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Original Research Article

Soft Tissue Sarcomas: Epidemiological, Clinical and Therapeutic Aspects

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Abstract: Soft-tissue sarcomas (STS) are a rare, and comprise a relatively heterogeneous group of malignant tumors arising from mesenchymal tissue. STS can affect any age group. In order to provide patients suffering from STS, with a functional extremity without local tumor relapse, treatment decisions must involve a multidisciplinary team decision-making approach. We conducted a retrospective, descriptive study, of 43 cases of soft tissue sarcoma, collected between January 2013 and December 2018, in the department of Radiation-Oncology of the Oncology and hematology hospital of Mohammed VI University Teaching Hospital. With this study we aimed to report the epidemiological, clinical, histological, therapeutic and evolutionary characteristics of soft tissue sarcomas in the Radiation-Oncology department, and to define the factors influencing patient survival in order to improve the quality of care. The items collected were: epidemiological, clinical, histological, radiological, and therapeutic. Univariate and then multivariate analyzes were performed looking for factors influencing 2-year survival. During the study period, we collected 43 cases, 22 Men and 21 Women, the average age was 45.23 years (Extreme = 11-78 years). The tumor was deep in 73% percent of the cases, and the lower limbs were the most affected (65%) especially in the thigh. The predominant histological type was Liposarcoma in 16 cases (37.20%). The tumor stage was localized in 35 cases (81.39%), metastatic in 8 cases (18.60%). Thirty-five tumors were treated with surgery, including 31 cases (88.57%) of conservative surgery and 4 cases (11.42%) of radical surgery. Radiotherapy was performed in 33 patients, and chemotherapy in 24 patients. Follow-up monitoring has detected 5 cases (28%) of local recurrence, and 13 other cases (72%) of distant metastases. In univariate analysis the prognostic factors were age ($p = 0.03$) and tumor stage ($p = 0.09$). In our study, radiation therapy is an integral part of the treatment of soft tissue sarcoma; it has been performed in most cases after conservative surgery. Age and tumor stage are prognostic factors influencing the survival of soft tissue sarcomas.

Keywords: Soft tissue sarcoma, surgery, radiation therapy, chemotherapy, prognostic factors.

INTRODUCTION

Soft-tissue sarcomas (STS) constitute a heterogeneous group of soft tissue neoplasia which arises from the nonepithelial extra-skeletal tissue of the body. They account for approximately 1% of all malignant tumors [1, 2]. STS are known for their extensive heterogeneity, with more than 100 histological subtypes associated with diverse and distinctive molecular and biological characteristics, clinical behavior, histopathological profiles, genetic make-up, response to tailored therapy, and prognosis. All age ranges can be affected by STS, however the median age at diagnosis is generally 55-70 years [3]. Malignancy seems to increases with age, compared to children, malignancy is significantly higher in adult patients. Extremities represent the most frequent location of STS, with approximately 70 % of cases involving limbs; however this group of tumors can arise anywhere in the body [3]. Generally soft tissue tumors are classified, based on the mature tissue they resemble, and presumed cell lineage according to the latest version of the World Health Organization (WHO) classification updated in 2013 [4]. The management of STS requires a multidisciplinary approach preferably in reference centers [5]. The treatment of Localized STS is mainly surgical, consisting of wide resection with a margin of 1 to 2 cm [6,7]. The conformity of the surgical procedures to Good Clinical Practice (GCP) guidelines is a major factor and independent predictor of progression-free survival of patients with STS and overall survival (OS) for patients with liposarcoma [8]. The objective of our study is to report the epidemiological, clinical, histological, therapeutic and

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evolutionary characteristics of patients treated for soft tissue sarcomas at the Radiation-Oncology Department of Marrakech.

MATERIALS AND METHODS

We conducted a retrospective, observational, descriptive study of 43 cases of soft tissue sarcoma, treated between January 2013 and December 2018 in the department of Radiation-Oncology of Mohamed VI University Teaching Hospital. The eligibility criteria were a histological evidence of a soft tissue sarcoma excluding gastrointestinal stromal tumors (GIST). The items collected were: Age at diagnosis, sex, tumor location and size, histological type and Grade, tumor stage, conservative or radical surgical treatment of localized forms, adjuvant or palliative radiotherapy, chemotherapy (neoadjuvant or palliative). Univariate and then multivariate analyzes were performed looking for 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.

RESULTS

Between 2013 and 2018, 43 patients with soft tissue sarcoma were treated at the Radiation-Oncology department of Mohamed VI University Hospital. Of these patients, 22 were male and 21 were female. The median age was 45.23 years (range: 11–78 years). The main reason for consultation was swelling with palpable soft-tissue mass, reported in 42 of our cases (96.6%). The tumor was deep located in 73% of cases, and the tumor size in physical examination ranged between 5 and 18cm, with a mean tumor size of 11cm. Due to the ubiquitous location of the soft tissues, 34 of our cases were located at the extremities (79%), 6 cases at the trunk (14%), 2 cases of retroperitoneal sarcomas (4.6%), and 1 case of head and neck sarcomas (2.32%). For primary tumor imaging, Magnetic Resonance Imaging (MRI) of the tumor site was performed in 30 cases (69.76%), while 25 cases (58.13%) had computed tomography (CT) of limbs. Imaging for metastatic disease consisted of a Chest-abdomen-pelvis Computed Tomography in 36 cases (83.7%). The tumor was localized in 35 cases (81.39%), and monitoring revealed 8 cases of lung metastasis (exclusive lung metastases in 6 cases, association to bone metastases in 1 case, and to adrenal metastases in 1 case). Histological evidence was obtained in 22 cases (51,16%) by a simple biopsy, while excisional biopsy was performed in 21 cases (48.83%). In our case series, histology revealed that the predominant histological types in decreasing order were: Liposarcoma in 16 cases (37.20%), Synovialosarcoma in 9 cases (20.93%), Leiomyosarcoma in 7 cases (16.27%), other histological types in 11 cases (25.58%) (Rhabdomyosarcoma 5 cases, 2 Peripheral neuroectodermal tumor (PNET), 1 Fibrosarcoma, 1 pleomorphic sarcoma and 2 undifferentiated sarcoma). Surgical resection of STS is the cornerstone of therapy for patients with localized disease; therefore all 35 localized cases of our study had surgery on the primary tumor, including 31 (88.57%) cases of conservative surgery and 4 (11.42%) cases of radical surgery. The limit of excision was > 1 cm in 2 cases, and <1 cm for the other cases (41 cases, 94.28%). Radiation therapy is usually combined with surgical resection in the management of patients with STS, in our study 33 patients required adjuvant external-beam irradiation, as they had equivocal or positive histologic margins, and/or were at high risk of recurrence. Palliative radiotherapy was performed in 2 cases. Chemotherapy was given in 24 patients (55.81%): neo-adjuvant chemotherapy in 3 cases, and palliative chemotherapy in 21 cases. Palliative chemotherapy was based on Antracycline in 19 cases (79%) including 7 cases (36.84%) in monotherapy and 12 cases (63.15%) in polychemotherapy. The response to chemotherapy was as follows: 9 patients (37.5%) had an objective response to chemotherapy (3 partial responses, 6 Stabilities), 10 patients (41%) progressed after chemotherapy, and the response to chemotherapy was not specified in 5 patients. Among the 35 patients with localized tumor, 18 (41.86%) relapsed after 6 months of follow-up (Range = 1-13 months), local relapse was reported in 5 cases (28%) and metastatic relapse in 13 cases (72 %). The site of metastasis recurrence was the lung in 12 cases, associated to bone metastases in 1 case and liver in 1 case, with only 1 case of isolated adrenal metastatic relapse. Local relapses were treated with the association of surgery and radiotherapy in 4 cases, and metastatic relapses were treated with chemotherapy. The median follow-up was 19.5 months (2-76 months). The median progression-free survival and overall survival were 12 and 19 months respectively.

We used a simple logistic regression to find the factors influencing the survival at 2 years: the factors having a p-value <0.30 in univariate analysis were introduced in the multivariate analysis. We retained as factors influencing 2-year survival, those with a p-value <0.05 in multivariate analysis. In univariate analysis, the factors which seem to influence survival at 2 years are: age (OR = 0.18 95% CI: 0.04-0.85; p = 0.03), disease stage (OR = 0.15 95% CI: 0.01-1.36; p = 0.09) and tumor size (OR = 0.41 95% CI: 0.08-2.06; p = 0.27). Multivariate analysis showed that only age is a factor of poor prognosis (OR = 0.17 95% CI: 0.03-0.82; p = 0.28). Medians of recurrence-free survival (RFS), and overall survival (OS) were calculated using the Kaplan Meier method. After a mean follow up of 18.5 months, median progression free survival was 11.3 months and median overall survival was 18.3 months.

DISCUSSION

Soft tissue sarcomas are a heterogeneous group of rare but anatomically and histologically diverse tumors. This heterogeneity is due to the nearly over 70 recognized histologic subtypes of soft-tissue sarcomas,

and the ubiquitous location of the soft tissues. During the period of our study, 43 soft tissue sarcomas were recorded in our department, which represent 1% of cancers in adults as described in the literature [2, 6]. The global incidence of STM is estimated at 3.6 cases per 100,000 populations per year [9]. The occurrence of STS can be seen over all age ranges; however, the median age at diagnosis is 55-65 years, with two peaks of incidence around 50 years and 80 years, with 25% of STS developing over 75 years old [9,10]. When comparing our results to those of the literature, we notice that our patients are slightly younger, with a median age of 45 years. This can be explained by the aging of the western population. There is a slight male predominance in our case series, with a male-to-female ratio of 1.04/1.0.

In the majority of cases of STS, no specific etiologic agent is identifiable; however several genetic predisposition syndromes as well as environmental risk factors have been recognized and well documented. In genetic predisposition syndromes, Li-Fraumeni syndrome is an autosomal dominant disease associated with loss of function of the tumor suppressor TP53 which can induce many types of cancer such as sarcoma [11]. Neurofibromatosis (NF1 gene) or Von Recklinghausen's disease, predisposes to the onset of cancer linked to the central nervous system but also to leukemia and malignant nerve sheath tumors [11, 12]. Other predisposing syndromes, such as mutation in the tumor suppressor gene RB1, show an increased incidence of the occurrence of sarcomas [13]. Several environmental predisposing factors have been recognized, such as radiation therapy. STS have been reported to originate in the radiation fields, following therapeutic irradiation for a variety of solid tumors. Radiation-induced sarcomas often develop decades later, and the majority are high-grade lesions (90%) [14]. Exposure to several chemicals in some occupations has been linked with the occurrence of STS. These chemicals include Chlorophenols, Thorotrast, Phenoxy acetic acids, Vinyl chloride, and Arsenic [15]. Exposure to alkylating chemotherapeutic agents has been associated with some pediatric soft-tissue sarcomas most commonly after the treatment of pediatric acute lymphocytic leukemia. The drugs implicated include procarbazine, cyclophosphamide, nitrosoureas, chlorambucil, and melphalan. Cumulative drug exposure appears to increase the relative risk of sarcoma. Some studies pointed out that some types of STS have been noted to occur in the chronically lymphedematous arms of women with breast cancer treated with radical mastectomy. In our study, no etiological investigation was made, but there was no notion of a personal or family history of genetic disease. None of our patients had a history of radiotherapy.

Generally, signs and symptoms of soft tissue sarcoma depend on the anatomic site of origin. This group of malignancies may develop at any site in the body where soft tissues are located, due to the ubiquitous location of the soft tissues. The most frequent locations are the limbs, the trunk, the retroperitoneum, and the head and neck [6, 16]. The results of our study are in accordance with findings in the literature, as more than two-thirds of cases (79%) were located at the extremities, and 14% at the trunk. We only reported 4.6% of retroperitoneal STS, and only 2.32 % of head and neck STS.

Soft tissue sarcomas encompass a variety of histologically distinct neoplasms, due to the wide spectrum of soft tissues. They are mainly classified according to the "WHO histological classification" which is based on the putative cell of origin of each lesion as well as its differentiation. Classifications, such as WHO classification, are based on histogenesis, therefore they are reproducible for only the more differentiated tumors. Consequently, the determination of cellular origin becomes increasingly difficult, as the degree of histologic differentiation declines. This process of dedifferentiation results in a variety of overlapping patterns, making identification of the cell of origin of an individual tumor a real challenge for experienced soft-tissue pathologists [17]. Histological findings of our cases showed the predominance of the following histological types: Liposarcoma, Synovialosarcoma, and Leiomyosarcoma. Only one case of discrepancy was reported in our case series, which required re-reading of the pathology slides.

The management of STS must follow a multidisciplinary approach. Since the majority of soft-tissue sarcomas arise in the extremities or superficial trunk, there are no standardized screening tests for this group of tumors.

First, physical examination should assess the size of the mass, its mobility relative to the underlying tissues, and its relationship to the investing fascia of the extremity, bony and nearby neurovascular structures. Assessment of regional lymph, and site-specific neurovascular examination should also be performed.

Optimal imaging of soft tissue sarcomas depends on the anatomic site. For tumors of the extremities, MRI is considered the imaging modality of choice because it provides a multiplanar definition of the lesion allowing the assessment of locoregional extension of the tumor; it also enhances the contrast between muscle and tumor and, between adjacent blood vessels and tumor. However, a study conducted by the Radiation Diagnostic Oncology Group (RDOG), that compared CT and MRI in 133 patients with STS showed no specific advantage of MRI over CT from a diagnostic standpoint. In our study MRI was performed in 30 cases (69.76%), this can be explained by the problem of availability and the cost of this examination [18]. Cost-effective imaging to exclude the possibility of distant metastatic disease depends on the anatomic

location of the primary tumor, grade, and size. Patients with low-grade or intermediate-grade tumors < 5 cm in diameter require only a chest x-ray. However, patients with high-grade tumors ⩾ 5 cm should undergo a more thorough staging of the chest by CT. Following the radiological assessment, a biopsy is necessary for carrying out the histological study. Therefore any soft-tissue mass located in extremity should be biopsied if it is symptomatic, has persisted beyond 4-6 weeks, is > 5 cm, or enlarging. Histological evidence can be obtained by percutaneous core biopsy or with fine-needle aspiration (FNA) for cytology. However In some cases, histologic evidence cannot be secured by percutaneous approaches. In these instances, open biopsy is indicated, with the exception of small superficial masses, which can be removed by excisional biopsy [19, 20]. In our study 22 (51%) patients underwent percutaneous core biopsy, while excisional biopsy was performed in the other cases (49%).

In soft tissue sarcomas, multidisciplinary treatment planning should precede the initiation of any therapy. Surgical resection is the cornerstone of therapy for resectable localized soft tissue sarcomas. The resection should encompass the previous biopsy site skin, soft tissues adjacent to the tumor, and subcutaneous tissues. Whenever possible, the tumor should be excised with a 2 to 3cm circumferential margin of normal surrounding tissue. This ideal margin is sometimes compromised since good adjuvant approaches are available to facilitate local control. This situation applies when resection of adjacent, possibly involved neurovascular or bone structures would result in significant functional loss [21]. The quality of the surgery is determined by the histological examination of the margins of the operative specimen, if the margins are invaded, a surgical revision must be considered [6, 7]. When external irradiation is indicated, surgeons should place metal clips at the margins of resection to facilitate radiation field planning. Positioning of drain sites should also be close to the wound to allow inclusion in radiation fields. Given the low prevalence (2-3%) of lymph node metastasis in patients with soft tissue sarcomas, there is no role for routine regional lymphadenectomy. It is only considered in case of clinically apparent lymphadenopathy [22, 23].

Management of patients with soft-tissue sarcomas of the extremities usually combines radiation therapy with surgical resection. The decision of whether to use neoadjuvant (preoperative) or adjuvant (postoperative) irradiation remains controversial and has been addressed in multiple randomized trials [24, 25]. Neoadjuvant irradiation has several practical and theoretical advantages. It may facilitate surgical resection from vital structures by producing tumor encapsulation. Smaller radiation portals can be utilized, as ecchymoses, hematomas, and the scar, do not need to be covered. Radiotherapy induces a reduction of the tumor size, thus decreasing the extent of surgical resection. It is easier, with preoperative, to spare a strip of skin and thereby lower the risk of lymphedema. In STS there are fewer relatively radioresistant hypoxic cells, therefore lower radiation doses can be utilized. However, neoadjuvant irradiation also has several drawbacks. They include increased problems with wound healing, and the inability to stage patients precisely based on pathology due to downstaging [26]. Studies from the M. D. Anderson Cancer Center, and Massachusetts General Hospital, and University of Florida, demonstrated that local control rates with preoperative radiotherapy reached 90% using doses of approximately 50 Gy. Distant metastases were the primary pattern of failure, and survival depended on the grade and size of the primary tumor [27].

Equivocal or positive surgical margins are associated with higher risks of local recurrence [6, 17]; therefore adjuvant irradiation should be indicated in all patients with close or positive histologic margins in whom re-excision is impractical. Doses of adjuvant external-beam radiation therapy are 60-65 Gy. In our study, only one case (4%) benefited from resection with a margin greater than 1 cm, for the twenty-four other patients with inadequate margins, adjuvant radiotherapy was performed [28]. A randomized study comparing, limb-sparing surgery plus postoperative irradiation to amputation, demonstrated the equivalence of the two approaches in terms of recurrence-free survival and overall survival [6]. For postoperative radiotherapy, a randomized trial from the National Cancer Institute (NCI), as well as a number of retrospective reports, have demonstrated that limb-sparing surgery plus adjuvant irradiation produces local control rates comparable to those achieved with radical surgery (amputation). With adjuvant radiation therapy, survival rates of 70%, five-year local control rates of 70%-90%, and limb-preservation rates of 85% can be expected [25]. The National Cancer Institute (NCI) of Canada Clinical Trials Group published the 5-year results of a randomized phase III trial comparing preoperative with postoperative irradiation for limb STS. A total of 190 patients were randomized in 2 treatment arms, preoperative versus postoperative irradiation. The updated results continue to show no difference in recurrence-free survival, local control, and metastatic relapse-free survival. Longer follow-up didn't show the previously reported difference in overall survival (OS). The 5-year OS rate was 73% vs 67% (P = .48). Grade and tumor size were the only significant predictors for overall survival, and cause-specific survival, metastatic relapse. Wound complications were observed in 35% of cases in the preoperative group versus 17% in the postoperative group (difference, 18% [95% CI: 5-30]; P = .01). In multivariate analysis, anatomical site and tumor size were also significant risk factors. Local control rates were identical in both arms of the trial. Results of five year outcomes showed no difference in cause specific survival, overall survival, or the occurrence of metastases [25].

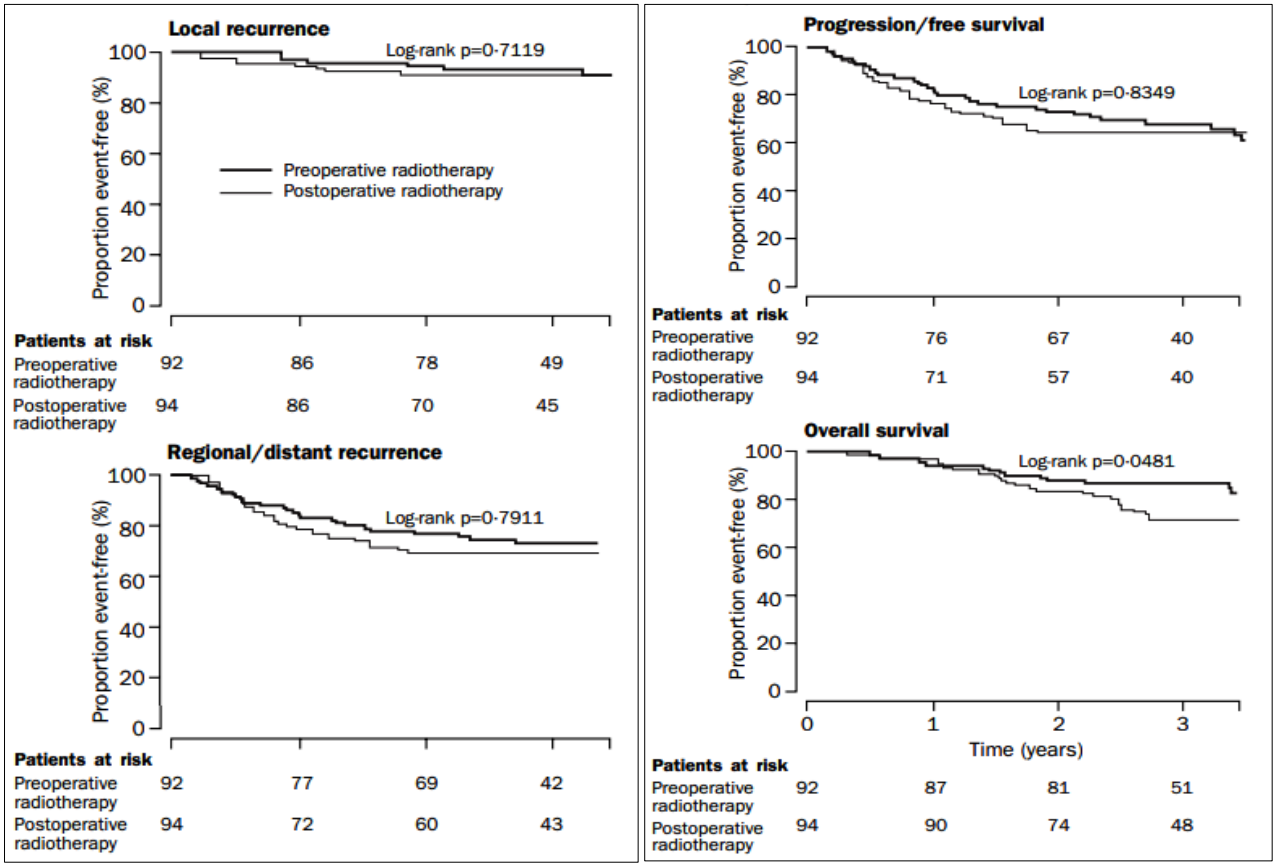

Figure 1: Kaplan-Meier plots for probability of local recurrence, metastatic (regional and distant) recurrence, progression-free survival, and overall survival [25]

Because neoadjuvant radiotherapy is associated with a higher risk of wound complications than adjuvant radiotherapy, but less edema, and fibrosis, the choice of treatment regimen for patients with STS should take into consideration the timing of surgery and radiotherapy and the anatomic site, and size of the tumor.

Some cancer treatment institutions use interstitial radiation therapy with iridium-192 as a radiation boost to the tumor bed following adjuvant external-beam irradiation. In a randomized trial, the 5-year local control rate with adjuvant brachytherapy was 82% versus 69% in with surgery alone. On subset analysis, local control rate in patients with high-grade lesions was 89% with postoperative brachytherapy versus 66% with surgery alone [29]. The results of this study and further studies have indicated that brachytherapy has no impact on local control for low grade soft tissue sarcomas. If brachytherapy is used, the dose is 40-45 Gy to a volume that includes all margins; when it's used as a boost in combination with external-beam irradiation, a dose of 20-25 Gy is utilized [30]. In a study conducted at Memorial Sloan-Kettering Cancer Center (MSKCC), over a 15-year period, 202 patients with high-grade sarcoma of the extremities were treated with complete gross resection followed by brachytherapy delivered over 5 days, with a median dose of 45 Gy. After a median follow-up of 61 months, distant relapse-free survival, 5-year local control, and overall survival rates were 63%, 84%, and 70%, respectively. Morbidity of brachytherapy was considered acceptable, with bone fractures in 3%, reoperation rates of 12%, and nerve damage in 5% [31]. These results compared favorably with data on external beam radiation therapy. Comparison of irradiation techniques (preoperative, postoperative, and interstitial techniques) showed comparable local control results (90%), although preoperative techniques were associated with higher rates of wound complications. A number of advantages can be offered with brachytherapy when it is employed as the sole adjuvant treatment. The entire treatment (surgery and adjuvant radiation) is completed in a 10 to 12 days, compared with the 10-12 weeks required for external beam radiation therapy and surgery. Moreover, with brachytherapy, smaller volumes can be irradiated, which could improve functional results. However, irradiation of smaller volumes may not be appropriate, depending on margins status, tumor size [32]. Another study of 911 patients treated by various techniques at MSKCC, demonstrated that local control is a highly achievable and worthwhile end point, regardless of the technique employed. Local recurrence occurred in 116 patients, metastases developed subsequently in 38 patients, and 34 patients died. Metastases after local

recurrence were predicted in patients with large (> 5cm) or high grade tumors [33].

Currently, treatment recommendations for soft tissue sarcomas include adjuvant radiotherapy for large (> 5 cm) low grade lesions, and all high grade sarcomas. Radiotherapy can be omitted, if small lesions (T1) were resected with clear margins. Postoperative therapy with either external beam irradiation or brachytherapy alone will achieve high rates of local control and, therefore, limb preservation. Preoperative radiotherapy, although equally efficacious, is associated with higher wound complication rate compared to the postoperative approach [34]. Several studies reported the results of treatment of unresectable or medically inoperable soft-tissue sarcomas with radiation therapy alone. 5-year survival rates ranged between 25% and 40%, and local control rates were of 30%. Subset analysis showed that local control depends largely on the size of the primary tumor. In case of treatment with exclusive radiation therapy, doses should be at least 65-70 Gy. However, tumor's location may be particularly important in determining this dose because of the potential for damage to critical structures by the higher doses normally prescribed [35].

Another modality in the treatment of soft tissue sarcomas is chemotherapy. For patients with large high grade sarcoma, many cancer treatment centers adopt neoadjuvant chemotherapy. The specific regimens generally contain both ifosfamide and anthracycline [36]. Neoadjuvant chemotherapy has been explored in a prospective trial conducted by the European Organization for Research on the Treatment of Cancer (EORTC). The trial included patients who had a STS of any grade measuring at least 8 cm, a locally recurrent or inadequately excised grade 2-3 sarcoma, or a primary or recurrent grade 2-3 sarcoma of any size. However, accrual was slow, and only 150 patients were included in this trial before its closure. Patients were randomized to receive either three cycles of chemotherapy with doxorubicin plus ifosfamide with mesna, or immediate surgery, followed by radiation therapy for close or positive margins. Among eligible patients (134), over 80% had primaries located in the extremities, but only 4% had 2-3 grade lesions > 8 cm. Among 49 patients assessable for response, major objective responses were achieved in 29% of the cases, including 4 complete responses. Progression of disease before surgery was reported in only 18% of the cases. Generally, administration of chemotherapy was well tolerated, and never prevented or delayed surgery. After a median follow-up of 7.3 years, 5 year survival rate among the 67 patients in the arm surgery alone was 64% versus 65% in the neoadjuvant chemotherapy arm (P = .22) [37]. Many trials were conducted with the aim of exploring the role of neoadjuvant chemotherapy and radiation therapy to decrease the rate of distant failure and possibly impact survival. Patients with high grade soft tissue sarcomas (8 cm or larger) were enrolled in a study from Massachusetts General Hospital. They were treated with three cycles of neoadjuvant chemotherapy consisting of Mesna, Adriamycin, Ifosfamide, and Dacarbazine (MAID) interdigitated with radiation therapy (44 Gy). This regimen was followed by surgery and 3 other cycles of adjuvant MAID chemotherapy. An additional 16 Gy of radiation therapy was delivered, in cases with positive surgical margins. Significant improvement in 5-year freedom from distant metastasis (75% vs 44%, P = .0016) was reported with this regimen in comparison with historic control patients. Furthermore, overall survival and 5-year disease free rates were 70% vs 42% (P = .0002) and 87% vs 58% (P = .0003) in favor of the MAID regimen versus control groups. In the MAID group a 29% rate of wound healing complications was reported [36]. Adjuvant chemotherapy was explored in multiple trials. This treatment modality was compared with observation alone in adults who had undergone resection of a primary or recurrent STS. However, some limitations were identified with these trials: small simple size (fewer than 100 patients in some trials), inadequate statistical power to detect a 15% difference in survival in some of the largest trials, and inclusion of low risk patients with small and/or low grade sarcomas. A meta-analysis of 14 trials including 1568 patients, as well as one Italian trial demonstrated a benefit with adjuvant chemotherapy [38]. However two randomized phase III trials from the EORTC assessing adjuvant chemotherapy, did not demonstrate benefit in terms of overall survival in intention to treat analysis. Subgroup analysis demonstrated that male patients and patients over 40 years had benefited of adjuvant chemotherapy, in terms of progression-free survival, while poor overall survival rates were reported with female gender and age< 40 years. In patients with R1 resection, administration of postoperative chemotherapy was associated with favorable progression-free survival and overall survival rates [39]. Aside from theoretic considerations, preoperative is preferred over postoperative chemotherapy for several pragmatic reasons. First, neoadjuvant chemotherapy permits a reduction in the size of large tumors, facilitating surgical resection with less morbidity. Second, compliance to treatment is reported to be better with preoperative therapy. One observation that supports the preoperative approach is that response to neoadjuvant chemotherapy, whether radiographic or pathologic, predicts improved survival and tumor control. In our study, none of our patients received adjuvant chemotherapy.

In soft tissue sarcomas, local recurrence develops in 10% to 50% of cases, with a median local recurrence free interval of 24 months, despite optimal multimodality therapy. Local recurrence rates depend on the primary site, and are highest for head and neck, and retroperitoneal sarcomas (adequate surgical margins are difficult to attain). In addition, relative radiosensitivity of surrounding structures of these sites,

often limits the prescription of high-dose adjuvant irradiation. These factors result in local recurrence rates of 50% for head and neck sarcomas, and 40% for retroperitoneal sarcomas, which are substantially greater than the 10% typically seen for sarcomas located in the extremities [40].

CONCLUSION

Soft tissue sarcomas comprise a relatively heterogenic and aggressive group of malignant tumors arising in mesenchymal tissues. Several factors such depth, tumor location, size, and grade, influence outcome. After diagnosis confirmation and optimal staging, treatment of soft tissue sarcomas involves a multidisciplinary approach. Most patients are eligible for surgical resection, usually combined with external beam radiation therapy. The unfavourable prognosis of soft tissue sarcomas is caused mainly by the propensity for metastasis. Moreover, local recurrence rates are relatively high, causing a substantial morbidity. Although soft tissue sarcomas have been studied quite extensively, several aspects of this group of tumors remain unclear.

REFERENCES

1. Hajdu, S. I. (1981). Soft tissue sarcomas: classification and natural history. *CA: A Cancer Journal for Clinicians*, *31*(5), 271-280.
2. Walker, E. A., Song, A. J., & Murphey, M. D. (2010, October). Magnetic resonance imaging of soft-tissue masses. In *Seminars in roentgenology* (Vol. 45, No. 4, pp. 277-297). WB Saunders.
3. Pollock, R. E., Karnell, L. H., Menck, H. R., & Winchester, D. P. (1996). The National Cancer Data Base report on soft tissue sarcoma. *Cancer: Interdisciplinary International Journal of the American Cancer Society*, *78*(10), 2247-2257.
4. Jo, V. Y., & Fletcher, C. D. M. (2014). WHO classification of soft tissue tumours: an update based on the 2013 (4th) edition. Pathology, 46(2), 95-104.
5. Blay, J. Y., Honore, C., Stoeckle, E., Meeus, P., Jafari, M., Gouin, F., ... & Bonvalot, S. (2019). Surgery in reference centers improves survival of sarcoma patients: a nationwide study. *Annals of Oncology*, *30*(7), 1143-1153.
6. Bonvalot, S., Vanel, D., Terrier, P., Le Pechoux, C., & Le Cesne, A. (2004). Principes du traitement des sarcomes des tissus mous de l'adulte. *EMC-Rhumatologie-Orthopédie*, *1*(6), 521-541.
7. ESMO Clinical Practice Guidelines. (2014). Soft tissue and Visceral Sarcoma. *Ann Oncol*.
8. Derbel, O., Cropet, C., Meeus, P., Gilly, F. N., Vaz, G., Thiesse, P., ... & Ray-Coquard, I. (2012). Adhesion to Clinical practices Guidelines (CPG'S) and role on survival for soft tissue sarcoma patients. Analysis of a population based cohort from Rhône-Alpes region. *Annals of Oncology*, *23*, ix478-491.
9. Coindre, J. M., Terrier, P., Bui, N. B., Bonichon, F., Collin, F., Le Doussal, V., ... & Contesso, G. (1996). Prognostic factors in adult patients with locally controlled soft tissue sarcoma. A study of 546 patients from the French Federation of Cancer Centers Sarcoma Group. *Journal of Clinical Oncology*, *14*(3), 869-877.
10. Nijhuis, P. H. A., Schaapveld, M., Otter, R., Molenaar, W. M., Van Der Graaf, W. T. A., & Hoekstra, H. J. (1999). Epidemiological aspects of soft tissue sarcomas (STS)—consequences for the design of clinical STS trials. *European Journal of Cancer*, *35*(12), 1705-1710.
11. SEER Research Data 1973-2015 -- ASCII Text Data:Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) Research Data (1973-2015), National Cancer Institute, DCCPS, Surveillance Research Program, released April 2018, based on the November 2017 submission.
12. Fletcher, C., Unni, K., & Mertens, F. (2013). World Health Organization Classification of Tumours Pathology and Genetics of Tumours of Soft Tissue and Bone Lyon: IARC Press.
13. Kleinerman, R. A., Schonfeld, S. J., & Tucker, M. A. (2012). Sarcomas in hereditary retinoblastoma. *Clinical sarcoma research*, *2*, 1-7.
14. Gandhi, S., & Chandna, S. (2017). Radiation-induced inflammatory cascade and its reverberating crosstalks as potential cause of post-radiotherapy second malignancies. *Cancer and Metastasis Reviews*, *36*, 375-393.
15. Lahat, G., Lazar, A., & Lev, D. (2008). Sarcoma epidemiology and etiology: potential environmental and genetic factors. *Surgical Clinics of North America*, *88*(3), 451-481.
16. Morère, J. F., Mornex, F., & Soulières, D. (2011). Thérapeutique du Cancer -2eme édition. France. Springer-Verlag.
17. Fletcher, C. D. (2014). The evolving classification of soft tissue tumours–an update based on the new 2013 WHO classification. *Histopathology*, *64*(1), 2-11.
18. Aga, P., Singh, R., Parihar, A., & Parashari, U. (2011). Imaging spectrum in soft tissue sarcomas. *Indian journal of surgical oncology*, *2*, 271-279.
19. Singh, H. K., Kilpatrick, S. E., & Silverman, J. F. (2004). Fine needle aspiration biopsy of soft tissue sarcomas: utility and diagnostic challenges. *Advances in anatomic pathology*, *11*(1), 24-37.
20. Puri, A., & Gulia, A. (2011). Management of extremity soft tissue sarcomas. *Indian Journal of Orthopaedics*, *45*, 301-306.
21. Eilber, F. R., & Eckardt, J. (1997, October). Surgical management of soft tissue sarcomas.

In *Seminars in oncology* (Vol. 24, No. 5, pp. 526-533).

22. Al-Refaie, W. B., Andtbacka, R. H., Ensor, J., Pisters, P. W., Ellis, T. L., Shrout, A., ... & Feig, B. W. (2008). Lymphadenectomy for isolated lymph node metastasis from extremity soft-tissue sarcomas. *Cancer: Interdisciplinary International Journal of the American Cancer Society*, *112*(8), 1821-1826.
23. Riad, S., Griffin, A. M., Liberman, B., Blackstein, M. E., Catton, C. N., Kandel, R. A., ... & Wunder, J. S. (2004). Lymph node metastasis in soft tissue sarcoma in an extremity. *Clinical Orthopaedics and Related Research (1976-2007)*, *426*, 129-134.
24. Lazarev, S., McGee, H., Moshier, E., Ru, M., Demicco, E. G., & Gupta, V. (2017). Preoperative vs postoperative radiation therapy in localized soft tissue sarcoma: Nationwide patterns of care and trends in utilization. *Practical radiation oncology*, *7*(6), e507-e516.
25. O'Sullivan, B., Davis, A. M., Turcotte, R., Bell, R., Catton, C., Chabot, P., ... & Zee, B. (2002). Preoperative versus postoperative radiotherapy in soft-tissue sarcoma of the limbs: a randomised trial. *The Lancet*, *359*(9325), 2235-2241.
26. Haas, R. L., Miah, A. B., LePechoux, C., DeLaney, T. F., Baldini, E. H., Alektiar, K., & O'Sullivan, B. (2016). Preoperative radiotherapy for extremity soft tissue sarcoma; past, present and future perspectives on dose fractionation regimens and combined modality strategies. *Radiotherapy and Oncology*, *119*(1), 14-21.
27. Scurr, M., & Judson, I. (2005). Neoadjuvant and adjuvant therapy for extremity soft tissue sarcomas. *Hematology/Oncology Clinics*, *19*(3), 489-500.
28. Tiong, S. S., Dickie, C., Haas, R. L., & O'Sullivan, B. (2016). The role of radiotherapy in the management of localized soft tissue sarcomas. *Cancer biology & medicine*, *13*(3), 373-383.
29. Pisters, P. W., Harrison, L. B., Leung, D. H., Woodruff, J. M., Casper, E. S., & Brennan, M. F. (1996). Long-term results of a prospective randomized trial of adjuvant brachytherapy in soft tissue sarcoma. *Journal of Clinical Oncology*, *14*(3), 859-868.
30. Bradley, J. A., Kleinman, S. H., Rownd, J., King, D., Hackbarth, D., Whitfield, R., & Wang, D. (2011). Adjuvant high dose rate brachytherapy for soft tissue sarcomas: initial experience report. *Journal of Contemporary Brachytherapy*, *3*(1), 3-10.
31. Alektiar, K. M., Leung, D., Zelefsky, M. J., Healey, J. H., & Brennan, M. F. (2002). Adjuvant brachytherapy for primary high-grade soft tissue sarcoma of the extremity. *Annals of Surgical Oncology*, *9*, 48-56.
32. Holloway, C. L., DeLaney, T. F., Alektiar, K. M., Devlin, P. M., O'Farrell, D. A., & Demanes, D. J. (2013). American Brachytherapy Society (ABS) consensus statement for sarcoma brachytherapy. *Brachytherapy*, *12*(3), 179-190.
33. Gronchi, A., Casali, P. G., Mariani, L., Miceli, R., Fiore, M., Lo Vullo, S., ... & Rosai, J. (2005). Status of surgical margins and prognosis in adult soft tissue sarcomas of the extremities: a series of patients treated at a single institution. *Journal of Clinical Oncology*, *23*(1), 96-104.
34. Kaushal, A., & Citrin, D. (2008). The role of radiation therapy in the management of sarcomas. *Surgical Clinics of North America*, *88*(3), 629-646.
35. Hoekstra, H. J., Koops, H. S., Molenaar, W. M., Mehta, D. M., Sleijfer, D. T., Dijkhuis, G., & Oldhoff, J. (1989). A combination of intraarterial chemotherapy, preoperative and postoperative radiotherapy, and surgery as limb-saving treatment of primarily unresectable high-grade soft tissue sarcomas of the extremities. *Cancer*, *63*(1), 59-62.
36. DeLaney, T. F., Spiro, I. J., Suit, H. D., Gebhardt, M. C., Hornicek, F. J., Mankin, H. J., ... & Harmon, D. C. (2003). Neoadjuvant chemotherapy and radiotherapy for large extremity soft-tissue sarcomas. *International Journal of Radiation Oncology* Biology* Physics*, *56*(4), 1117-1127.
37. Gortzak, E., Azzarelli, A., Buesa, J., Bramwell, V. H. C., Van Coevorden, F., Van Geel, A. N., ... & Verweij, J. (2001). A randomised phase II study on neo-adjuvant chemotherapy for 'high-risk'adult soft-tissue sarcoma. *European Journal of Cancer*, *37*(9), 1096-1103.
38. Bui-Nguyen, B., Italiano, A., Delva, F., & Toulmond, M. (2010). Chimiothérapie adjuvante des sarcomes des tissus mous de l'adulte. *Bulletin du cancer*, *97*(6), 673-678.
39. Le Cesne, A., Ouali, M., Leahy, M. G., Santoro, A., Hoekstra, H. J., Hohenberger, P., ... & Van Der Graaf, W. T. A. (2014). Doxorubicin-based adjuvant chemotherapy in soft tissue sarcoma: pooled analysis of two STBSG-EORTC phase III clinical trials. *Annals of Oncology*, *25*(12), 2425-2432.
40. Karakousis, C. P., Proimakis, C., Rao, U., Velez, A. F., & Driscoll, D. L. (1996). Local recurrence and survival in soft-tissue sarcomas. *Annals of surgical oncology*, *3*, 255-260.

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