Clinicopathologic Prognostic Factors of Pure Myxoid Liposarcoma of the Extremities and Trunk Wall

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Abstract

Background Myxoid liposarcoma is generally considered a low grade tumor but the presence of areas of round cells exceeding 5% is reportedly associated with a worse prognosis. Whether “pure” tumors without round cells are low grade has not been confirmed. While radiotherapy has been used for patients’ myxoid liposarcoma it is unclear whether it reduces local recurrences.

Questions/purposes We therefore determined the survival, roles of radiotherapy for local control, and prognostic factors of pure myxoid liposarcoma of the extremities and trunk wall.

Methods We retrospectively reviewed 53 patients histologically diagnosed with pure myxoid liposarcoma arising in extremities and the trunk wall. Nine patients of the 53 received radiotherapy for primary tumors. Clinical features and prognosis was determined, and various factors were analyzed as to their usefulness as prognostic factors (age,

gender, location, size, depth, surgical margin, and adjuvant radiotherapy). The minimum followup was 12 months (mean, 60 months; range, 12–226 months).

Results Seven (13%) and 6 (11%) patients developed a local recurrence and distant metastasis, respectively. The 5- and 10-year disease-specific and disease-free survival rates were 90% and 83% and 77% and 77%, respectively. Radiotherapy had no impact on either overall or disease free survival. Age (older than 60 years) independently predicted worse overall and disease-free survival.

Conclusions In pure myxoid liposarcoma located in the extremities and trunk wall, relatively few patients developed distant metastasis suggesting the tumor is generally low grade. Local control could be achieved with wide surgical margins without radiotherapy. Age was associated with lower survival but size and depth were not. Myxoid liposarcoma in older patients requires special consideration for treatment and followup.

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

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Each author certifies that his institution has approved the human protocol for this investigation, that all investigations were conducted in conformity with ethical principles of research, and that informed consent was obtained.

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Introduction

Liposarcoma is one of the most common soft tissue sarcomas, accounting for 20% of all soft tissue sarcomas in adults [19]. Authors have described several subtypes: well-differentiated, dedifferentiated, pleomorphic, and myxoid/round cell liposarcoma [10]. Low-grade myxoid and well-differentiated subtypes have a 5-year survival rate of 90% [17, 18, 20]. However, high-grade subtypes such as pleomorphic, and dedifferentiated liposarcomas have 5-year survival rates of only 30% to 62% [11, 13] and 44% to 75% [5, 20], respectively. Treatment

modalities should be altered in these subtypes because of differences in their sensitivity to chemotherapy, radiotherapy, and risk of local relapse following surgery. Predicting clinical outcome for patients with liposarcoma facilitates appropriate treatment decisions and informing patients about their prognosis.

Myxoid liposarcoma is the second most common type of liposarcoma, representing approximately one-third of all liposarcomas [7] and 6% of all adult soft tissues sarcomas. The tumor is low grade according to one report [7]. However, when they do metastasize, in contrast to other liposarcoma variants they tend to metastasize to unusual locations with worse prognosis [3, 8, 22]. Further, when areas of round cells exceed 5% myxoid liposarcomas reportedly have a worse prognosis [2] but the number of cases with areas of round cells greater than 5% is small, and these tumors are often included in reported series making confirmation of the low grade nature of “pure” tumors difficult, particularly from single centers given the low incidence. In addition, in most of the previous series [5, 6, 9, 16, 23] radiation therapy was used so the effects of surgery alone could not be determined.

The aims of this study were to determine (1) whether pure myxoid liposarcoma (those with fewer than 5% areas of round cells) arising in the extremities and trunk wall is a low grade disease by establishing survival; (2) whether the tumor could be locally controlled without radiotherapy; and (3) whether any of several clinicopathologic and treatment characteristics influenced survival.

Patients and Methods

From 1984 to 2005, 685 patients were histologically diagnosed with soft tissue sarcomas in four institutions (Nagoya University Hospital, Aichi Cancer Center Central Hospital, Aichi Cancer Center Aichi Hospital, Nagoya Memorial Hospital). Among these patients, 117 patients had liposarcomas, the subtypes of which were divided into four groups: well-differentiated, myxoid/round cell, pleomorphic, and dedifferentiated types. A pathologist with expertise in sarcoma reviewed all cases for diagnostic accuracy, paying attention to contemporary definitions of this disease given these have occurred over time. Excluding 64 patients with tumors diagnosed as other subtypes or diagnosed as myxoid liposarcoma but containing greater than 5% round cell component, there were 53 patients with myxoid liposarcomas diagnosed on histologic criteria. No patients had metastatic disease at the time of initial referral. These 53 patients formed the basis for this study. Thirty-one patients were male and 22 were female. Average age was 51 years (range, 17–85 years). Forty tumors arose in the extremities; 24 in the thigh, four around the knee, three

in the arm, four in the forearm, four in the leg, and one in the foot. Although 13 patients had liposarcoma in the trunk, none was located in the retroperitoneum. The mean major axis of tumor burden was 8.8 cm (range, 1.5–25 cm), and 63% were deep-seated excluding cases with unknown location (Table 1). We included data on patients lost to followup until the time when their health status was last known. Minimum followup was 12 months (mean, 60 months; range, 12–226 months). Institutional Review Board approved this study.

Surgery was performed in all patients with a wide surgical margin obtained whenever possible. A wide surgical margin was defined that a resection margin was designated outside of a reactive zone by imaging and confirmed microscopically to be negative. All 53 patients had limb salvage surgery. There were 12 patients with prereferral unplanned surgery; unplanned surgery was defined as

Table 1. Demographic details of the 53 patients

Variables	Patients	%
Gender		
Male	31	58.5
Female	22	41.5
Age (range)	51 (17–85)	
Site		
Upper extremity		13.2
Arm	3	5.7
Forearm	4	7.5
Lower extremity		62.3
Thigh	24	45.4
Knee	4	7.5
Leg	4	7.5
Foot	1	1.9
Trunk		24.5
Chest Wall	6	11.3
Groin	5	9.4
Gluteus	2	3.8
Depth		
Superficial	15	28.3
Deep	26	49.1
Unknown	12	22.6
Tumor size (range)	8.8 (1.5–25)	
< 5 cm	12	22.5
5–10	22	41.6
10≤	19	35.9
AJCC staging		
Stage I	53	100
Stage II–IV	0	0
Adjuvant	83	87.4
Chemotherapy	5	9.4
Radiotherapy	9	17.0

resection of presumed benign masses without appropriate preoperative imaging, or attention to surgical margin [12]. Subsequently, additional wide resection was performed for those patients in our institutions. Pathologic evaluation of the surgical margin, which was determined by a pathologist with expertise in sarcoma, was wide in 44, marginal in seven, and unknown in two.

Chemotherapy was not commonly used in the adjuvant setting during the study period but was administered to patients with distant metastasis for palliative purposes or for tumor reduction preoperatively in cases of tumors located close to neurovascular structures. Nine patients were treated with chemotherapy (five as adjuvant treatment and four for palliative purposes). The most common anti-cancer agents used were doxorubicin and ifosfamide, and commonly, four cycles were performed. Twelve patients were treated with radiotherapy. Four of the patients treated with chemotherapy and three with radiotherapy were so treated after occurrence of distant metastasis. After excluding the three patients with metastatic disease who had radiotherapy, we were left with nine patients with primary tumors who were included in the analysis of the influence of radiotherapy on survival.

We determined overall and disease-free survival by the Kaplan-Meier method [14]. Age at presentation (older than 60 years), gender, location (upper extremity, lower extremity, trunk), tumor size (less than 5 cm, 5–10 cm, 10 cm or greater), depth, surgical margin, and radiotherapy were analyzed to correlate with patient prognosis. We calculated overall survival from the date of diagnosis until death or the last followup visit. Disease-free survival was defined as the period from diagnosis until local or systemic disease recurred. We performed multivariate analysis using the Cox proportional hazard method with variables chosen using a forward conditional stepwise approach. We used SPSS 15.0 for Windows (SPSS Corp, Chicago, IL) for the statistical analysis.

Results

Overall survival for all 53 patients was 90% at 5 years (Table 2) and 83% at 10 years. Because all 53 patients underwent definitive surgery, they were analyzed with respect to disease-free survival, which was 77% at both 5 and 10 years. No patient had distant metastasis at the time of diagnosis, but six (11%) developed distant metastasis during followup. Three patients had the initial metastasis in the lung, two in the spine, and one in the brain. Only one of seven patients with recurrence had distant metastasis during followup. At last followup, 47 of the 53 patients had no evidence of disease, two were alive with disease, and four had died of their tumor.

Table 2. Overall (OAS) (53 patients) and disease free (DFS) (53 patients) survival at 5 years

Variable	OAS (%)	DFS (%)
All	90.3	76.5
Gender		
Male	82.8	77.5
Female	85.7	74.1
Age		
> 60	77.3	57.4
< 60	96.6	84.7
Depth		
Superficial	100	77.8
Deep	85.4	69.5
Size		
10≤	86.9	66.0
5–10	88.0	85.1
< 5	100	77.1
Location		
Trunk	87.5	64.9
Upper extreme.	80.0	68.6
Lower Extrem.	93.3	81.0
Surgical margin		
Wide	88.3	80.2
Marginal	50.0	66.7
Radiotherapy		
(+)	83.3	76.2
(–)	91.8	76.9
Local recurrence		
(+)	75.0	
(–)	92.1	

Seven patients (13%) had local recurrence. Although only nine patients (17%) had adjuvant radiotherapy in this study, two of the nine patients (22%) had local recurrence. Among 44 patients without radiotherapy, five patients (11%) had local recurrence. Of these seven patients, four had excision with wide margins, two with marginal, and one with an unknown margin. The five year overall survival of patients with radiotherapy was similar ($p = 0.85$) to that of patients without radiotherapy (83% versus 91%, respectively).

The only factor associated with a lowered overall survival was age older than 60 years ($p = 0.039$; hazards ratio [HR] = 10.2, 95% confidence interval [CI]: 1.1–91) (Table 3) (Fig. 1). Factors associated with a shortened disease-free survival were age older than 60 years ($p = 0.012$; HR = 5.38, [CI]: 1.44–20). There was no difference between the age with distant metastasis and that without distant metastasis (Mann-Whitney U test), nor 45 years as cut-off age (log-rank). Patients with larger tumors (mean; 10.6 cm) tended to have a higher rate of

Table 3. Multivariate analysis for overall (OAS) and disease-free (DFS) survival in 53 patients with myxoid liposarcoma

	Variable	<i>P</i> value (Hazards ratio) (95% CI)
OAS	Age (> 60)	0.039 (10.2) (1.1–91)
DFS	Age (> 60)	0.012 (5.38) (1.4–20)

OAS = overall survival; DFS = disease-free survival; CI = confidence interval.

Fig. 1A–B Kaplan-Meier curves show overall survival (**A**) and disease-free survival (**B**) for age older than 60 (dotted line) and younger than 60 years (solid line). Five-year overall survival for age older than 60: 86% (95% confidence interval: 78–104%), younger than 60 years 97% (95% CI: 90–103%). Five-year disease-free survival for age older than 60: 58% (95% CI: 31–85%), younger than 60: 85% (95% CI: 70–99%).

local recurrence compared to those without recurrence (mean; 8.5 cm), but the numbers were too small to achieve statistical significance and we do not know if this is clinically important.

Discussion

Patients with myxoid liposarcoma containing areas of round cells exceeding 5% reportedly have a worse prognosis than those containing no round cell components [2]. We asked whether (1) pure myxoid liposarcoma is a low grade sarcoma; (2) the tumor could be locally controlled without radiotherapy; and (3) whether any of several clinicopathologic and treatment characteristics influenced survival.

There are several limitations of this study. First, because chemotherapy was used selectively, chemotherapy could not be subjected to statistical analysis in this study. Second, the minimum followup was 12 months, and nine patients were followed up for less than 2 years, which was shorter than in other studies. This may have accounted for the low incidence of extrapulmonary metastases. Longer followup will clarify this issue. Although the followup period was short, 50% of initial metastasis occurred in nonpulmonary sites, which is consistent with the previous reports of unusual high incidence of nonpulmonary metastasis in this disease. Third, tumor sites were limited to the extremity and trunk wall and tumor grade was similar since we excluded all tumors with a greater than 5% round cell component; while these limitations create a more homogeneous group for analysis, they might reduce the importance of other factors for prognosis. Fourth, we had few patients with radiotherapy, so we had inadequate power to discern whether there was any added benefit. However, surgery alone achieved local control in most patients.

A number of studies have reported recurrences and metastases in patients with myxoid liposarcoma (Table 4). Although most of these studies analyzed pure myxoid liposarcoma together with the round cell liposarcoma, the findings are worth comparing with ours. We found a local recurrence rate of 13%, which is lower than reported in other studies (14%–33%) [2, 21, 23]. There may be several reasons for this low recurrence rate. The relative number of tumors located in the extremities in this study was higher than in other studies, and most tumors were resected with a wide margin. The high rate of wide margin status (83%) obtained lowered not only the recurrence rate, but also the frequency of radiotherapy. According to the treatment modality in our musculo-skeletal oncology group, radiotherapy is not indicated after surgery with wide surgical margins. A previous report demonstrated no major difference was seen in the local recurrence rates between patients treated with marginal resection with radiotherapy versus wide surgical resection alone [16]. Together, myxoid liposarcoma, relatively low-grade soft tissue sarcoma, located in an extremity or trunk where easily approached by the

Table 4. Comparison to previous reports of patients with myxoid liposarcoma

Author	No. of cases	Age median	Site Extremity %	Pure MLS %	Local recurrence %	Distant metastasis %	DSS % (Year)
Smith et al. [21]	29	44	100	73	31	34	70 (5)
Kilpatrick et al. [16]	86	44	96	57	14	35	82 (5)
Antonescu et al. [2]	79	46	84	68	28	38	80 (5)
ten Heuval et al. [23]	49	44	86	83	33	27	85 (5)
Dalal et al. [5]	144	NA	NA	100	NA	NA	92 (5)
Engstrom et al. [6]	64	NA	NA	NA	8	10	NA
Fiore et al. [9]	269	NA	NA	75	24	14	77 (10)
Nishida et al. [current study]	53	52	75	100	13	11	90 (5)

MLS = myxoid liposarcoma; DSS = disease specific survival; NA = not available.

surgeon and treated with a wide surgical margin, can be locally controllable with surgery alone.

Other studies have reported most metastases occurred in extrapulmonary sites, including the retroperitoneum, pericardium, subcutaneous tissues, and bone, which is a typical feature of myxoid liposarcoma [3, 8, 22]. Patients with high predilection for unusual sites of metastasis in previous studies were mostly composed of relatively higher-grade tumors and/or a higher rate of round cell component. However, given that six (11%) of 53 patients had distant metastasis and three (50%) of six patients with distant metastasis had extrapulmonary sites (two in the spine and one in the brain) in this study, it is suggested that even pure myxoid liposarcoma should be considered a relatively higher grade of tumor.

Overall and disease-free survivals at 5 years were 90% and 77%, respectively, in this series of 53 patients with myxoid liposarcoma of extremity and trunk wall sites that underwent surgery aiming at complete resection. These results are similar or superior to those reported from previous published reports [2, 5, 9, 16, 21, 23]. In one study the 12-year disease-specific survival rate was 86% for myxoid liposarcoma and 53% for round cell liposarcoma [5] while in another the 10-year disease-specific survival rates for myxoid liposarcoma and round cell liposarcoma were 90% and 82%, respectively [9]. Results of other studies for disease-specific survival have been relatively low (47%–73%) [2, 16, 21, 23]. This difference in outcomes may reflect mainly differences in tumor location and inclusion of round cell subtype between this study and previous reports. Previous studies included 56–96% of extremity myxoid liposarcoma [5, 9, 16, 23]. There were few patients with round cell liposarcoma in our institutions, and they were excluded from this study. Therefore, risk stratification in the round cell liposarcoma group should be investigated prospectively. Regarding chemotherapy, because this variable was not prospectively randomized in

previous studies, it was omitted from the study [5] or reported to have no impact on prognosis [9].

Although patients with larger tumor size (10 cm or greater) had more local recurrence, no impact of tumor size was evident in this study. According to the American Joint Committee on Cancer classification, the cutoff size of 5 cm seemed to single out two different risk categories [1]. However, the cutoff size of 5 cm did not have any impact in this study either. We found (unpublished data) tumor size (less than or greater than 10 cm) predicted ($p = 0.044$) disease-free survival with all subtypes of liposarcoma in our institutions, but size may have a more influence on higher-grade liposarcomas.

Age independently predicted both overall and disease-free survival. Several other studies suggest older patients have a worse prognosis [6, 16, 23]. Possible reasons for the poor prognosis of older patients may be an age-related decrease in host immunity, decreased DNA repair ability, or defects in tumor suppressor genes with advancing age [4, 16]. Other explanations might be attributable to the cohort in this study, which was composed of patients with pure myxoid liposarcomas restricted to the extremities and trunk wall. Age may emerge as a major prognostic factor analyzed in this homogeneous cohort of low-grade myxoid liposarcoma.

Previous studies established postoperative nomograms for soft tissue sarcoma or liposarcoma to predict patient prognosis [5, 15]. Although they are important for selecting patients for careful observation, aggressive adjuvant therapy, and stratifying patients for clinical trials, specific consideration will be necessary for more limited groups of patients. Among patients with pure myxoid liposarcoma arising in the extremity or trunk wall, presentation with older age should require special consideration. Patients should be followed routinely for lung metastasis, and paid attention to abnormal findings and symptoms on routine examination, which suggest unusual sites of metastasis.

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