease-free survival (B), distant recurrence-free interval (C), distant disease-free survival (D), overall disease-free survival (E), and disease-specific survival (F) for chemotherapy versus no chemotherapy.

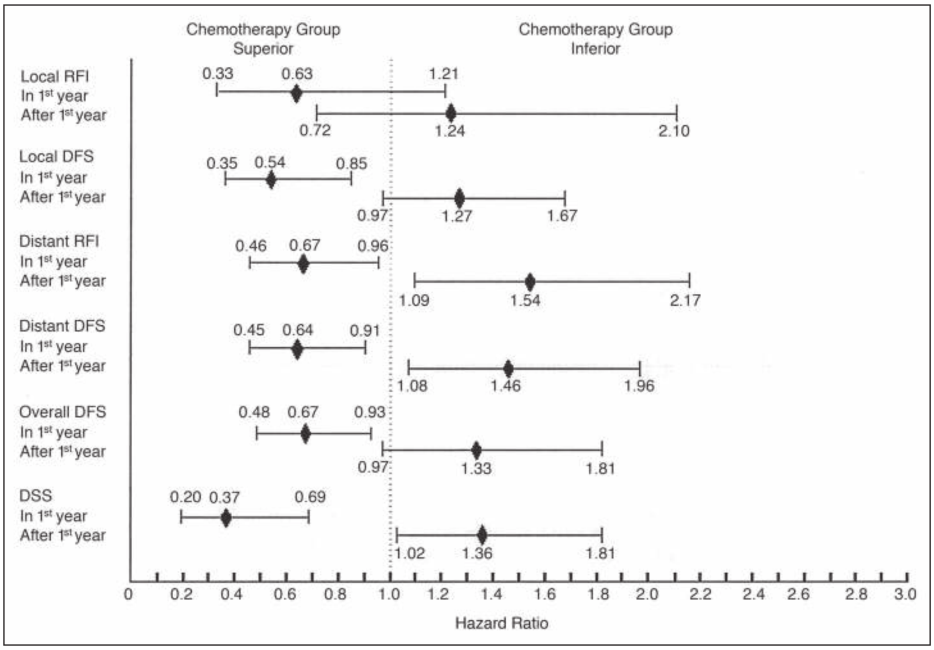

Fig 3. Hazard ratio and 95% CI for time-to-event outcomes in the chemotherapy group. RFI, recurrence-free interval; DFS, disease-free survival; DSS, disease-specific survival.

DISCUSSION

In our covariate-adjusted analysis of 674 patients with stage III extremity STS, the observed effects of chemotherapy varied over time. The instantaneous hazard function curves for patients treated with chemotherapy compared with patients treated without chemotherapy crossed at approximately 1 year after the initiation of treatment. Given that the proportional hazards assumption is violated, the effects of being treated with chemotherapy cannot be characterized by a single parameter. Consequently, we analyzed these effects over two distinct time periods: the interval up to 1 year and the interval beyond 1 year. Total benefits associated with chemotherapy in the first year were estimated to be 7%, 6%, 6%, and 8% for local, distant, and overall DFS and DSS, respectively. However, at 5 years, the use of chemotherapy was associated with higher rates of disease recurrence and lower DFS and DSS, with cumulative 2%, 1%, 2%, and 2% decrements in local, distant, and overall DFS and DSS, respectively. Thus, chemotherapy seemed to result in no long-term benefits.

This study included a homogeneous population of high-risk patients with STS traditionally considered likely to benefit from chemotherapy. The chemotherapy and no-chemotherapy subgroups were balanced with respect to known prognostic factors, except that younger patients were more likely to have received chemotherapy ($P < .001$). Given that our model adjusted for age as well as all other known prognostic factors, its estimates of the effects of chemotherapy were unlikely to have been confounded by the observed difference in the age distribution. Nevertheless, if the effects of chemotherapy were confounded by age, this might explain the early benefits seen with chemotherapy but not the subsequent adverse effects.

Although the patient population in this study was homogeneous and the analyses were adjusted for known prognostic factors, interpretation of these data must take into account that patients were not randomly assigned between chemotherapy and no chemotherapy. Although the Cox model can adjust for known clinicopathologic and treatment factors, we cannot exclude the possibility that the time-varying effects of chemotherapy arose as a consequence of an imbalance in unknown confounding factors. For example, the use of potentially less efficacious chemotherapy regimens (doses and agents) in one group might account for some of the effects observed. These and additional subset analyses will be addressed in subsequent reports. The retrospective nature of our analysis also does not allow us to draw conclusions about the mechanism(s) underlying the time-varying effects of chemotherapy. There may be biologic reasons for the eventual unfavorable effects associated with chemotherapy.

To our knowledge, the current report of 674 patients is the largest observational study evaluating the effects of chemotherapy in patients with high-risk extremity STS. When considering sample size and number of observed events, the current report may be compared and contrasted with the SMAC meta-analysis.[6] Several points merit comment. First, the meta-analysis was based on pooled individual patient data from randomized trials in heterogeneous patient populations with STS, whereas this report is a retrospective analysis comparing nonrandomized treatments in a homogeneous population. Second, the meta-analysis included patients with primary (89%) or recurrent (11%) STS arising in extremity (58%) and nonextremity (42%) anatomic sites, whereas this report was restricted to patients with primary extremity tumors. Third, the meta-analysis combined data from a number of treatment centers and was performed with significant missing covariate data. For example, 28% and 37% of patient cases were missing tumor grade and size, respectively. In contrast, this analysis was based on a data set from two institutions with no missing covariate data. Fourth, the SMAC meta-analysis included patients with significant tumor heterogeneity. For example, 17% of patients had uterine sarcomas and 5% of patients had low-grade sarcomas. In addition, in the subset of patients with extremity STS in the SMAC meta-analysis, 40% of patient cases had tumor size less than 5 cm—a subset of patients with generally more favorable outcomes.[19,20] In contrast, our report was based on a homogeneous patient population; all patients had large ($>$ 5 cm), high-grade sarcomas located beneath the investing fascia of the extremity. Given the general limitations of meta-analysis,[21,22] the specific limitations of the SMAC meta-analysis,[10] and the conflicting body of relatively small randomized trials, there is no consensus on the role of chemotherapy in patients with localized high-risk STS. In this context, retrospective reports such as ours may provide important observations that add to the existing body of literature.

In summary, this retrospective analysis of patients with high-risk extremity STS treated at two cancer centers over a 16-year period suggests that the use of chemotherapy is associated with time-varying clinical effects. During the first year, there seem to be improvements in clinical end points; thereafter, the effect seems to be reversed, with the use of chemotherapy associated with lower DFS and DSS. These results suggest that caution should be used in interpreting randomized clinical trials of adjuvant chemotherapy that seem to demonstrate clinical benefits with relatively short-term follow-up. Given the ongoing controversy regarding the role of chemotherapy for high-risk localized STS, we recommend that patients with stage III extremity STS who are considering doxorubicin-based chemotherapy be informed that the initial clinical benefits of chemotherapy may not be sustained over time.

Acknowledgment

We thank Melissa Burkett for her editorial assistance.

Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

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