Clin Orthop Relat Res (2013) 471:926–931
DOI 10.1007/s11999-012-2568-0

Clinical Orthopaedics and Related Research®
A Publication of The Association of Bone and Joint Surgeons®

SYMPOSIUM: HIGHLIGHTS FROM THE FIRST COMBINED 2011 MEETING OF THE MUSCULOSKELETAL TUMOR SOCIETY AND CONNECTIVE TISSUE ONCOLOGY SOCIETY

Lymphadenectomy and Histologic Subtype Affect Overall Survival of Soft Tissue Sarcoma Patients With Nodal Metastases

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Published online: 7 September 2012

Abstract

Background Lymph node metastases in patients with soft tissue sarcomas are rare and these metastases are frequently associated with certain histologic subtypes. The survival is believed to be poor if lymph node metastases occur and the potential benefit of lymphadenectomy is unclear.

Questions/purposes We determined whether lymph node metastases affect overall survival with regard to the status of lymphadenectomy, histologic subtypes, isolated or systemic metastasis, and the timing of presentation of lymph node metastases.

Methods We retrospectively reviewed all 871 patients diagnosed with soft tissue sarcomas between 1983 and 2008 to determine whether they had lymph node metastases at diagnosis or subsequently and whether they had lymphadenectomy for treatment. Overall survival was assessed and the effect of prognostic variables was examined by a log rank test.

Results Forty-nine of the 871 patients (6%) had lymph node metastases. The estimated 5-year survival rate for the group of 49 patients with lymph node metastases was 27%. Those who had lymphadenectomy had better survival at 1.5 years although there was no difference between those who did not undergo lymphadenectomy at 5 years. Patients with nonrhabdomyosarcoma had better overall survival than patients with rhabdomyosarcoma. Timing of development of lymph node involvement and whether lymph node metastases were an isolated site did not affect the overall survival.

Conclusions Overall survival of patients with lymph node metastases was related to histologic subtypes and patients with nonrhabdomyosarcoma had better survival than those with rhabdomyosarcoma. Resection of the metastatic lymph node did not improve long-term survival of patients with soft tissue sarcomas.

Level of Evidence Level II, prognostic study. See Guidelines for Authors for a complete description of levels of evidence.

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This work was performed at the Cancer Institute Hospital for Japanese Foundation for Cancer Research, Tokyo, Japan.

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Introduction

Lymph node metastases in patients with soft tissue sarcomas are rare and the overall prevalence is 1.75% to 5.9% [2, 5, 8, 12]. Certain histologic subtypes such as epithelioid sarcoma, rhabdomyosarcoma, and clear cell sarcoma have a higher frequency of lymph node metastases, reportedly

17% to 50% [3, 5, 8], compared with other soft tissue sarcomas. Overall survival is possibly related to histologic subtype, although the rarity of the lymph node metastases has made the study of their natural history difficult.

Prognosis of patients with lymph node metastases and the potential benefit of lymphadenectomy are unclear. Some consider lymph node metastases an indicator of disseminated disease [2, 5, 9] because lymph node metastases present at diagnosis may reflect more aggressive behavior of the tumor rather than regional disease progression. Collin et al. [4] found positive regional lymph nodes independently predicted poor survival in multivariate analysis of 423 patients. Several studies have reported patients who had lymph node metastases at diagnosis of the primary tumor had a poorer survival than those who developed lymph node metastases later [2, 5], whereas others found the timing of the identification of nodal involvement in relation to the initial diagnosis of the primary tumor did not influence the overall survival [1, 12].

Several authors [8, 12] suggest an aggressive approach of treatment improves long-term survival and have reported better survival rates in patients with lymph node metastases as the only distant site and who subsequently underwent lymphadenectomy. Fong et al. [8] reported that those who underwent curative lymphadenectomy for lymph node-only metastases had a 16.3-month median survival, which was superior to that seen in patients who underwent lymphadenectomy (4.3-month median survival). In another study, 26 patients with isolated lymph node metastases underwent lymphadenectomy with a 4-year survival rate of 71% [12]. Other studies have found similar 5-year survival in patients with isolated lymph node metastases and patients with distant metastases and that the resection status of the metastatic lymph nodes did not influence overall survival [2, 5]. Behranwala et al. [2] reported radical lymphadenectomy did not confer a substantial survival benefit; patients with surgically managed isolated regional lymph node metastases had a 47.4% and 23.9% 2-year and 5-year survival, respectively. According to these studies, it is possible that lymphadenectomy may offer a benefit in short-term survival less than 5 years but it has less impact on overall survival in the long term.

We therefore determined whether (1) lymphadenectomy improves overall survival of patients with lymph node metastases; (2) overall survival of patients with lymph node metastasis differs between histologic subtypes; (3) patients with isolated lymph node metastases have better survival compared with those presenting with both lymph node and other metastases such as lung, bone, and soft tissue; and (4) those who present with lymph node metastases at diagnosis have a poorer prognosis than those who developed them later.

Patients and Methods

We retrospectively reviewed the charts of all 871 patients with soft tissue sarcomas from 1983 to 2008. Because treatment strategies, including adjuvant therapies, have been changed over the years, we excluded patients diagnosed before 1983. Patients were identified who presented with lymph node metastases at diagnosis or had lymph node metastases develop after their initial visit. Lymph node metastases were identified by presence of a palpable mass and were confirmed on cross-sectional imaging by CT or MRI. We obtained chest CT routinely for all patients. In addition, abdominal and pelvic CT scans were obtained for patients with liposarcoma. Because PET-CT was not covered by the health insurance system in Japan before 2010, none of these patients was evaluated with PET-CT. Biopsy of the suspected lymph nodes metastases was performed for all cases except two; one had paraaortic lymph node metastases and the other presented with multiple systemic metastases. We did not perform sentinel lymph node biopsy. No patients were recalled specifically for this study; all data were obtained from the medical records.

Demographic data collected included age, sex at the time of diagnosis, and duration of followup. The median age of the study population was 49 years (range, 7–88 years). There were 25 males (51%) and 24 females (49%). We recorded the length of patient followup and tumor characteristics. Data of metastases other than lymph nodes (lung, bone, and soft tissue) were collected. Isolated lymph node metastases (N1M0) were defined as lymph node-only metastases without other metastases such as lung, bone, or soft tissue. Primary tumor characteristics were tabulated with tumor size (equal to or less than 5 cm, greater than 5 cm), the site of the primary tumor (trunk, extremity), depth (superficial, deep), grade, and histologic subtype. Tumor size was determined by the imaging studies at diagnosis using maximal diameter measured on CT or MRI. If patients had unplanned excision elsewhere, the tumor size was determined by outside images if available. We reviewed the pathology report when tumors were excised without preoperative imaging studies. Thirty-two patients (65%) presented with tumors larger than 5 cm, whereas 35% had tumors equal to or less than 5 cm (Table 1). A tumor was considered to be in the extremity if it was at or beyond the shoulder or at or below the hip. Other tumors were considered to be in the trunk. Most patients had tumors located in the extremity (44 patients [90%]). Tumors located superficial to the fascia were considered to be superficial and tumors on or deep to the fascia were considered as deep soft tissue sarcomas. Grade 1 in the FNCLCC grading system [14] was categorized as low grade and Grade 2; Grade 3 was considered as high grade in this study. Histologic subtypes were categorized as

Table 1. Patient and tumor characteristics of 49 patients with lymph node metastases.

Patient characteristics	Number	Percent
Lymph node metastasis at diagnosis		
Yes	22	45
No	27	55
Isolated lymph node metastases		
Yes	41	84
No	8	16
Tumor size		
≤ 5 cm	17	35
> 5 cm	32	65
Primary tumor site		
Trunk	5	10
Extremity	44	90
Depth		
Superficial	20	41
Deep	29	59
Grade		
Low (FNCLCC 1)	5	10
High (FNCLCC 2-3)	44	90

Table 2. Surgical treatment and adjuvant therapies administered

Type of treatment	Number	Percent
Surgical procedure		
Amputation	7	14
Limb-sparing procedure	40	82
Biopsy only	2	4
Radiation therapy		
Preoperative		
Yes	17	35
No	32	65
Postoperative		
Yes	10	20
No	39	80
Chemotherapy		
Preoperative		
Yes	11	22
No	38	78
Postoperative		
Yes	17	35
No	32	65
Lymph node excision		
Yes	36	73
No	13	27

rhabdomyosarcoma and nonrhabdomyosarcoma for analysis because rhabdomyosarcoma differs from nonrhabdomyosarcoma in terms of its natural history, higher sensitivity to chemotherapy, and radiotherapy [6]. Histologic diagnosis was confirmed by our pathologists (RM, NH) experienced in musculoskeletal pathology.

Surgical procedures for primary tumor (limb-sparing, amputation), chemotherapy (preoperative, postoperative) and radiotherapy for primary tumor (preoperative, postoperative), and resection of metastatic lymph nodes were reviewed for each patient. Seven patients were treated with amputation proximal to the wrist or ankle (Table 2). Limb-sparing tumor excision was performed in 40 patients and two patients had biopsy only. We excised metastatic lymph nodes for most N1M0 cases and excised metastatic lymph nodes for N1M1 cases when other distant metastases could be excised. We removed metastatic lymph nodes from distal to proximal and all specimens were sent for histologic analysis with frozen section. We determined that lymphadenectomy was complete when the proximal most lymph nodes were negative for tumor. In some N1M1 cases, we excised lymph nodes hoping to prevent progression of metastatic lesions. We did not operate on those who had multiple distant metastases that were unresectable. Tumor beds were radiated including the proximal area of metastatic lymph nodes after lymphadenectomy in all cases.

We defined overall survival as the time interval between the initial visit to death and survival was assessed by the method of Kaplan and Meier. In this series, short-time survival was defined as survival less than 5 years and long-term survival was defined as survival equal to or longer than 5 years. The effect of lymph node excision, histologic subtype (rhabdomyosarcoma or non rhabdomyosarcoma), isolated lymph node metastases or not, and the timing of lymph node metastases on overall survival was examined with a univariate method in a log rank test. All data were analyzed using statistical software Stata 10 (StataCorp, College Station, TX, USA).

Results

Forty-nine (6%) of 871 patients with soft tissue sarcoma had lymph node metastases. Of 49 patients with lymph node metastases, 22 patients presented with lymphatic involvement at the time of diagnosis of their primary tumor. Twenty-seven patients developed lymph node metastases during the followup period. The minimum followup was 3 months (median, 31.4 months; range, 3–233 months). The minimum followup after lymph node metastases was 1 month (median, 18.4 months; range, 1–230 months). The estimated 5-year survival for the group of 49 patients with lymph node metastases was 27% (95% confidence interval [CI], 15%–41%).

The 1.5- and 5-year survival for those who had lymphadenectomy was 65% (95% CI, 47%–79%) and 30% (95% CI, 15%–46%). The 1.5- and 5-year survival for those who did not have lymphadenectomy was 19% (95% CI, 3%–46%) and 19% (95% CI, 3%–46%). There was no difference in survival ($p = 0.12$) between those who underwent surgical resection and those who did not have resection of metastatic lymph nodes in the long term (Fig. 1). Three patients survived more than 12 months without lymphadenectomy in our series; one patient received both chemotherapy and radiation and the other two patients had low-grade tumor.

Lymph node metastases occurred most frequently in patients with clear cell sarcoma (three of eight patients [38%]), rhabdomyosarcoma (seven of 19 patients [37%]), epithelioid sarcoma (six of 20 patients [30%]), angiosarcoma (two of 10 patients [20%]), and Ewing's sarcoma of soft tissue (three of 19 patients [16%]). The number of patients who survived after lymphadenectomy is shown (Table 3). Patients with nonrhabdomyosarcoma had better survival ($p = 0.006$) compared with patients with rhabdomyosarcoma (Fig. 2).

Patients with isolated lymph node metastasis had similar survival ($p = 0.20$) compared with those who had both lymph node and other metastases. We found no difference in survival ($p = 0.46$) in those who presented with lymph node metastases versus those who developed them later.

Discussion

Lymph node metastases in patients with soft tissue sarcomas are rare and the rarity of the metastases has made the study difficult. The overall survival is believed to be poor if

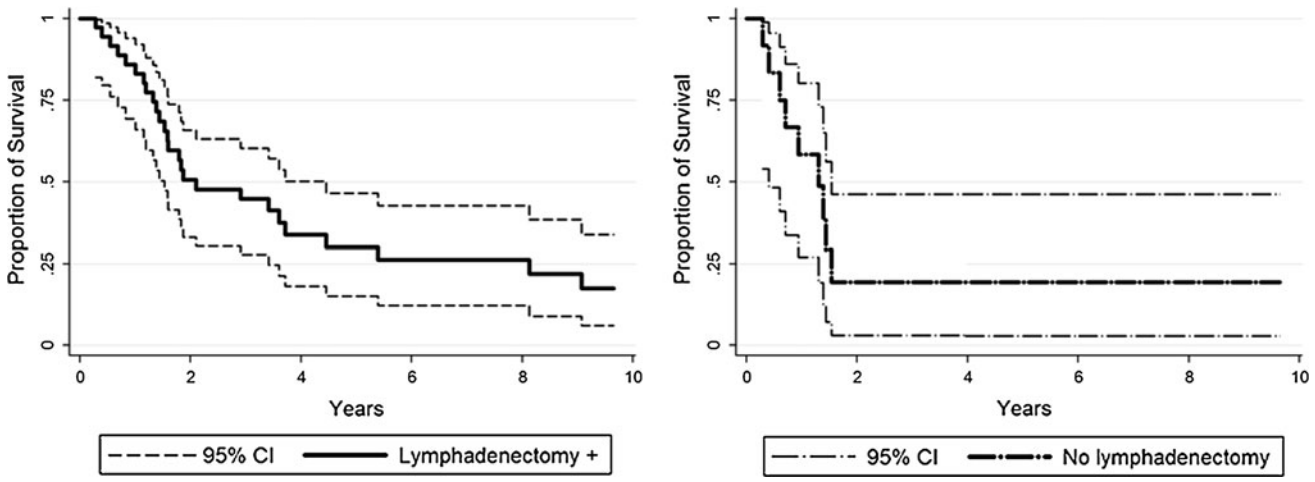

Fig. 1 Survival curves comparing those who had lymphadenectomy and those who did not are shown. Lymphadenectomy may improve short-term survival, although there was no difference ($p = 0.12$) in the long term.

Table 3. Histologic subtypes and frequency of lymph node metastases

Histologic subtype	Number of patients	Number of lymph node metastases (%)	Number of lymphadenectomies	Number of survivors after lymphadenectomy (%)
Clear cell sarcoma	8	3 (38)	3	1 (33)
Rhabdomyosarcoma	19	7 (37)	4	0 (0)
Epithelioid sarcoma	20	6 (30)	6	2 (33)
Angiosarcoma	10	2 (20)	1	1 (100)
Ewing sarcoma	19	3 (16)	2	1 (50)
Chondrosarcoma	27	3 (11)	2	0 (0)
Fibrosarcoma	20	2 (10)	2	1 (50)
Synovial sarcoma	64	5 (8)	4	1 (25)
Malignant fibrous histiocytoma	276	16 (6)	10	2 (20)
Liposarcoma	123	2 (2)	2	1 (50)

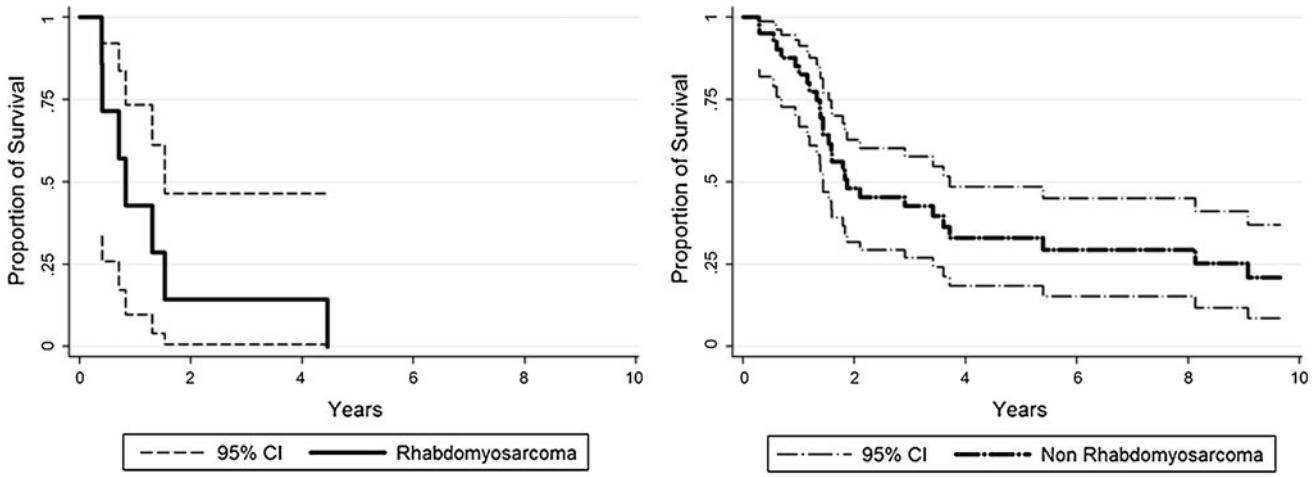

Fig. 2 Survival curves comparing rhabdomyosarcoma with nonrhabdomyosarcoma are shown. Patients with nonrhabdomyosarcoma had better overall survival ($p = 0.006$).

lymph node metastases occur and the potential benefit of lymphadenectomy is unclear [4, 9, 10, 15]. Whether lymph node metastases present at diagnosis have a different impact on survival compared with those patients who develop them subsequently is controversial, although some believe they may represent disseminated disease similar to metastases at other sites [1]. Patients with isolated lymph node metastases may have better survival rates compared with those who had other metastases. Lymph node metastases are frequently associated with certain histologic subtypes [3, 5, 8] and the survival is possibly related to the histologic diagnosis rather than lymph node metastases themselves. We questioned if (1) lymphadenectomy improves the overall survival; (2) survival is different between histologic subtypes; (3) patients with isolated lymph node metastases have better survival than those with other metastases; and (4) those who presented with lymph node metastases at diagnosis have a poorer survival than those who developed them later.

We acknowledge several limitations in this study. First is the limited number of patients with lymph node metastases because the frequency of lymph node metastases of soft tissue sarcoma is as low as 1.75% to 5.9% in previous literature [2, 5, 8, 11, 12] and 6% in our series. We found that lymphadenectomy did not improve overall survival but the chance of a Type II error is substantial. However, our study is a relatively large series of soft tissue sarcomas with 871 patients and the survival curve with or without lymphadenectomy showed a trend to improved short-time survival in patients with lymph node metastases who had them resected. Second, our study is limited by the fact that it is nonrandomized. Thus, there is the potential for patient selection bias, which could have influenced the survival outcomes. For example, patients who presented with isolated nodal disease are more likely to be offered lymphadenectomy. As a result, the potential selection bias could have conferred a survival benefit that was actually a result of the biology of the disease rather than an effect of the lymphadenectomy. Nevertheless, our results indicated lymphadenectomy did not improve overall survival. Patients with lymph node metastases only do not have better survival after lymphadenectomy. Third, MFH is the term used in our study period, although that designation has been changed to undifferentiated pleomorphic sarcoma according to the WHO classification of soft tissue tumors in 2002 and essentially represents a diagnosis of exclusion [7]. This may have some influence on the results if the sarcomas were classified differently. Fourth, this study has all the limitations of a retrospective study, especially as a result of the different adjuvant chemotherapy protocols used in these years, which may affect the result of the study.

Lymphadenectomy did not confer a substantial survival benefit in the long term in our series. A possible explanation is that involvement of lymph nodes represents a clinical expression of the biological aggressiveness of the sarcoma as previously reported [5]. Several authors concluded that patients who underwent lymphadenectomy had better overall survival than that for patients treated by chemotherapy and radiotherapy only [8, 12], although this finding may be confounded by the fact that patients with progressive disease were less likely to be offered lymphadenectomy. Another explanation is that lymphadenectomy primarily affects the short-term survival and its effect disappears beyond that time (Fig. 1). Our findings do not imply that lymphadenectomy should not be performed in selected cases because it does appear to improve the short-term survival, avoids ulceration, and may improve quality of life. Our results imply that lymph

node metastases represent systemic involvement of sarcoma and are an indicator of disseminated disease.

Lymph node metastases independently predict shorter survival times in several sarcoma subtypes [4, 8, 13]. Fong et al. [8] reported that patients with lymph node metastases for malignant fibrous histiocytoma had worse survival compared with other histologic subtypes. We found patients with nonrhabdomyosarcoma had better survival compared with patients with rhabdomyosarcoma. The result is consistent with the study by Rodeberg et al. [13] because patients with lymph node metastases had worse prognoses for alveolar rhabdomyosarcoma. Our results suggested the influence of lymph node metastases possibly varies between each histologic subtype. Our data of number of survivors after lymphadenectomy in each histologic subtype are shown (Table 3), although we were not able to prove this hypothesis in the study because of limited statistical power to analyze each histologic subtype.

Patients with isolated lymph node metastases had similar survival compared with those who had lymph node and other metastases such as lung, bone, and soft tissue. Contradictory to the findings of Riad et al. [12] but in agreement with the result of Daigeler et al. [5], our results suggest that lymph node metastases represent a component of disseminated disease rather than regional disease progression.

The relation of lymph node involvement to the time to primary tumor diagnosis did not affect the overall survival in our study. Our result is consistent with previous studies [1, 12] and the timing of the identification of nodal involvement in relation to the initial diagnosis of the primary tumor does not appear to correlate with biological behavior of the soft tissue sarcomas. Because our result suggests that the survival of patients with lymph node metastases at diagnosis is similar to those who developed later, the timing of lymph node metastases should have less impact to decide treatment options.

In conclusion, we observed that lymph node metastases were more frequently seen in patients with clear cell sarcoma, rhabdomyosarcoma, and epithelioid sarcoma (approximately 30%). Resection of the metastatic lymph node did not improve overall survival of patients with lymph node metastases from soft tissue sarcomas after 5 years. Overall survival of patients with lymph node metastases may be related to histologic subtypes in that patients with nonrhabdomyosarcoma had better overall survival than patients with rhabdomyosarcoma. We did not find a difference in survival in those who had isolated lymph node metastases compared with those who had other metastases. Those presented with lymph node metastases had similar survival compared with those who developed them later.

Acknowledgments We thank Rikuo Machinami, MD, PhD, and Nobuyuki Hiruta, MD, PhD, for evaluation of pathologic specimens.

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