Primary Sarcoma of the Mediastinum

A Report of 16 Cases Referred to the British Columbia Cancer Agency

Matthew Paquette, BSc, Pauline T. Truong, MDCM,*† Jason Hart, MD,*† Stuart O. Jones, BSc,* Benjamin Martens, BA,*† Jennifer L. Christie, BSc,* Cheryl Alexander, CCHRA(C),* and Howard Joe, MD*†*

Background: Sarcoma arising in the mediastinum is a rare entity. This study evaluates treatment and survival in a cohort of patients with primary mediastinal sarcoma.

Methods: Between 1990 and 2006, 16 patients were referred to the British Columbia Cancer Agency with histologically confirmed sarcoma of mediastinal origin. Outcomes examined were disease-free survival (DFS) and overall survival (OS).

Results: There were nine male and seven female patients. The median age at diagnosis was 56 years (range 21–70 years). Thirteen (81%) patients had localized disease, and three (19%) patients had distant metastasis at diagnosis. Surgical resection was performed in 8 of 13 patients with localized disease. At a median follow-up of 18 months, 12 patients have died of disease, three were alive with disease, and one was alive with no evidence of disease. In the entire cohort, median DFS was 12 months (range 0–107 months), and median OS was 18 months (range 1–193 months). Patients who underwent surgery experienced improved DFS ($p = 0.054$) and OS ($p = 0.034$). Eastern Cooperative Oncology Group performance status 0 to 1 was associated with improved DFS ($p = 0.038$) and OS ($p = 0.007$). The histologic subtype with the longest survival was well-differentiated liposarcoma. Age, gender, tumor location, T and N stage, tumor size, location, and grade were not associated with significant survival differences.

Conclusion: Surgical resection was associated with more favorable survival in patients with mediastinal sarcoma. However, the high rates of progression and mortality underscore the need for more effective adjuvant treatments.

Key Words: Sarcoma, Mediastinum, Surgery, Radiotherapy, Chemotherapy, Survival.

(*J Thorac Oncol.* 2010;5: 898–906)

Soft tissue sarcomas are a heterogeneous group of malignant mesenchymal tumors that can affect various anatomic locations, most commonly the extremities.[1] Primary sarcoma arising in the mediastinum is a rare entity, comprising less than 10% of all adult primary mediastinal tumors and less than 2% of all soft tissue sarcoma cases.[2–4] There are few data defining optimal therapy for this rare disease. Current knowledge on treatment and outcomes in patients with mediastinal sarcoma is primarily based on institutional series,[4–8] case studies,[9–15] and data from sarcoma involving other anatomic sites.[16–24] Surgical resection has been reported to confer survival benefit,[4] but late presentation and delayed diagnosis due to nonspecific symptoms can result in locally advanced or metastatic disease at presentation. The role of radiation therapy (RT) and systemic therapy and their impact on prognosis have remained unclear.

This study is a population-based analysis of the clinicopathologic characteristics, local and systemic treatment, and survival in adult patients referred to a Canadian provincial cancer care institution with primary sarcoma arising in the mediastinum.

METHODS

Study Setting

The British Columbia Cancer Agency (BCCA) is a tertiary care institution providing a province-wide, population-based cancer control program for the residents of British Columbia, Canada. All patients referred to the BCCA Sarcoma Tumor Group are discussed in a multidisciplinary forum by a specialized team of surgeons, radiation and medical oncologists, pathologists, and radiologists convening weekly to review all pertinent records, investigations, and pathology of each case. Individualized management recommendations are made by the multidisciplinary team and communicated to the referring physicians and treating oncologists. The chemotherapy regimens used were consistent with systemic therapy regimens endorsed provincially by the BCCA Sarcoma Tumor Group.

Study Subjects

Between January 1, 1990, and December 31, 2006, 2767 patients were referred to the BCCA with newly diagnosed primary sarcoma. Of these, 19 (0.7%) cases were

*British Columbia Cancer Agency, Vancouver Island Centre, Victoria; †University of British Columbia, British Columbia, Canada.

Disclosure: The authors declare no conflicts of interest.

Address for Correspondence: Pauline T. Truong, MDCM, British Columbia Cancer Agency, Vancouver Island Centre, 2410 Lee Avenue, Victoria, BC V8R 6V5, Canada. E-mail: ptruong@bccancer.bc.ca

ISSN: 1556-0864/10/0506-0898

mediastinal in origin. Three cases were excluded, one with age <18 years, one with lacking pathologic and treatment information, and one with a final diagnosis of sclerosing mediastinitis rather than malignant sarcoma. The remaining 16 patients formed the study cohort of this analysis.

Data Abstraction and Analysis

Retrospective chart review was performed to abstract data on patient, tumor, and treatment characteristics, response to treatment, and survival outcomes. Response to therapy was classified as complete response, partial response, or no response based on the World Health Organization Handbook for Reporting Results of Cancer.[25] Complete response was defined as the disappearance of all known disease. For patients treated with surgery, we also defined complete response as the resection of all gross disease. Partial response was defined as 50% or more decrease in total tumor size, with no new lesions or progression of any lesion. No response was defined as no change or when a 50% decrease in total tumor size could not be established.[25]

Performance status was graded using the Eastern Cooperative Oncology Group criteria.[26]

Disease-free survival (DFS) and overall survival (OS) were computed using Kaplan-Meier methods. The log-rank test was used to compare survival between different subgroups. Statistical tests were two sided, with significance established at $p < 0.05$. All analyses were conducted using Statistical Package for Social Sciences software, version 14.0.2 (SPSS, Chicago, IL).

The study was approved by the University of British Columbia research ethics board.

RESULTS

Patient and Tumor Characteristics

Clinicopathologic characteristics of the study cohort are summarized in Table 1. There were nine male and seven female patients. The median age at diagnosis was 56 years (range 21–70 years). Thirteen (81%) patients had localized disease, and three (19%) patients had distant metastasis at diagnosis.

Treatment Characteristics

Local and systemic treatment, response to treatment, time to progression, and survival are summarized in Table 2. Surgical resection was performed in 8 of 13 patients with localized disease. Of these, one had wide local excision with negative surgical margins, six had positive margins, and one had unknown margin status. The characteristics of patients treated with versus without surgery are presented in Table 3. There were higher proportions of patients with poor performance status and metastatic disease in the no surgery group. In the five patients with localized disease who did not undergo surgery, the disease was deemed to be unresectable because of disease extent or intimacy with the major vessels and heart structures. Four of these five patients had poor performances status, Eastern Cooperative Oncology Group score ≥2. In the six patients with positive margins, the median tumor size was 11.5 cm (range 6.5–16 cm).

RT as part of initial treatment was used with radical intent in 7 of 13 patients with localized disease and with palliative intent in two of three patients with metastatic disease at diagnosis. Among seven patients with localized disease who underwent RT, five patients had postoperative RT and one patient had RT alone, all targeting the mediastinum, with total doses ranging from 40 to 60 Gray, in 20 to 30 fractions.

Chemotherapy, alone or in combination with local therapy, was used in 4 of 13 patients with localized disease and 1 of 3 patients with metastatic disease. Chemotherapy alone was used in two patients with unresectable localized disease. One patient with synovial sarcoma received doxorubicin and ifosfamide but discontinued treatment after one cycle because of local progression. One patient with undifferentiated pleomorphic sarcoma received single-agent doxorubicin, with no response, and died of disease after one cycle. Preoperative chemotherapy, using ifosfamide-mesna and etoposide, alternating with vincristine, doxorubicin, and cyclophosphamide, total eight cycles, was used in one patient with embryonal rhabdomyosarcoma, resulting in partial response. One patient with a Ewing family tumor received ifosfamide-mesna and etoposide alternating with vincristine, doxorubicin, and cyclophosphamide, total six cycles, with no response. This patient subsequently underwent total body irradiation and autologous stem cell transplant, followed by mediastinal RT, also with no response.

Relapse and Survival Outcomes

Relapse and survival in each subject are summarized in Table 2. At a median follow-up of 18 months, 9 of 13 patients with localized disease have experienced disease progression: two local, six distant, and one both local and distant progression (Table 2). The median time to progression was 9 months (range 0–38 months).

Overall, 12 patients have died of disease, three were alive with disease, and one was alive with no evidence of disease. In the entire cohort, mean and median DFS were 21 months and 12 months, respectively (range 0–107 months), and mean and median OS were 34 months and 18 months, respectively (range 1–193 months) (Figures 1*A* and *B*).

Performance status was associated with DFS ($p = 0.038$) and OS ($p = 0.007$) (Table 1). The histologic subtype associated with the most favorable survival was well-differentiated liposarcoma (Table 2). Age, gender, tumor location, T and N stage, tumor size, location, and grade were not associated with significant survival differences.

Survival According to Treatment Characteristics

In patients with localized disease, surgical treatment was associated with improved OS ($p = 0.034$) and a trend for improved DFS ($p = 0.054$) (Figures 2*A* and *B*). The median OS was 27 months (range 6–193 months) in eight patients treated with surgery, when compared with 5 months (range 1–38 months) in five patients who did not undergo surgery (Figure 2*B*).

OS was not significantly different in patients treated with surgery alone compared with surgery and postoperative

TABLE 1. Clinical Characteristics and Associated Disease-Free Survival and Overall Survival

Variables	*n* (%)	Disease-Free Survival Median, Range (mo)	*P*[a]	Overall Survival Median, Range (mo)	*P*[a]
All	16 (100)	11.5 (0–107)	—	18 (1–193)	—
Gender			0.704		0.908
Male	9 (60)	9 (0–107)		11 (1–193)	
Female	7 (40)	14 (0–35)		26 (4–38)	
Age (yr)			0.658		0.945
≤50	7 (40)	9 (0–40)		16 (1–193)	
>50	9 (60)	17 (0–107)		26 (1–107)	
Eastern Cooperative Oncology Group performance Status			0.038		0.007
0–1	3 (19)	40 (14–67)		67 (28–193)	
≥2	8 (50)	3 (0–17)		4.5 (1–26)	
Unknown	5 (31)	24 (0–107)		26 (6–107)	
Histologic subtype			0.009		0.002
Liposarcoma, well differentiated	2 (13)	87 (67–107)		87 (67–107)	
Liposarcoma, not otherwise specified	1 (6)	24		26	
Synovial sarcoma	3 (19)	35 (2–40)	.	38 (5–193)	
Unspecified sarcoma/Spindle cell sarcoma	3 (19)	2 (0–14)		6 (2–28)	
Leiomyosarcoma	2 (13)	8.5 (0–17)		23 (20–26)	
Embryonal rhabdomyosarcoma	1 (6)	15		16	
Ewing family tumor	1 (6)	9		11	
Angiosarcoma	1 (6)	4		4	
Undifferentiated pleomorphic sarcoma	2 (13)	1 (0–1)		1 (1–1)	
T stage			0.789		0.417
T1B	1 (6)	0		20	
T2B	14 (88)	14.5 (0–107)		21 (1–193)	
TX	1 (6)	0		1.0	
N stage			0.515		0.515
N0	3 (19)	35 (2–40)		38 (6–193)	
N1	1 (6)	9		11	
NX	12 (75)	9 (0–107)		18 (1–107)	
M stage			0.002		0.262
M0/MX	13 (81)	15 (1–107)		26 (1–193)	
M1	3 (19)	0		2 (1–20)	
Tumor size (cm)			0.348		0.512
<10	5 (31)	9 (0–35)		20 (2–38)	
10–15	5 (31)	24 (4–107)		26 (4–193)	
≥15	5 (31)	2 (1–67)		6 (1–67)	
Unknown	1 (6)	0		1	
Tumor location			0.519		0.309
Anterior	4 (25)	14.5 (1–40)		22 (1–193)	
Posterior	3 (19)	2 (0–17)		5 (2–26)	
Not specified	9 (56)	9 (0–107)		20 (1–107)	
Grade			0.888		0.952
I and II	4 (25)	1.5 (0–107)		13 (1–107)	
III and IV	8 (50)	20.5 (0–67)		26 (2–193)	
Unknown	4 (25)	6.5 (0–14)		7.5 (1–28)	

[a] Log-rank statistics performed on known values only.

RT ($p = 0.107$) and in patients with localized disease treated with versus without RT ($p = 0.852$).

Among patients with localized disease at diagnosis, median OS durations were 8 months (range 1–16 months) in four patients treated with chemotherapy and 28 months (range 4–193 months) in nine patients treated without chemotherapy ($p = 0.010$).

Response to therapy was significantly associated with DFS ($p = 0.001$) and OS ($p = 0.007$) (Figures 3*A* and *B*). Mean OS durations were 95 months (range 26–193 months)

TABLE 2. Local and Systemic Treatment, Response, Time to Progression, and Survival in Patients with Mediastinal Sarcoma

Cases	Histologic Subtype	Surgery	Radiation Thearapy	Chemotherapy	Response	Time to Progression	Status	Overall Survival
Localized								
1	Liposarcoma, well differentiated	Wid5e excision	No	No	R0	None	ANED	67 mo
2	Liposarcoma, well differentiated	Marginal excision	No	No	R1–R2	None	AWD	107 mo
3	Liposarcoma, not otherwise specified	Wide excision	Postop mediastinum 54 Gy/30F	No	R0	Distant 21 mo	DWD	26 mo
4	Synovial sarcoma	Wide excision	Postop mediastinum 45 Gy/xxF	No	R0	Distant 38 mo	AWD	193 mo
5	Synovial sarcoma	No	Primary mediastinum 50 Gy/25F	No	PR	Local 32 mo	DWD	38 mo
6	Synovial sarcoma	No	No	Doxorubicin & ifosfamide	NR	Local 1 mo	DWD	5 mo
7	Unspecified sarcoma/Spindle cell sarcoma	Intralesional excision	Postop mediastinum 60 Gy/30F	No	R1–R2	Distant 12 mo	DWD	28 mo
8	Unspecified sarcoma/Spindle cell sarcoma	Marginal excision	Postop mediastinum 50 Gy/20F	No	R1–R2	Both local and distant 0 mo	DWD	6 mo
9	Leiomyosarcoma	Wide excision	Postop mediastinum 40 Gy/xxF	No	R1–R2	Distant 17 mo	DWD	26 mo
10[a]	Embryonal rhabdomyosarcoma	Wide excision	No	Preop IME, VAC	R1–R2	Distant 6 mo	DWD	16 mo
11	Ewing family tumor	No	TBI 12 Gy/6F; mediastinum 55 Gy/30F	IME/VAC; autologous stem cell transplant	NR	Distant 1 mo	DWD	11 mo
12	Angiosarcoma	No	No	No	—	—	DWD	4 mo
13	Undifferentiated pleomorphic sarcoma	No	No	Doxorubicin	NR	—	DWD	1 mo
Metastatic								
1	Leiomyosarcoma	No	Palliative spine 8 Gy/1F	Doxorubicin	NR	—	AWD	20 mo
2	Unspecified sarcoma/Spindle cell sarcoma	No	Palliative mediastinum 20 Gy/5F	No	NR	—	DWD	2 mo
3	Undifferentiated pleomorphic sarcoma	No	No	No	—	—	DWD	1 mo

[a] Negative margins after surgery.

Gy, gray; F, fractions; xx, unknown; IME, ifosfamide-mesna/etoposide; VAC, vincristine/doxorubicin/cyclophosphamide; TBI, total body irradiation; CR, complete response; PR, partial response; NR, no response; mo, months; AWD, alive with disease; ANED, alive, no evidence of disease; DWD, dead with disease.

TABLE 3. Clinical Characteristics, Overall Survival, and Disease-Free Survival of Patients Treated with Versus without Surgery

Variable	Surgery ($n = 8$) n (%)	No Surgery ($n = 8$) n (%)	p^a
OS (mo)			0.034
Median (range)	27 (6–193)	4.5 (1–38)	
DFS (mo)			0.054
Median (range)	20.5 (2–107)	1.5 (0–35)	
Gender			0.614
Male	4 (50)	5 (62.5)	
Female	4 (50)	3 (37.5)	
Age (yr)			
≤50	3 (37.5)	4 (50)	
>50	5 (62.5)	4 (50)	
Eastern Cooperative Oncology Group Performance Status			0.026
0–1	3 (37.5)	0	
≥2	2 (25)	6 (75)	
Unknown	3 (37.5)	2 (25)	
T stage			0.268
T1B	0	1 (12.5)	
T2B	8 (100)	6 (75)	
TX	0	1 (12.5)	
N stage			0.513
N0	2 (25)	1 (12.5)	
N1	0	1 (12.5)	
NX	6 (75)	6 (75)	
M stage			0.055
M0/MX	8 (100)	5 (62.5)	
M1	0	3 (37.5)	
Tumor size (cm)			0.153
Median (range)	8 (2–24)	13 (6.5–20)	
<10	1 (12.5)	4 (50)	
10–15	4 (50)	1 (12.5)	
≥15	3 (37.5)	2 (25)	
Unknown	0	1 (12.5)	
Grade			0.679
I and II	2 (25)	2 (25)	
III and IV	5 (62.5)	3 (37.5)	
Unknown	1 (12.5)	3 (37.5)	

[a] Statistics performed on known values only.

in three patients with complete response, 43 months (range 16–107 months) in five patients with partial response, and 8 months (range 1–20 months) in six patients with no response (Figure 3*B*).

DISCUSSION

Primary sarcomas arising in the mediastinum are rare. At the BCCA, they account for less than 1% of all referred sarcoma cases, a finding comparable with other reports.[4] Available data on treatment and outcomes specific to patients with mediastinal sarcoma are limited to institutional series,[4–8] anecdotal case reports,[9–13] and collective reviews of case reports.[14,15]

Table 4 summarizes published series reporting treatment and outcomes in patients with primary mediastinal sarcoma to place in context with the current report. Relative to other studies, this study is among the more contemporary series available. Distinct from other populations, the patients in this analysis were derived from a geographically defined population with universal health care access, including oncologic treatment services coordinated by a centralized provincial program funding all chemotherapeutic drugs and RT delivery. Although there were no standard treatment protocols specific to mediastinal sarcoma because of its rarity, general consensus guidelines in soft tissue sarcoma management were available.[27] In addition, all patients were reviewed in a multidisciplinary forum by the BCCA Sarcoma Tumor Group, a team of specialists with expertise in the diagnosis, pathologic examination, and treatment of soft tissue sarcoma.

Our study has documented a range of individualized treatment strategies for patients with mediastinal sarcoma and corroborated others' findings of heterogeneity in disease response and survival outcomes.[4–8] The mean OS of 34 months in the present series is comparable with other series reporting mean survival ranges of 4 to 30 months.[4–8] Although the study has identified several clinical factors associated with more favorable survival, the high rates of progression and limited survival emphasize the need for more effective treatments.

The impact of patient demographics and clinicopathologic characteristics on survival in patients with mediastinal sarcoma is unclear. The median age of 56 years in our cohort is comparable with other series reporting median ages of 35 to 58 years.[4–8] Although the male to female ratio in our cohort was 1.3, others have found a higher male predominance with male to female ratios of 1.6 to 2.0.[4,7] Age and gender were not associated with significant survival differences in the current analysis. The finding that performance status was significantly correlated with survival corroborates other studies[16,17] and suggests that this factor can be used in clinical decisions and prognosis estimates.

Distinct from some series limited to one histologic subtype,[5,7,8] this study evaluated all histologic subtypes to assess whether there may be survival variations associated with different subtypes. Survival was most favorable in patients with well-differentiated liposarcoma and least favorable in patients with undifferentiated pleomorphic sarcoma and angiosarcoma. These findings, however, should be interpreted with caution because of small patient samples with this rare disease. Acknowledging the caveat with small samples, the relatively longer survival seen in association with well-differentiated liposarcoma is consistent with some case reports[12,15] and institutional series.[8] Similarly, the rapid rates of tumor progression and poor survival observed with undifferentiated pleomorphic sarcoma and angiosarcoma have also been described by others, suggesting that these subtypes have a more aggressive biology.[13,17,18]

The guiding principle in the surgical management of soft tissue sarcoma is to achieve complete removal of the

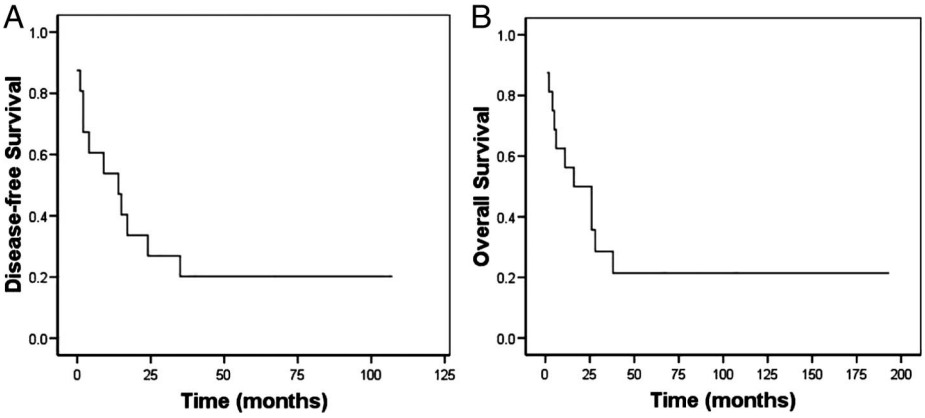

FIGURE 1. *A,* Disease-free survival and *B,* overall survival of the entire cohort.

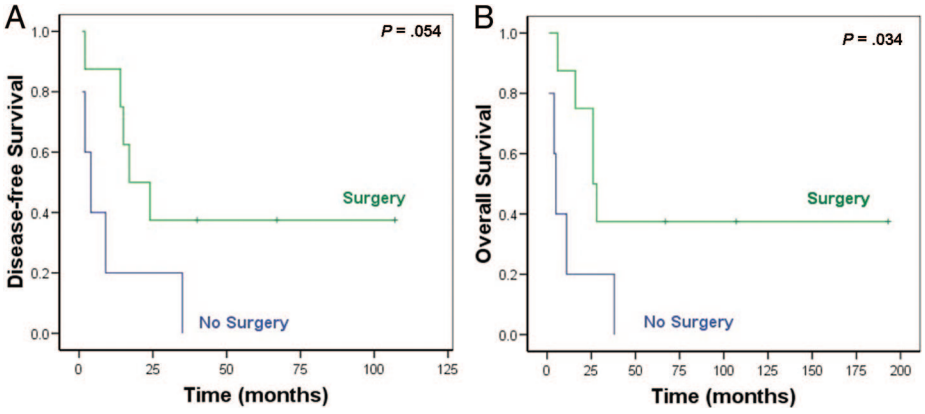

FIGURE 2. *A,* Disease-free survival and *B,* overall survival according to surgery for localized disease.

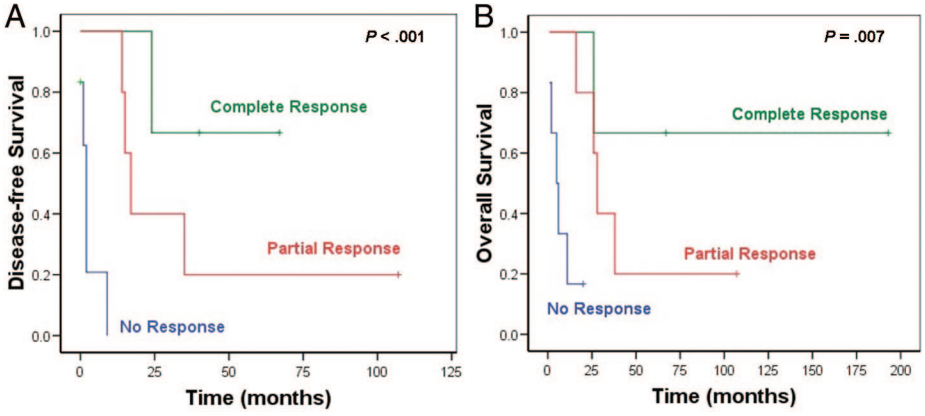

FIGURE 3. *A,* Disease-free survival and *B,* overall survival according to response to therapy.

primary tumor, preserve function, and minimize the risk of local recurrence.[19,27] In this series, patients with localized disease treated with surgery experienced significantly improved survival relative to patients treated without surgery. Although the demonstration of survival benefits with surgical resection is clear, the ability to perform wide local excision with negative resection margins in patients with mediastinal sarcoma can be challenging, particularly with extensive, bulky disease invading major vessels and adjacent cardiopulmonary structures.

The difficulty in achieving complete tumor clearance is reflected by the high rates of positive margins in our series, with only one patient having negative margins after surgery. In our series, the reasons for positive margins were predominantly large tumors with invasion into blood vessels and adjacent critical structures. Similarly, in a series of 24 patients with mediastinal liposarcoma reported by Hahn and Fletcher,[8] among 14 patients who underwent surgery, nine had positive margins, three had close margins, and two had unknown margin status. In a study of 395 patients with soft tissue sarcoma of various primary sites, Stefanovski et al.[16] identified positive margin to be a strong prognostic predictor for both local relapse and mortality. Burt et al.[4] reported similar findings in an analysis of the Memorial Sloan Ketter-

TABLE 4. Summary of Published Series from 1990—Present Reporting Treatment and Outcomes in Adult Patients with Mediastinal Sarcoma

Institution, Year of Publication	Study Period	Cases	Histologic Subtypes	Age (yr)	Surgical resection	RT Use	CT Use	Overall Survival (mo)
Mount Sinai Medical Center, 1994[5]	NR	4	All rhabdo myosarcoma	Mean 23	2/4 (2 incomplete)	0/4	3/4	Mean 4 (range 1–6)
Memorial Sloan-Kettering Cancer Center, 1998[4]	1940–1991	47	Varied	Median 39	34/47 (22 complete and 12 incomplete)	32/47	30/47	Median 13 (range NR)
University of New Mexico, 2000[6]	1973–1995	11	Varied	NR	8/11	4/11	5/11	36% at 5 yr mean/median NR
Ohio State University, 2005[7]	1985–2000	15	All synovial sarcoma	Median 35	12/15 (10 complete and 2 incomplete)	5/15	0/15	NR
Harvard Medical School, 2007[8]	1992–2005	24 (15 had outcomes data)	All liposarcoma	Median 58	14/24 (3 complete, 9 incomplete, and 2 unknown)	2/24[a]	5/24[a]	Mean 30 (range 2–59)
British Columbia Cancer Agency, 2010	1990–2006	16	Varied	Mean 50 median 57	8/16 (1 complete, 6 incomplete, and 1 unknown)	9/16	5/16	Mean 34, median 18 (range 1–193)

[a] Information regarding treatment not available in 8 of 24 patients.
NR, not reported; RT, radiation therapy; CT, chemotherapy.

ing Cancer Center's experience treating 47 patients with mediastinal sarcoma more than five decades from 1940 to 1991. The most significant factor associated with survival was complete surgical resection. In that series, the 5-year survival with complete resection was 49%, when compared with 18% with incomplete or no resection.[4] These outcomes underscore the importance of early diagnosis to improve the feasibility to perform complete resection and the need for new treatment strategies to address the problem of residual disease or positive margins after surgery.

Evidence-based recommendations guiding RT decisions for soft tissue sarcoma have been primarily based on prospective trials of patients with sarcoma involving the extremities.[19–22] These trials have demonstrated that combined surgery and RT confer improved local control, but not survival, in patients with nonmetastatic disease.[19–21] Our analysis did not find survival differences in patients who underwent surgery plus postoperative RT compared with patients treated with surgery alone. Interestingly, the two patients treated with surgery alone had well-differentiated liposarcoma, and both have remained alive without local or distant progression. In contrast, among the five patients who underwent surgery plus postoperative RT, all of whom had positive margins, five had local disease control but developed distant metastasis within 12 to 38 months, and one patient developed rapid progression both locally and distantly. These outcomes are likely related to patients with higher risk disease being selected for postoperative RT whereas patients with lower risk disease were managed with surgery alone.

We acknowledge that our retrospective study is limited by small samples and inherent biases in patient and treatment selection and that there are few data reporting outcomes after RT in patients with mediastinal sarcoma with which to compare our results. Despite these caveats, the observation in this series that the majority (4 of 5) of patients who received postoperative RT were locally controlled and the concern that thoracic disease progression can lead to symptom distress and reduced quality of life support the consideration of using mediastinal RT to optimize local control, particularly in cases of unresectable tumors or residual disease after surgery.

The role of chemotherapy in mediastinal sarcoma management has not been established because of limited data. The BCCA Sarcoma Tumor Group's treatment policy acknowledged that routine postoperative chemotherapy for soft tissue sarcoma is controversial.[27] In other studies reporting chemotherapy use in patients with mediastinal sarcoma, most have used doxorubicin-based regimens, in various combinations with agents including cyclophosphamide, ifosfamide, etoposide, and cis-platin.[4,8,14,15] These studies, similar to ours, found varied tumor response and survival outcomes.[4,8,14,15] The small numbers of patients treated with chemotherapy in this and other studies preclude the ability to draw conclusions regarding what constitutes optimal systemic therapy and whether neoadjuvant or adjuvant approaches should be used.

At the BCCA, general guidelines are available for specific settings where chemotherapy is an integral component of multimodality therapy for sarcoma.[27] These include

rhabdomyosarcoma, Ewing sarcoma, and other small round blue cell tumors.[27] Accordingly, alternating ifosfamide-mesna/etoposide and vincristine/doxorubicin/cyclophosphamide were used as preoperative therapy in one case of embryonal rhabdomyosarcoma and as primary therapy in conjunction with RT and bone marrow transplant in one case of Ewing family tumor. In both cases, survival was poor with distant dissemination occurring within 6 months after therapy.

Although our series is among the largest available series, it remains small in absolute numbers because of the rarity of this disease. Given the small numbers and heterogeneity in clinical and treatment characteristics, it is not possible to perform multivariate analyses to control for confounders and that interpretation of small subgroup comparisons must be done with caution. These limitations prohibit the ability to formulate guidelines as the management of patients with this rare disease must be individualized depending on the extent of disease at diagnosis and the patient's physiologic reserve. Thus, we advocate the policy of thorough review of each case, including imaging and pathologic review, in an interdisciplinary forum to obtain consensus regarding optimal treatment, with the understanding that the final treatment recommendations for each patient can only be made after careful, individualized assessment by the surgeon and oncologist.

Research efforts are warranted to examine new local and systemic treatments that may be used in conjunction with surgery to improve disease control and survival in patients with mediastinal sarcoma. Innovative RT techniques including intensity-modulated RT and conformal treatment planning incorporating functional imaging data have the potential to improve intrathoracic tumor targeting and reduce normal tissue exposure.[28,29] Intraoperative brachytherapy using permanent Iodine-125 interstitial planar seed implants applied to high-risk intrathoracic regions at the time of surgery is a new strategy that may be particularly useful for patients with close or positive margins.[30] Molecular analysis of sarcoma pathology and identification of targets for molecular therapy have also advanced in recent years.[31] The evaluation of these prognostic and therapeutic innovations to advance care for patients with mediastinal sarcoma will succeed only with continued multidisciplinary clinical and research collaboration.

CONCLUSION

In patients with mediastinal sarcoma, good performance status, well-differentiated liposarcoma, surgical resection, and complete response to therapy were associated with more favorable survival. The majority of patients treated with surgery and postoperative RT had local disease control but progressed distantly. The high rates of disease progression and mortality emphasize the need for more effective local and systemic treatments. Given the rarity and complexity of mediastinal sarcomas, a policy of reviewing each case in an interdisciplinary forum is advocated to optimize individualized treatment decisions for these patients.

REFERENCES

1. Brennan ME, Alektiar KM, Maki RG. Soft tissue sarcoma. In VT DeVita, S Hellman, SA Rosenberg, (Eds.), Cancer: Principles and Practice of Oncology, 6th Ed. Philadelphia, NY: JB Lippincott, 2001. Pp. 1841–1890.
2. Macchiarini P, Ostertag H. Uncommon primary mediastinal tumours. *Lancet Oncol* 2004;5:107–118.
3. Silverman NA, Sabiston DC Jr. Mediastinal masses. *Surg Clin North Am* 1980;60:757–777.
4. Burt M, Ihde JK, Hajdu SI, et al. Primary sarcomas of the mediastinum: results of therapy. *J Thorac Cardiovasc Surg* 1998;115:671–680.
5. Suster S, Moran CA, Koss MN. Rhabdomyosarcomas of the anterior mediastinum: report of four cases unassociated with germ cell, teratomatous, or thymic carcinomatoous components. *Hum Pathol* 1994;25:349–356.
6. Temes R, Allen N, Chavez T, et al. Primary mediastinal malignancies in children: report of 22 patients and comparison to 197 adults. *Oncologist* 2000;5:179–184.
7. Suster S, Moran CA. Primary synovial sarcomas of the mediastinum: a clinicopathologic, immunohistochemical, and ultrastructural study of 15 cases. *Am J Surg Pathol* 2005;29:569–578.
8. Hahn HP, Fletcher CD. Primary mediastinal liposarcoma: clinicopathologic analysis of 24 cases. *Am J Surg Pathol* 2007;31:1868–1874.
9. Katakura H, Fukuse T, Shiraishi I, et al. Mediastinal synovial sarcoma. *Thorac Cardiovasc Surg* 2009;57:183–185.
10. Kaira K, Ishizuka T, Sunaga N, et al. Primary mediastinal synovial sarcoma: a report of 2 cases. *J Comput Assist Tomogr* 2008;32:238–241.
11. Barbetakis N, Samanidis G, Samanidou E, et al. Primary mediastinal liposarcoma: a case report. *J Med Case Reports* 2007;1:161.
12. Grewal RG, Prager K, Austin JH, et al. Long term survival in non-encapsulated primary liposarcoma of the mediastinum. *Thorax* 1993;48:1276–1277.
13. Kardamakis D, Bouboulis N, Ravazoula P, et al. Primary hemangiosarcoma of the mediastinum. *Lung Cancer* 1996;16:81–86.
14. Gotoh M, Furukawa S, Motoishi M, et al. Synovial sarcoma of the mediastinum: report of a case. *Surg Today* 2004;34:521–524.
15. Hirai S, Hamanaka Y, Mitsui N, et al. Surgical resection of primary liposarcoma of the anterior mediastinum. *Ann Thorac Cardiovasc Surg* 2008;14:38–41.
16. Stefanovski PD, Bidoli E, De Paoli A, et al. Prognostic factors in soft tissue sarcomas: a study of 395 patients. *Eur J Surg Oncol* 2002;28:153–164.
17. Nascimento AF, Raut CP. Diagnosis and management of pleomorphic sarcomas (so-called "MFH") in adults. *J Surg Oncol* 2008;9:330–339.
18. Fayette J, Martin E, Piperno-Neumann S, et al. Angiosarcomas, a heterogeneous group of sarcomas with specific behavior depending on primary site: a retrospective study of 161 cases. *Ann Oncol* 2007;18:2030–2036.
19. Pisters PWT, O'Sullivan B, Maki RG. Evidence-based recommendations for local therapy for soft tissue sarcomas. *J Clin Oncol* 2007;25:1003–1008.
20. Yang JC, Chang AE, Baker AR, et al. A randomized prospective study of the benefit of adjuvant radiation therapy in the treatment of soft tissue sarcoma of the extremity. *J Clin Oncol* 1998;16:197–203.
21. Rosenberg SA, Tepper JE, Glatstein EJ, et al. The treatment of soft-tissue sarcomas of the extremities: prospective randomized evaluations of (1) limb-sparing surgery plus radiation therapy compared with amputation and (2) the role of adjuvant chemotherapy. *Ann Surg* 1982;196:305–315.
22. O'Sullivan B, Davis AM, Turcotte R, et al. Preoperative versus postoperative radiotherapy in soft tissue sarcoma of the limbs: a randomized trial. *Lancet* 2002;359:2235–2241.
23. Adjuvant chemotherapy for localised resectable soft tissue sarcoma of adults: meta-analysis of individual data. Sarcoma Meta-analysis Collaboration. *Lancet* 1997;350:1647–1654.
24. Pervaiz N, Colterjohn N, Farrokhyar F, et al. A systematic meta-analysis of randomized controlled trials of adjuvant chemotherapy for localized resectable soft tissue sarcoma. *Cancer* 2008;113:573–581.
25. Miller AB, Hodgstraten B, Staquet M, et al. Reporting results of cancer treatment. *Cancer* 1981;47:207–214.
26. Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria

of the Eastern Cooperative Oncology Group. *Am J Clin Oncol* 1982;5: 649–655.
27. British Columbia Cancer Agency cancer management guidelines. Available at: http://www.bccancer.bc.ca/HPI/CancerManagementGuidelines/MusculoskeletalandSarcoma/Management/Referral+Info.htm. Accessed October 1, 2009.
28. Choe KS, Salama JK. Advances in radiotherapy for tumors involving the mediastinum. *Thorac Surg Clin* 2009;19:133–141.
29. Sharma N, Neumann D, Macklis R. The impact of functional imaging on radiation medicine. *Radiat Oncol* 2008;15:3–25.
30. Stewart AJ, Mutyala S, Holloway CL, et al. Intraoperative seed placement for thoracic malignancy: a review of technique, indications, and published literature. *Brachytherapy* 2009;8:63–69.
31. Wunder JS, Nielsen TO, Maki RG, et al. Opportunities for improving the therapeutic ratio for patients with sarcoma. *Lancet Oncol* 2007;8:513–524.