Prognostic factors for the recurrence of myxoid liposarcoma: 20 cases with up to 8 years follow-up

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**Abstract**

*Introduction:* Myxoid liposarcomas (MLS) are the second most common type of liposarcoma. Although some MRI findings are distinctive characteristics of MLS, the diagnosis can be tricky in tumors with a large portion of round cells (RC). Known predictors of an unfavorable outcome include age, tumor size, high RC content and positive resection margins. The goal of this retrospective study was to define prognostic factors for recurrence, with special emphasis on the percentage of RCs and medical care provided in a non-specialized center.

*Patients and methods:* Twenty patients (11 women, 9 men) with a mean age of 44.3 years (18–73) were reviewed after a mean of 55.9 months. Six of these patients had been operated at a non-specialized center. The diagnostic MRI was read by a specialized radiologist and the resection procedures performed by two specialized surgeons. Tumors were labeled as either “pure myxoid liposarcoma” or “myxoid/round-cell liposarcoma”. The local recurrence-free survival rate and mortality rate were calculated. Results: Fifteen patients had undergone an MRI during the initial assessment. The typical MRI findings of MLS were present in four of them. The MRI suggested a non-specific lesion in the other 11 patients. After correlation with pathology findings, these tumors contained more than 5% round cells. The fourteen patients treated at our facility had undergone a biopsy, while none of the ones treated outside did. Five patients had R0 resection margins and 15 had R1 margins. Prognostic factors for recurrence consisted of age, tumor size > 10 cm, R1 resection margins, FNCLCC grade 2 + R1 margins, medical care at a non-specialized center, and > 5% round cells. There were eight local recurrences and three metastases (15%). Two patients died (90% overall survival rate).

*Discussion:* The risk of local recurrence was 3.86 times greater in this study when the tumor contained more than 5% RCs, which is consistent with published data. The MLS diagnosis was made only four times based on the initial MRI because misleading nature of high RC tumors. R1 resection margins are a risk factor for local recurrence. However, cases with R1 margins have a recurrence rate that is similar to R0 cases when the surgery is performed at a specialized cancer center. Treatment of MLS in a non-specialized center is a key negative prognostic factor. The reported rate of metastasis varies. Atypical extrapulmonary localizations are common, and often multifocal, MRI has been shown to be superior at detecting secondary lesions and some have suggested that a full-body MRI should be performed.

*Conclusion:* Prognostic factors for the recurrence of myxoid liposarcomas have been identified. MRI analysis is not definitive and must be supplemented by a biopsy.

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1. Introduction

Liposarcomas are soft-tissue tumors in a broader class of mesenchymal tissue neoplasms, which have an adipocyte-derived cell population. These tumors make up 17–25% of all sarcomas, which have an incidence of 30 cases per million [1,2].

The World Health Organization classification includes five sub-types, including myxoid liposarcomas (MLS) and round-cell liposarcomas (RCLS) [3] (Fig. 1). MLS is the second most common type of liposarcoma. The disease spectrum is consistent with that of other tumor types, ranging from well-differentiated pure liposarcoma to dedifferentiated liposarcoma with high round-cell content [4]. Well-known negative prognostic factor are patient age...
(> 45 years), tumor size (> 10 cm), sub-aponeuritic location, high histological grade, large percentage of round cells and positive resection margins [5–7].

Magnetic resonance imaging (MRI) is essential for the diagnosis of liposarcoma [4,8–10]. Although there are disease-specific MRI criteria, the diagnosis can be tricky in tumors containing a large number of round cells [4,10]. Treatment of these lesions requires a multidisciplinary team in a specialized cancer center [11–13]. MLS have the ability to metastasize to other soft tissues, including serous ones, which can make patient monitoring more challenging [5,14,15].

The goal of the current study was to define prognostic factors for local recurrence and metastasis, with special emphasis on the percentage of round cells and treatment at a non-specialized center.

2. Patients and methods

A series of 20 patients who were treated surgically for MLS between January 2004 and February 2012 were reviewed retrospectively. Patients were included if they had been referred within our hospital network for consultation and treatment of MLS. Patients who were diagnosed and underwent tumor resection at our facility were included, as well as those who underwent an unplanned tumor resection at another facility.

All patients were treated and monitored. Patients who experienced a recurrence during the follow-up period were compared to those who did not. The initial MRI analysis was performed by a single specialized radiologist. All of the surgical procedures were performed by two surgeons who were specialized in the care of adult sarcomas.

The definitive diagnosis was made by a pathologist who specializes in sarcomas. The liposarcomas were labeled as either “pure myxoid liposarcoma (MLS)” or “myxoid/round-cell liposarcoma (MRCLS)”. Histological grading was performed based on the FNCLCC system (French Federation of Comprehensive Cancer Centers). The quality of the surgical resection was defined according to the “R” classification of the Union for International Cancer Control. The need for additional treatment was determined in multidisciplinary meetings: radiation therapy for R1 tumors or FNCLCC grade 2 or 3 tumors; chemotherapy for metastatic lesions.

The data were analyzed statistically using the Xlstat® software (Addinsoft SARL, Paris, France). The local recurrence-free survival time was defined as the period between the initial diagnosis and the date of the last visit. The mortality rate was calculated. Differences between the “local recurrence” and “recurrence–free” groups were analyzed with a Chi² test for the qualitative variables and Student’s t-test for quantitative variables. A multivariate analysis was carried using a Cox proportional hazards model. Statistical tests where the P-value was below 0.05 were considered as being statistically significant. Survival rates were analyzed using Kaplan-Meier curves to determine the risk of local recurrence, metastasis and death.

3. Results

The series consists of 20 patients (11 women, 9 men) who were operated for curative purposes between January 2004 and February 2012 (Table 1). The average age was 44.3 years (range 18 to 73). The average follow-up was 55.9 months. The tumor was located in the lower limb in all patients: popliteal fossa in five patients (25%), anterior aspect of thigh and sartorius muscle in four patients (20%), adductor fossa in seven patients (35%) and gluteal area in two patients (10%). The tumor was located in the anterior compartment of the tibia in one patient and was located in the infrapatellar fat pad in one other patient.

Fifteen patients had undergone an MRI during the initial assessment. The disease-specific MRI finding of a homogeneous mass with combined T1 hypersignal and T2 hypointense and intralesional adipose tissue was present in four patients, all of whom had pure myxoid liposarcomas. In the other patients, the MRI report listed the presence of a non-specific heterogeneous mass with malignant appearance. After correlation with pathology results, these tumors contained more than 5% round cells. The five patients who

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Summary of study results.</th>
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<tbody>
<tr>
<td>Variable</td>
<td>Value</td>
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<tr>
<td>Age</td>
<td>Average: 44.3</td>
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<td></td>
<td>Range: 18–73</td>
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<tr>
<td>Gender</td>
<td>Male: 9</td>
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<td></td>
<td>Female: 11</td>
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<tr>
<td>Presentation</td>
<td>Primary: 14</td>
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<tr>
<td></td>
<td>Post-resection R2: 4</td>
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<tr>
<td></td>
<td>Post-recurrence: 2</td>
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<tr>
<td>Tumor size</td>
<td>Average: 11.675</td>
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<tr>
<td></td>
<td>Range: 2–26</td>
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<td>Biopsy</td>
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<td>CT scan</td>
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<tr>
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<td>&gt; 25%: 1</td>
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<tr>
<td>Local recurrence</td>
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<tr>
<td>Metastasis</td>
<td>3</td>
</tr>
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<td>Death</td>
<td>2</td>
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</table>
had sought treatment at non-specialized centers did not initially undergo an MRI evaluation.

Fourteen patients underwent a biopsy at our facility (8 under CT control), while none of the ones treated outside had a biopsy. An analysis of the biopsied tissue led to the final diagnosis of MLS.

Surgical treatment was performed on 14 patients at our facility. The resection was recorded as marginal in 3 patients (21.4%), wide in 6 patients (42.8%) and radical in 5 patients (35.7%). The excision was labeled as “intraläsional” when the tumor was opened during the surgery, thereby contaminating the surgical site, which leads to a high local recurrence rate. The excision was labeled as “marginal” when the tumor was removed macroscopically without opening it but the dissection plane was located near the tumor’s pseudocapsule; this leads to a risk of microscopic amounts of residual tumor tissue, which is also a cause of recurrence. This type of excision is often performed when the presence of nerve and vascular elements prevents a more extensive excision from being performed. The excision was labeled as “wide” when the entire tumor was removed with its pseudocapsule and a sleeve of healthy tissue around it from the same compartment. This however does not prevent the possibility of “skip” metastasis in cases of highly malignant tumors. The excision was labeled as “radical” or compartmental when the entire compartment containing the tumor and its pseudocapsule were removed, including fascia, muscle insertions and septa. The risk of recurrence is very low (<2%) in such cases [16].

The tumor resection surgery had been performed at a non-specialized center in the six other patients. Four were referred to us for consultation after a type R2 resection and two after local recurrence.

The pathology evaluation identified tumors that were 2 to 26 cm in size. Nine were pure myxoid liposarcomas and 11 were classified as myxoid/round-cell liposarcomas, 6 of which had >5% round cells. There were 11 grade 1 tumors and 9 grade 2 tumors (FNCLCC scale). The resection margins were graded as R0 in 5 cases and R1 in 15 cases, 10 of which were from “planned” surgical procedures. The diagnosis was confirmed by the detection of t(12;16) chromosome translocation, specifically TLS-CHOP fusion [5]. Adjuvant radiation therapy was carried out in the 15 patients with R1 resection margins or grade 2 tumors. The lesions were subfascial in all of these cases; a small tumor size did not exclude the patient from adjuvant radiation therapy. Adjuvant chemotherapy was prescribed in the three patients with metastasis.

There were eight cases of local recurrence. Negative prognostic factors consisted of higher age (mean of 52.25 in those with recurrence), tumor size (>10 cm) in combination with age, R1 resection margins, FNCLCC grade 2 tumor with R1 margins, treatment carried out in non-specialized center and >5% round-cell content. Only the latter component was a statistically significant predictor of recurrence (P = 0.047).

Three patients had a metastasis; all had tumors with a large portion of round cells. Secondary lesions were found in extrapulmonary locations such as bone, muscle and the retroperitoneal space. The estimated metastasis risk was 15%. Two of these patients died. The survival rate for the patient cohort was 90% with a maximum follow-up of 8 years.

4. Discussion

This was a retrospective study of a rare disease with short inclusion and follow-up periods; all of these factors combine to reduce the statistical power of this study. There are only seven published studies on myxoid/round-cell liposarcoma [5,6,17–21]. The small number of patients also limits the interpretation of any statistical tests for prognostic factors.

The percentage of round cells was the strongest prognostic factor, as it negatively impacted local recurrence, metastasis and survival. Grading of the round-cell content of tumors is based on three levels and a 5% threshold. The lowest grade corresponds to pure MLS; intermediate-grade tumors contain 0 to 5% RCs and the highest-grade tumors contain more than 5% RCs. In this study, 11 of the 20 patients (55%) had RCs in their tumor; 6 of them had more than 5%. Among these 6 patients, 5 had a local recurrence. This resulted in an 83% rate of recurrence for tumors with >5% RCs and 21.5% rate for tumors with ≤5% RCs.

In this study, the risk of local recurrence was 3.86 times greater if the tumor contained more than 5% RCs; this is consistent with the 3.4 fold increase in risk found in a recent study [17]. There is also evidence that the “low-grade” nature of pure myxoid liposarcomas results in a 77% recurrence-free survival rate at 10 years [22].

Imaging findings are not definitive; many pitfalls have been described [4,8–10]. Disease-specific MRI findings only occur with pure myxoid liposarcoma or tumors with a low percentage of RCs (Fig. 2). Tumors with a high percentage of RCs have an atypical appearance (Fig. 3). In the current study, the MLS diagnosis was strongly suggestive in only 4 of 20 patients based on the initial MRI.

R1 resection margins are an important risk factor for local recurrence [5,6,17–21,23]. However, a local recurrence rate similar to R0
surgery can be obtained when the excision procedure is planned by a specialized surgeon who has decided before the surgery to accept narrow margins in high-risk areas or areas in close proximity to vascular, nerve or bone structures [12,23–25]. The local recurrence rate was 23% in the current study when the surgery was planned accordingly, which is comparable to published rates [5,6,17–21].

Treatment of MLS at a facility that is not specialized in cancer care is an important risk factor for local recurrence. Engström et al. [12] found a 47% recurrence rate for tumors operated in this setting. Chandrasekhar et al. [11] found a 59% rate of residual tumors out of 363 cases. In the current study, six patients were initially treated in a non-specialized center. Four of them had a recurrence; four had an “intralesional” excision; only one had a preoperative MRI; none of the patients had a preoperative biopsy; two experienced a metastasis and one died. The French National Cancer Institute (INCa) has set up an accredited network of facilities in 2010 that includes three specialized centers and 25 expert centers throughout France. Patients with a suspected sarcoma must be referred to one of these centers so they can benefit from care given by a specialized team.

The published rate of MLS metastasis ranges from 14 to 32% [5,6,17–21]. Atypical extrapolumal localizations are common, and often multifocal [5,14–16,21,26]. MRI has been shown to be superior at detecting secondary lesions [27,28]. It has also been suggested that patients undergo a whole-body MRI [29]. This examination was shown to be feasible in a small series of patients and has good sensitivity and specificity. Nevertheless, it cannot be performed in all patients and should be limited to those who have the highest risk of an unfavorable outcome based on the prognostic factors.

MLS are atypical when it comes to adjunct treatments. They are more sensitive to radiation therapy [30–32] and chemotherapy [33,34] than other soft-tissue sarcomas. Trabectedin is a promising therapeutic candidate [35]. The relatively high recurrence rate when compared to other centers (28% vs. 10%) highlights the benefit of treatment in a specialized center and also points to a benefit of neoadjuvant radiation therapy [18,19,36]. This could be particularly relevant for large tumors with a high risk of recurrence, as it may be possible to reduce the tumor’s volume before it is surgically resected. Radiation therapy was used as an adjuvant in certain patients in the current study. The studies reporting a better survival rate were performed on patients who received neoadjuvant chemotherapy [6,17]. Nevertheless, the treatment protocols are not well defined and have not been standardized.

5. Conclusion

The goal of this study was to define prognostic factors for myxoid liposarcomas. The risk factors for local recurrence found in this study were consistent with the ones outlined in previously published studies: patient above 45 years of age, tumor size greater than 10 cm, positive resection margins with or without FNCLCC grade 2, more than 5% round-cell content and treatment carried out at a facility that is not specialized in sarcoma care.

Non-planned surgery was a predictor of unfavorable outcomes. Based on these findings, sarcoma patients should only be treated in specialized centers, especially since MRI and biopsy examinations can be tricky and misleading. Sarcoma patients who are referred after being treated in non-specialized centers have a greater risk of local recurrence.

MLS are atypical tumors that are very sensitive to radiation therapy and chemotherapy, and have an unusual ability to metastasize in locations other than the lungs. The threshold between intermediate-grade and high-grade corresponds to a 5% round-cell content. High-grade tumors (> 5% round cells) have a higher risk of metastasis. The potential benefit of neoadjuvant radiation therapy and adjuvant chemotherapy must be evaluated in these patients. This subset of patients is also a candidate group for research into new treatments.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

References


