Title

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Lymph Node Metastases in Pediatric and Young Adult Patients with Non-Rhabdomyosarcoma Soft Tissue Sarcoma (NRSTS): Findings from Children's Oncology Group (COG) Study ARST0332

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Abstract

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AUTHOR CONTRIBUTIONS

Conception and design: SLS, AHJ, SCK, DMP
Provision of study materials or patients: SLS, AHJ, LM, SXS, ARW
Collection and assembly of data: SLS, AHJ, SCK, DMP, LM
Data analysis and interpretation: EA, JH, SLS, DAB
Manuscript preparation: EA, SLS
Manuscript review and revisions: EA, SLS, DAB
Final approval of manuscript: EA, JH, SLS, AHJ, SCK, DMP, LM, SXS, ARW, DAB

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Purpose—To better define the clinical features and outcomes of young patients with non-rhabdomyosarcoma soft tissue sarcoma (NRSTS) with regional and distant lymph node (LN) metastases treated in a standardized fashion, we analyzed lymph node involvement in COG study ARST0332, which evaluated a risk-based treatment strategy for young patients with all stages of NRSTS.

Patients and Methods—Patients <30 years old with newly diagnosed NRSTS and LN metastases enrolled on ARST0332 were studied. Regional LN sampling was required for those with epithelioid sarcoma, clear cell sarcoma, or clinically/radiographically enlarged LNs. Tumor features and extent of pre-enrollment resection determined treatment, including chemotherapy, radiotherapy, and delayed surgery. Recommendations for LN metastases included LN dissection at the time of primary tumor resection and dose-adapted radiotherapy based on extent of LN resection.

Results—Twenty of 529 eligible and evaluable ARST0332 patients with NRSTS had LN metastases; epithelioid sarcoma had the highest incidence (18%, 5 of 28). Pre-treatment imaging identified LN enlargement in 19 of 20 patients; 1 had no pre-treatment LN imaging. At 6.9 years median follow-up for surviving patients, 5-year overall survival (OS) was 85.7% (95% CI: 33.4%, 97.9%) for 7 patients with isolated LN metastases and 15.4% (95% CI: 2.5%, 38.8%) for 13 patients with additional extranodal metastases. LN recurrence occurred in only 1 patient without LNs sampled at initial diagnosis.

Conclusion—LN metastases occur in about 4% of pediatric/young adult NRSTS, are limited to a few histologic subtypes, and are rare in patients who did not have clinical or imaging evidence of lymphadenopathy, suggesting that biopsies of non-enlarged LNs are not necessary to identify occult involvement. Patients with isolated LN metastases have high 5-year OS (~85%) and should be treated with curative intent.

Keywords

Pediatric; non-rhabdomyosarcoma soft tissue sarcoma (NRSTS); lymph node metastases; prognostic factor

INTRODUCTION

The non-rhabdomyosarcoma soft tissue sarcomas (NRSTS) are a heterogeneous group of tumors varying in histologic appearance and clinical behavior that represent about 4% of childhood cancers.[1] Although most pediatric patients with NRSTS have localized disease and a relatively good outcome, those with metastatic disease fare poorly.[2–6] In adults with soft tissue sarcomas (STS), lymph node (LN) metastases are uncommon and are restricted to a handful of histologic subtypes including epithelioid sarcoma, clear cell sarcoma, and angiosarcoma. Adults with STS with isolated LN involvement may fare better than those who also have extranodal metastases,[7,8] although recent changes to the American Joint Commission on Cancer (AJCC) staging system have been controversial in their handling of this subgroup.[9–11] Retrospective pediatric studies have found that LN involvement occurs in 1.75% to 7.5% in young patients with NRSTS,[2,3,5,12–17] but few details have been reported. To better define the clinical features and outcomes of pediatric and young adult patients with NRSTS with regional and distant LN metastases managed in a standardized fashion,

we performed a planned subset analysis of COG clinical trial ARST0332, which evaluated a risk-based treatment strategy for patients under 30 years of age with all stages of NRSTS.

PATIENTS AND METHODS

Patient Population

This analysis included newly diagnosed patients with NRSTS under 30 years of age who were enrolled on COG study ARST0332 and had LN metastases at study entry. The eligibility criteria, treatment guidelines, and outcomes observed in ARST0332 have been previously reported.[18] The study was IRB-approved at all participating institutions, and enrolling patients and/or their legal guardians, as appropriate, signed IRB-approved consent/assent document(s) prior to study participation. Computed tomography or magnetic resonance imaging of the LN bed draining the tumor was required prior to study entry. Sites of metastasis and surgical outcomes were confirmed by central review of imaging studies, operative notes, and pathology reports as previously reported.[18] The two experienced radiology reviewers used best practices to determine the presence or absence of LN involvement, including the size, number, location, and asymmetry of lymph nodes and loss of the fatty hilum; cases where the first reviewer felt uncertain were reviewed on a second occasion by both reviewers simultaneously to establish a consensus opinion. LN involvement was categorized as regional for involved LNs in the first bed anatomically expected to drain lymph from the primary tumor site, and distant if the involved LNs were located elsewhere. Pathology central review determined the diagnosis according to the 4th edition of the World Health Organization classification[19] and the histologic grade by both the Pediatric Oncology Group (POG)[20] and Federation Nationale des Centres de Lutte Contre le Cancer (FNCLCC)[21] criteria as previously described.[18] Regional LN sampling was required prior to study entry for patients with epithelioid sarcoma, clear cell sarcoma, and for those with enlarged LNs on physical exam or on required imaging of the LN bed draining the tumor unless central imaging review confirmed that the LNs were sufficiently enlarged that a biopsy was not necessary to confirm LN involvement. Sentinel LN mapping and biopsy was permitted to document LN status, but fine needle aspiration was not allowed due to sampling error and specimen interpretation difficulties.

Treatment Approach

In the risk group and treatment assignment schema for ARST0332,[18] patients with LN metastases were assigned to the high-risk group and received ifosfamide/doxorubicin chemotherapy. In those who had not undergone definitive resection of the primary tumor prior to study entry, surgery was performed after 4 chemotherapy cycles and concomitant 45 Gy radiotherapy (RT). Those with microscopic residual disease after definitive surgery received a cumulative dose of 55.8 Gy RT, either adjuvantly after upfront surgery or via a postoperative boost of 10.8 Gy following neoadjuvant RT and delayed surgery. A postoperative boost of 19.8 Gy (total dose 64.8 Gy) was given for gross residual disease despite maximal surgery. Resection of LN metastases was recommended at the time of definitive resection of the primary tumor. For those with LN involvement, the entire LN drainage chain was included in the clinical target volume for primary site RT. The involved LNs received either 45 Gy for no residual disease, 55.8 Gy for microscopic residual

disease or 64.8 Gy for gross residual disease. Patients with extranodal metastases underwent excision of any resectable metastases and irradiation of any unresectable metastases to a total dose of 50 Gy at the end of therapy.

Statistical Methods

The clinical features of patients with and without LN metastases were compared using the two-sample t-test or Fisher's Exact Test, which were also used to compare the features of patients with LN metastases based on the presence or absence of extranodal metastases. Age at enrollment was analyzed both as a continuous and categorical variable (0–9, 10–17, 18–30 years). Other *a priori* variables evaluated included demographic features, diagnosis, and known clinical prognostic factors, primary tumor site, primary tumor size, POG histologic grade, FNCLCC histologic grade, primary tumor depth, primary tumor invasiveness, presence/absence of extranodal metastases, treatment arm, and institutional assessment that the tumor was unresectable.

Each variable was tested for univariate association with event-free survival (EFS) and overall survival (OS) using the Log-rank test. EFS was defined as the time from enrollment date to the date of tumor recurrence, second malignancy, death, or date of last follow-up, whichever occurred first. OS was defined as the time from enrollment to the date of death or last follow-up.

A univariate Cox proportional-hazard modeling among all patients with and without LN metastases and with and without extranodal metastases as independent variables was performed to further understand the role of LN and extranodal metastases in EFS and OS. Depth of the primary tumor was not included in the predictive univariate model analysis due to extreme distribution.

The analyses were performed in R 4.0.1 using the cmprsk package and *SAS* 9.4 using PROC LIFETEST, PROC FREQ and PROC PHREG. Data current to 30 June 2018 when the data were frozen for publication were used for this analysis.

RESULTS

ARST0332 enrolled 529 eligible, evaluable patients with NRSTS between 2/5/07 and 2/20/12 (Figure 1). Of the entire cohort, 104 patients had LN procedures: 35 were performed in patients with epithelioid or clear cell sarcoma and 69 in patients with LN enlargement by exam or imaging.

Twenty patients (3.8%) had LN metastases at study entry; all had radiologic evidence of LN involvement except for one epithelioid sarcoma patient without imaging of the draining LNs (a protocol violation) but with pathologic confirmation of nodal involvement. Thirteen of the 20 patients with LN metastases had histologic confirmation (2 core biopsy, 2 incisional biopsy, 6 enlarged LN resection, 3 formal LN dissection); the remaining 7 had LN involvement confirmed by central imaging review. Diagnoses with the highest incidence of LN metastases were epithelioid sarcoma (18%, 5 of 28), angiosarcoma (17%, 1 of 6), and clear cell sarcoma (14%, 1 of 7). The incidence of LN metastases for the four most common

diagnoses were 4% (6 of 138) for synovial sarcoma, 5% (3 of 63) for undifferentiated sarcoma, 0% (0 of 58) for malignant peripheral nerve sheath tumor (MPNST), and 0% for undifferentiated embryonal sarcoma of the liver (UESL; 0 of 39). LN metastases were regional only in 16, distant only in 2, and both regional and distant in 2 patients. There were no patients with nodal metastases among those with superficial tumors or POG or FNCLCC grade 1 tumors.

Table 1 shows the clinical features of the 20 patients with and the 509 patients without LN metastases. There was a statistically significant difference in primary tumor size (11.9 cm ± 6.0 with versus 7.7 cm ± 5.4 without, $p < 0.001$) and extranodal metastases (65% with versus 11.8% without, $p<0.001$). Among patients with > 5 cm tumors, the cumulative incidence of LN involvement at diagnosis or first recurrence was 71% in epithelioid sarcoma (5 of 7), 67% in clear cell sarcoma (2 of 3), 6% in synovial sarcoma (6 of 96), and 4% in other diagnoses (8 of 228).

The demographic and clinical features of patients with LN metastases and those with exclusively extranodal metastases were compared (Table 2). Patients with extranodal metastases were older (16.0 ± 5.0 years vs. 13.1 ± 6.4 years; $p = 0.037$) and the distribution of diagnoses differed. Extranodal metastases but no LN metastases were observed in MPNST, alveolar soft part sarcoma and UESL.

Treatment

Five patients with LN metastases underwent gross total resection of the primary tumor and enlarged LNs prior to study entry, including 3 who underwent a formal LN dissection. All received protocol-specified chemotherapy and radiotherapy to the primary tumor (55.8 Gy) and involved LNs (median dose 45 Gy, range 45 Gy-55.8 Gy), except one patient who did not receive LN radiotherapy for uncertain reasons. Three of these 5 patients also had extranodal metastases. Only one underwent resection of metastases (a solitary liver nodule); none received RT to extranodal metastases.

Nine of the 15 patients with unresected tumor at the primary site underwent delayed resection after neoadjuvant chemotherapy and 45 Gy RT (8 negative and 1 positive microscopic margins); the one with positive margins received a post-operative RT boost to a total dose of 55.8 Gy. Seven patients underwent LN resection during delayed surgery (4 formal LN dissection, 3 enlarged LN resection); residual tumor was present in 3 cases (2 epithelioid, 1 undifferentiated sarcoma round cell type). All 7 patients who underwent delayed LN resection received RT to the involved LNs (median dose 45 Gy, range 45–55.8 Gy). Eight patients on the neoadjuvant treatment arm did not undergo delayed resection of LNs: 7 had been removed from protocol therapy for PD (n=2), intolerable toxicity (n=1), or patient/physician decision (n=4) and 1 had other unresectable distant metastases. Five of the 8 patients who did not undergo delayed resection of LNs received RT to the involved nodes (median dose 45 Gy, range 43.2–45 Gy); the other 3 did not receive LN irradiation due to age <2 years (n=1), early removal from protocol therapy for toxicity (n=1), and protocol violation (n=1). Nine of the 15 patients with LN metastases and unresected primary tumor at study entry also had extranodal metastases; none underwent resection of extranodal metastases, but 2 received RT to lung (n=1) or bone (n=1).

Outcomes

The median follow-up for surviving patients with LN metastases was 6.9 years (range 2.2–10.6 years). Fifteen of the 20 patients with LN metastases (75%) experienced an event including: 14 tumor recurrence (1 local/distant, 2 LN/distant, 11 distant only) and one second cancer (acute myeloblastic leukemia) (Figure 2). Both patients with LN recurrence had major RT deviations (1 inadequate dose, 1 inadequate volume). Four of the 5 patients without an event had undergone gross total resection of enlarged LNs (one was a LN dissection) and received RT to the involved LN bed (median 45 Gy, range 45–55.8 Gy). The remaining patient was a <2-year-old child removed from protocol therapy early in treatment because the physician felt it was in the child's best interest; the patient was confirmed to be a >10 year survivor but the treatment given after removal from protocol therapy is unknown.

In addition to the 2 patients with LN metastases at study entry who experienced nodal failure, 3 patients without LN metastases at study entry experienced LN recurrence. All 3 had > 5 cm tumors and no imaging evidence of lymphadenopathy at study entry, and included a patient with pleural clear cell sarcoma and negative LN sampling who later developed contralateral mediastinal and retroperitoneal LN metastases, a patient with epithelioid sarcoma of the foot and negative sentinel LN biopsies (1 popliteal, 2 inguinal) at initial diagnosis who later developed inguinal LN metastases, and a patient with paratracheal synovial sarcoma who later developed ipsilateral pericardiophrenic LN metastases.

In a univariate Cox proportional hazards model among patients with LN metastases, distant metastatic disease was the only factor associated with poorer survival (EFS: HR 4.6, CI 1.3–16.9; OS: HR 11.3, CI 1.6–88.5) (Supplemental Table 1). The development of distant metastatic disease among patients with LN metastases was not predicted by any of the other factors evaluated in the univariate model.

Figure 3 shows the estimated 5-year OS for all patients by the presence or absence of LN metastases and distant metastases at study entry. Patients with isolated LN metastases fared similarly to those without distant metastases (point estimate, 95% CI: 85.7% [33.4%, 97.9%] vs. 87.4% [83.7%, 90.3%] respectively, Log-rank p=0.99), and had a significantly higher 5-year OS than patients with both LN and distant metastases (15.4% [2.5%, 38.8%], Log-rank p=0.004).

DISCUSSION

In this large, prospective clinical trial that included central review of pathology and diagnostic imaging, we found that LN metastases occur in about 4% of pediatric and young adult patients with NRSTS. Patients with LN metastases had larger tumors, a higher incidence of distant metastases, and more often had unresected tumors at study entry than those without LN metastases. The diagnoses most associated with LN metastases (>10%) were epithelioid sarcoma, undifferentiated sarcoma, clear cell sarcoma, and angiosarcoma of soft tissue. Although the proportion of synovial sarcoma patients with LN metastases was low (4.3%), it was the most frequent diagnosis with LN metastases because there were proportionally more synovial sarcoma patients. LN involvement was not observed in patients with MPNST or UESL, other common diagnoses in pediatric and young adult patients.

Our patients with isolated LN involvement fared significantly better than those who also had extranodal metastases, with outcomes similar to those with non-metastatic disease. A better prognosis had not been documented for pediatric patients with isolated LN metastases previously. Several adult studies suggest that isolated LN involvement has a better prognosis than extranodal metastases, including one showing that adult patients with isolated LN metastases had a 4-year survival of 71%.[22] In another study, combined LN and distant metastases (2-year survival, 21.76%) were associated with significantly worse prognosis than LN metastases alone (2-year survival, 47.36%).[23] Despite evidence that isolated LN metastases have a more favorable prognosis, categorizing isolated LN metastases separately from distant metastases in adult STS in the AJCC staging system remains controversial.[9,24] Although there is no standard staging system for NRSTS in children and adolescents, the more favorable outcomes of young patients with isolated LN metastases suggests that they be treated with curative intent.

Based on the high incidence of LN involvement in epithelioid sarcoma and clear cell sarcoma in the adult literature,[25] our study required LN sampling or sentinel LN biopsies for these patients even when LN enlargement was absent. However, all of our patients with confirmed LN involvement at study entry had obvious enlargement of LNs on imaging except for one patient who did not have imaging of the draining LNs, suggesting that clinical/radiographic detection is a reliable method to identify patients with LN metastases. Furthermore, of the entire study cohort of 529 patients, only 3 had LN metastases at first recurrence without having LN metastases at diagnosis, 2 of whom had negative LN biopsies at study entry. Although the conclusions we can draw from our small sample size are limited, LN sampling in young patients without clinically or radiologically evident lymphadenopathy may not be warranted regardless of the histologic subtype, with the possible exception of >5 cm epithelioid sarcoma and clear cell sarcoma where the incidence of nodal disease is very high. Eliminating sampling of LNs may accelerate initiation of other therapy by limiting postoperative healing time and may reduce anesthesia risks, lower the lymphedema risk, and decrease overall costs.

The role of sentinel LN biopsy in adult STS remains uncertain, as the incidence of occult LN metastases is low except in clear cell sarcoma.[26] Our study yields limited information about the role of sentinel LN biopsy in young patients with NRSTS since none of our patients with LN metastases had occult disease detected by sentinel LN biopsy. Whether this procedure missed involved LNs in the single patient with negative sentinel LN biopsies who went on to develop LN metastases in the same region later or whether the LN involvement developed later in the course of the disease is unclear.

Given the very low incidence of LN metastases in NRSTS, clinically or radiographically enlarged LNs in these patients should not routinely be assumed to be LN metastases. Indeed, only 14 of the 69 patients who underwent LN biopsies for enlarged LNs (20%) had metastatic involvement. Alternate explanations for regional LN enlargement include healing following tumor biopsy, infections and inflammatory conditions. Published literature suggests that FDG-avidity of LNs on positron emission tomography also is not specific for metastases in STS.[27] Because the implications for treatment and prognosis are significant, enlarged and/or FDG-avid LNs may warrant biopsies unless there is sufficient enlargement

to be diagnostic of metastasis. In patients with a soft tissue mass highly suspicious for malignancy, LN imaging prior to tumor biopsy may decrease the need to sample LNs that become enlarged as a result of surgery. To avoid missing nodal involvement, selective LN sampling may be indicated in patients with marginally enlarged regional nodes, particularly when the histologic entity is strongly associated with nodal metastases.

The main limitation of this analysis is the small number of patients with LN metastases, which limits the reliability of our conclusions. In addition, we also did not include all soft tissue tumors that can have lymph node involvement, so it is possible that we underestimate the rate of lymph node involvement. However, given the large size of the overall cohort and the low incidence of LN metastases in these very rare sarcomas, it is unlikely that more complete pediatric data that includes baseline imaging review for nodal enlargement and standardized guidelines for LN sampling will be forthcoming. Recognizing that the data are somewhat limited, we recommend that routine LN sampling or sentinel LN biopsy not be required in future pediatric NRSTS studies, except in patients with suspicious lymphadenopathy on physical exam or diagnostic imaging. A possible exception might be >5 cm epithelioid sarcoma and clear cell sarcoma given their high rate of nodal involvement. Lymph node involvement was detected in all of these patients in our study by diagnostic imaging, but the small overall number of patients enrolled precludes us from making a definitive recommendation about whether routine nodal sampling is warranted for this subgroup in future studies.

Considering their relatively favorable outcomes, patients with isolated LN metastases deserve treatment with curative intent. Event-free survival in our cohort correlated with grossly complete excision of enlarged LNs and adequate RT to the nodal bed, so we recommend this therapeutic approach for local tumor control in potentially curable patients with LN metastases. Due to the small number of cases, we cannot comment on whether outcomes with LN dissection are superior to those with excision of enlarged nodes only. However, most of our event-free survivors did not have a formal LN dissection, suggesting that removal of grossly enlarged nodes and adequate LN bed irradiation may be sufficient. Finally, it is clear that patients with concomitant LN and extranodal metastases have an extremely poor prognosis that reflects particularly aggressive tumor biology. More effective therapies are desperately needed for these patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- Large prospective study of NRSTS with lymph node (LN) involvement in young patients
- Occult lymph node involvement is exceedingly rare
- Isolated LN metastases have a favorable prognosis so should be treated aggressively
- Complete enlarged LN excision and nodal bed radiation correlate with better outcome

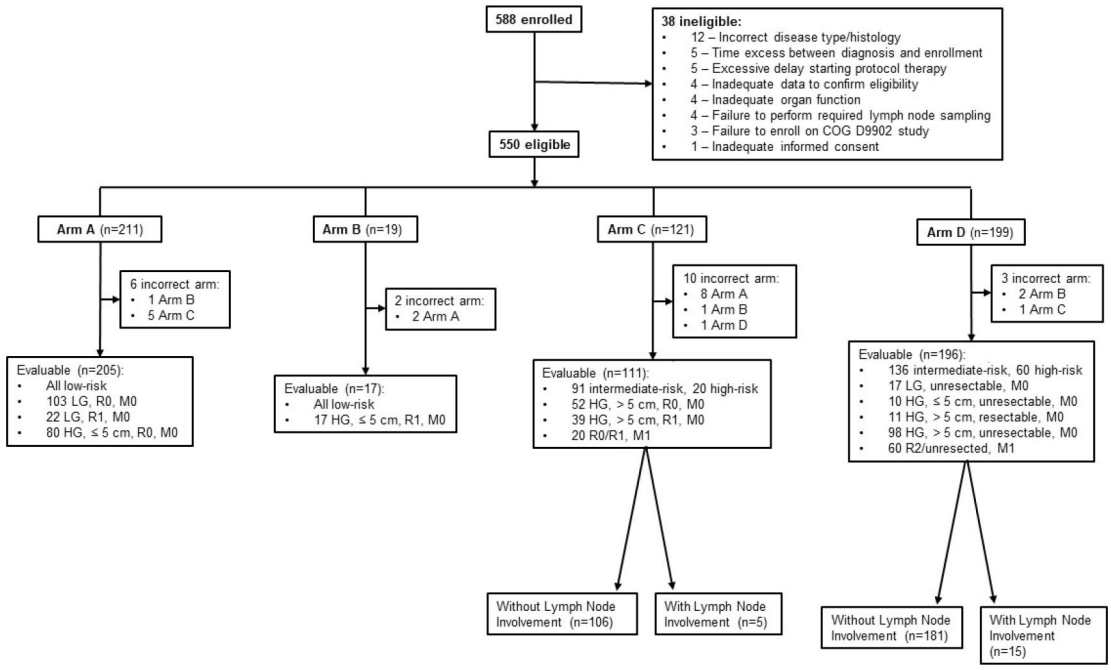

Figure 1.
Consort Diagram

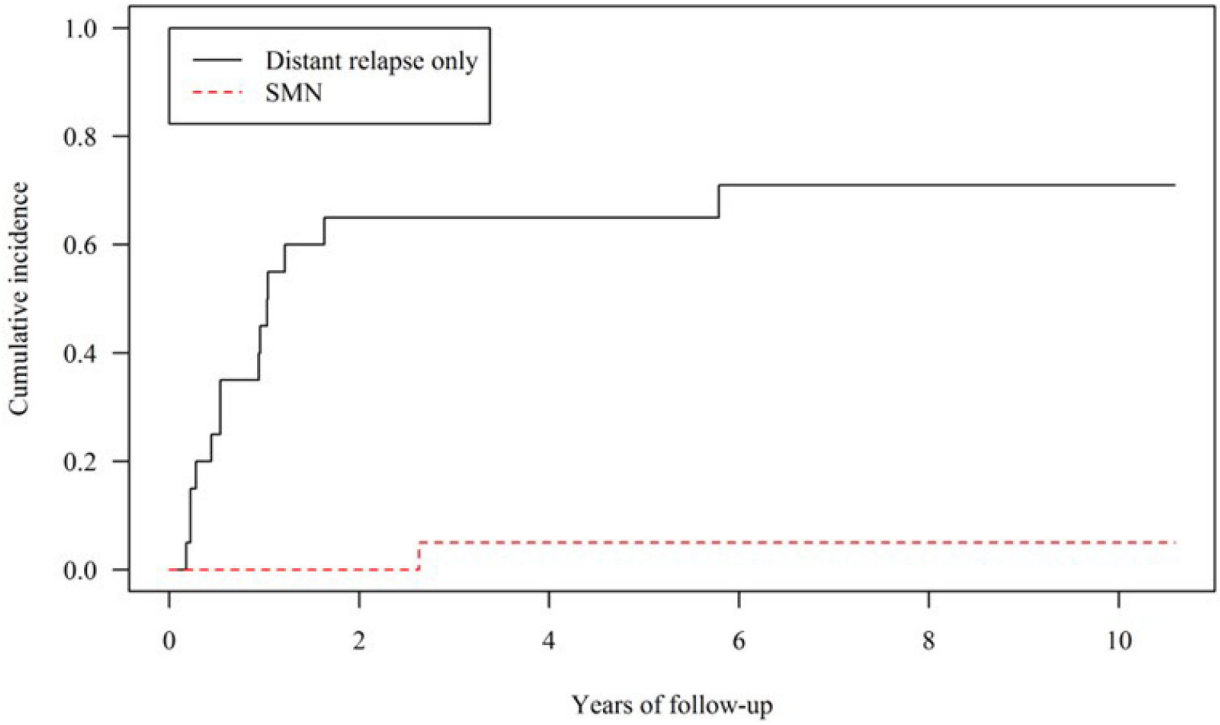

Figure 2.

Estimated Cumulative Hazard Rate with Competing Risk for Patients with NRSTS with Lymph Node Metastases

SMN = second malignancy

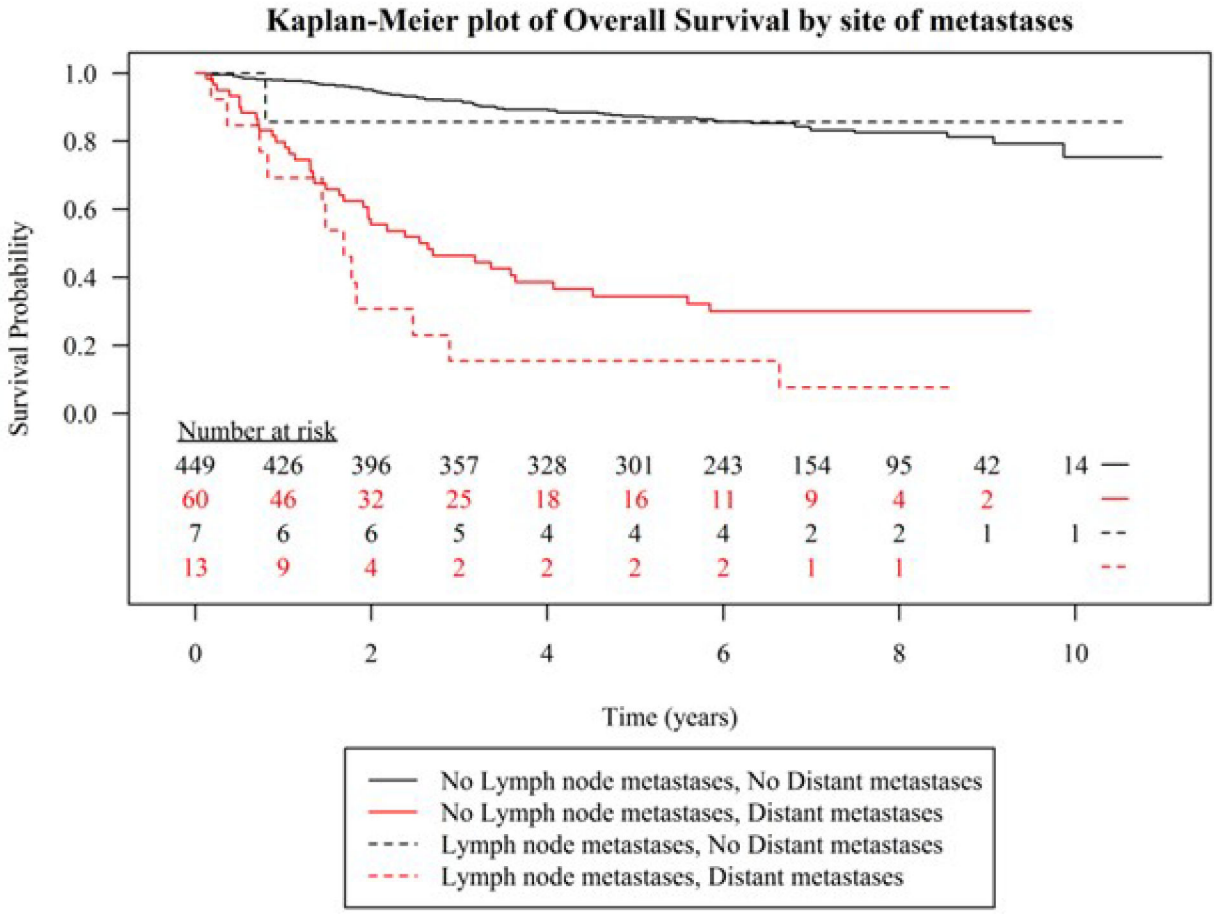

Figure 3.
Estimated Overall Survival for all Patients by Site of Metastases

Table 1.

Characteristics of Patients with and without Lymph Node Metastases at Study Entry

Characteristics	Lymph Node Metastases (N=20)	No Lymph Node Metastases (N=509)	*p*-value
Age at enrollment (years) (continuous)	13.1 ± 6.4	13.0 ± 5.5	0.931
Age at enrollment (years)			1.0
0–9	5 (25%)	141 (27.7%)	
10–17	12 (60%)	289 (56.8%)	
18–30	3 (15%)	79 (15.5%)	
Sex			0.651
Male	8 (40%)	237 (46.6%)	
Female	12 (60%)	272 (53.4%)	
Race			0.609
White	13 (65%)	362 (71.1%)	
Black or African American	4 (20%)	76 (14.9%)	
Other		24 (4.7%)	
Unknown	3 (15%)	47 (9.2%)	
Ethnicity			0.780
Hispanic or Latino	4 (20%)	76 (14.9%)	
Not Hispanic or Latino	16 (80%)	414 (81.3%)	
Unknown		19 (3.7%)	
Histologic Diagnosis			0.005
Synovial sarcoma	6 (30%)	132 (25.9%)	
Epithelioid sarcoma	5 (25%)	23 (4.5%)	
Undifferentiated sarcoma	3 (15%)	60 (11.8%)	
Clear cell sarcoma	1 (5%)	6 (1.2%)	
Malignant peripheral nerve sheath tumor	-	58 (11.4%)	
Angiosarcoma	1 (5%)	5 (1.0%)	
Alveolar soft part sarcoma	-	24 (4.7%)	
Embryonal sarcoma of the liver	-	39 (7.7%)	
Other	4 ** (20%)	162 (31.8%)	
Primary tumor site			0.271
Extremity	9 (45%)	280 (55.0%)	
Body Wall	2 (10%)	73 (14.3%)	
Visceral	8 (40%)	103 (20.2%)	
Head/neck	1 (5%)	53 (10.4%)	
Primary tumor size (cm) (continuous)	11.9 ± 6.0	7.7 ± 5.4	<0.001
Primary tumor size (cm)			0.001
0–5	2 (10%)	193 (37.9%)	
5.1–10	6 (30%)	162 (31.8%)	

Characteristics	Lymph Node Metastases (N=20)	No Lymph Node Metastases (N=509)	*p*-value
10.1–15	4 (20%)	102 (20.0%)	
>15.1	8 (40%)	52 (10.2%)	
Distant metastases			<0.001
Yes	13 (65%)	60 (11.8%)	
No	7 (35%)	449 (88.2%)	
Tumor POG histologic grade			0.070
1	0 (0%)	60 (11.8%)	
2	1 (5%)	85 (16.7%)	
3	19 (95%)	364 (71.5%)	
Tumor FNCLCC histologic grade			0.039 *
1	0 (0%)	70 (13.8%)	
2	6 (30%)	216 (42.4%)	
3	14 (70%)	222 (43.6%)	
Indeterminate	0 (0%)	1 (0.2%)	
Primary tumor depth			0.033
Superficial	0 (0%)	92 (18.1%)	
Deep	20 (100%)	417 (81.9%)	
Invasiveness			0.257
Non-invasive	6 (30%)	223 (43.8%)	
Invasive	14 (70%)	286 (56.2%)	
Treatment Arm			—
A: No adjuvant treatment	0 (0%)	205 (40.3%)	
B: Adjuvant radiotherapy	0 (0%)	17 (3.3%)	
C: Adjuvant chemotherapy + radiotherapy	5 (25%)	106 (20.8%)	
D: Neoadjuvant chemo-radiotherapy	15 (75%)	181 (35.6%)	
Tumor resectable by institutional assessment			<0.001
Yes	15 (75%)	173 (34.0%)	
No	5 (25%)	336 (66.0%)	

*p-value obtained by ignoring the “Indeterminate” category.

**These 4 patients had soft tissue sarcomas that were study-eligible but could not be more specifically categorized based on available pathologic material.

Table 2:

Demographics and Tumor Characteristics of Patients with NRSTS with Lymph Node Metastases

Characteristic	Lymph Node Metastases ± Distant Metastases (n=20)	Distant Metastases Only (n=60)	*p*-value
Median Follow-up time for patients alive at last contact (years)	6.86	6.76	—
Age at enrollment (years) (continuous)	13.1 ± 6.4	16.0 ± 5.0	0.037
Age at enrollment (years)			0.407
0–9	5 (25%)	8 (13.3%)	
10–17	12 (60%)	37 (61.7%)	
18–30	3 (15%)	3 (5.0%)	
Sex			0.443
Male	8 (40%)	31 (51.7%)	
Female	12 (60%)	29 (48.3%)	
Race			0.281
White	13 (65%)	42 (70.0%)	
Black or African American	4 (20%)	13 (21.7%)	
Other		3 (5.0%)	
Unknown	3 (15%)	2 (3.3%)	
Ethnicity			0.727
Hispanic or Latino	4 (20%)	9 (15.0%)	
Not Hispanic or Latino	16 (80%)	51 (85.0%)	
Histologic Diagnosis			0.009
Synovial	6 (30%)	15 (75.0%)	
Epithelioid	5 (25%)	1 (1.7%)	
Undifferentiated	3 (15%)	6 (10%)	
Clear Cell	1 (5%)	1 (1.7%)	
Malignant Peripheral Nerve Sheath Tumor		6 (10.0%)	
Angiosarcoma	1 (5%)	2 (3.3%)	
Alveolar Soft Part		11 (18.3%)	
Embryonal sarcoma of the liver		4 (6.7%)	
Other	4 (20%)	14 (23.3%)	
Primary tumor site			0.779
Extremity	9 (45%)	34 (56.7%)	
Body Wall	2 (10%)	6 (10.0%)	
Visceral	8 (40%)	17 (28.3%)	
Head/neck	1 (5%)	3 (5.0%)	
Primary tumor size (cm) (continuous)	11.9 ± 6.0	12.6 ± 5.3	0.650
Primary tumor size (cm)			0.202
0–5	2 (10%)	3 (5.0%)	
5.1–10	6 (30%)	18 (30.0%)	

Characteristic	Lymph Node Metastases ± Distant Metastases (n=20)	Distant Metastases Only (n=60)	*p*-value
10.1–15	4 (20%)	25 (41.7%)	
>15.1	8 (40%)	14 (23.3%)	
Tumor POG histologic grade			1.0
2	1 (5%)	3 (5%)	
3	19 (95%)	57 (95%)	
Tumor FNCLCC histologic grade			0.601 *
2	6 (30%)	22 (36.7%)	
3	14 (70%)	37 (61.7%)	
Indeterminate	-	1 (1.7%)	
Primary tumor depth			1.0
Superficial	-	2 (3.3%)	
Deep	20 (100%)	58 (96.7%)	
Invasiveness			0.345
Non-invasive	6 (30%)	11 (18.3%)	
Invasive	14 (70%)	49 (81.7%)	
Treatment Arm			1.0
C: Adjuvant chemotherapy + radiotherapy	5 (25%)	15 (25.0%)	
D: Neoadjuvant chemoradiotherapy	15 (75%)	45 (75.0%)	
Tumor “Unresectable” by Institutional Assessment			1.0
Yes	15 (75%)	44 (73.3%)	
No	5 (25%)	16 (26.7%)	
Margins after Maximal Surgery			1.0
Negative	2 (10%)	5 (8.3%)	
Positive	3 (15%)	10 (16.7%)	
Unresected	15 (75%)	45 (75.0%)	

* p-value calculated ignoring the “Indeterminate” case