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Clinical Investigation

Radiation Therapy in Resectable Intrathoracic Sarcomas. A Rare Cancer Network Study

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Summary

This clinical study examines the use of adjuvant radiation therapy for resected intrathoracic sarcomas. Adjuvant radiation therapy was associated with improved local control. The impact of these results on long-term survival requires further evaluation in prospective clinical studies.

Purpose: Intrathoracic sarcomas (ITS) are considered rare tumors and have a dismal prognosis. We investigated outcomes and risk factors for local control (LC), disease-free survival (DFS), and overall survival (OS) in patients with resected nonmetastatic ITS treated with or without adjuvant radiation therapy (RT) and/or chemotherapy.

Methods and Materials: Patients from the Rare Cancer Network database were studied. A Kaplan-Meier estimate was used to assess survival curves, and Cox proportional hazards regression was used to assess risk factors for LC, DFS, and OS.

Results: Between 2000 and 2017, 121 patients met inclusion criteria. The primary site was lung in 30%, mediastinum in 34%, and pleura in 36%. Thirty-nine percent and 32% received RT and chemotherapy. Median follow-up was 34 months (range, 2-141). LC, DFS, and OS at 10 years were 52%, 18.7%, and 7.2%, respectively. In multivariate analysis, RT ($P = .003$) and R1 margin status ($P = .041$) retained a significant association with LC. Only R1 resection ($P = .002$) remained associated with an increased risk of death in multivariate analysis. Overall, 7 patients (6%) developed grade 3 treatment-related chronic toxicity events.

Conclusions: This joint analysis revealed that OS remains modest in this group of patients, mainly given by the high risk of local and distant failure. Our results suggest that resected ITS can benefit from adjuvant RT.

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Introduction

Primary intrathoracic sarcomas (ITS) are a very rare subtype of soft-tissue sarcoma with heterogenous biological properties and histologic findings.[1] Surgical resection is the primary therapy for localized ITS, but a completely negative resection margin is often difficult to achieve. Adjuvant radiation therapy (RT) and chemotherapy (CT) have improved outcomes in other subtypes of sarcoma.[2] Therefore, multimodal approaches should be implemented to further improve patient outcomes and to optimize disease control and survival for ITS.[3] In this complex context, few retrospective studies have specifically analyzed the prognosis of patients with ITS.[3-13] The Rare Cancer Network (RCN, www.rarecancer.net) supports cooperative research projects on rare tumors that could be studied by multicenter retrospective data collection. In November 2017, the RCN launched a study aiming to analyze treatment strategies and long-term outcomes in this clinical scenario.

Methods and Materials

On November 9, 2017, a letter describing the project was sent to institution members of the RCN. Ultimately, 7 centers (3 American, 4 European) agreed to participate in this retrospective study. The study population comprised adult patients (age >18 years) with pathologically confirmed resected nonmetastatic ITS treated between March 2000 and November 2017. Patients with Ewing sarcoma or rhabdomyosarcoma were not included. Adjuvant therapy was recommended after taking into account tumor location, resectability, and clinical status. Data were collected using hospital electronic records and charts, updated to the date of this analysis (February 2, 2018). Details of surgery, RT, and adjuvant CT followed international standards.[7] A range of multiagent CT protocols based on institutional recommendations was used because of the wide treatment period included in this study. The most commonly used agents were doxorubicin and ifosfamide.

Table 1 Patient, tumor, and treatment characteristics

Parameter	Variable	n (%)	Adjuvant radiation therapy	No adjuvant radiation therapy	*P* value
Patient variables		121 (100)	39 (32)	82 (68)	
Sex	Female	58 (48)	17 (44)	41 (40)	.89
	Male	63 (52)	22 (56)	41 (50)	
Age (y)	Median (range)	60 (19-83)	59 (19-77)	60 (21-83)	.76
Symptoms	Yes	89 (74)	29 (74)	60 (73)	.93
	No	32 (26)	10 (26)	22 (27)	
Location	Pleural	43 (36)	14 (36)	29 (35)	.88
	Mediastinum	41 (34)	13 (33)	28 (34)	
	Lung	37 (30)	12 (31)	25 (31)	
Surgical variables					
Surgical resection protocol	Tumorectomy	75 (62)	23 (59)	52 (63)	.42
	Extended resection	46 (38)	16 (41)	30 (37)	
Pathologic specimen					
Histologic subtype	UPC	35 (29)	12 (31)	23 (28)	.56
	Synovial sarcoma	26 (22)	8 (20)	18 (22)	
	Leiomiosarcoma	23 (19)	9 (23)	14 (17)	
	Liposarcoma	11 (9)	3 (8)	8 (10)	
	Others	26 (21)	7 (18)	19 (23)	
Tumor stage	T1	21 (17)	4 (10)	17 (21)	.31
	T2	30 (25)	10 (26)	20 (25)	
	T3	43 (36)	13 (33)	30 (39)	
	T4	27 (22)	17 (31)	12 (15)	
Nodal stage	N0	90 (74)	27 (69)	63 (77)	.62
	N1	10 (8)	4 (10)	6 (7)	
	N2	21 (18)	8 (21)	13 (16)	
Histologic grade	I	13 (11)	3 (8)	10 (12)	.45
	II	48 (39)	13 (33)	35 (43)	
	III	60 (50)	23 (59)	37 (47)	
Margin status	R0	55 (45)	16 (41)	39 (48)	.47
	R1	66 (55)	23 (59)	43 (52)	
Adjuvant therapy					
Chemotherapy	Yes	47 (39)	15 (38)	32 (39)	.94
	No	74 (61)	24 (62)	50 (61)	

Abbreviation: UPC = undifferentiated pleomorphic sarcoma

Differences in median and frequencies were calculated using the Mann-Whitney and χ^2 test. Staging system was American Joint Committee on Cancer, 8th edition and the pathologic grading system was French Federation of Comprehensive Cancer Centers.

The goal of surgery was gross total resection. A complete resection was possible in 45% and R1 resection in 55%. Tumorectomy (62%) was defined as the surgical removal of the tumor along with the minimum of healthy tissue. Extended resection (38%) was defined as the resection of a major vessel or lung. A total median external beam RT dose of 50 Gy (range, 45-60 Gy) was applied postoperatively and delivered with megavoltage equipment (6-15 MV) using 3-dimensional conformal field (n = 115, 95%) or intensity modulated RT (n = 6, 5%).

We performed a descriptive analysis of the whole population. Local control (LC), disease-free survival (DFS), and overall survival (OS) were calculated, using the date of surgical resection as initial reference date. The Statistical Package for the Social Sciences, version 19.0 (SPSS, Inc, Chicago, IL) was used for statistics. The primary endpoint of the analysis was LC. Secondary endpoints were DFS and OS. To prevent immortal time bias, all patients needed have survived for at least 1 month after surgery. The Kaplan-Meier method was used to estimate the survival, and the log-rank test was used to compare the impact of clinical or therapeutic variables. Confidence intervals were computed from standard errors, and $P < .05$ was considered significant. Potential associations for survival outcomes were assessed in the univariate and multivariate analyses using the Cox proportional hazards model. Based on P values (<.05) in the univariate analysis and clinical relevance, multivariate analysis was performed using a stepwise regression model to identify variables that have an effect on survival outcomes ($P < .05$, 2-sided). The study data

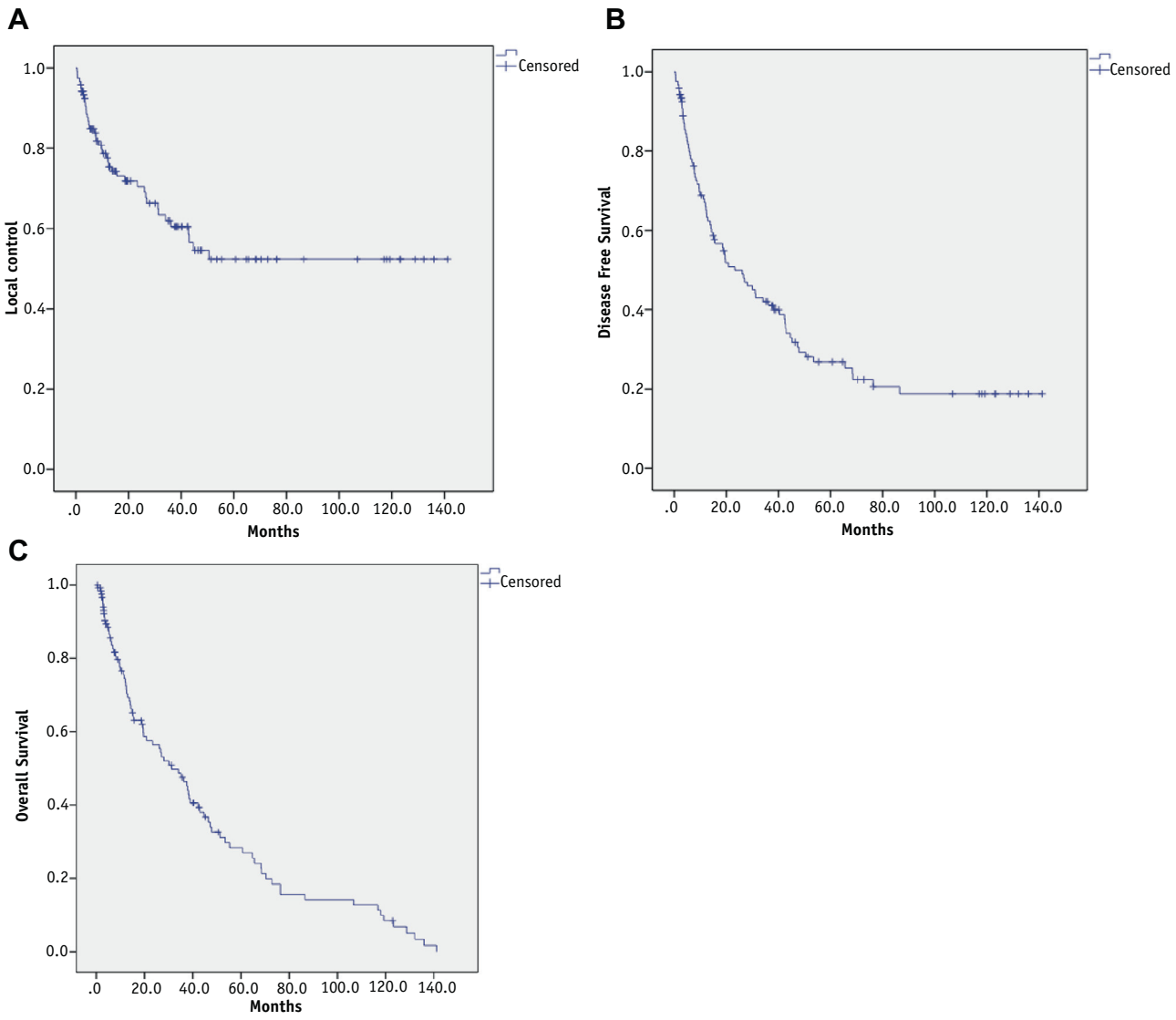

Fig. 1. (A) Actuarial local control curve for all patients (n = 121): 5- and 10-year local control of 52% (41 events). (B) Disease-free survival curve for all patients (n = 121): 5-year (26.8%) and 10-year (18.7%) disease-free survival (81 events). (C) Actuarial overall survival curve for all patients (n = 121): 5-year (27.3%) and 10-year (7.2%) overall survival (86 events).

collection protocol was designed in accordance with the ethical guidelines and was approved by the independent ethics committees at all participating hospitals.

Results

Median follow-up time for all patients was 34 months (range, 2-141 months). Table 1 summarizes patient, pathologic, and treatment characteristics. One hundred twenty-one patients met the inclusion criteria. The primary site was lung in 30%, mediastinum in 34%, and pleura in 36%. Thirty-nine percent and 32% received RT and CT. A total of 35 patients remained alive at the time of the analysis. Of the 86 deceased patients, 82 (95%) died of progression of sarcoma, and 4 (5%) died of causes unrelated to sarcoma or treatment.

The crude local relapse rate was 34% (n = 41); 43% of the patients (n = 53) developed distant metastases. LC for the study population at 5 and 10 years was 52% (Fig. 1A). Univariate Cox proportional hazard analyses showed that tumor location ($P = .010$), nodal stage ($P = .002$), margin ($P = .023$), and no RT administered to treat the ITS ($P = .033$) were associated with local relapse (Table 2). After adjustment for other covariates, the variables that remained significantly associated with local relapse were the absence of RT ($P = .003$) and R1 margin status ($P = .041$) (Table 3). DFS at 5 and 10 years was 26.8% and 18.7%, respectively (Fig. 1B). Univariate analysis showed that tumor location ($P = .028$) and no RT ($P = .050$) led to a higher probability of overall relapse (Table 4). In the multivariate analysis, no RT ($P = .027$) and tumor location ($P = .007$) retained a significant association with regard to DFS (Table 3). OS at 5 and 10 years was 27.3% and 7.2% (Fig. 1C). Univariate analysis showed that patients with R1 resection ($P = .030$) and no RT ($P = .001$) had a higher probability of death (Table 5). In the multivariate analysis, only margin status ($P = .002$) retained a significant association with regard to OS (Table 3).

Overall, 7 patients (6%) developed grade 3 treatment-related chronic toxicity events (pulmonary [n = 3], cardiac [n = 3], and skin [n = 2]). No grade 4 or 5 toxicities were reported, and no second malignancies were observed during the follow-up period. We found no difference between patients treated with or without RT: 7.7% (n = 3) versus 5.9% (n = 4) ($P = .63$).

Discussion

To the best of our knowledge, this is the largest study in the literature reporting and analyzing long-term outcomes in

Table 2 Univariate analysis of associations between patient, tumor, and treatment characteristics and local control

		Local control				
Parameter	Variable	HR	95% CI	*P*- value	5-year	*P*- value
Patient variables						
Sex	Female	1.0	0.60-1.29	.501	46.8%	.502
	Male	0.88			56.2%	
Age (y)	<60	1.0	0.71-1.43	.970	53.5%	.971
	≥60	1.06			46.7%	
Symptoms	Yes	1.0	0.53-3.18	.572	50.9%	.573
	No	1.30			45.5%	
Location	Pleural	1.0	1.24-6.99	.014	69.9%	.010
	Mediastinum-lung	2.95			44.7%	
Surgical variables						
Surgical resection protocol	Tumorectomy	1.0	0.84-2.40	.192	71.4%	.193
	Extended resection	1.14			45.2%	
Pathologic specimen						
Tumor stage	T1-2	1.0	0.47-6.09	.231	61.7%	.232
	T3-4	2.03			47.1%	
Nodal stage	N0	1.0	1.17-2.17	.003	56.7%	.002
	N1-N2	1.59			40.0%	
Histologic grade	I-II	1.0	0.83-2.64	.166	62.3%	.167
	III	1.56			40.4%	
Margin status	R0	1.0	1.09-4.03	.027	60.1%	.023
	R1	2.10			45.1%	
Adjuvant therapy						
Chemotherapy	Yes	1.0	0.49-1.52	.625	53.2%	.626
	No	0.87			65.5%	
External beam radiation therapy	Yes	1.0	1.22-2.08	.037	68.7%	.033
	No	1.46			41.2%	

Abbreviations: CI = confidence interval; HR = hazard ratio.

Table 3 Univariate analysis of associations between patient, tumor, and treatment characteristics and disease-free survival

Parameter	Variable	Disease-free survival				
		HR	95% CI	*P*- value	5-year	*P*- value
Patient variables						
Sex	Female	1.0	0.44-1.36	.544	45.6%	.545
	Male	0.77			50.2%	
Age (y)	<60	1.0	0.67-2.07	.711	56.5%	.712
	≥60	1.23			45.2%	
Symptoms	Yes	1.0	0.47-1.55	.612	50.8%	.613
	No	0.73			54.2%	
Location	Pleural	1.0	1.14-2.45	.027	63.3%	.028
	Mediastinum-lung	1.67			47.2%	
Surgical variables						
Surgical resection protocol	Tumorectomy	1.0	0.95-3.48	.070	58.1%	.070
	Extended resection	1.81			25.9%	
Pathologic specimen						
Tumor stage	T1-2	1.0	0.61-3.77	.443	46.1%	.444
	T3-4	1.45			35.3%	
Nodal stage	N0	1.0	0.73-1.44	.741	47.5%	.742
	N1-N2	1.27			42.0%	
Histologic grade	I-II	1.0	0.78-5.57	.246	60.1%	.247
	III	2.36			48.7%	
Margin status	R0	1.0	0.84-2.88	.164	54.5%	.161
	R1	1.55			46.4%	
Adjuvant therapy						
Chemotherapy	Yes	1.0	0.64-1.91	.632	46.7%	.634
	No	1.17			42.5%	
External beam radiation therapy	Yes	1.0	0.99-3.78	.050	62.0%	.050
	No	1.93			43.0%	

Abbreviations: CI = confidence interval; HR = hazard ratio.

patients with ITS treated with surgery with and without adjuvant therapy. Our most relevant findings can be summarized as follows. First, we noted that the omission of adjuvant RT was associated with an increased risk of overall disease progression. Second, we observed that patients with ITS located in the pleura had improved progression-free survival compared with mediastinum or lung location. Finally, having positive margins was linked to worse LC and OS.

Results comparable to those in the present analysis have been previously reported by other expert institutions.[3-13] The present retrospective multicenter analysis included only patients with primary ITS. Selection criteria were not based on location site, volume of tumor, margin status, or adjuvant treatment modalities. ITS represent a rare entity and, compared with non-ITS, have a worse prognosis.[3-13] Moreover, long-term survival (approximately 25%) has not improved in the last decades.[7] This difference is likely multifactorial in origin, and possible reasons include the difficulty of obtaining R0 resection, the lack of a standard treatment, and differences in the metastatic pattern.[4] Although it is commonly accepted that the quality of the surgical margin is of extreme importance, it is not well established what constitutes an adequate margin. In the current study, only 45% of patients had complete resections, and only 32% received adjuvant RT. These findings probably indicate the need for more aggressive local treatment, combining surgery and RT in all nonmetastatic cases. We observed that patients receiving adjuvant RT had a 27.5% absolute improvement in LC at 5 years. Additionally, in the present analysis, the predominant pattern of failure was distant; nonetheless, the use of CT was scarce (39%) and not associated with improved disease control. Based on this observation, recruitment into well-conducted clinical trials offering novel systemic approaches should be strongly considered in all patients with ITS.

The main limitations of our study are related to several uncertainties, biases, and limitations that deserve to be mentioned. First, because patients were treated over a long period, the analyzed population was heterogeneous. Second, a selection criterion for the present analysis was not prospectively defined. Third, the decision to use adjuvant RT was defined by each institution and recommended after taking into account tumor location, resectability, and clinical status. This may have contributed to the worse outcomes observed in the setting of patients not receiving RT. Fourth, results should be interpreted with caution because the small sample size may limit the ability to examine prognostic factors.

Acknowledging these limitations, the findings of effectiveness of the present study suggest the actual need for a multimodal RT-containing approach. Furthermore, for

Table 4 Univariate analysis of associations between patient, tumor, and treatment characteristics and overall survival

Parameter	Variable	Overall survival				
		HR	95% CI	*P*- value	5-year	*P*- value
Patient variables						
Sex	Female	1.0	0.60-1.29	.634	26.8%	.635
	Male	0.82			28.2%	
Age (y)	<60	1.0	0.71-1.78	.881	29.5%	.882
	≥60	1.17			25.7%	
Symptoms	Yes	1.0	0.57-2.65	.762	30.9%	.763
	No	1.20			25.5%	
Location	Pleural	1.0	0.66-1.66	.862	28.1%	.851
	Mediastinum-lung	0.95			26.6%	
Surgical Variables						
Surgical resection protocol	Tumorectomy	1.0	0.91-2.38	.117	33.5%	.115
	Extended resection	1.47			16.5%	
Pathologic Specimen						
Tumor stage	T1-2	1.0	0.82-1.97	.284	30.2%	.282
	T3-4	1.27			24.3%	
Nodal stage	N0	1.0	0.79-1.36	.823	29.9%	.824
	N1-N2	1.03			16.8%	
Histologic grade	I-II	1.0	0.91-2.20	.121	33.8%	.119
	III	1.42			21.7%	
Margin status	R0	1.0	1.02-1.59	.032	31.4%	.030
	R1	1.27			21.9%	
Adjuvant Therapy						
Chemotherapy	Yes	1.0	0.44-1.83	.713	27.4%	.714
	No	0.82			29.5%	
External beam radiation therapy	Yes	1.0	1.20-1.97	.001	48.6%	.001
	No	1.54			19.5%	

Abbreviations: CI = confidence interval; HR = hazard ratio.

Table 5 Factors associated with local control, disease-free survival, and overall survival in multivariate analyses

Parameter	Variable	Local control		
		HR	95% CI	*P*- value
Margin status	R0	1.0	1.03-4.01	.041
	R1	2.03		
External beam radiation therapy	Yes	1.0	1.33-2.88	.003
	No	2.06		

Parameter	Variable	Disease-free survival		
		HR	95% CI	*P*- value
Location	Pleural	1.0	1.17-2.57	.007
	Mediastinum-lung	1.73		
External beam radiation therapy	Yes	1.0	1.10-4.55	.027
	No	2.23		

Parameter	Variable	Overall survival		
		HR	95% CI	*P*- value
Margin status	R0	1.0	1.33-3.47	.002
	R1	2.15		

Abbreviations: CI = confidence interval; HR = hazard ratio.

patients with resected ITS, this study provides important preliminary data that adjuvant RT improves long-term clinical outcomes.

Conclusions

This study, performed within the framework of the RCN, was able to collect many patients who were treated by surgery alone or by surgery plus adjuvant therapy. Surgery and adjuvant RT is a well-tolerated therapy; the associated incidence of late morbidity is low enough to justify its use as part of radical treatment. In this complex clinical scenario, universal treatment recommendations still have not been defined; therefore, an individualized treatment approach should be followed for each case.

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