Head and neck soft tissue sarcomas treated with radiation therapy

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Abstract

Head and neck soft tissue sarcomas (HNSTSs) are rare and heterogeneous cancers in which radiation therapy (RT) has an important role in local tumor control (LC). The purpose of this study was to evaluate outcomes and patterns of treatment failure in patients with HNSTS treated with RT. A retrospective review was performed of adult patients with HNSTS treated with RT from January 1, 1998, to December 31, 2012. LC, locoregional control (LRC), disease-free survival (DFS), overall survival (OS), and predictors thereof were assessed. Forty-eight patients with HNSTS were evaluated. Five-year Kaplan-Meier estimates of LC, LRC, DFS, and OS were 87, 73, 63, and 83%, respectively. Angiosarcomas were found to be associated with worse LC, LRC, DFS, and OS. Patients over the age of 60 had lower rates of DFS. HNSTSs comprise a diverse group of tumors that can be managed with various treatment regimens involving RT. Angiosarcomas have higher recurrence and mortality rates.

Introduction

Head and neck soft tissue sarcomas (HNSTSs) are a rare and heterogeneous group of malignancies that pose a considerable therapeutic challenge owing to their location and the paucity of data related to their management. HNSTS makes up approximately 1% of head and neck cancers and 10% of soft tissue sarcomas.[1] Surgery is considered necessary for curative treatment; however, the anatomy of the head and neck often makes wide local excision difficult, placing patients at risk for locoregional recurrence in the absence of adjuvant therapy.[2] In addition to survival implications of local recurrence, the high density of critical structures in the head and neck make local control (LC) especially important because treatment failure can be highly morbid and challenging to salvage. Radiation therapy (RT), when used as part of a multimodal regimen with surgery, has been shown to improve LC of soft tissue sarcomas in the extremities.[3]

Limited published series describe the treatment and outcome of HNSTS.[2,4-19] Even fewer reports address the role of RT in HNSTS.[13,15] Defining optimal management of HNSTS is further complicated by the great heterogeneity within this diverse group of tumors, which possess a range of clinical and pathologic characteristics.[2] Herein, we report the outcomes, patterns of recurrence, and potential prognostic factors in patients treated for HNSTS with RT at our institution.

Materials and Methods

Patient population

With the permission of the Mayo Clinic Institutional Review Board, a retrospective review was performed of patients with soft tissue sarcomas of the head and neck treated with RT between January 1, 1998, and December 31, 2012. Included were adult patients presenting with nonmetastatic disease who received RT as a component of treatment with curative intent. Patients with less than 3 months of follow-up were excluded, as were those with embryonal type rhabdomyosarcoma, extraosseous Ewing sarcoma, and desmoid tumors. Fifty patients met inclusion criteria for the study. In compliance with Minnesota statutes, all living patients consented to review of their medical records for research purposes.

Surgery

Surgical intervention typically consisted of wide local excision with gross total resection and primary closure or pedicled flap reconstruction. *Positive margin* was defined as disease present within 1 mm of the final resected edge.

Radiation therapy

All patients received RT and were treated with intensity-modulated RT (IMRT), 3-dimensional (3-D) conformal RT, or en face electron beam RT. The RT dose and modality differed depending on the timing of RT relative to surgery; clinical characteristics of the tumor, including depth; proximity to adjacent critical structures; and availability of technology at the time. Our institution began using IMRT to treat head and neck malignancies in September 2003. Patients were treated preoperatively or postoperatively at the discretion of the oncologic team. Patients received treatment once daily, with 5 fractions per week. The median dose per fraction was 2 Gy (range, 1.8-2.4 Gy). Two patients with disease in the neck received intraoperative RT (10 and 11 Gy) at the time of tumor resection following a course of preoperative RT. One other patient was treated with Gamma Knife (Elekta AB) stereotactic radiosurgery postoperatively. He received 20 Gy, prescribed to the 50% isodose line.

Chemotherapy

Chemotherapy was given preoperatively, postoperatively, or concurrently with RT at the discretion of the oncologic team. Common regimens included neoadjuvant or adjuvant paclitaxel or neoadjuvant methotrexate, doxorubicin, and cisplatin.

Analysis and statistical methods

Descriptive statistics are reported as frequency (percentage) or mean, as appropriate. Events are reported from the patient's last day of RT. Estimates of LC, locoregional control (LRC), disease-free survival (DFS), and overall survival (OS) were computed using the Kaplan-Meier product-limit method.[20] The Wilcoxon test among groups was performed to analyze differences in LC, LRC, DFS, and OS when patients were grouped in accordance with presenting location (*i.e.,* scalp or face, neck, and paranasal sinus) or histologic finding (leiomyosarcoma, malignant peripheral nerve sheath tumor, malignant fibrous histiocytoma or undifferentiated pleomorphic sarcoma (MFH/UPS), spindle cell sarcoma not oth-

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erwise specified, synovial sarcoma, angiosarcoma, liposarcoma, and *other*). Univariate analysis was performed using Cox proportional hazards regression for the outcomes LC, LRC, DFS, and OS with potential prognostic factors.[20] Multivariate analysis was applied in certain cases to further elucidate the effects of competing factors. Statistical significance was defined as P value equal to or less than .05. Data were analyzed using JMP software (SAS Institute Inc, Chicago, IL, USA).

Histologic grade was obtained through retrospective chart review. To compare tumors graded on various systems, including the French Fédération Nationale des Centres de Lutte Contre le Cancer (FNCLCC) and the American Joint Commission on Cancer and International Union Against Cancer (AJCC/UICC), a designation of *high grade* or *low grade* was assigned. High-grade tumors were defined as FNCLCC grade 2/3 and AJCC/UICC grade 3/4. Toxicity was graded with the National Cancer Institute's Common Terminology Criteria for Adverse Events.[21] *Acute toxicity* was defined as toxicity occurring within 3 months of completing RT.

Results

Patient and treatment characteristics

Forty-eight patients were included in our analysis. Table 1 summarizes patient and tumor characteristics, subdivided with presenting location of the tumor. Of the 48 patients, 10 were treated with RT for recurrent disease. Three patients presented with HNSTS in sites that previously had received RT. Indications for their prior RT were Hodgkin lymphoma, glottic cancer, and acne control (treated in the 1950s). Time to development of the HNSTS after RT ranged from 6 to 50 years.

Table 2 summarizes treatment characteristics for the presenting tumor location. Of the 48 patients, 44 (92%) underwent surgical resection of their tumor. The majority of patients treated with surgery and RT (34, 77%) received RT postoperatively. Of all patients, 10 (21%) were treated with elective nodal irradiation (ENI). Among these 10 patients, the presenting location occurred in the neck, scalp, and supraclavicular areas for 5, 4, and 1 patient, respectively. Histologic entities that received ENI were leiomyosarcoma (n=2), MFH/UPS (n=1), synovial sarcoma (n=1), angiosarcoma (n=3), liposarcoma (n=1), interdigitating cell sarcoma (n=1), and hemangioendothelioma (n=1). Chemotherapy was given in 16 (33%) patients. Angiosarcomas and synovial sarcomas had the highest rates of treatment with chemotherapy, at 64% (9/14) and 50% (3/6), respectively.

Survival analysis

Median follow-up for all patients was 4.8 years (range, 0.3-14.8 years). Median follow-up for the 40 patients alive at last contact was 5.1 years (range, 0.4-14.8 years). Kaplan-Meier estimates of LC, LRC, DFS, and OS at 5 years were 87, 73, 63, and 83%, respectively (Figure 1). Five-year estimates of local recurrence, regional recurrence, and distant recurrence were 13, 16, and 16%, respectively. Concurrent regional recurrence and distant metastasis developed in 1 patient. Of the 15 patients with recurrent disease, all had recurrence within the first 3 years and 9 (60%) had recurrence within the first 18 months.

Patterns of recurrence

Five patients had local recurrence, all of whom had primary disease of the face or scalp. Four patients had angiosarcoma; 1 had

Table 1. Patient and tumor characteristics by site of presentation.

Characteristic	Patient and tumor characteristics by site*				
	Neck (n=16)	Paranasal sinus (n=3)	Scalp/face (n=27)	Supraclavicular (n=2)	Total (N=48)
Age at diagnosis, y					
Median	48.8	74.4	70.0	27.6	68.5
Range	(19.1-85.6)	(41.8-82.6)	(23.5-86.9)	(25.9-29.2)	(19.1-86.9)
Sex					
Female	4 (25.0)	1 (33.3)	9 (33.3)	0 (0.0)	14 (29.2)
Male	12 (75.0)	2 (66.7)	18 (66.6)	2 (100.0)	34 (70.8)
Presentation					
Recurrent	5 (31.3)	0 (0.0)	4 (14.8)	1 (50.0)	10 (20.8)
Primary	11 (68.8)	3 (100.0)	23 (85.2)	1 (50.0)	38 (79.2)
Histologic finding					
DFSP	1 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.1)
Leiomyosarcoma	2 (12.5)	0 (0.0)	3 (11.1)	0 (0.0)	5 (10.4)
MPNST	0 (0.0)	0 (0.0)	1 (3.7)	0 (0.0)	1 (2.1)
MFH/UPS	3 (18.8)	0 (0.0)	4 (14.8)	2 (100.0)	9 (18.8)
Spindle cell	2 (12.5)	0 (0.0)	2 (7.4)	0 (0.0)	4 (8.3)
Synovial sarcoma	5 (31.3)	0 (0.0)	1 (3.7)	0 (0.0)	6 (12.5)
Angiosarcoma	0 (0.0)	1 (25.0)	13 (48.1)	0 (0.0)	14 (29.2)
Liposarcoma	1 (6.3)	0 (0.0)	2 (7.4)	0 (0.0)	3 (6.3)
Other°	2 (12.5)	1 (25.0)	0 (0.0)	0 (0.0)	3 (6.3)
Hemangiopericytoma	0 (0.0)	1 (25.0)	1 (3.7)	0 (0.0)	2 (4.2)
Rhabdomyosarcoma	0 (0.0)	1 (25.0)	0 (0.0)	0 (0.0)	1 (2.1)
Grade					
Low	2 (12.5)	0 (0.0)	4 (14.8)	0 (0.0)	6(12.5)
High	7 (43.8)	1 (33.3)	18 (66.8)	2 (100.0)	28 (58.3)
Not available	7 (43.8)	2 (66.7)	5 (18.5)	0 (0.0)	14 (29.1)
Size, cm					
≤5	11 (68.8)	3 (100.0)	17 (63.0)	2 (100.0)	33 (68.8)
>5	5 (31.3)	0 (0.0)	10 (37.0)	0 (0.0)	15 (31.2)
Depth					
Superficial	2 (12.5)	0 (0.0)	16 (59.3)	1 (50.0)	19 (39.6)
Deep	14 (87.5)	3 (100.0)	11 (40.3)	1 (50.0)	29 (60.4)

DFSP, dermatofibrosarcoma protuberans; MFH, malignant fibrous histiocytoma; MPNST, malignant peripheral nerve sheath tumor; UPS, unclassified pleomorphic sarcoma. *Values are presented as number and percentage of patients unless specified otherwise. °Other histologic findings include interdigitating dendritic cell sarcoma, chordoma, and hemangioendothelioma.

leiomyosarcoma. Three patients had recurrences within the RT treatment volume and 2 had recurrences at the margin of the treatment volume. The patients with in-field recurrences were treated with 60 Gy in 30 fractions, 66 Gy in 33 fractions, and 69.96 Gy in 33 fractions. All local recurrences occurred within the first 2 years of follow-up. Two patients had positive margins at the time of surgery and one had gross residual disease after resection; none of these patients experienced local recurrence. Regional nodal recurrence developed in 5 patients. No patients had concurrent local and regional nodal recurrence. Four of these patients had angiosarcoma of the face or scalp and 1 had synovial sarcoma of the neck. Of the 10 patients who underwent ENI, 1 patient (10%) with an angiosarcoma had recurrence within the treated nodal volume. Thirty-eight patients did not undergo ENI, 4 (11%) of whom developed nodal recurrence in the neck.

One patient with angiosarcoma developed a nodal recurrence and distant metastasis that were discovered simultaneously. Isolated distant metastasis occurred in 6 patients. Of these patients, 3 had angiosarcoma; 1, synovial sarcoma; 1, spindle cell sarcoma not otherwise specified; and 1, MFH/UPS. Sites of distant metastasis were the lungs, vertebrae, brain, and peripheral bony sites.

Univariate and multivariate analysis

Univariate analysis is presented in Table 3. Patients over the age of 60 had lower rates of DFS than those younger that 60. Angiosarcomas were compared with all other histologic entities and were found to be associated with poorer LC, LRC, DFS, and OS.

RT without surgery was associated with significantly lower LC, LRC, DFS, and OS. The 4 patients treated with RT alone or chemotherapy and RT were either not medically fit for surgery or had inoperable tumors.

No significant difference in any outcome measured was observed for IMRT *vs.* 3-D conformal RT or preoperative RT *vs.* postoperative

Table 2. Treatment characteristics by site of presentation.

Characteristic	Treatment by site*				
	Neck° (n=16)	Paranasal sinus# (n=3)	Scalp/face (n=27)	Supraclavicular (n=2)	Total (N=48)
Treatment					
Trimodality	3 (18.8)	2 (66.7)	8 (29.6)	1 (50.0)	14 (29.2)
Surgery and RT	13 (81.3)	1 (33.3)	15 (55.6)	1 (50.0)	30 (62.5)
RT alone	0 (0.0)	0 (0.0)	2 (7.4)	0 (0.0)	2 (4.2)
Chemotherapy and RT	0 (0.0)	0 (0.0)	2 (7.4)	0 (0.0)	2 (4.2)
Timing of RT					
Definitive	0 (0.0)	0 (0.0)	4 (14.8)	0 (0.0)	4 (8.3)
Preoperative	4 (25.0)	1 (33.3)	4 (14.8)	1 (50.0)	10 (20.8)
Postoperative	12 (75.0)	2 (66.7)	19 (70.4)	1 (50.0)	34 (70.8)
Type of closure					
Report unavailable	1 (6.3)	1 (33.3)	0 (0.0)	0 (0.0)	2 (4.2)
Nonoperative	0 (0.0)	0 (0.0)	4 (14.8)	0 (0.0)	4 (8.3)
Primary closure	10 (62.5)	0 (0.0)	8 (29.6)	2 (100.0)	20 (41.7)
Skin graft	0 (0.0)	0 (0.0)	6 (22.2)	0 (0.0)	6 (12.5)
Pedicle flap	4 (25.0)	1 (33.3)	4 (14.8)	0 (0.0)	9 (18.8)
Free flap	1 (6.3)	1 (33.3)	5 (18.5)	0 (0.0)	7 (14.6)
Margin					
Nonoperative	0 (0.0)	0 (0.0)	4 (14.8)	0 (0.0)	4 (8.3)
Negative	15 (93.8)	2 (66.6)	22 (81.5)	2 (100.0)	41 (85.4)
Positive	1 (6.3)	0 (0.0)	1 (3.7)	0 (0.0)	2 (4.2)
Gross positive	0 (0.0)	1 (33.3)	0 (0.0)	0 (0.0)	1 (2.1)
Type of RT					
IMRT	7 (43.8)	3 (100.0)	17 (63.0)	1 (50.0)	28 (58.3)
Electrons	0 (0.0)	0 (0.0)	5 (18.5)	0 (0.0)	5 (10.4)
3-D conformal	9 (56.3)	0 (0.0)	5 (18.5)	1 (50.0)	15 (31.3)
Preoperative EBRT dose, Gy					
Median	50.4	50.4	58.8	39.6	50.4
Range	(50.0-56.3)	(50.4-50.4)	(50.0-66.0)	(39.6-39.6)	(39.6-66.0)
Postoperative EBRT dose, Gy					
Median	61.0	59.4	60.0	63.0	60.0
Range	(56.3-70.0)	(55.8-59.4)	(59.4-70.0)	(63.0-63.0)	(55.8-70.0)
Definitive					
Median	NA	NA	66.0	NA	66.0
Range			(60.0-70.0)		(60.0-70.0)
Dose per fraction, Gy					
Median	2.0	1.8	2.0	2.0	2.0
Range	(1.8-2.3)	(1.8-1.8)	(1.8-2.4)	(1.8-2.1)	(1.8-2.4)
ENI					
Yes	5 (31.2)	0 (0.0)	4 (14.8)	1 (50.0)	10 (20.8)
No	11 (68.8)	3 (100.0)	23 (85.2)	1 (50.0)	38 (70.2)
RT treatment time, days					
Median	43	39	43	34.5	42.5
Range	(34-49)	(38-46)	(32-50)	(31-38)	(31-50)

EBRT, external beam radiation therapy; ENI, elective nodal irradiation; IMRT, intensity-modulated radiation therapy; NA, not applicable; RT, radiation therapy; 3-D, 3-dimensional. *Values are presented as number and percentage of patients unless specified otherwise. °Two patients with neck disease received intraoperative RT (10 and 11 Gy) after a course of preoperative RT. #One patient with paranasal sinus disease was treated with 20 Gy postoperative radiosurgery with Gamma Knife.

RT. Similarly, no differences in any measured outcomes were found among those who received ENI and those who did not. Patient presentation (*i.e.* primary *vs.* recurrent), and sex were not associated with a significant difference in outcome. In addition, tumor size, tumor grade, and depth of tumor invasion were not associated with a significant difference in observed outcome.

Radiation therapy complications

Seven (15%) of the 48 patients reported grade 3 RT-related acute toxicity. Two patients required percutaneous endoscopic gastrostomy tube placement because of poor oral intake. Other grade 3 adverse effects were severe dermatitis (n=2), wound infection requiring intravenous antibiotics (n=3), severe mucositis (n=1), and split thickness skin graft failure (n=1). One patient had both percutaneous endoscopic gastrostomy tube placement and severe dermatitis, and 1 patient had both abscess formation and skin graft failure. No statistically significant difference was found in toxicity of grade 3 or higher among patients treated with IMRT and those treated with 3-D conformal RT (P=0.84). No grade 4 or grade 5 RT-related acute toxicity was observed.

Long-term grade 3 toxicities included cataracts requiring surgery (n=1) and osteonecrosis (n=1) requiring surgical debridement of the zygoma and maxilla 9 years after receiving RT of 70 Gy. One patient had grade 2 Lhermitte syndrome that gradually improved over 5 years. No grade 4 or grade 5 long-term RT complications were documented.

Discussion

Survival and patterns of recurrence

In this cohort of patients with HNSTS treated with RT, we report the 5-year actuarial rates of LC, LRC, DFS, and OS as 87, 73, 63, and 83%, respectively. Although comparison across heterogeneous HNSTS studies is difficult, our series shows slightly higher rates of LC and OS than previously reported outcomes, which range from 60 to 81 and 45 to 75% for LC and OS, respectively (Table 4).[2,4-19] In these series, 32% to 100% of patients received RT as a part of their treatment regimen. An interesting temporal comparison can be made with the 1995 study by Willers and colleagues[15] that described 52 patients treated from 1972 to 1993 and our 48 patients treated from 1998 to 2012. The 2 cohorts have relatively similar numbers of angiosarcomas (29 *vs.* 19%) and rhabdomyosarcomas (2 *vs.* 0%), but our study shows higher rates of LRC (73 *vs.* 60%) and OS (83 *vs.* 66%). Advancements in imaging and staging likely contributed to improvements in survival, while improvements in surgical and RT techniques

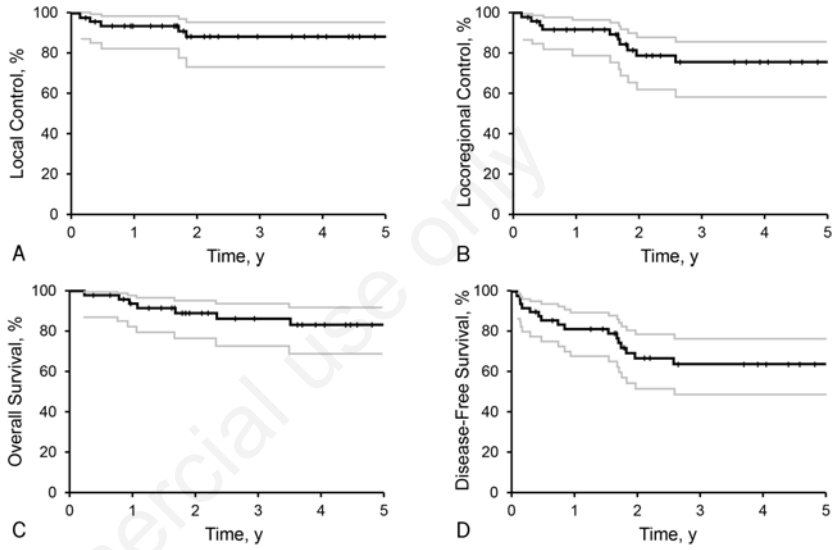

Figure 1. Kaplan-Meier plots for rates of local (A) and locoregional (B) control and for overall (C) and disease-free (D) survival. Hash marks in lines represent excluded patients. The number of patients still at risk is plotted below the x-axis. Lighter graph lines indicate 95% confidence interval.

Table 3. Univariate analysis of local control, locoregional control, disease-free survival, and overall survival for various patient, tumor, and treatment characteristics.

Characteristic	Univariate analysis*							
	LC		LRC		DFS		OS	
	HR (95% CI)	P Value	HR (95% CI)	P Value	HR (95% CI)	P Value	HR (95% CI)	P Value
Sex, male *vs* female	1.8 (0.2-16.0)	0.60	1.1 (0.3-4.1)	0.93	1.4 (0.4-4.3)	0.58	1.4 (0.4-5.5)	0.63
Age, >60 *vs* ≤60	3.4 (0.5-67.2)	0.22	3.5 (0.88-23.4)	0.08	3.7 (1.18-16.1	0.02	3.6 (0.9-23.7)	0.07
Size, >5 cm *vs* ≤5 cm	3.0 (0.5-23.1)	0.24	2.1 (0.6-7.5)	0.25	2.1 (0.8-5.7)	0.15	1.25 (0.32-4.4)	0.73
Histology								
High *vs* low grade	0.6 (0.1-12.6)	0.71	1.0 (0.2-18.7)	0.99	0.85 (0.22-5.6)	0.80	0.66 (0.15-4.5)	0.62
Angio *vs* other	15.5 (2.3-306.5)	<0.005	17.7 (4.4-118.1)	<0.001	8.9 (3.2-28.5)	<0.001	4.5 (1.3-17.8)	0.02
Deep *vs* superficial	0.4 (0.05-2.3)	0.29	0.57 (0.16-2.1)	0.39	0.74 (0.28-2.1)	0.43	0.33 (0.08-1.2)	0.08
Presentation, recurrent vs. primary	1.3 (0.11-14.7)	0.80	0.62 (0.03-29.7)	0.63	1.2 (0.23-3.6)	0.78	1.0 (0.15-4.1)	0.99
RT								
>60 Gy *vs* ≤60 Gy	3.3 (0.54-24.9)	0.19	2.6 (0.7-9.4)	0.14	2.4 (0.86-6.4)	0.09	2.3 (0.6-8.5)	0.19
Preoperative *vs* post-operative	0 (-)	0.30	0.63 (0.03-3.9)	0.66	0.66 (0.10-2.5)	0.57	0.56 (0.03-3.3)	0.57
Alone *vs* with surgery	28.2 (4.5-218.8)	<0.001	15.1 (3.8-53.8)	<0.001	6.9 (1.9-20.4)	0.006	6.1 (1.3-22.0)	0.03
IMRT *vs* 3-D RT	0.82 (0.14-6.2)	0.83	2.2 (0.55-14.7)	0.28	1.12 (0.4-3.6)	0.83	2.0 (0.45-13.6)	0.57
Elective nodal RT	0.93 (0.05-6.3)	0.95	0.92 (0.14-3.7)	0.92	0.87 (0.20-2.7)	0.82	1.3 (0.28-4.7)	0.72

Angio, angiosarcoma; DFS, disease-free survival; HR, hazard ratio; IMRT, intensity-modulated radiation therapy; Inf, infinite; LC, local control; LRC, locoregional control; OS, overall survival; RT, radiation therapy; 3-D, 3-dimensional. *Boldface type indicates statistically significant data.

may have contributed to improved LRC in the present series.

Most recurrences occurred early in our series, with 100% of local recurrences and 90% of locoregional recurrences occurring within the first 2 years. These data are corroborated by previous studies showing that up to 96% of recurrences occurred within the first 3 years.[7]

Prognostic factors

Angiosarcoma has been shown to be associated with poorer LC, greater risk of distant metastasis, and poorer OS[10,15] relative to other HNSTS. Our study corroborates these findings and shows that in the era of modern RT modalities and concurrent chemotherapy, angiosarcomas continue to portend a poorer prognosis. A recent study by Chang and colleagues found that patients over the age of 60 had lower cause specific survival (CSS) compared to younger patients.[18] Our study found patients 60 and older had significantly lower rates of DFS and a non-significant trend towards poorer OS (P=0.07). These results can largely be explained by the later onset of angiosarcomas, with a median age of 79 years old at diagnosis. Angiosarcomas accounted for 43% (12/28) of the HNSTS in patients older than 60 compared to 5% (1/20) of patients under 60 years of age. Previous studies have implicated tumor size, grade, and margin status with poorer cause-specific survival.[6,9,12,15-17] We were not able to duplicate those findings. Larger tumor size and positive margin status has been associated with poorer LC.[6,9,17] We were not able to demonstrate the same. Having only three patients in our cohort with positive surgical margins limited our ability to observe the effects of this proven prognostic factor.

Role of radiation therapy

Maximal safe tumor resection continues to be the primary treatment modality for HNSTS. Total compartmental resection results in high rates of LC but is often not feasible anatomically.[10] RT is given for tumors with close (<1 cm) or positive surgical margins[2,10] and other high risk features. Although the rarity of the disease has prevented studies directly evaluating the benefit of RT in the head and neck, RT for soft tissue sarcomas of the extremities has been shown to increase rates of LC in prospective randomized trials.[3,22] In the present study, a range of RT modalities and regimens were used, including preoperative, postoperative, and definitive fractionated therapy, stereotactic radiosurgery, and intraoperative RT. No prospective study has compared preoperative to postoperative RT in HNSTS. However, O'Sullivan and colleagues[23] performed a prospective trial for soft tissue sarcomas of the extremities and found that although preoperative RT was associated with higher rates of severe wound complications, patients treated

Table 4. Summary of relevant prior studies with survival data and treatment with radiation therapy data.

Institution, Country	Authors, year	Study dates	Patients, no.	Angio, %	Rhabdo, %	Med FU, y	Tx with RT, %	RT regimen	Median dose, Gy	LC or LRC, % (y)	DM, % (y)	DFS, % (y)	OS,) % (y)
MGH, USA	Willers *et al.*,[15] 1995	1972-1993	57	19	0	4.3	100	Preoperative, postoperative, definitive	64.80	LRC: 60 (5)	23 (5)	NR	66 (5)
TMH, India	Dudhat *et al.*,[5] 2000	1981-1995	72	0	0	NR	53	Postoperative	NR	NR	NR	45 (5)	60 (5)
University of Miami, USA	Chen *et al.*,[19] 2005	1996-2003	39	0	10	8.7	100	Preoperative, postoperative, definitive	NR	78 (5)			63 (5)
University , of Florida USA	Trifiletti *et al.*,[13] 2012	1981-2009	24	0	0	11.1	100	Postoperative	64.80	LC: 73 (10)	0 (10)	73 (10)	73 (10)
IRCCS, Italy	Mattavelli *et al.*,[9] 2013	1990-2010	167	5	0	5.5	36	Preoperative, postoperative	NR	LC: 81 (10)	11 (10)	NR	NR
AMC, South Korea	Park *et al.*,[17] 2014	1995-2012	122	12	20	6	53	Postoperative, definitive	60.00	LRC: 76 (5), 64 (10)	NR	NR	75 (5), 66 (10)
NCCS, Singapore	Yeang *et al.*,[16] 2013	2002-2011	83	16	6	6.9	53	Postoperative, definitive	NR	LRC: 49 (5)	29 (5)	37 (5)	45 (5)
University of Washington, USA	Chang,[18] 2014	2000-2012	97	23	11	1.8	55	Preoperative, Postoperative, Definitive	NR	NR	NR	NR	78 (5)
Present study	Vitzthum *et al.*	1998-2012	48	29	2	4.8	100	Preoperative, postoperative, definitive	60.00	LC: 87 (5) LRC: 73 (5)	16 (5)	63 (5)	83 (5)

AMC, Asan Medical Center; Angio, angiosarcoma; DM, distant metastasis; DFS, disease-free survival; IRCCS, Fondazione Instituto Nazionale del Tumori; LC, local control; LRC, locoregional control; Med FU, median follow-up; MGH, Massachusetts General Hospital; NCCS, National Cancer Centre Singapore; NR, not reported; OS, overall survival; Rhabdo, rhabdomyosarcoma; RT, radiation therapy; TMH, Tata Memorial Hospital; Tx with RT, treatment (or treated) with radiation therapy.

with postoperative RT tended to have higher risk of fibrosis and edema. The investigators observed no difference in survival outcomes between preoperative and postoperative RT. Because of tumor bed hypoxia following surgical resection, higher doses of RT are typically administered postoperatively, and larger fields are often required to encompass surgical changes. Thus, for soft tissue sarcomas of an extremity, preoperative RT is typically favored in order to reduce treatment-associated toxicity. However, in patients with HNSTS, only those patients with advanced, marginally resectable tumors are routinely considered for preoperative RT.[2] Preoperative RT often is avoided in operations that violate mucosal membranes because of risk of fistula formation.[13] In our study, no difference was observed in any outcomes between preoperative RT and postoperative RT. No prospective studies have looked at dose effect for RT in HNSTS. In soft tissue sarcomas of the extremities, preoperative RT doses are typically about 50 Gy and postoperative doses range from 64 to 66 Gy.[10] In our study, median doses for preoperative, postoperative, and definitive fractionated RT were 50.5, 60, and 66 Gy, respectively.

Small patient numbers and selection bias make it difficult to assess the efficacy of RT without surgery because these patients tend to have comorbid illnesses and more advanced disease. Indeed, in our study, RT alone was associated with worse outcomes for DFS, LC, LRC, and OS; however, this small group of patients had advanced disease or serious medical comorbidities, or both. Chen and colleagues[3] also report lower crude rates of LC with RT alone *vs.* RT with surgery (50 *vs.* 82%) that are attributed to higher-risk disease in the cohort receiving RT alone. The role of ENI is unclear in the treatment of HNSTS. For angiosarcomas presenting in any location of the body, Ward and colleagues[24] have recommended ENI for large tumors (>5 cm). In our study, we observed no difference in LRC among patients treated with ENI and those who were not; however, our sample size was small, there is inherent selection bias in the determination of which patients should receive ENI, precluding meaningful comparison.

Limitations

The present study is limited by its retrospective nature, the relatively small sample size and subsequent small subgroups, and the heterogeneity of the included histologic entities. Variations in the medical, surgical, and RT treatments made identifying prognostic factors difficult. Our study also investigated a large number of univariate analyses. Four end points were assessed for 12 unique variables, resulting in a total of 48 significance tests. At an α level of 0.05, it can be expected that 2 or 3 significant results may be type I errors. Despite these limitations and given the rarity of HNSTS, this study adds a valuable contribution to understanding the prognosis, patterns of recurrence, and prognostic factors associated with this disease.

Conclusions

This study describes a diverse group of HNSTS with treatment regimens involving RT and reviews the literature and current practices using RT in HNSTS. Angiosarcomas have significantly higher rates of recurrence and disease-specific death. Patients older than 60 years of age were found to have lower rates of DFS. Further studies are required to elucidate indications for RT, as well as the optimal dose and timing of RT.

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