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SOFT TISSUE SARCOMAS OF THE LIMBS: MULTIDISCIPLINARY TREATMENT

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Abstract: *Soft Tissue Sarcomas (STS) are rare tumors that arise from mesenchymal tissues. Although STS can arise at any site within the body, 40% typically originate in the limbs. At onset, sarcomas are characterized by a painless mass discovered casually or through an ultrasonographic scan performed for other reasons.*

Any superficial mass of 5 cm or more in diameter or a deep mass equal to or greater than 3 cm should be considered suspicious of malignancy. Work-up for an extremity mass suspicious for a STS includes cross-sectional imaging with computerized tomography (CT) and magnetic resonance imaging (MRI), and a core biopsy made in line with the planned incision. For years, STS limbs were treated with amputation. Now, limb-sparing surgery is considered the mainstay therapy for the treatment of STS.

Radiotherapy and adjuvant chemotherapy are used in combination with surgery to prevent local recurrence and metastasis. Radiation therapy should be considered for tumors with high risk of local recurrence. The timing of radiation is best determined by weighing the increased risk of wound complications from neoadjuvant radiation against the increased risk of side effects to surrounding tissues. The use of adjuvant chemotherapy is controversial; however, there are relative indications for neoadjuvant chemotherapy for tumors with moderate or high risk of distant metastases.

KEYWORDS: *Soft tissue sarcoma, Limb sparing surgery, Radiotherapy, Chemotherapy, Sarcoma of the limbs.*

INTRODUCTION

Soft tissue sarcomas (STS) are a heterogeneous group of rare tumors, arising from the mesenchymal tissues of the body. Under this term, more than 100 different histological types are grouped together with different biological characteristics and distinct behaviors. These tumors account for less than 1% of adult cancer. Every year, in fact, only about 12,000 new cases are diagnosed in the United States[1].

The incidence of these neoplasms has remained stable over time, with a modest tendency to increase in women. Age-related tumor distribution shows a first peak in pediatric age, followed by a constant increase trend from 30 years with a peak after age 60[2,3].

The etiology of sarcoma is largely unknown, although some rare inherited disorders increase the risk of sarcoma cancerogenesis. Patients with type I neurofibromatosis have a risk of over 10% of developing a malignant tumor of peripheral nerve conduits. Li-Fraumeni syndrome, caused by a mutation of the p53 suppressor gene, results in an increased risk for bone sarcomas and soft tissues. Radiation-induced sarcoma has been recognized after treatment for lymphomas, uterine carcinomas or breast cancer. Chronic lymphedema may be a factor in the development of angiosarcoma.

Sarcomas have also been noted to emerge in the chronically lymphedematous arms of women who were treated for breast cancer with radical mastectomy (Stewart-Treves syndrome). In addition, an association between viral infections, such as Ebstein Barr virus in patients with AIDS and leiomyosarcoma, was noted[4-6].

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The STS can grow anywhere in the body, even though in 40% of cases the limbs are the preferred site. Liposarcoma, pleomorphic undifferentiated sarcoma, myxofibrosarcoma and synovial sarcoma are the most common histotypes observed. These neoplasms clinically appear as a painless mass that causes a swelling of a limb, or are sometimes detected casually during a US scan performed for other reasons. Any superficial lesion greater than 5 cm or any deep mass should be considered as highly suspicious[7].

For years, STS limbs were treated with extremely mutilating operations such as amputation. However, a clinical trial has changed the paradigm of the treatment for this tumor. In this study, patients underwent surgery with preservation of limbs ("limb-sparing surgery") associated with post-operative radiotherapy, achieving comparable results in terms of local recurrence and overall survival to the amputation group. Limb-sparing surgical procedures are therefore considered the mainstay therapy for the treatment of STS[8].

Radiotherapy and adjuvant chemotherapy are used in combination with surgery to prevent local recurrence and metastasis[9,10]. However, while the indication for radiotherapy appears relatively clear, the role of chemotherapy is more controversial, with significant differences in treatment strategies used in highly specialized sarcoma centers[11]. In this review we want to analyze the role of combined therapy in the treatment of limb sarcoma.

CLINICAL PRESENTATION AND IMAGING

Sarcomas of the limbs emerge as a swelling of the soft tissue. The patient often does not report pain because the mass, while growing, has room to infiltrate and dislocate the tissues. In most cases, the patient reports a more or less rapid increase in swelling size. The increase can take place in a few months, sometimes even years. At the objective examination, a sarcoma usually appears as a mass of hard-elastic consistency (unlike the lipoma soft consistency), which is not mobile on superficial and/or deep planes. A superficial mass greater than 5 cm or more or a deep (underfascial) mass equal to or greater than 3 cm should be suspected of malignancy and thoroughly investigate[12].

Radiological imaging is crucial both in the initial stages of diagnosis and in the staging. The ultrasound examination makes it possible to measure the size of the mass, highlights the relationship with the fascia, detects morphology, margins (regular, irregular, with or without pseudocapsules), echostructures (solid, liquid, mixed) and studies the involvement of neurovascular bundle and vascularization[13].

Both computerized tomography (CT) and magnetic resonance imaging (MRI) have their advocates as the mode of choice for studying soft-tissue sarcomas. Both methods provide information on local aggression, presence of necrotic areas in the context of mass and the infiltration of surrounding structures[14].

High-quality contrast-enhanced CT is a fast and well-tolerated method. It will show all necessary anatomical details of the tumor and may identify features that preclude resection.

Although MRI is not necessarily superior to CT, it makes it possible to demonstrate with extreme accuracy the size, morphology and contours of the tumor, and the presence of pseudocapsules and peritumoral edema. It allows precise definition of the compartment and relationships with vascular and nervous structures. The use of contrast medium contributes to the definition of benign / malignant tumors. The growing use of MRI in the last few years has consolidated this as the technique of choice in local-regional STS study[15].

Staging is completed by the evaluation of pulmonary parenchyma with CT since this is the most frequent metastatic site (44-92%).

PATHOLOGY, GRADING, BIOPSY

The current American Joint Committee for Cancer (AJCC) Staging System for Soft Tissue Sarcomas manual incorporates the tumor stage, extent of tumor, and tumor grade (Table 1). This TNM system evaluates tumor size (whether greater than 5 cm or not), depth (whether suprafascial or deep to fascia), and localized or disseminated (presence or absence of lymph node or distant metastases)[16].

Soft tissue sarcomas are heterogeneous tumors, which prove very difficult to uniformly grade. However, the grading system proposed by French Federation of Cancer Centers (Federation Nationale des Centres de Lutte Contre le Cancer, FNCLCC) has been validated by the largest number of patients studied, and its reproducibility has been tested with a large number of pathologists[17,18].

The FNCLCC grading system of soft tissue sarcomas is based on the total score obtained from the summation of points for 3 factors: differentiation, mitotic rate, and tumor necrosis for each soft tissue sarcoma type, points are assigned (1-3) for level of differentiation mitotic count, and tumor necrosis. The sum of the points is then categorized as either grade 1 (2-3 points), grade 2 (4-5 points), or grade 3 (6-8 points). The mitotic count refers to the number of mitotic figures counted in 10 high-power fields (HPF; field size of 0.174 mm^2).

TABLE 1. AJCC staging for soft tissue sarcoma.

CLASSIFICATION OF SOFT TISSUE SARCOMA *AJCC Cancer Staging Manual 7th ed, Springer New York, Usa, 2010*				
Primitive Tumor (T)	TX: Primitive cancer cannot be assesed T0 there is no evidence of primitive tumor T1: tumor <= 5 cm in the larger diameter T1a: surface tumor (not involving underlying fascia) T1b: deep tumor (involving or deep to fascia) T2: tumor> 5 cm in the larger diameter T2a: surface tumor T2b: deep tumor			
Regional lymph nodes (N)	NX: Regional lymph nodes cannot be assessed NO: no metastasis in regional lymph nodes N1: metastasis in regional lymph nodes			
Distant metastasis (M)	M0: No distance metastasis a M1: Distant metastasis			
Histologic grade (G)	Gx: Grade cannot be assesed G1: Grade 1 G2: Grade 2 G 3: Grade 2			
Stage	**T**	**N**	**M**	**G**
IA	T1a-b	N0, NX	M0	G1,GX
IB	T2 a-b	N0, NX	M0	G1,GX
IIA	T1a -b	N0, NX	M0	G2,G3
II B	T2 a-b	N0, NX	M0	G2
III	T2a-b	N0, NX	M0	G3
	Any T	N1	M0	Any G
IV	Any T	Any N	M1	Any G

The classification and characterization of STS are based on the integration of morphology, immunohistochemistry and genetics. The most important prognostic factors are the degree of differentiation depth and volume of the tumor. The presence of metastasis is another prognostic factor. 5-year survival for Stage I is about 90%, for Stage II 70%, Stage III 50% and 10% for Stage IV[2].

When a sarcoma is diagnosed, it is necessary to proceed with a tumor tissue sampling to determine the histological diagnosis. The biopsy should indicate the histotype and grade of the neoplasm as accurately as possible so as to allow the most appropriate therapeutic planning.

The histological characterization of malignant mesenchymal neoplasia can be obtained by cytological examination by aspirated needle biopsy, core biopsy, incision biopsy, excisional biopsy.

Cytological pathology by needle aspiration has limited use and is mainly used in suspected recurrences where the definition of malignancy is sufficient. Excisional biopsy should only be used in highly selected and appropriated cases[19,20].

Fine needle biopsies are not recommended for the initial diagnosis because it is very difficult to distinguish well-differentiated sarcomas from benign neoplasms. Core needle biopsy is now considered the procedure of choice in most cases of STS of the limbs. The incision biopsy can be used every time you do not get enough information from needle biopsy [21].

It is important to properly perform the biopsy to avoid the risk of contaminating the surrounding tissues and therefore possibly making subsequent surgery more complex. The core biopsy must be performed by the same access route as the incision biopsy so as to allow the tumor to be removed with the needle track.

SURGERY

For years, STS of the limbs were treated with extremely invalidating operations such as amputation[22]. However, a clinical trial changed the treatment of this tumor. In this study, 43 patients were

randomized to surgery with preservation of limbs ("limb-sparing surgery") associated with post-operative radiotherapy or amputation; only 15% of patients who underwent limb-sparing surgery showed local recurrence and the two groups did not differ in terms of 5-year disease-free or overall survival. Limb-sparing surgical procedures have now become the main therapy for STS[8].

Originally, this surgery was performed by sacrificing all the muscle involved, now a free margin of 1 cm is generally considered to be oncologically adequate[7,23]. For superficial lesions, the underlying fascia is removed with the tumor, while for deep tumors (under the fascia) it is necessary to remove the entire muscle group.

The skeletonization of vessels and nerves is considered adequate oncologically but an infiltration of a high-grade lesion may require resection of the neurovascular bundle[24]. If the artery is clearly involved, a vascular resection and reconstruction should be programmed. In addition, patients should be advised regarding the expected results of a nerve resection[25].

The type of excision that is obtained with surgery is classified according to the Musculoskeletal Tumor Society as intralesional, marginal, wide or radical. The microscopic resection test allows a precise definition of the margins and hence the quality and type of excision. The detection of areas of marginality and / or contamination of the resection is always crucial as it affects post-surgical therapy. The quality of surgery is to be defined on the basis of the worst margin. Surgical margins are defined as appropriate when they are radical or wide, or not appropriate when they are either marginal or intralesional[26].

Occasionally, in some advanced and nowadays rare cases, sarcomas of the limb require amputation due to the involvement of large or multifocal masses or in the case of neurovascular bundle infiltration. Isolated limb perfusion (ILP) has been used in patients who would otherwise require amputation in an attempt to convert them to the limb-sparing operation[27]. ILP with melphalan alone had limited success. However, combination therapy with tumor necrosis factor-α has been shown to have a good clinical response with limb salvage rates up to 60-70% [28, 29].

RADIOTHERAPY

Radiotherapy (RT) plays a key role in the multidisciplinary management of soft tissue sarcomas. Combined with surgery, radiation therapy represents a standard treatment for patients with STS.

The role of radiotherapy in preventing local recurrence was studied in a series of clinical and prospective trials, such as an RCT of the National Cancer Institute. This study showed the same oncological results of amputation versus surgery with wide margins plus radiotherapy, prompting the move to a conservative approach. Furthermore, a second randomized study, by researchers at the National Institutes of Health, showed that RT reduces the local recurrence rates [9,30].

Radiation therapy can be administered pre-, intra and after the surgery. However, the ideal mode of association between surgery and radiation therapy has not yet been defined. No RCT has demonstrated a statistically significant difference between the pre- and the postoperative approach as regards local control, distant metastasis and survival[31].

Risks of RT were defined in a randomized study on 94 patients by O'Sullivan et al[32]; 43 patients received 50 Gy pre-operatively or 66 Gy administered after surgery. For a median follow-up of 3.3 years, the two groups had equivalent rates of local recurrence. However, wound complications were more frequent in those who received neoadjuvant radiation than those who received adjuvant treatment (35% *vs.* 17%; p =0 .01)[32].

Since pre-operative treatment is burdened by greater morbidity in terms of wound healing (31% *vs.* 8%; p = 0.0014) compared to post-operative treatment, it is believed that pre-operative radiotherapy should be reserved for cases of initially inoperable tumors. Post-operative radiotherapy is the most conventional mode of association with surgery [33].

Radiotherapy is used together with surgery in the case of high-grade sarcomas of large diameter (> 5 cm) and in the case of local recurrence of any grade and dimension. In low-grade sarcomas, radiotherapy completes surgery in the case of marginal resection and other possible risk factors.

On the other hand, it is only reasonable to consider surgery as an appropriate RT treatment in the following cases: all small tumors ≤ 5 cm, low-level (over-spasms) tumors, deep-level (sub-spasms, intramuscular) tumors even larger than 5 cm which have been operated with extensive surgery.

Brachytherapy (intraoperative catheter placement with perioperative treatment), as well as intraoperative radiotherapy (IORT), are procedures for achieving a dose escalation associated with external beam radiotherapy to improve local disease control and to improve surgery in cases of surgical marginality at critical anatomical structures[34]. IORT has the advantage of delivering a single high boost dose to sarcoma residues and the surgical bed area near radiosensitive structures, with limited toxicity.

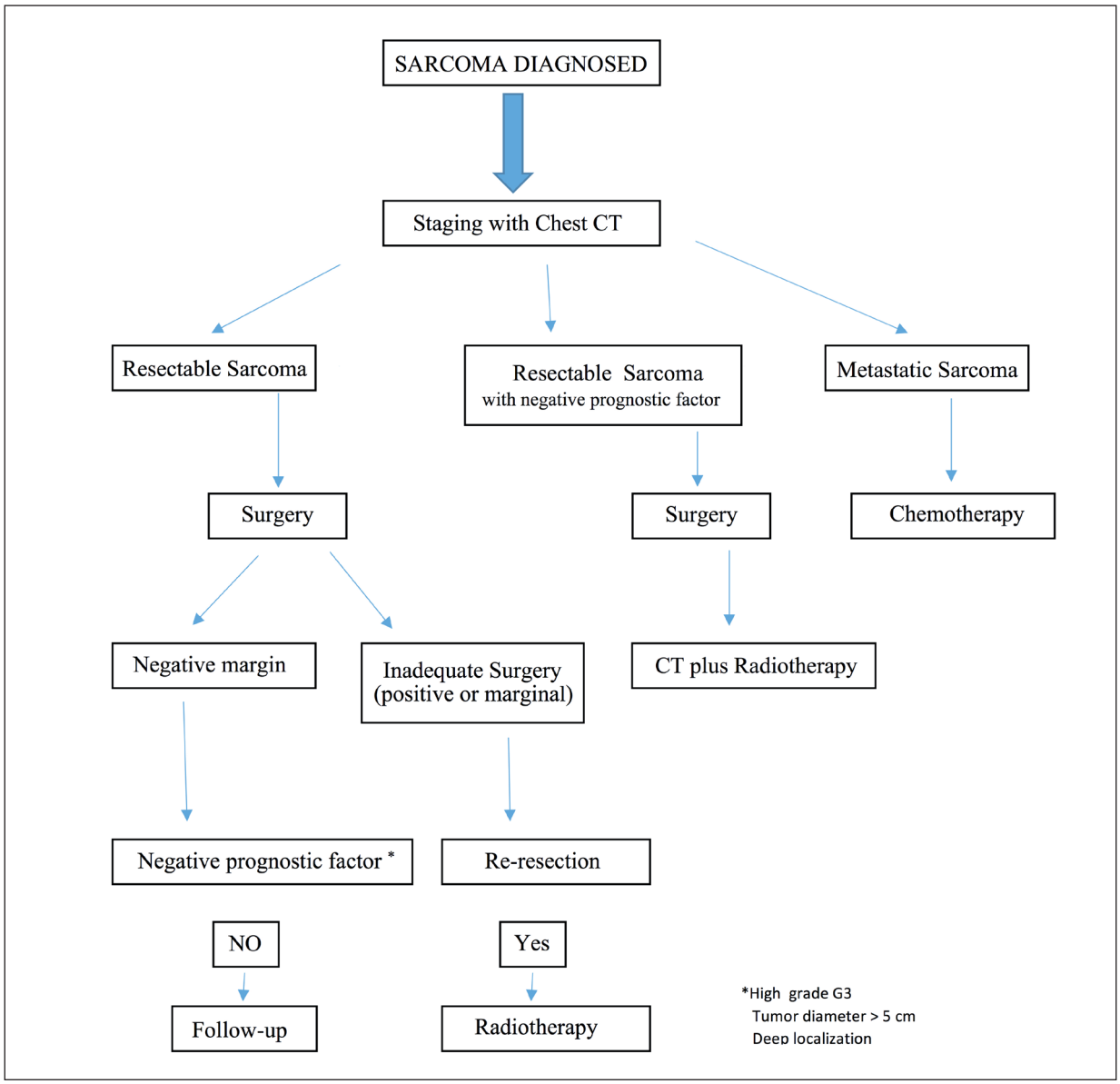

Fig. 1. Flow-chat of limb sarcoma treatment.

CHEMOTHERAPY

Recommendations regarding the prescription of adjuvant chemotherapy in patients with STS of the limbs vary greatly, even among high-volume specialized centers[35].

Conventionally active drugs in STS include anthracyclines (doxorubicin and epirubicin), ifosfamide and dacarbazine[36]. Chemotherapy may be used as a neoadjuvant to make the mass easily resectable or to sterilize micrometastatic foci, or post-operatively to reduce the risk of local or distant recurrence (for high grades tumors)[36,37].

There is no evidence that prior use of chemotherapy in surgically resectable forms can offer an advantage in local control [38].

Chemotherapy should not be considered a standard treatment for STS but should be reserved for special clinical situations. This clinical variability ensues from the conflicting results of a clinical trial[11]. The argument in favor of chemotherapy was further supported by subset analysis of the cohort of patients enrolled in the EORTC 62931 study[39]. In this study, the patients with the best results were those in the adjuvant arm with grade III tumors or with a diameter >10 cm. The analysis of this subset group of patients did not reach statistical significance, but the results may define cohorts who would receive the most benefit from adjuvant chemotherapy[40].

Based on these results, there is consensus that adjuvant chemotherapy can be proposed to pa-

tients with high grade STS, informing patients of the risk of the result based on the studies available so far. High grade superficial STS with ≥ 10 cm of diameter or ≥ 5 cm deep tumors are defined as high risk. The risk of developing distant metastases in patients with high-grade lesions with 5-10 cm volume is 34%, rising to 43% for lesions of 10-15 cm and 58% for lesions> 15 cm.

CT as the primary and only treatment should be reserved for unresectable or metastatic forms as a palliative procedure.

FOLLOW-UP

"Follow-up" refers to the set of periodic controls in patients with long-lasting pathology with the purpose of early detection of disease recurrences that can potentially be treated with appropriate therapeutic measures. Patients with recurrent STS of the limb can potentially be salvaged either by resection of local recurrence or by resection of distant (usually lung) metastases. The proposed examinations and their timing are based on limited experience and not on randomized studies[13].

The situations that may benefit from periodic controls are local recurrences still operable and limited number and size lung metastases whose radical surgical removal can prolong patient survival. Accurate instrumental re-evaluation in postoperative (ultrasound and/or MRI and/or CT) that excludes a residual disease allows comparison with subsequent follow-up examinations. In low-grade STS, controls are recommended every 4-6 months for 5 years and then every 12 months up to 10 years. In high-grade forms, checks should be performed every 3 months for 2 years and then every 4-6 months up to the 5th year. Then the timing can be annual. For primary tumors, the clinical examination supported by ultrasound and/or MRI from the anatomic site are the methods to be recommended[41].

CONCLUSIONS

Soft tissue sarcomas (STS) arising in the extremities pose a therapeutic challenge due to concerns of functional morbidity. The perioperative management of primary extremity soft-tissue sarcomas is multidisciplinary including, surgery, radiation therapy and chemotherapy.

Resections with negative margins "Limb-sparing surgery" is considered the mainstay therapy for the treatment of STS. Radiotherapy improves local control of STS of the limbs compared with surgery alone. Radiation therapy for soft tissue sarcoma continues to evolve with changes in timing, techniques, and targets. Chemotherapy is increasingly used to limit loss of function after wide surgical excision with the ultimate aim of improving patient survival. Since STS of extremities is prone to recurrence despite apparently complete treatment, a close follow-up is highly recommended.

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