Genetic Profiling Identifies Two Classes of Soft-Tissue Leiomyosarcomas with Distinct Clinical Characteristics


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Conflicts of interest:
None
TRANSLATIONAL RELEVANCE

Leiomyosarcomas (LMS) represent one of the most frequent sarcoma subtypes and can occur in the soft tissue compartment or visceral sites. This study focused on soft-tissue LMS in order to identify their prognostic factors and their molecular characteristics. Our results showed that soft tissue LMS were a heterogeneous group of tumors with at least two categories retroperitoneal and peripheral LMS having peculiar clinical and molecular features.
Abstract

Purpose: Data regarding the prognostic factors of soft-tissue leiomyosarcomas (LMS) and their correlation with molecular profile are limited.

Study design: From 1990 to 2010, 586 adult patients with a primary soft-tissue LMS were included in the French Sarcoma Group (GSF) database after surgery of the primary tumor. Multivariate analyses were carried out by Cox's regression model in a backward stepwise procedure. Genetic profiling was performed for 73 cases.

Results: Median age was 59 years (range 21-98). The median follow-up of patients alive was 46 months. The 5-year metastasis-free survival (MFS) rate was 51% (95% location, and grade > 1 were independent adverse prognostic factors for MFS. The 5-year overall survival rate was 63% (95% CI 59–67). On multivariate analysis, age ≥ 60 years old, tumor size > 5 cm, deep location, and grade > 1 were independent adverse prognostic factors for OS. Molecular profiling identified specific clusters with activation of different biological pathways: retroperitoneal LMS are characterized by overexpression of genes involved in muscle differentiation and non-retroperitoneal LMS characterized by overexpression of genes mainly involved in extracellular matrix, wounding and adhesion pathways. The CINSARC signature but not CGH profiling was predictive of outcome.

Conclusion: Soft-tissue LMS represent a heterogeneous group of tumors with at least two categories retroperitoneal and extremities LMS having specific clinical outcome and molecular features. Future clinical trials should consider this heterogeneity for a better stratification of patients.

Key words: leiomyosarcoma, soft-tissue, prognosis, treatment, array-CGH, expression profiling

Running title: Prognosis and Molecular Profiling of Leiomyosarcomas
INTRODUCTION

Leiomyosarcoma (LMSs) are an uncommon group of malignant tumors composed of cells showing distinct smooth muscle differentiation (1). These tumors occur mainly in adults in any location of the body (soft-tissue or viscera). Soft-tissue LMS represent 10-15% of all soft-tissue sarcomas. The most frequent locations are the limbs followed by the retroperitoneum. Data related to the clinical outcome of soft-tissue LMSs are mainly limited to small, single institution, non-exhaustive or out of date series (2-7). Moreover, only few data regarding the molecular characteristics of LMS are available. Most of such studies analyzed a small number of cases and/or mixed visceral and soft-tissue and primary and metastatic specimens (8-18). The main objective of our study was to investigate the clinical outcome, the prognostic factors of soft-tissue LMS and the correlation between molecular profiles and clinical characteristics.

MATERIAL AND METHODS

Patients

From 1990 to 2010, 586 adult patients (≥18 years old) with a non-metastatic soft tissue LMS underwent surgery of the primary tumor and were included in the French Sarcoma Group (GSF) database. All the cases were reviewed by the members of the pathological sub-committee of the GSF. The histological diagnosis was established according to the World Health Organization Classification of Tumors (1). The histological grade was determined after central review as previously described according to the Fédération Nationale des Centres de Lutte Contre le Cancer (FNCLCC) grading system (19-20).

Selection of cases for genetic profiling
Genetic profiling included array comparative genomic hybridization and gene expression array. The selection of cases was based on the following inclusion criteria: availability of frozen tumor material from the primary tumor; absence of chemotherapy or radiotherapy given before tumor sampling; patient consent. Seventy-three cases followed these criteria. Their characteristics (supplementary table 1) were similar to that of the entire cohort except for the proportion of small tumors (< 5 cm) which was significantly lower in the molecular cohort (9.5% vs 36%, p=0.03) as the result of the obvious lower probability to collect frozen material from small samples.

**Array comparative genomic hybridization**

Genomic DNA was isolated using a standard phenol-chloroform extraction protocol. Array-based comparative genomic hybridization (array-CGH) experiments were done with a DNA microarray developed in our laboratory. Three thousand eight hundred seventy-four BAC/PAC DNAs (BACPAC Resources Center, Children’s Hospital, Oakland Research Institute) were spotted in triplicate on UltraGAPS slides (Corning). These clones cover the whole genome with a resolution of 1 Mb. The probes were prepared and hybridized as previously described (21). The data were analyzed with software developed at Institut Curie (CAPweb, http://bioinfo-out.curie.fr/CAPweb/). Cyanine-5/cyanine-3 ratios >2 were considered as amplifications, and ratios >1.2 and <0.8 were considered as gains and losses, respectively. Analysis of array-CGH (computation of genomic alterations) was provided by the VAMP interface (http://bioinfo.curie.fr/vamp) (22).

**Gene expression profile**
Total RNAs were extracted from frozen tumor samples with TRIzol reagent (Life Technologies, Inc.) and purified using the RNeasy® Min Elute™ Cleanup Kit (Qiagen) according to the manufacturer’s procedures. We checked RNA quality on an Agilent 2100 bioanalyzer (Agilent® Technologies). Samples were then analyzed on Human Genome U133 Plus 2.0 array (Affymetrix®), according to the manufacturer’s procedures (GEO access number: GSE21050). We simultaneously normalized all microarray data using the GCRMA algorithm (23). T-tests were performed using Genespring (Agilent Technologies) and $P$-values were adjusted using the Benjamini-Hochberg procedure. The $P$-value and fold change cut-off for gene selection were 0.001 and 3, respectively. Gene ontology (GO) analysis was performed to establish statistical enrichment in GO terms using Genespring (Agilent Technologies).

**Statistical analysis**

The statistical analysis of baseline demographics and clinical outcome are based on all data available up to the cut-off date of 31 July 2011. Descriptive statistics were used to show the distribution of variables in the population. Overall survival (OS) was defined as the interval between histological diagnosis and the time of death or last follow-up. Metastasis-free survival (MFS) was defined as the interval between histological diagnosis and the time of distant recurrence or the last follow-up. Patients who did not develop metastasis (for MFS) or remained alive (for OS) at final follow-up were censored at that time. Follow-up times were described as median by use of the inverse Kaplan Meier estimator (24). Survival rates were estimated with the use of the Kaplan–Meier method and compared using the log-rank test. Multivariate analyses were carried out by Cox’s regression model in a backward stepwise
procedure. Univariate and multivariate analyses included the following variables: age, sex, anatomic site, tumor size, tumor location (superficial or deep), FNCLCC grade. Variables associated with survival with a \( P \) value <0.05 in the univariate analysis were included in the multivariate regression. Analyses were carried out using SAS 19.0 statistical software. All statistical tests were two sided, and \( P < 0.05 \) indicated statistical significance.

**RESULTS**

**Patients**

The patients’ characteristics are described in Table 1. Median age was 59 years (range 21-98). The majority of patients had a LMS of the extremities (62.5%), larger than 5 cm (59%) and deeply located (79%). Twelve per cent of patients had grade 1 disease, 36% had grade 2 and 47% had grade 3. Grading was missing in 5% of cases. Three hundred and seven patients (52%) received adjuvant radiotherapy. One hundred and nine patients (18%) received adjuvant chemotherapy. In all the cases, doxorubicin was delivered either alone or in combination with other drugs (dacarbazine with or without cyclophosphamide and vincristine: CYVADIC protocol, or ifosfamide with or without dacarbazine and mesna: AI or MAID: protocols). The factors significantly associated with a higher likelihood to receive adjuvant chemotherapy were: age < 60 years (25.5% versus 11.5%, \( p < 0.0001 \)), deep location of the tumor (21% versus 9.5%, \( p=0.005 \)), and grade 3 disease (30% versus 10.5% for grade 2 versus 1.5% for grade 1, \( p < 0.0001 \)).

**Prognostic Factors**

*Metastasis-free survival*
The median follow-up of patients alive was 46 months. At the time of analysis, 246 patients (42%) had metastatic recurrence. The median MFS was 82 months (95% CI 46-118) (Supplementary Figure 1). The 1-year, 5-year and 10-year MFS rates were 83% (95% CI 80-86), 51% (95% CI 47- 55) and 45% (95% CI 41-49), respectively (Supplementary Figure 1). On multivariate analysis (supplementary table 2 and table 2), retroperitoneal location, tumor size > 5 cm, deep location, and grade > 1 were independent adverse prognostic factors for MFS. The most significant adverse prognostic factor for MFS was grade 3 (Hazard ratio: 3.5, 95% CI 1.7-7.4, p=0.001) (Supplementary Figure 2).

Overall survival

At the time of analysis, 209 patients (35%) had died and 377 (65%) were still alive. One hundred sixty four deaths (78%) were the result of sarcoma (including 2 deaths related to the treatment) and 45 (22%) the result of other causes. The median OS was 116 months [95% CI 92–140]. The 1-year, 5-year and 10-year OS rates were 95% (95% CI 93–97), 63% (95% CI 59–67) and 49% (95% CI 45–53), respectively (Supplementary Figure 1). On multivariate analysis (supplementary table 2 and table 2), age ≥ 60 years old, tumor size > 5 cm, deep location, and grade > 1 were independent adverse prognostic factors for OS. As for MFS, the most significant adverse prognostic factor for OS was grade 3 (Hazard ratio: 6.2, 95% CI 1.9-19.8, p=0.001) (Supplementary Figure 3).

Genomic profiling

Genomic profiling was performed on 73 LMS and except for 5 cases which presented a flat profile, we observed for 68 LMS a characteristic complex profile with the most frequent alterations being losses of chromosomes 10q, 13q, 16q and 17p, and gains of 17p (Figure 1). According to both the number and the type of alterations,
we identified two types of recurrent profiles (Figure 1). A first group of 29 tumors (43 %) had few alterations (less than 30) mainly involving the full chromosome arm or entire chromosomal gain or loss. We called this group the “arm” profile group. A second group of 39 tumors (57%) was characterized by a high level of chromosomal complexity with more than 30 alterations. We called this group the “rearranged” profile. We identified a significant correlation between the genomic profile and the tumor location since 69 % of tumors of the “arm” profile group were retroperitoneal whereas 76% of the tumors of the “rearranged” profile group were located in the extremities (p=0.02). However, on univariate analysis, the genomic profile (“arm” versus “rearranged”) was not predictive of metastasis-free survival (p=0.18; data not shown).

Expression profiling

Gene-expression profiles of the 73 LMS were re-examined to test the hypothesis that gene expression in the tumor is associated to genome profile, tumor location or metastatic outcome. We thus performed three t-tests to compare the expression profiles of tumors classified according to 1) genomic profile type (arm vs rearranged); 2) tumor location (retroperitoneal vs extremities); and 3) metastatic outcome (metastasis vs non-metastasis). We identified 445 genes that were up-regulated (Fold change [FC] >3; p>0.001) in the “arm” profile group in comparison with the “rearranged” profile and 423 genes that were up-regulated (FC>3; p>0.001) in LMS located in the internal trunk in comparison with LMS located in the extremities. As expected, most of the differentially expressed genes are common to both comparisons (Fig 2a) and the pathways overrepresented were extremely similar in both groups and were mainly involved in muscle differentiation (Supplementary table 3). We also found that the MYOCD gene (17p12 chromosomal region) was the
most over-expressed in LMS of the internal trunk as compared to LMS of the extremities (absolute FC = 100.2). Since MYOCD was previously reported as amplified in a subset of LMS, we have assessed the genomic status of this gene in our series. We found a high level amplification and a gain of the MYOCD gene in 7 and 17 cases respectively. Amplification of the MYOCD gene was significantly associated with high expression (p<0.0001). Moreover, we identified 248 and 156 genes that were up-regulated in the “rearranged” profile group in comparison with the “arm” profile group and in LMS of the extremities in comparison with retroperitoneal LMS. The majority of these genes were common to both comparisons (Fig 2b) and encoded proteins involved mainly in extracellular matrix, wounding and adhesion pathways (Supplementary table 4). At the contrary, no common gene or pathway were observed between “Retroperitoneal” and “Rearranged” LMS on one hand and between “Extremities” and “Arm” LMS on the other hand (data not shown).

Regarding metastasis outcome, few genes were significantly differentially expressed between LMS with or without metastasis (18 up regulated and 9 down regulated in metastatic cases, FC > 2; p < 0.05). Of note, up regulated genes are involved in muscle differentiation and down regulated ones in lipids metabolism (Supplementary table 5). This signature failed to predict significantly metastatic outcome (data not shown), we thus tested a previously published signature, i.e. CINSARC, and survival analysis (Figure 3) revealed that the CINSARC classification split the tumors into two groups with very different metastasis-free survival (MFS, P = 5.8 x 10-5).

DISCUSSION

We report here the first large series investigating the prognostic factors and the molecular profile of soft-tissue LMS.
The 5-year OS (63%) rate was similar to that reported by Svarvar et al. in a series of 206 patients with localized LMS (7). Of note, in this series, the 5-year MFS was higher than in our study (74% versus 51%). This result is probably explained by the exclusion of retroperitoneal LMS in the study of Svarvar et al, LMS in this location being characterized by an higher risk of metastatic relapse as we have shown here. Although the majority or metastatic recurrence (64%) occurred within 2 years after the initial diagnosis, a significant proportion of patients experienced late treatment failure up to 11 years after initial diagnosis. This underscores the need for a prolonged follow-up of patients with primary resected LMS. Interestingly, patients with metastatic recurrence occurring >2 years after the initial diagnosis had a significantly better outcome than patients who relapsed earlier. We and others have previously reported such a correlation between a longer time to recurrence and a better postrecurrence survival in soft-tissue and bone sarcomas (25-27). Nevertheless, this finding should be interpreted with caution. Indeed, the design of our study did not allow us to analyse the impact on postrecurrence survival of several key variables such as the type of management of metastatic recurrence and particularly the role of resection of metastases or the role of an additional lines of palliative chemotherapy in patients already treated with chemotherapy in the adjuvant setting.

The large cohort included in our study as well as the mature follow-up allowed us to identify robust prognostic factors for patients with localized LMS. In our series, grade 3, retroperitoneal tumor site, deep location, and tumor size > 5 cm were independent predictors of poor MFS. These findings were consistent with the data from smaller series which have already shown a significant correlation of grade, tumor depth and tumor size with the risk of metastatic relapse (3, 5-7). Previous series focusing on retroperitoneal sarcomas have already shown the higher
metastatic risk of LMS in comparison to other retroperitoneal histological subtypes including liposarcomas (28-29). Our study demonstrates that retroperitoneal LMS represent among soft-tissue LMS a specific clinical and molecular entity. Indeed, in comparison with LMS of the extremities, retroperitoneal LMS are characterized by a higher risk of metastatic relapse and a distinct genomic and expression profile. Most of the genes overexpressed in retroperitoneal LMS encodes proteins involved in muscle differentiation. Non-retroperitoneal LMS are on the contrary characterized by overexpression of genes encoding proteins mainly involved in extracellular matrix, wounding and adhesion pathways. The capacity of molecular profiling to identify LMS clusters was previously suggested by a study from Beck et al. analyzing a limited series of cases and showing that LMS include distinct molecular subtypes including one characterized by an overexpression of muscle associated genes (18). However, in the study of Beck et al., 26 out of the 52 samples were not primary but metastatic samples with potential changes in gene expression patterns in comparison to the primary tumor and only six retroperitoneal cases were included, precluding any possible correlation with clinical characteristics or outcome. Interestingly, a recent study has shown that retroperitoneal LMS carry a frequent amplification of the MYOCD gene which is also the most differentially expressed gene between LMS and retroperitoneal undifferentiated sarcomas (30). MYOCD is involved in smooth muscle differentiation but also in the regulation of cell migration (31-32). Its inactivation has been shown to reduce not only smooth muscle differentiation gene expression but also cell migration in LMS cell lines, suggesting a potential role in metastatic progression.

In this regard, we have observed that muscle differentiation pathways are over-represented in metastatic cases versus nonmetastatic cases, reflecting the high
metastatic potential of retroperitoneal LMS which are often well differentiated. However, the simple comparison of expression profiling of LMS patients with and without metastases did not allow us to identify a specific prognostic molecular signature for LMS. We recently published a 67 gene expression prognostic signature related to genome complexity (CINSARC for Complexity INdex in SARComas) which predict outcome in sarcomas with complex genomics such as LMS (33). As expected, this signature was able to predict outcome in the present series of soft-tissue LMS. Further investigations are needed to investigate how this molecular signature can help to identify patients who are more likely to benefit of adjuvant treatments such as chemotherapy in order to prevent metastatic relapse.

Clinicians involved in the management of soft-tissue sarcomas are well aware of the high heterogeneity of this group of rare malignancies including more than 50 histological subtypes. By focusing our investigations on soft-tissue leiomyosarcomas, we were able to clarify the prognostic factors of LMS and to identify even more heterogeneity with at least two categories retroperitoneal and peripheral LMS having peculiar clinical and molecular features. The next step of our work will be to identify “druggable” specific molecular aberrations in these specific LMS categories.

REFERENCES


study of 48 patients, including cellular DNA content. Cancer 1992; 70: 114–119.


## Tables

### Table 1. Patients characteristics (N=586)

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Table 2. Significant Prognostic Factors for Metastasis-free Survival (MFS) and Overall survival (OS) (multivariate analysis)
FIGURE LEGENDS

Figure 1. Genomic profiles (comparative genomic hybridization) a) one case of LMS of extremity with a “rearranged profile” and b) one case of LMS of internal trunk with an “arm” profile.

Figure 2. Up-regulated genes in a) Internal trunk LMS and “Arm profile” LMS and b) Extremities LMS and “Rearranged profile” LMS.

Figure 3. Kaplan-Meier analysis of metastasis-free survival (MFS) of 73 LMS according to the CINSARC category (C1: patients with low expression of CINSARC genes; C2: patients with high expression of CINSARC genes).
Figure 1

A

B

Pam-geonomic representation

Pam-geonomic representation

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Figure 2

A

Entity List 1: Up-regulated in "Internal Trunk" LMS
423 entities

Entity List 2: Up-regulated in "Arms" LMS
445 entities

164
259
186

B

Entity List 1: Up-regulated in "Recurrent" LMS
246 entities

Entity List 2: Up-regulated in "Extremities" LMS
156 entities

163
85
71
Figure 3

**Kaplan-Meier curves for metastasis-free survival.**

- Hazard ratio: 7.862 (95% CI: 2.41 - 25.64)
- Log rank: 5.86; p = 0.05
- Meta C1 = 3 cases
- Meta C2 = 40 cases

**Legend:**
- C1: 17 cases
- C2: 56 cases

Years
Genetic Profiling Identifies Two Classes of Soft-Tissue Leiomyosarcomas with Distinct Clinical Characteristics

Antoine Italiano, Pauline Largarde, Celine Brulard, et al.

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