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Soft Tissue Sarcomas: Descriptive Study of 232 Cases Collected, over a Period of 10 Years, at the Hospital of Oncology, Department of the Hassan II Hospital FEZ

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Abstract

Soft-tissue sarcomas are uncommon tumors that have traditionally been managed by wide excisional surgery and radiotherapy; the use of chemotherapy has been reserved for advanced disease. Advances in multidisciplinary care have improved the evaluation and care of patients with this disease. Limb-conserving surgical paradigms, superior radiotherapy delivery, and novel adjuvant agents for specific tumors are now available. The objective of this study is to report the epidemiological, clinical, histological, therapeutic and evolutionary characteristics of soft tissue sarcomas at the oncology hospital: Chu Hassan II in FEZ, and to define the factors influencing patient survival. This is a retrospective study of 232 cases of soft tissue sarcoma, collected between January 2010 and June 2020. The eligibility criteria were an age greater than 16 years, and histological evidence of a soft tissue sarcoma excluding gastrointestinal stromal tumors (GIST). Items collected were: epidemiological, clinical, histological, radiological, and therapeutic. These are 232 cases, 120 Men and 112 Women, the mean age was 48.89 years (Extreme = 18 - 76 years). The tumor was localized to the extremities at (58.72%). The predominant histological type was Leiomyosarcoma in 61 cases (26.29%). The tumor stage was localized in (17.67%) of cases, locally advanced in 34.05% and metastatic in 44.08% of patients, all localized cases were treated surgically including (84%) conservative surgery and (16%) radical surgery. Radiation therapy was performed in 32.75% of patients. Chemotherapy was performed in 74.14% of patients. Age and tumor stage are prognostic factors influencing the survival of soft tissue sarcomas.

Keywords

Soft Tissue Sarcomas, STS, Chemotherapy, Leiomyosarcoma

1. Introduction

Soft tissue sarcomas (STS) are rare tumors that represent 1% of solid tumors in adults, including a wide variety of malignant tumors of mesenchymal origin, occurring at all ages and in multiple locations, their management charge requires a multidisciplinary approach from the initial diagnosis, preferably in reference centers [1].

The treatment of Localized STS is above all surgical, consisting of wide excision with a margin of 1 to 2 cm [1] [2]. Compliance with the surgical procedure with good clinical practice guidelines is a major and independent predictor of progression-free survival for patients with STS and overall survival (OS) for patients with liposarcomas [3].

The objective of this study is to report the epidemiological, clinical, histological, therapeutic and evolutionary characteristics of soft tissue sarcomas at the oncology department of CHU HASSAN II in Fez, and to define the factors influencing patient survival.

2. Methods

This is a retrospective study of 232 cases of soft tissue sarcoma, collected between January 2010 and June 2020, at the oncology hospital: Chu Hassan II in FEZ. The eligibility criteria were an age greater than 16 years, and histological evidence of a soft tissue sarcoma excluding gastrointestinal stromal tumors (GIST).

The elements collected were: age at the time of diagnosis, sex, tumor location and size, histological type and grade, tumor stage, conservative or radical surgical treatment of localized forms, adjuvant or palliative radiotherapy, and chemotherapy (neoadjuvant or palliative). Time to progression, and survival.

Univariate and then multivariate analyzes were carried out in search of factors influencing 2-year survival. Median recurrence-free survival and overall survival were calculated using the Kaplan Meier method. The log-Rank test was used for the comparison of the curves.

3. Results

These are 232 cases, of which 112 are women (48.71%) (**Figure 1**), the average age was 48.89 years (Extremes = 18 - 76 years), the average tumor size was 16.06 cm (extremes = 5 - 35 cm), the tumor was localized at the extremities in (58.72%) of the cases, at the level of the trunk in (20.18%) of the cases, (10.2%) at the gynecological level, (8.07%) of the cases at the Retroperitoneal level and (3.03%) at the head and neck level (**Figure 2**). The initial radiological workup included

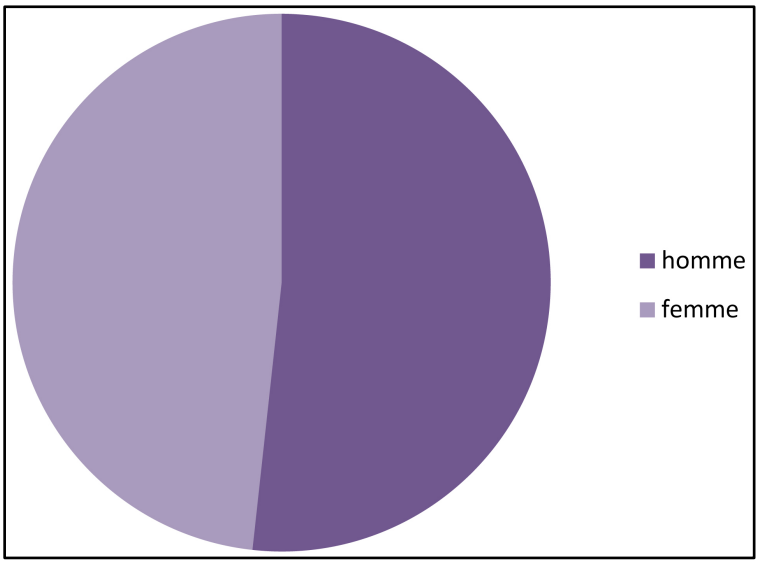

Figure 1. Gender breakdown.

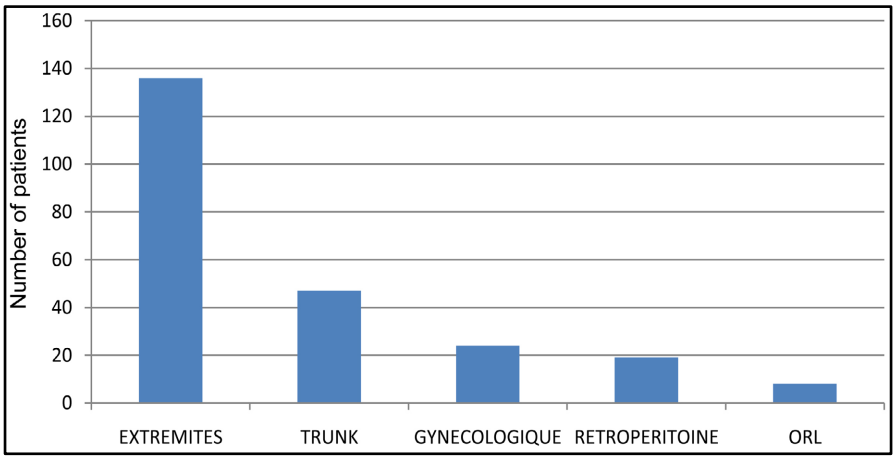

Figure 2. Breakdown by location.

computed tomography (CT) of the tumor site in 50% of cases, magnetic resonance imaging (MRI) in (47.4%) of cases, thoracic CT in 66.7%; an initial biopsy was done in (53.02%) of the patients, the others underwent an excisional biopsy.

The predominant histological types were leiomyosarcoma in 61 cases, liposarcoma in 51 cases, and synovial sarcoma also in 51 cases, the other histological types (29.74%) (Rhabdomyosarcoma 16 cases, 14 PNET (Peripheral neuroectodermal tumor), 12 Fibrosarcoma, 11 Dermatofibrosarcoma (DMFS), 9 pleomorphic sarcomas and 7 Undifferentiated sarcomas) (**Figure 3**).

The tumor was metastatic in (44.8%), locally advanced in (34.05%), and localized in 17.67% (**Figure 4**), all metastases were pulmonary, alone, or associated with another site (OS, folds, adrenals). All the localized cases had surgery on the primary tumor, including (84%) cases of conservative surgery and (16%) cases of radical surgery.

Radiotherapy was carried out in (32.75%) of the patients including 36.84% of

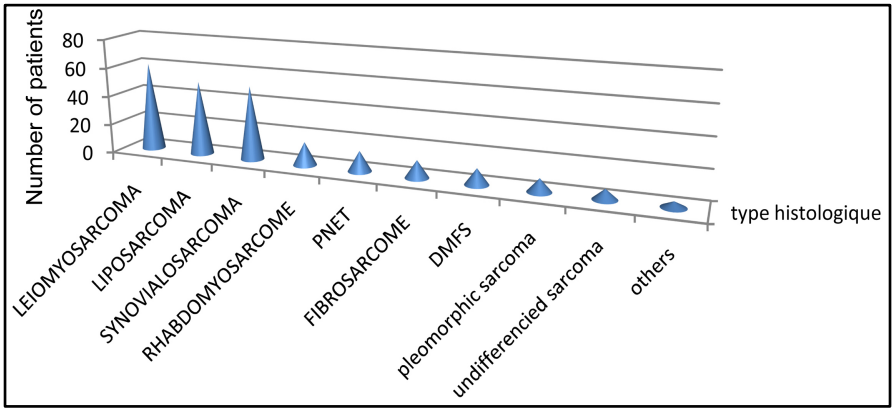

Figure 3. Histological type.

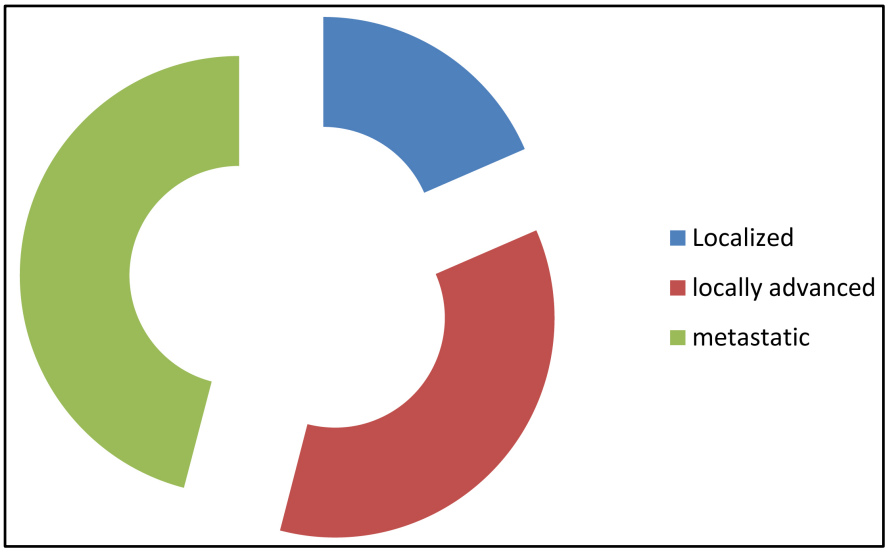

Figure 4. Tumor stage.

the cases in adjuvant and 63.16% of the cases in palliative. Chemotherapy was performed in (74.14%) patients, including 37.2% of cases in a neoadjuvant situation and 62.79% of cases in a palliative situation. Palliative chemotherapy was based on Anthracyclines in (85%) of the cases, including (47.05%) in monotherapy and (50.95%) in polychemotherapy; (35%) had an objective response to chemotherapy (12% partial responses, 23% Stability), (40%) progressed after chemotherapy, (20.26%) Relapsed after an average of 6 months (Extreme = 1 - 13 months) at local level in (20%) and remotely in (80%).

The site of metastases was the lung in 48% of cases, associated with bone in 32% of cases and the liver in 37% of other cases. Local relapses were treated by surgery with radiotherapy in 26 cases. Metastatic relapses were treated with chemotherapy.

The median follow-up was 19.5 months (Extremes = 2 - 76 months). Median progression-free survival and overall survival were 12 and 19 months respectively.

We used a simple logistic regression to search for factors influencing 2-year survival: factors with a p-value < 0.30 in univariate analysis were introduced in

the multivariate analysis. The factors influencing 2-year survival were those with a p-value < 0.05 in multivariate analysis. In univariate analysis, the factors that seem to influence 2-year survival are age (OR = 0.19 95%CI: 0.04 - 0.85; p = 0.03), stage of the disease (OR = 0.14 95%CI: 0.01 - 1.36; p = 0.09) and tumor size (OR = 0.40 95%CI: 0.08 - 2.06; p = 0.27). Multivariate analysis showed that only age is a poor prognostic factor (OR = 0.15 95%CI: 0.03 - 0.82; p = 0.28).

Median recurrence-free survival and overall survival were calculated using the Kaplan Meier method. After a mean follow-up of 19.5 months, the median progression-free survival was 12 months and the median overall survival was 19 months.

4. Discussion

STS are rare tumors, they represent 1% of adult cancers. The worldwide incidence varies between 3 - 5/100,000 H per year. These tumors can occur at any age, but most often after 40 years, the average age in our study was 48.89 years. There is a slight male predominance in our study (sex ratio 1.07 Male to 1 Female). The causative factor of STS remains unknown, however, certain genetic diseases and environmental factors are recognized as predisposing factors. Radiotherapy, especially at high doses, is a well-known factor in the development of soft tissue sarcoma.

In our study, there was no notion of a personal or family history of genetic disease. None of our patients had a history of radiotherapy. The most frequent locations are the limbs, trunk, retroperitoneum, then head and neck [1] [4]. In our study, the extremities represented more than half (58.72%), the trunk (20.18%), gynecological 10.2%, the retroperitoneum (8.07%), and the head and neck (3.03%), which is described in the literature. The revealing clinical manifestations of sarcomas are pain and swelling, in our study the tumor size varied between 5 and 35 cm (mean = 16.06 cm). The heterogeneity of soft tissue sarcomas explains the complexity of the histological study which must be carried out by a pathologist specializing in this field, if not a second opinion must be systematically requested to ensure the diagnosis [2]. In our study the most frequent histologic types were leiomyosarcoma, liposarcoma and synovial sarcoma. The histological diagnosis of the majority of our patients was made in our training, and in 12 cases a re-reading was made objecting to a partial discrepancy.

The management of STS must be multidisciplinary from the initial stage of diagnosis with the realization of a radiological assessment before the biopsy. MRI is the reference examination because it allows the study of the anatomical relationships with the adjacent structures, and the locoregional extension, to guide the biopsy and to assess the resectability of the tumor. In our study this examination was carried out at (47.4%), this can be explained by the problem of availability and the cost of this examination. Following the radiological assessment, a biopsy is necessary for carrying out the histological study, however, small superficial lesions may benefit from a biopsy excision from the outset

while avoiding tumor invasion [4]. Only (53.02%) of our patients underwent an initial biopsy, an immediate resection was performed in the other cases (46.98%).

The standard treatment for resectable localized soft tissue sarcomas is surgery, which consists of a large, single-block resection removing the biopsy scar and tumor with a 2 cm circumferential margin of non-tumor tissue or an anatomical barrier (R0 resection). The quality of the surgery is determined by histological examination of the margins of the surgical specimen, if the margins are invaded, a surgical revision must be done [1] [2] [4]. Insufficient surgical margins are the factors of local recurrence [1] [4]; A randomized study demonstrated the equivalence in terms of recurrence-free survival and overall survival of non-radical resection associated with radiotherapy and amputation in localized limb sarcomas [1].

Two randomized studies have demonstrated the benefit of adjuvant radiotherapy in terms of survival without recurrence but not in terms of overall survival [1]. This adjuvant radiotherapy should be reserved for STMs greater than 5 cm, deep or high grade (G2, 3). Superficial, low-grade lesions 5 cm or less will not require radiotherapy after surgical excision in healthy margins [2] [4].

A meta-analysis of data from 1568 patients in 14 trials and one Italian trial demonstrated a benefit from adjuvant chemotherapy [5], however two randomized phase 3 trials from the EORTC (European Organization for Research and Treatment of Cancer) assessing adjuvant chemotherapy did not demonstrate a benefit in terms of overall survival, but subgroup analysis demonstrated that Male patient, as well as patients >40 years of age, have a benefit in terms of survival progression-free, while female sex and age <40 years are associated with poor overall survival; patients with R1 resection have better progression-free survival and overall survival after adjuvant chemotherapy [6].

In locally advanced STS, the goal of neoadjuvant chemotherapy is to decrease tumor size to allow conservative treatment and to test tumor sensitivity to this chemotherapy.

Anthracycline-based chemotherapy with a dense dose regimen gives an objective response of 94% with an R0 resection rate of 82% and a rate of progression-free survival and 5-year overall survival of 48% and 64% respectively [7]. The benefit of neoadjuvant chemotherapy is increased by local hyperthermia [4].

In our study, 62.79% of patients received palliative chemotherapy, of which (47.05%) were metastatic from the outset and (52.95%) had a metastatic relapse. Chemotherapy was anthracycline-based in 85% of cases.

Monochemotherapy was performed in 47.05% of patients, and Polychemotherapy in (50.95%) of cases. The treatment of metastatic STS is palliative chemotherapy; to the 3 substances classically active in STMs which are Doxorubicin, Ifosfamide and Dacarbazine is added a new molecule, Trabectedin.

Doxorubicin is the agent most used in the first line at doses between 60 and 75 mg/m^2 every 3 weeks with an activity rate between 16% and 30% [4] [8], its cumulative cardiotoxicity limits its use. in the long term and to overcome this cardiotoxicity other formulations have been developed including pegylated Dox-

orubicin which has demonstrated, at a dose of 50 mg/m^2 every 4 weeks, an efficacy equivalent to Doxorubicin with less toxicity and which is especially mucocutaneous hand-foot syndrome type [4].

An interesting new formulation is Aldoxorubicin, A prodrug of Doxorubicin derived from its binding with an acid-sensitive bond, after passing into the bloodstream it binds rapidly and covalently with albumin and preferentially passes intra tumoral, the acidic medium of which causes the cleavage of the link and the Doxorubicin is thus delivered directly to the tumor level which makes it possible to bypass the heart and avoid cardiac toxicity. In a phase I study, Aldoxorubicin at a dose of 350 mg/m^2 every 3 weeks demonstrated an objective response rate of 76% in soft tissue sarcomas. Recently, a randomized phase II study compared Doxorubicin (75 mg/m^2 D1, D21, 6 cycles) and Aldoxorubicin (350 mg/m^2 D1 every 3 weeks) in the first line until progression. One hundred and twenty-three patients were included. An objective response rate of 25% versus 0% and median progression-free survival (PFS) of 5.6 months versus 2.8 months ($p = 0.02$) are observed in favor of Aldoxorubicin.

Aldoxorubicin, however, causes more episodes of grade 3 - 4 neutropenia (29% vs. 15%), but less febrile grade 3 - 4 neutropenia (14% vs. 18%), no acute cardiotoxicity in both arms but a decrease in left ventricular ejection fraction (LVEF) of less than 50% in 3 of the 40 patients who received Doxorubicin [9].

A phase III study. Ifosfamide is an alkylating agent from the oxazaphosphorine family which has dose dependent activity in STMs. High doses of 6 to 14 g/m^2 give response rates that increase with the dose administered but require the use of granulocyte growth factors, its effectiveness also depends on its mode of administration, in fact, the bolus mode is more active than administration continues [4]. Response rates are around 38% for doses of 5 to 8 g/m^2 every 3 weeks [8]. Its toxicity is mainly hematological, bladder, renal, hepatic and neurological.

Trabectedin, Extracted from a mother's tunicate (the ascidian Ecteinascidiaturbinata) and currently obtained by synthesis, is a DNA minor groove agent preventing cell cycle progression, its activity was initially demonstrated in patients with STM in escape to anthracyclines with an objective response of 38%, then confirmed by retrospective and prospective studies, the response was mediocre in the order of 4% to 8% but with prolonged stability in more than 20% of patients [8], has currently demonstrated, in a randomized phase II study, its first-line efficacy in uterine leiomyosarcoma in combination with doxorubicin with an objective response of 87% [10].

Dacarbazine gives objective responses of 18% at a dose of 1200 mg/m^2, haematological toxicity is more severe in bolus administration than in fractional administration [8].

The standard is to use mono-chemotherapy with anthracycline in the first line in soft tissue sarcomas. Combinations of anthracycline-based polychemotherapy give objective responses between 19% and 34% and have not demonstrated any benefit in overall survival. Compared with Doxorubicin-based monotherapy,

this was confirmed by a metanalysis as well as a phase III randomized trial of the EORTC [11]. However, a new combination, which seems interesting, of Doxorubicin with Evofosfamide (TH 302) which is an alkylating agent close to Ifosfamide, active only in hypoxia environment. It is a prodrug of Bromo-is ophospharamide mustard (Br-ISPM). TH 302 is reduced at its nitroimidazole site by intracellular reductases under hypoxic conditions thus causing the release of Br-ISPM which is the active metabolite and which acts by the formation of stable bridges, by covalent bonds, between the two chains DNA thus preventing its duplication and consequently prevents mitosis. In a study Phase II, Doxorubicin at a dose of 75 mg/m^2 every 3 weeks was combined with TH 302 at a dose of 300 mg/m^2 D1 and D8 every 21 days in 92 patients with metastatic STS naïve to any chemotherapy, after 6 cycles, responder or stable patients received TH 302 for maintenance. The objective response rate was 36%, the 6-month progression-free survival rate was 58%, and the medians of progression-free and overall survival were 6.5 months and 21 months respectively. During the maintenance phase, the objective response was improved by 12.5%. The main toxicities were fatigue, nausea, mucocutaneous toxicity, anemia, leukopenia and thrombocytopenia but less severe in the maintenance phase. There was no cardiac, hepatic or renal toxicity linked to TH 302, a phase III is in progress [12]. Polychemotherapy remains preferable for patients with potentially resectable metastases.

The objective response rate for first-line chemotherapy in metastatic soft tissue sarcomas varies between 15% and 34% [11]. In our study, (35%) of patients who received palliative chemotherapy, had a response to chemotherapy (12% partial responses and 23% stabilities), (40.09%) progressed, and the response did not was determined in (24.01%) of patients who lost sight. (23%) developed grade 3 - 4 hematological toxicities within (5%) cases of febrile neutropenia.

Currently, the second-line treatment of STS after anthracycline escape depends on the histological type and the existence of a molecular anomaly potentially sensitive to targeted therapy. Trabectedin has demonstrated, in phase II studies, second-line activity in several histological types such as uterine leiomyosarcoma [13], myxoid liposarcoma [13] [14], and translocation sarcomas [15]. Combinations of Gemcitabine with Docetaxel or Dacarbazine are effective second-line in uterine leiomyosarcoma after anthracycline escape [8]. Pazopanib, a multikinase inhibitor blocking the transduction of messages transmitted by the VEGF and PDGF receptors as well as the KIT and FLT3 pathways and thus blocking tumor angiogenesis, represents a new second-line therapeutic option for soft tissue sarcomas with exception of liposarcoma. In a Phase III study, Pazopanib at a dosage of 800 mg/day was compared with a placebo in patients with progressing soft tissue sarcomas after standard chemotherapy. Three hundred and sixty-nine patients were randomized, the primary objective being progression-free survival. The median progression-free survival was 4.6 months for Pazopanib versus 1.6 months in the placebo arm ($p < 0001$) with more toxicities in the Pazopanib arm (Fatigue, nausea, diarrhea and hypertension), the objective response rate was 73% for Pazopanib. This is the only phase III study that has

demonstrated an improvement in progression-free survival in STS [16].

For patients who achieved partial responses or stabilization after first-line chemotherapy, the concept of maintenance therapy was explored in a Phase III trial evaluating Ridaforolimus, an inhibitor of the mammalian target (mTOR) pathway of Rapamycin), for maintenance in responder patients after chemotherapy in soft tissue sarcomas. This trial was positive demonstrating a significant improvement in progression-free survival, the primary objective of the trial [17].

Metastatic soft tissue sarcomas have a poor prognosis with progression-free survival rates at 6 months varying between 30% and 56% depending on the histological type and the substances used [18], overall survival is around 12 months [19].

In our series, after a median follow-up of 19.5 months (Extremes = 2 - 76 months), the median progression-free survival and overall survival were 12 and 19 months respectively. The factors influencing survival were tumor stage ($p < 0.0001$) and age ($p = 0.067$).

5. Conclusion

Soft tissue sarcomas are rare tumors, their management requires a multidisciplinary approach from the initial stage of diagnosis. Age and tumor stage are prognostic factors influencing patient survival.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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