Received: 8 November 2019 | Accepted: 5 January 2020

DOI: 10.1002/jso.25847

RESEARCH ARTICLE

Journal of SURGICAL ONCOLOGY WILEY

Brazilian consensus on the diagnosis and treatment of extremities soft tissue sarcomas

Ranyell M. S. S. B. Spencer MD, PhD[1] | Veridiana P. de Camargo MD[2] | Maria L. G. Silva MD, MSc[3] | Fabio F. E. Pinto MD, PhD[4] | Felipe D'Almeida Costa MD, PhD[5] | Wagner S. Cequeira MD[6] | Rodrigo R. Munhoz MD, MSc[2] | Celso A. Mello MD, PhD[2] | Rafael A. Schmerling MD[2] | Waldec J. D. Filho MD, MSc[2] | Tharcisio M. Coelho MD[3] | Alexandre V. A. Ambrosio MD[3] | Elton T. T. Leite MD[3] | Samir A. Hanna MD, PhD[3] | Sueli A. Nakagawa MD[4] | Andre M. Baptista MD, PhD[4] | Rodrigo N. Pinheiro MD, MSc[1] | Jadivan L. de Oliveira MD[1] | Marcelo Sá de Araújo MD[1] | Raphael L. C. de Araujo MD, PhD[1] | Gustavo A. Laporte MD, PhD[1] | Claudio de Almeida Quadros MD, PhD[1] | Alexandre F. de Oliveira MD, PhD[1] | Ademar Lopes MD, PhD[1]

[1]Department of Directory, Brazilian Society of Surgical Oncology (BSSO), Rio de Janeiro, Brazil

[2]Department of Directory, Brazilian Society of Clinical Surgical (BSCO), São Paulo, Brazil

[3]Department of Directory, Brazilian Society of Radiation Oncology (BSRO), São Paulo, Brazil

[4]Department of Directory, Brazilian Society of Orthopaedics and Traumatology (BSOT), São Paulo, Brazil

[5]Department of Directory, Brazilian Society of Pathology (BSP), São Paulo, Brazil

[6]AC Camargo Cancer Center, Department of Diagnosis and Imaging, São Paulo, Brazil

Correspondence
Ranyell M. S. B. Spencer, MD, PhD, HAOC, São Joaquim st 94, São Paulo, SP 01508-000, Brazil.
Email: ranyell.spencer@gmail.com

Abstract

Introduction: Soft tissue sarcomas (STSs) are rare tumors and constitute only 1% of all tumors in adults. Indeed, due to their rarity, most cases in Brazil are not treated according to primary international guidelines.

Methods: This consensus addresses the treatment of STSs in the extremities. It was made by workgroups from Brazilian Societies of Surgical Oncology, Orthopaedics, Clinical Oncology, Pathology, Radiology and Diagnostic Imaging, and Radiation Oncology. The workgroups based their arguments on the best level of evidence in the literature and recommendations were made according to diagnosis, staging, and treatment of STSs. A meeting was held with all the invited experts and the topics were presented individually with the definition of the degree of recommendation, based on the levels of evidence in the literature.

Results: Risk factors and epidemiology were described as well as the pathological aspects and imaging. All recommendations are described with the degree of recommendation and levels of evidence.

Conclusion: Recommendations based on the best literature regional aspects were made to guide professionals who treat STS. Separate consensus on specific treatments for retroperitoneal, visceral, trunk, head and neck sarcomas, and gastrointestinal stromal tumor, are not contemplated into this consensus.

KEYWORDS
multidisciplinary sarcoma, sarcoma consensus, sarcoma reference cancer centers, soft tissue sarcomas

1 | INTRODUCTION AND METHODOLOGY

Soft tissue sarcomas (STSs) are rare tumors that originate from a primitive mesenchymal cell. They comprise over 80 histological types, divided by molecular subtype, and primarily affect the extremities. STSs correspond to only 1% of all tumors in adults.[1]

This consensus serves as a manual for the treatment of STSs in the extremities. STSs in other areas, gastrointestinal stromal tumors, and other histological types that have specific treatments, such as Kaposi sarcoma and Ewing sarcoma, will be covered in another document, as embryonic and alveolar rhabdomyosarcomas, which are more common in children, and their treatment extends into adulthood, with the exception of pleomorphic rhabdomyosarcoma, the treatment of which that has been proposed in this manual is based on high-grade adult STS. The treatment of the histological subtypes of adult STS, which affects adolescents, can be managed according to what is determined in this consensus.

On the basis of the rarity of STS, most cases in Brazil are not treated according to primary international guidelines. Despite the differing histologies, in most cases, the treatment of STS is based on clinical criteria that determine the use of therapeutic methods that follow a certain order to achieve better functional and oncological results. Some international treatment guidelines have been developed with algorithms to improve the clinical management of patients with STS.[2] However, as Brazil is a huge country with regional particularities, we were motivated to develop the Brazilian Consensus on Extremity STS, considering such regional aspects in defining the degrees of recommendation.

This consensus was produced by the Brazilian Societies of Surgical Oncology, Clinical Oncology, Radiation Oncology, and Orthopedics, presenting the findings and recommendations of a panel of specialists, based on the degree of expertise and area of activity of those who are involved in the diagnosis, staging, and treatment of STS. All topics were determined by a committee and distributed to members. A meeting that was attended by all invited experts was held, at which the topics were presented individually with the definition of the degree of recommendation, based on the levels of evidence in the literature (Tables 1 and 2).[3,4] The medical literature was selected from the MEDLINE database. In the absence of sufficient evidence for a clear conclusion, the final recommendation was based on all votes and consensus among the specialists who were present.

1.1 | Epidemiology

In the United States, sarcomas represent an estimated 1% of all tumors in adults versus 15% in children.[1] In 2018, 13,040 people were diagnosed with STS, and approximately 5150 deaths occurred.[1] In Brazil, we infer that there are 3400 new cases that arise each year, and its incidence continues to rise, perhaps as a result of better recognition and diagnosis. However, no official data have been collected by governmental entities due to the difficulty of its diagnosis and the erratic decentralization in the care of these patients.

The incidence of STS is equal between sexes but varies according to age: 20.7% in patients aged under 40 years, 27.6% in those aged between 40 and 60 years, and 51.7% in patients aged over 60 years.[5] The American statistics show a higher number of cases in Caucasians (87%), followed by African-Americans (10%) and other races (4%).[5]

1.2 | Risk factors

The main risk factors for the development of STS are genetic syndromes, immunosuppression, chronic lymphedema, and infection. Immunosuppressive agents, such as HIV, and the use of immunosuppressive medications, such as posttransplant and chemotherapy medications, are related to the development of Kaposi sarcoma.[6] The presence of chronic lymphedema after mastectomy correlates with the occurrence of angiosarcomas.[7]

The incidence of STS ranges from 12% to 21% in patients with Li-Fraumeni syndrome—that is, those with mutations in TP53.[8] In Brazil, the pR337H is the most prevalent mutation in Li-Fraumeni patients, especially in the southeast and south, and this variant is associated with several peculiarities, such as high incidence of adrenocortical

TABLE 1 Strength of Recommendations and Levels of evidence—Classification of CDC System—Adapted from Riechelmann et al[3]

A—At least one randomized controlled trial (RCT) of good methodological quality or meta-analysis of well-designed RCT and without heterogeneity
B—Small RCTs or large RCTs with low methodological quality or meta-analysis of trial with a high risk of bias
C—Prospective cohort studies
D—Retrospective series or case-control studies
E—Case reports and expert opinion.
Levels of evidence—CDC grading system—Adapted from Riechelmann et al[3]
I—At least one randomized controlled trial (RCT) of good methodological quality or meta-analysis of well-designed RCT and without heterogeneity
II—Small RCTs or large RCTs with low methodological quality or meta-analysis of trial with a high risk of bias
III—Prospective cohort studies
IV—Retrospective series or case-control studies
V—Case reports and expert opinion

carcinoma in childhood; earlier breast cancer; and a higher prevalence of papillary thyroid tumor, kidney cancer, and pulmonary adenocarcinoma in relation to the classical form of Li-Fraumeni.[9]

Desmoid tumors are described in 7.5% to 16% of patients with FAP.[10] We will not consider the treatment of desmoid tumors for this consensus.

Hereditary retinoblastoma that is related to germinal mutations in the tumor suppressor gene (RB1) and neurofibromatosis with mutations in the neurofibrin 1 (NF1) and 2 (NF2) genes[11] are associated with an increased risk of developing STS.[12]

Other risk factors for the development of STS are radiotherapy (RT) and exposure to chemical agents. STSs emerge in areas that have received RT for other types of tumors. Frequently, they occur in low-dose regions in the periphery of the previously treated area, also called the penumbra. By definition, radiation-induced sarcomas do not appear before 3 years after treatment and often take decades after RT to develop. They are usually high-grade tumors (90%), of which osteosarcoma is the predominant histological type. High-grade undifferentiated pleomorphic sarcoma, angiosarcoma, and other subtypes have also been described.[13,14]

Finally, a positive relationship exists between intensive exposure to chlorophenols and the appearance of STS (odds ratio [OR] = 1.79; 95% confidence interval [CI], 1.10-2.88).[15] Exposure to industrial oils that are used for cutting metal is also associated with STS (OR = 1.65; 95% CI, 1.04-2.61).[16]

2 | DIAGNOSIS AND STAGING

2.1 | Image

Often, patients report that they have suffered local trauma, which may cause confusion with regard to the origin of STS and may incorrectly lead to associating STS with trauma. The clinical suspicion of STS occurs frequently after the identification by the patient of a new nodule or the rapid growth of an existing nodule. In this situation, the next step is to correctly assess and characterize it through an imaging exam.

Imaging exams are intended to confirm the presence of the lesion and provide the information that is necessary for the diagnosis, local staging, remote staging, and biopsy planning.[17] Thus, an appropriate systematic approach must be in place for the management of these lesions. Despite our recent belief in the superiority of magnetic resonance imaging (MRI) in the management of these patients, it remains limited in its ability to establish the histological diagnosis of soft tissue lesions, achieving only one-quarter to one-third of cases.[18]

2.1.1 | Recommendations

- Any patient with a suspected soft tissue tumor in an extremity should initially undergo ultrasonography. If the benign nature of this lesion cannot be confirmed, the diagnostic investigation should continue, ideally in a specialized center (IIIA).

  Note: Virtually every patient with a deep soft tissue lesion or superficial lesion above 5.0 cm should receive care in an oncological center[19] (IIIA).
- In a case of suspected or confirmed STS, MRI is the main modality for locoregional staging and defining related neurovascular structures (IVB). Contrast-enhanced CT is used for patients with contraindications to MRI and is the most frequently available method in Brazil (IVB).

  Note: (a) Computed tomography (CT) and X-ray are used to exclude bone tumors, detect bone erosions, demonstrate calcification, and assist in the diagnosis of ossifying myositis, for example. (b) Angio-CT and angio-MRI do not provide additional information, which is relevant to neurovascular status.
- Diagnostic confirmation can be performed by excisional biopsy for lesions smaller than 3.0 cm with a favorable anatomical location or by multiple percutaneous thick-needle biopsies using 14G to 16G[20] needles. Incisional open biopsy, provided that it is performed in a referral cancer center, is an option in certain cases; however, it is a more expensive procedure and is subject to potential complications (IIIB).

  Note: Percutaneous biopsy should be performed in a specialized center and planned by the surgeon to ensure that the biopsy scar is removed in the definitive surgery (IIIB).
- Remote staging should be performed by X-ray or chest CT. For patients with superficial tumors less than 5.0 cm and low histological grade, a chest X-ray is recommended[21] (IVB). Conversely, tumors greater than 5.0 cm, deep in relation to the fascia, from intermediate- to high-grade, should be staged with chest CT[21] (IIIA).
- Abdominal and pelvic CT should be requested in cases of high-grade myxoid liposarcoma, leiomyosarcoma, epithelium sarcoma, and angiosarcoma[22] (VC). MRI can be considered in select cases of myxoid liposarcoma[23,24] (VB).

  Note: For the preparation of an adequate imaging report, the surgical staging of the tumor should be based on the TNM/AJCC[25] classification, and it must contain the following information on the MRI[20]:
  1) Size of the lesion, measured in three dimensions
  2) Location in relation to the fascia (superficial or deep); compartment, muscle involvement, extension through the fascia and into the skin
  3) Contours, well or poorly defined, and presence of satellite lesions
  4) Signal characteristics, suggesting fat, cystic, or solid lesion
  5) Signal characteristics, suggesting myxoid or hemosiderin tissue
  6) Description of the presence of peritumoral edema; neurovascular involvement (proximity, contact, partial, or complete involvement, incarceration); bone involvement: proximity or invasion (cortex and marrow); lymph node involvement; joint extension (capsule, joint space); and the prominence of intratumor veins (presurgical embolization).
- There is no consensus on PET-CT. This diagnostic method appears to be useful in staging, prognosis, grading, and

determining the response to chemotherapy.[20,26] The recommendation of this consensus is that PET-CT can be used to evaluate the results of patients with high-grade sarcomas who were initially treated with chemotherapy or to indicate radical surgery (amputation) after relapse, ruling out remote disease (IVB).[5,26]

2.2 | Pathology

After an adequate radiological evaluation is performed, it is necessary to plan the acquisition of material for histopathological diagnosis. The amount of tissue material that is obtained has a direct influence on the accuracy of the diagnosis, subclassification, and grading of tumors and the eventual availability of tissue for molecular pathology tests or storage.

2.2.1 | Recommendations

- The preferred method to obtain histologic tissue for pathological examination is imaging-guided core needle biopsy (IVB). This approach aims to avoid inadequate representation—for example, of the necrotic areas—and obtain the samples that represent the highest-grade component of the neoplasm in cases of very heterogeneous tumors. Incisional and excisional biopsies can be performed in select cases, after discussion with multidisciplinary teams. Fine-needle aspiration is not recommended for the diagnosis of soft tissue tumors (IVC).[2]
- At least two fragments should be obtained, ideally three to six.[27] In institutions that have a bank of biological material and other diagnostic methods, additional material must be obtained, on informed consent by the patients (IVC).
- During the procedure, a cytological evaluation or freezing examination can be performed by a pathologist to assess the suitability of the sample but not to establish an immediate diagnosis—this practice that should be discouraged.[5]
- For histopathological and immunohistochemical examinations and conventional molecular pathology techniques, such as in situ hybridization and sequencing, formalin-fixed and paraffin-processed specimens with good representation are usually adequate. After removal, tissues should be stored for the shortest time possible in an appropriate container with 10% buffered formalin. The ideal volume of the fixing agent is at least 10 times the volume of the sample. In the case of excessively bulky materials, the sample should be at least completely covered by the fixing agent. The fixation time varies according to the type of material. For biopsies, the fixation time is 6 to 48 hours, and for surgical specimens, 24 to 72 hours is recommended. The processing, inclusion, cutting, and staining of the slides should follow the standard procedures of each pathology service, preferably in accordance with national or international laboratory quality control programs (IVC).[28]
- The diagnosis should be made following the most recent World Health Organization (WHO) classification for soft tissue tumors.[29] The diagnosis of well-established entities that are not included in the WHO classification should be accompanied by bibliographic references in the pathological report. The histological grading should follow the system of Fédération Nationale des Centers de Lutte Contre le Cancer (FNCLCC) (IIIC). This system that takes into account the differentiation, mitotic index, and the presence and extent of necrosis.[30]

  Note: The use of immunohistochemistry and molecular pathology examinations should be done wisely, with reasonable use of diagnostic markers to avoid unnecessary wear of the material. Cases that are difficult to resolve should be referred to a pathologist with more specific experience and dedication to soft tissue pathology (IIIC).[31]
- For specimens from surgical resections, the general recommendation is to represent at least one slice per cm of the neoplasm. Data, such as situation regarding the superficial fascia (ie, determination of whether the neoplasm is superficial or deep), size, tumor integrity, and evaluation of surgical margins, should be reported in the pathological report. For the latter, integration with information from the surgical team about the intraoperative findings and spatial orientation of the specimen is essential. The identification of specific topographies can be performed with surgical wires and special dyes. In general, a margin is considered to be compromised when there is direct contact between the edge and neoplastic cells. The distance between the tumor and the nearest margin should also be reported. When applicable, the presence of lymph node metastases should be evaluated. When all of the necessary information is available to pathologists, the pathological report must also contain the TNM staging, per the eighth edition of the American Joint Committee on Cancer (AJCC) *Cancer Staging Manual*.[25] For precise staging, whenever necessary, the pathologist should resort to imaging exams and surgical procedure data (IVD).[32]
- Cases that are subjected to neoadjuvant treatment protocols should provide an estimate of the pathological response to treatment. There is no single validated system for STSs; however, approaches that are similar to those that are used for osteosarcoma and Ewing sarcoma can be used. It is important to correlate the macroscopic findings of the specimen to the radiological aspects to perform a more accurate evaluation.[2]

For a detailed guide and complementary information regarding the parameters that should be included in the anatomopathological report of biopsies and surgical resections of soft tissue tumors, the protocols of the Brazilian Society of Pathology and the College of American Pathologists, available free of charge on the internet, can be found at the following websites: http://www.sbp.org.br/mdlhisto/partes-moles/, https://documents.cap.org/protocols/cp-other-softtissue-biopsy-19-4011.pdf, and https://documents.cap.org/protocols/cp-other-softtissue-resection-19-4011.pdf.

2.3 | Staging and risk stratification

The AJCC staging system designates the stage by tumor criteria, nodal status, metastasis, and histological grade (TNMG).[33] The eighth edition of the AJCC Cancer Staging Manual indicates that the TNMG staging classification has various T staging criteria and prognostic groups, depending on the location of the sarcoma, and determines the histological grade classification system of the Sarcoma Group of the French Federation of Cancer Centers (FNCLCC), a three-level system that is based on the differentiation of tumor cells, mitotic activity, and extent of necrosis.[25,30,33]

2.3.1 | Recommendations

- Molecular markers are not formally incorporated into the staging system, awaiting further evaluation of their impact on the prognosis,[34] and recurrent or residual sarcomas are subjected to staging tests using the same system as primary tumors, with the specification that the tumor is recurrent (IVC).[33]
- For complete staging, a complete study of all biopsy samples (including those from the primary tumor, lymph nodes, and other suspicious lesions) is essential. In the planning phase, clinical staging is obtained with data from the clinical examination and imaging exams, local and remote, with the focus on the lung. Exceptions are made when the possibility of extrapulmonary dissemination exists, which can occur in cases of myxoid liposarcoma, and specific examinations by imaging of the abdomen and pelvis might be necessary (IIIC).[2,33]

  Note: Although lymph node involvement in STS is rare (<3%), some histological subtypes can evolve with lymph node metastasis more frequently, such as rhabdomyosarcoma, vascular sarcomas, synovial sarcomas, clear-cell sarcomas, and epithelial sarcomas.[35,36]
- The prognosis of STS should be determined in a multifactorial manner, considering the factors that are related to a worse prognosis, such as age over 60 years, tumor size greater than 5 cm^2 and high histological grade.[2,37] In summary, high-grade histologies, positive margins after resection or relapse, and depth in relation to the fascia are considered as the main factors that are linked to worse clinical outcomes.[33,37]
- Specific symptoms should be properly investigated at the discretion of the service team. We recommend that all knowledge of risk factors be applied to risk stratification and that it be based on the current studies and good clinical practice (IVB).
- Scores and nomograms (such as sarculator[38] and MSK sarcoma nomogram[39]) that are drawn from the risk factors that have been cited are found in the literature with strong support. These tools allow stratification and grouping according to clinical characteristics in high-risk, intermediate-risk, and low-risk patients and can assist in clinical studies, guide management, and predict outcomes.[40] The recommendation of this consensus is that the use of nomograms and validated statistical tools lies with the discretion of the assisting team, always remembering their obvious utility (IVB).

3 | MANAGEMENT OF LOCAL/LOCALIZED DISEASE (see Figure 1)

3.1 | Surgery

STSs should be treated in specialized centers, guided by a multidisciplinary approach, involving clinical oncologists, radiologists, pathologists, radiation oncologists, and surgeons who are specialized in the subject. Surgery, with three-dimensional (3D) resection, is the basis for the treatment of STS of the extremities and should be performed by an experienced surgeon, preferably in a Reference Center for the disease. Studies show that this approach has better clinical outcomes.[41]

3.1.1 | Recommendations

- Resectability should be evaluated in the preoperative phase, based on imaging exams, the clinical conditions of the patient, and staging[42] (IVC).
- The standard surgical procedure is resection with adequate 3D oncological margins—that is, with a normal tissue margin of 1 to 2 cm (IIA). R0 resection should always be sought and is an important prognostic factor in the treatment of STS.[43]

  Note: When the tumor is not indicated for adequate resection, which occurs when the tumor is close to vessels, nerves, or main bone structures, the preoperative period can be planned adequately using neoadjuvant or adjuvant strategies with chemotherapy or RT, to preserve the limb (IIIA).[44-46]
- In the case of atypical lipomatous tumors, which are considered low-grade tumors with a low risk of local relapse and metastasis, the appropriate treatment can be the planned marginal excision without the need for neoadjuvant or adjuvant (IVB) strategies.[47]
- Major surgeries such as disarticulation or amputation might be the appropriate surgical option to achieve local control and offer the chance of a cure—especially in cases in which there is an invasion of noble structures that do not respond to neoadjuvant treatment for nonmetastatic patients. Vascular or nerve reconstruction should be discussed individually (IVC).
- In cases in which compartmental resection or significant muscle resection is required to achieve free margins, reconstruction with a local muscle flap or microsurgical reconstruction should be considered at the time of the primary surgery. The main advantage of this type of reconstruction is that it can be completed in a single surgical procedure, although the morbidity is increased (IIIC).[48]
- In patients who undergo an unplanned resection or who have compromised margins that are confirmed in a histopathological report, a new surgical approach (enlargement of margins) should be offered when possible.[2,43] Residual disease in the surgical bed (macroscopic or

microscopic) confers a worse prognosis, and local control is unlikely to be achieved, even in combination with adjuvant RT (IVA).

3.2 | Surgical reconstruction

Surgical reconstruction is often necessary after resection of STS of the lower limbs to provide adequate coverage of the wound and allow functional preservation of the limb.[49] Recent studies have reported successful esthetic and functional results using free tissue transfer as the main reconstruction modality after resection of the limb due to sarcoma.[48,50]

3.2.1 | Recommendations

- Repairs with pedicled muscle or fasciocutaneous flaps vascularized free flaps, and vascular or nerve grafts should be used as needed. Pediculated flaps have traditionally been preferred for oncological resections, but their use can be disregarded when using neoadjuvant RT[51] (IVB).
- Free tissue transfer allows the application of healthy vascularized tissue to the defect while providing the freedom to position the flap and avoiding elongation or elbowing of the vessels.[52] This reconstructive strategy is recommended for large areas that have undergone RT or when deemed necessary (IVB).
- The flap for bone reconstruction is chosen, based on the location of the lesion, the level of activity of the individual, the need for adjuvant therapy, and growth potential. The most commonly harvested bone flap is the free flap of the fibula, which can be used in three main ways for reconstruction: vascularized fibular flap; vascularized fibular flap, combined with allograft; and double vascularized fibula[53] (IVB).

  Note: Bone reconstruction with an unconventional stent-graft might produce satisfactory results as a comprehensive limb-saving and excision strategy for patients with large extracompartmental STSs with just an articular bone involvement. The 2- and 5-year overall survivals are 61.6% and 30.0%, respectively.[54]
- Reconstruction of motor nerves should be considered when limb preservation surgery is indicated, wherein an important motor nerve (IVB) will be killed.
- When vascular resection is necessary to obtain adequate margins after conservative limb surgery, arterial reconstruction is always the most important procedure to prevent ischemia, whereas the need for venous reconstruction is not well-established[51] (IVB).

3.3 | Surgical wound complications

Preservative resection of STS limbs is a procedure with a high risk of postoperative complications of the wound. Factors, such as diabetes, smoking, obesity, tumor diameter, location of the tumor in the proximal portion of the lower extremity, and preoperative RT, are predictors of complications in STSs that are subjected to surgical treatment.[55] The use of neoadjuvant RT can increase the risk of these complications to 30% to 40%, with most complications occurring within 6 weeks of resection.[56]

3.3.1 | Recommendations

- Seromas are the most common complication after surgery for resection of an extremity site. Planned thoracentesis is the treatment for most cases. In situations of relapse, whether there is a concomitant infection should be determined. Sclerosis strategies with chemical agents can be used, but their recommendation is doubtful, given the absence of randomized studies (IVB).[56]
- As *Staphylococcus aureus* is the most commonly isolated organism and because most anaerobic infections are polymicrobial, the use of antibiotics that cover aerobic and anaerobic bacteria should be considered in the treatment of these complications (IVB).[57]
- In cases of postoperative infections, a planned, multistage surgical treatment can be considered, given the high failure rate with single-stage debridement attempts (IVB).[56]

  Note: There is no difference in survival, local relapse, or metastasis between patients with or without postoperative infection—that is, a postoperative infection does not confer a protective effect or increase the risk of adverse oncological outcomes after resection of STS.[57]

3.4 | Limb perfusion/infusion therapy

After being used successfully in melanoma, isolated limb perfusion (ILP) initially showed disappointing results in the treatment of STS. However, the interest was renewed with the addition of tumor necrosis factor-α (TNF-α) to melphalan in ILP. ILP applies high-dose local chemotherapy (melphalan), with TNF-α and hyperthermia, which is restricted to the affected limb through arterial and venous cannulation and a tourniquet.[58]

Recent studies have shown that ILP reduces tumors, rendering them passive to resection and that it should be considered in select cases.[59] It can be used as an adjuvant treatment in cases of marginal surgical resections, in which the RT dose has already been exhausted.[60]

A meta-analysis and systematic review evaluated 19 studies on patients with advanced or marginally resected STS who were treated with perfusion therapy or limb infusion with or without TNF-α regimens. The study showed no difference between those who were given TNF-α with melphalan or not. However, in nonrandomized studies, the level of evidence is generally weak.

3.4.1 | Recommendation

- When possible, ILP can be used in a neoadjuvant manner (preoperative) to reduce the dimensions of the primary tumor or

improve local conditions, increasing the probability of limb preservation surgery.[61] However, alpha and melphalan NTT are unavailable in most centers in Brazil; thus, we do not recommend this type of treatment outside of institutional protocols with experienced surgeons (IIC).[62]

3.5 | Radiotherapy

Surgical resection with adequate margins that is followed by RT is considered the standard treatment, with excellent rates of local control and maintenance of limb function and quality of life, without affecting the overall survival.[58,63] No randomized study has specifically defined the subgroup of patients with high-grade tumors who do not require RT. Given the conflicting outcomes of nonrandomized trials and the clear benefit in local control that is offered by adjuvant RT in randomized trials, the standard treatment for most high-grade lesions remains limb preservation surgery that is followed by RT.[64]

3.5.1 | Recommendations

- Wide excision, followed by RT, is indicated in high-grade disease (grades 2 and 3), deeper or greater than 5 cm (IIB).[58,59,65]
- With exceptions to be discussed in a multidisciplinary context and in the absence of a consensus among large reference centers, tumors that are high-grade and deeper and less than 5 cm have to be treated with surgery, followed by RT (IVC).[58,59]
- RT can also be considered in select cases of the superficial lesions, greater than 5 cm (any grade), and of low-grade deep and greater than 5 cm. In these cases, RT should be discussed in a multidisciplinary setting, considering the anatomical location, histological aggressiveness, and expected sequelae of treatment (IIB).[58,59]

  Note: (a) In the absence of definitive data, patients with superficial tumors that are smaller than 5 cm; unequivocally free 3D margins; and intact facial planes are candidates for treatment with surgery only.[66] (b) To help identify these subgroups, a tool was developed by MSKCC—a nomogram to estimate the likelihood of local relapse in 3 and 5 years in operated patients, without chemotherapy or adjuvant RT, incorporating five independent prognostic factors: age, grade, size, margins, and histology.[60]
- RT should be omitted in the rare cases of actual compartmental resection, in which the entire lesion is contained in the anatomical compartment that has been removed (IVC).[2]
- In cases of marginal resections or R1-R2, RT is also indicated, this decision of which is individualized according to the possibility of surgical enlargement of the margins and the impact on future approaches (IVC).[2]
- In rare cases with lymph node involvement, adjuvant treatment can be recommended after lymphadenectomy and should be reserved for cases with many affected lymph nodes or extracapsular extravasation. In these cases, the benefit on local control should be balanced against the toxicity (especially lymphedema) (IVC).[2]
- There is no consensus on the exact time for initiating adjuvant RT. It is recommended that in patients who will not undergo adjuvant chemotherapy, adjuvant RT should be started 4 and 8 weeks after surgery.
- Related to neoadjuvant RT, the surgery should be performed between 4 and 8 weeks after the end of the RT (IVC).

  Note: (a) Local control and overall survival are influenced by acute or late local complications, not by the time of RT. (b) The choice of neoadjuvant or adjuvant treatment with RT remains under discussion, and the only randomized study was concluded prematurely due to greater surgical wound complications in the neoadjuvant group. However, at the late follow-up, patients in the adjuvant group experienced high rates of late grade 2 or 3 toxicity, such as fibrosis, edema, and joint stiffness.[45] Therefore, a multidisciplinary evaluation is recommended to define the treatment sequence, taking into consideration the time between surgery and RT, tumor size, anatomical location, and histological type.[67,68]
- If severe complications in the surgical wound can be predicted, a surgery that is followed by adjuvant RT might be the best option. If these complications are considered manageable or avoidable, then preoperative treatment should be prioritized.[67,68]
- For the adjuvant scenario, doses of 60 Gy in 30 fractions are recommended for patients who undergo R0 resection and 66 Gy in 33 fractions for those who are subjected to R1 resection. For the neoadjuvant scenario, a dose of 50 Gy in 25 fractions (IA) is recommended.[2,45]

  Note: (a) The 60- to 66-Gy scheme in 2-Gy/day fractions that were used by the NCI and O'Sullivan is the most frequently used regimen in the adjuvant scenario, whereas the 50-Gy plan in 25 2-Gy fractions per O'Sullivan is the most commonly used protocol in the neoadjuvant scenario (IIA).[45,58] (b) For patients who undergo neoadjuvant RT and are operated on with positive margins, the recommendation is to proceed with an adjuvant boost at a dose of 16 to 20 Gy.[58] However, the need for this complementary therapy has been questioned by several retrospective series (IIC).[69,70]

3.6 | Chemotherapy

The value of adjuvant chemotherapy in the treatment of STS still conflicting in literature adding the fact that the high hematological and gastrointestinal toxicity associated with chemotherapy allows only few patients to be candidates for treatment.

A 2008 meta-analysis comprised of four studies from a previous meta-analysis published in 1997 and evaluated the value of ifosfamide, combined with doxorubicin, as adjuvant therapy for sarcomas, demonstrating a small benefit for overall survival and local relapse-free survival in favor of chemotherapy.[71,72] However, the study with the most patients, EORTC 62931, was not included, which did not find any benefit with regard to overall survival with the same chemotherapy regimen.[46,73,74]

TABLE 2 Scheme of adjuvant treatment with chemotherapy and histological types to be considered

Chemotherapy schemes
Ifosfamide and doxorubicin for three to five cycles
Ifosfamide and epirubicin for three to five cycles
Chemotherapy doses
Ifosfamide 9 g/m^2 (divided into 3 to 5 d)
Epirubicin 120 mg/m^2 (divided into 2 d)
Doxorubicin 75 mg/m^2 (divided into 3 d)
Histological types
Pleomorphic/Undifferentiated sarcoma
High-grade leiomyosarcoma
High-grade myxoid liposarcoma
Synovial sarcoma
High-grade myxofibrosarcoma
Epithelioid sarcoma
Malignant tumor of the peripheral nerve sheath

3.6.1 | Recommendations

- The indications for adjuvant or neoadjuvant chemotherapy should be discussed in a multidisciplinary meeting with specialists and be based on a scheme that includes the combination of ifosfamide and doxorubicin[74] (IIA).
- Adjuvant chemotherapy should be indicated for patients with good performance status and no comorbidities, with high-grade deep sarcomas that are at least 5 cm and have been adequately resected, regardless of having undergone RT[46,74] (IIA).

  Note: Alternative regimens should not be considered, even if there is a better expectation of response in metastatic disease. Patients who are not healthy enough to receive the combination should not have their treatment adapted. They should be monitored by a more intensive follow-up regimen (IVB).[74]
- Neoadjuvant chemotherapy can be indicated for patients with deep, high-grade sarcomas that are at least 5 cm and not subject to resection with adequate margins (IIB).[46,73]

  Note: (a) The use of neoadjuvant chemotherapy today is based primarily on a phase III study that compared the standard ifosfamide- and anthracycline-based regimen with one that targeted the histological subtype for three cycles.[75] The standard regimen was superior to the other protocols with regard to overall survival in all subtypes. (b) Alternative regimens should not be considered, even if there is an expectation of a better response in metastatic disease. Patients who do not have a sufficient clinical profile to receive the combination should not have their treatment adapted. They should have their treatment rediscussed to broach neoadjuvant RT or radical, nonconservative surgeries.
- The suggested regimens for adjuvant or neoadjuvant treatment and the histological types that are to be considered are shown in Table 2.

3.7 | Follow-up

After the treatment, with or without chemotherapy or RT, the follow-up begins. Several follow-up strategies are used, considering the periodicity of the exams. The clinical history and physical examination should look for relapse signs and symptoms or eventual sequelae due to treatment.[76] Imaging tests are complementary and are intended to the study of locoregional and distant relapse.

3.7.1 | Recommendations

- The imaging tests should be defined by the medical team, considering its care conditions and patient financial status. MRI, contrast-enhanced CT, and even USG can be used for locoregional evaluation, whereas chest X-ray and CT can be used for routine lung evaluation (IVA).[76]
- In stage I and low-grade tumors, consider noncontrast-enhanced chest CT every 12 months in the first 2 years, intercalated with simple chest X-ray every 4 to 6 months and every 6 to 12 months for the subsequent 3 to 5 years (IVB).[76] Chest radiography can be performed as a follow-up due to the very low risk of metastases that are associated with low-grade tumors (IIIB).[33]

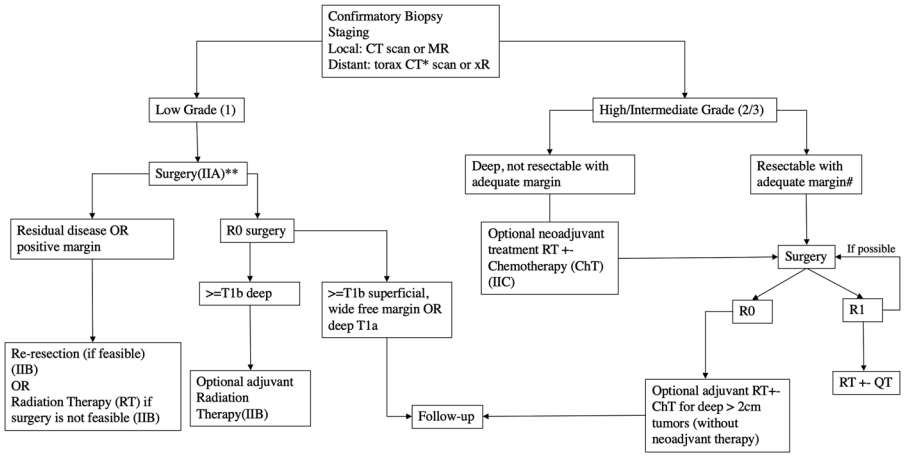

FIGURE 1 Management of localized resectable STS. OR, odds ratio; RT, radiotherapy; STS, soft tissue sarcoma; *, for high-grade tumors; **, optional neoadjuvant OR adjuvant RT for deep tumors greater than 5 cm with predictive R1 margin; #, predictive R1 margin or marginal resection from great neurovascular boundaries or bone

- MRI with or without contrast and contrast-enhanced CT can be recommended for evaluation of the primary site,[33] preferably 3 months after the surgical procedure, serving as a baseline and comparison for future examinations. Ultrasonography can be considered for small superficial lesions—to be performed by an examiner who is experienced in musculoskeletal disease (IVB).[33,76,77]
- For stages II and III, local clinical evaluation, local imaging (MRI or CT), and chest imaging (CT without contrast, alternated with plain radiography) are recommended every 3 to 6 months for 2 to 3 years, every 6 months for the next 3 to 5 years, and then annually up to 8 to 10 years (IVA).[2,33,76]

  Note: Although the use of MRI to detect local relapse and chest CT for pulmonary metastases is likely to detect earlier relapses, it has not been demonstrated that it is beneficial or cost-effective compared with the clinical evaluation of the primary site and regular chest radiographs.[2]
- Further exams or evaluations might be necessary to diagnose relapses in common sites and atypical relapses or to clarify signs and symptoms that are revealed during the follow-up, and their request should be made at the discretion of the assisting team (IVA).

  Note: Nonroutine MRI of the total spine can be considered for myxoid liposarcoma; central nervous system (CNS) MRI or CT can be considered for alveolar sarcoma and angiosarcoma; and pelvic CT or MRI can be considered for proximal end liposarcomas (IVB).[33]

3.8 | Metastatic disease (see Figure 2)

Metastases in STS develop preferentially in the lungs. The main factors that increase the risk for metastasis are tumor size, depth, and degree. Patients with deep, high-grade tumors that are larger than 10 cm have a 50% to 60% chance of developing distant metastasis. We need to drive the treatment, taking into consideration whether the metastasis is synchronous or metachronic, the volume of the metastasis, and the treatment of the primary tumor.[78]

3.8.1 | Recommendations

- We recommend that the evaluation of and therapeutic decision for patients with metastatic disease to be performed in multidisciplinary team (IVB).
- Confirmatory biopsy of the first metastasis site is recommended in atypical presentations cases and a long interval between treatment of the primary tumor rise and the appearance of metastasis or suspicion for other primary neoplasms, provided that the morbidity and risk of the procedure are manageable (IVB).[79]
- The value of sequencing techniques using broad panels of genes for determining the systemic treatment is unknown in most situations, and their routine use is not recommended (IIIC).[80]
- Research on fusions that involved the TRK gene can be considered, as they are associated with high sensitivity to such agents as Larotrectinib (approved in Brazil). However, such fusions have a low prevalence in STSs, especially in adults (IIIA).[80]

3.9 | Surgery of metastatic disease

Surgery remains the main therapeutic option for the treatment of metastatic disease in patients with ECIV STS.[78] We reiterate the recommendation that all cases that are considered should be discussed in a multidisciplinary meeting.[79] The decision for surgery should take into consideration the following factors to improve the prognosis, provided that the predicted morbidity is acceptable: histology of indolent course, relapse-free interval greater than 12 months, and up to 5 outbreaks of disease in the same organ.[81]

3.9.1 | Recommendations

- Patients who are indicated for pulmonary metastasectomy should have their treatment defined in a multidisciplinary meeting (IVB).
- The performance of PET-CT (FDG) should be considered, when available, before performing metastasis surgery (IVC)[82]

  Note: In performing pulmonary metastasectomy, the following criteria should be considered[83,84]:
  - Controlled or controllable primary tumor
  - Predictability of complete resection of lesions in previous radiological evaluation
  - Pulmonary reserve that allows surgery
  - Absence of metastatic lesions in other locations
  - Absence of superior treatment to surgery.

- The primary surgery can be performed at the same time to metastases resection or later, provided that resection of the primary tumor is predicted (IVC).[84]
- We should preserve as much of the pulmonary parenchyma as possible. The recommended surgical margins are 5 to 10 mm, but larger resections, such as lobectomy and pneumonectomy, can be performed (IVC).[84]
- We do not recommend performing mediastinal lymphadenectomy. Its impact is negligible (IVD).[85]
- We recommend, when possible, video thoracoscopy in cases of oligometrical disease or peripheral lesions (IVB).[86]
- For patients with synchronous metastases at the diagnosis, in the absence of extrapulmonary disease, the initial treatment of choice is systemic chemotherapy. Surgery is indicated to residual pulmonary lesions, especially in cases of stable disease or response[84] (IIIB).
- Initially, the extrapulmonary metastatic disease should not be treated with surgery, for which systemic treatment is the most acceptable. After systemic chemotherapy and evaluation of the

response, consider a discussion of the case in a multidisciplinary meeting (IIA).[87]

- In cases of relapse after metastasectomy, a new surgical approach can be offered if the lesions are completely resectable (IIIB).[88]

  Note: Interval time between surgery and the appearance of new lesions, a fewer number of lesions, and patient performance status are considered factors of good prognosis (IVC).[89]

3.10 | Surgery of primary tumor in metastatic disease patient

There are no data that indicate the best approach for the primary tumor in synchronous disease. The primary tumor treatment directions depend primarily on its size, location, and the volume of the metastatic disease. Efforts should be made to preserve the limb, considering that the prognosis is related to metastases and that the oncological principles must be obeyed.

3.10.1 | Recommendations

- We recommend that all patients with the synchronic disease be discussed in a multidisciplinary meeting (IVB).
- The treatment sequence should be based on patients' status performance, the primary tumor volume, and metastatic disease. However, our recommendation is that systemic treatment with chemotherapy be prioritized at the beginning of treatment (IIIB).[84]
- Surgery for primary resection, when indicated, must obey oncological principles with regard to margin (as discussed), and RT is considered in neoadjuvant and adjuvant settings for tumors that are not subject to adequate resection (IIB).[58,59,65]
- Limb amputation should be indicated only in cases in which the limb becomes a hindrance to the quality of life and when it is not possible to preserve the affected limb (IVC).

3.11 | Radiotherapy

RT has a well-established role in the palliation of symptoms of metastatic disease due to its antalgic, hemostatic, and decompressive function. There are general treatment recommendations and specific recommendations regarding the site of involvement, such as with bone,[90] pulmonary, and cerebral[91] metastases. However, in very specific situations, it can be indicated for palliation and local control of metastases, notably in the case of oligometastases.[92]

STS is a radioresistant disease,[90] and in this context, extracranial stereotactic RT (SBRT or SABR), which supplies restricted ablative doses to the tumor while delivering lower doses to adjacent structures, is an interesting modality for achieving satisfactory response rates. Nevertheless, the efficacy of SABR in pulmonary metastases has been demonstrated in several institutional series. This technique effects 2-year local control rates between 86% and 96%,[93] with low complication rates. As it is a noninvasive procedure and easy to tolerate, it can be considered as an option other than surgery in the treatment of pulmonary metastases, meeting some selection criteria, such as a progression-free period after primary treatment, the number of lesions per lung, and evolution of the systemic disease.[92] Another situation in which SBRT is widely used is paraspinal tumors. Local control rates with this strategy of 85.9% have been achieved.[92] SABR can also be performed in intracranial, hepatic, intra-abdominal, lymph node, and subcutaneous lesions.

Finally, the nonsurgical option should always be discussed with the patient and in a multidisciplinary manner to control the metastatic disease, without any detriment to the quality of life.

3.11.1 | Recommendations

- RT should be considered in the palliation of such symptoms as pain; bleeding; obstruction; and hollow organs, bones, central or peripheral nervous system, and viscera (IA).
- The fractionation regimens can vary from a single dose to treatments in 10 fractions, depending on the location that is treated, the objective of the treatment, and the performance status of the patient (IA).
- Extracranial stereotactic RT (SABR or SBRT) can be considered when local control is desired, especially in oligometastatic patients (synchronic or metachronic metastases), and in situations of oligoprogression (up to 5 lesions) (IIB).

  Note: Possible locations for treatment with SABR or SBRT are the lung, bone, liver, soft tissues, and lymph nodes.
- CNS metastases follow general treatment recommendations: surgery or ablative RT for patients with few lesions (up to 4) and total brain irradiation for patients with multiple lesions, low-performance status, or extra-CNS progression disease (IA).

3.12 | Chemotherapy

The aim of the systemic treatment of patients with metastatic STS is to relieve symptoms and improve quality of life.

Certain histologies should be considered separately and follow specific management algorithms in metastatic disease: rhabdomyosarcomas, PEComas, alveolar STS, dermatofibrosarcoma protuberans, and solitary fibrous tumors.

This section will describe the systemic treatment options and several situations for their use in metastatic patients.

3.12.1 | Recommendations

Nonresectable local relapse

- Consider systemic treatment with preoperative chemotherapy and subsequent surgery. The choice of a chemotherapy regimen in this

scenario should take into consideration the previous use of anthracycline and adjuvant ifosfamide (IVB).

Lymph node relapse

- A rare situation with a poor prognosis without standard treatment. Consider surgical treatment, followed by RT and chemotherapy, in sensitive histologies. In certain cases, consider neoadjuvant treatment to avoid mutilating surgeries (IVB).

Systemic relapse

- Patients with exclusive pulmonary disease can be treated with surgery exclusively of the lung if they fit the criteria for metastasis surgery.
- Patients with a relapse interval less than 12 months or with more than 3 pulmonary lesions should be treated initially with systemic chemotherapy for subsequent surgical procedure evaluation, depending on the tumor response, despite the absence of evidence of an improvement in overall survival (IIIB).

3.13 | First-line palliative chemotherapy

First-line treatment should be indicated for patients who have not been previously subjected to neoadjuvant or adjuvant chemotherapy and who present metastatic disease or local relapse that is not resectable (IA).

The first-line and second-line regimens are described in Table 2.

3.13.1 | Recommendations

- Conventional doxorubicin continues to be the preferred first-line drug in metastatic disease, with no better scheme in terms of overall survival to date. The response rate is 10% on average, with progression-free survival (SLP) of 3 months and overall survival (SG) of 12 months.
- Ifosfamide can be used as a first-line regimen in patients with contraindications to anthracycline or histologies that are sensitive to ifosfamide, such as synovial sarcoma.[94]

  Note: (a) In a phase III study, two ifosfamide regimens were compared with doxorubicin alone. The superiority of doxorubicin over ifosfamide was maintained with response rates of 8.4%, an SLP of 3 months, and an overall survival of 10.92 months.[94] (b) The recommended histologies are undifferentiated high-grade pleomorphic sarcoma, synovial sarcoma, and malignant peripheral neural sheath tumor.
- Liposomal doxorubicin can be used primarily for patients who are not candidates for conventional doxorubicin due to its lower toxicity.[95]

  Note: (a) In a phase II study that compared both drugs, there was no significant difference in survival.[95]
- The combination of doxorubicin and ifosfamide in the first line did not show better overall survival in a randomized phase III study compared with doxorubicin alone, only higher local response rate compared with doxorubicin alone (26% vs 14%) with a higher rate of gastrointestinal and hematological toxicity.[96] Our recommendation is that the combination be a therapeutic option in cases of the synchronic disease with the possibility of resection of the primary tumor and metastases, after discussion in a multidisciplinary environment (IIIB).

3.14 | Second-line palliative chemotherapy

The second-line schemes are based on gemcitabine only, have response rates ranging from 4% to 18% and an SLP and GS of approximately 3 months and 13.9 months, respectively. Gemcitabine in combination with docetaxel, dacarbazine or vinorelbine have response rates ranging from 12.5% to 16%, SLP ranges from 3.4 to 6.2 months, and GS ranges from 16.8 to 17.9 months.[97–99]

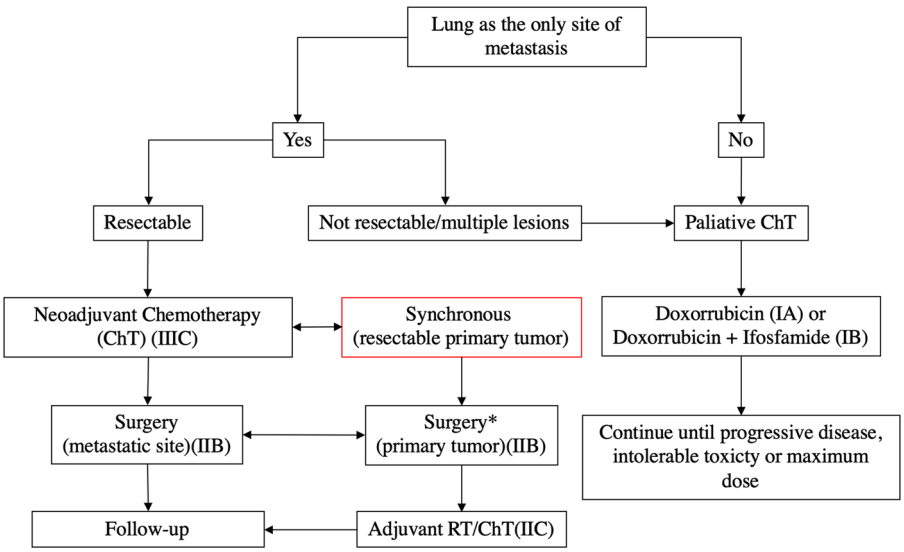

FIGURE 2 Management of metastatic STS. STS, soft tissue sarcoma; *, all patients go to multidisciplinary team discussion; **, same principles for nonmetastatic disease [Color figure can be viewed at wileyonlinelibrary.com]

3.14.1 | Recommendation

- Second-line treatment is indicated after failure of the anthracycline or ifosfamide regimen in adjuvant, neoadjuvant, or first-line metastatic disease (IBI).

  Note: Recommended histologies are nonuterine and uterine leiomyosarcomas, high-grade undifferentiated pleomorphic sarcoma, undifferentiated liposarcoma, pleomorphic liposarcoma, and synovial sarcoma.

3.15 | Patients refractory to two lines of palliative chemotherapy

3.15.1 | Drugs approved for use in Brazil

A situation in which the disease progresses despite the first and second lines of treatment is common. Several studies and drugs are being developed primarily for these situations, often supported by phase II studies. In Brazil, pazopanib and eribulin are approved. Dacarbazine can also be used as a third-line treatment in cases of leiomyosarcomas and high-grade liposarcomas (IIB).[100]

Pazopanib is a tyrosine kinase inhibitor against VEGF, PDGF, and FGF receptors used orally at a dosage of 800 mg per day in patients who have failed at least one line of chemotherapy with metastatic sarcomas, excluding liposarcomas. The Palette study was a randomized, double-blind phase III study that compared pazopanib with placebo in these patients, demonstrating a 3-month increase in progression-free survival and a 46% reduction in the risk of progression, especially in patients with synovial sarcoma and leiomyosarcomas.[100] The regimen for pazopanib is 800 mg orally continuously, and the histological subtypes that are considered for treatment are metastatic nonliposarcomas (Tables 3 and 4).

Another drug that has been approved for use in Brazil is eribulin. An important phase III study compared eribulin with dacarbazine in patients with leiomyosarcoma and metastatic liposarcomas. There was no difference in progression-free survival, but there was an increase in overall survival of 2 months in favor of eribulin. There were greater hematological toxicity and peripheral neuropathy in the eribulin group, in addition to a higher cost. In a subgroup analysis, the overall survival benefit was seen only in patients with liposarcomas, not in those with leiomyosarcomas. Therefore, eribulin should preferably be considered in patients with good performance status and a diagnosis of undifferentiated, pleomorphic, or high-grade myxoid liposarcoma.[101] The recommended dosage is 1.4 mg/m^2 on days 1 and 8 every 21 days (IA).

As a third-line option, dacarbazine is an older, low-cost drug with limited activity in metastatic sarcomas. The histological subtype that derives the greatest benefit is nonuterine leiomyosarcoma, according to the main studies, including a phase III study that compared dacarbazine with eribulin.[101] The recommended dosage is 850 to 1800 mg/m^2 on day 1 every 21 days (IB).

TABLE 3 Schemes and doses of first-line and second-line chemotherapy for metastatic disease

	Dose	Interval
First line		
Scheme—one drug		
Doxorubicin[a]	60-75 mg/m^2 day 1	21 d
Doxorubicin Lipos	40-50 mg/m^2 day 1	21-28 d
Combined scheme		
Doxorubicin[a]	25 mg/m^2 day 1	21 d
Ifosfamide	3 g/m^2 days 1 to 3	21 d
Granulokine	300 mcg days 4 to 10	
Second line		
Scheme 1		
Gemcitabine	900-1000 mg/m^2 days 1 and 8	21 d
Docetaxel	75 mg/m^2 day 8	21 d
Granulokine	300 mcg days 9 to 15	
Scheme 2		
Gemcitabine	800 mg/m^2 days 1 and 8	21 d
Vinorelbine	25 mg/m^2 days 1 and 8	21 d
Scheme 3		
Gemcitabine	1800 mg/m^2 days 1 15	21 d
Dacarbazine	500 mg/m^2 days 1 and 15	21 d

[a]Maximum of six cycles.

3.15.2 | Drugs not approved for use in Brazil

Trabectedin is a drug that has been used in patients with leiomyosarcomas or metastatic liposarcomas that are refractory to at least two lines of chemotherapy, including anthracyclines. The use of this drug is based on a phase III study that compared it with dacarbazine. There was a gain in progression-free survival of 2.7 months in favor of trabectedin.[102] This drug is recommended for patients with uterine and nonuterine leiomyosarcomas, undifferentiated and pleomorphic liposarcomas, and high-grade myxoid liposarcoma. The recommended dosage is 1.5 g/m^2 on day 1 every 21 days (IID).

Pembrolizumab was evaluated for use in SARC 028. This phase II study evaluated the use of pembrolizumab in patients with bone sarcomas and metastatic soft tissues. Patients with undifferentiated liposarcoma and high-grade pleomorphic sarcoma experienced the greatest benefit and were thus evaluated in a phase III study.[103] The recommended dosage is 2 mg/kg every 21 days (IIID).

TABLE 4 Selected histologies and treatment options

Histology	Treatment options
Soft tissue alveolar sarcoma	TK inhibitors
Solitary fibrous tumor	Pazopanib, Temozolomide, and Bevacizumab
Angiosarcomas	Taxanes, Anthracyclines
Dermatofibrosarcoma protuberans	Imatinib
PEComas	mTOR inhibitors
Sarcomas with TRK gene fusions	Larotrectinib

Abbreviation: TK, tyrosine kinase.

3.16 | Special histologies

Angiosarcomas have a high sensitivity to taxanes, especially primary angiosarcomas of the scalp. Other options for treatment of this histological type include doxorubicin (conventional or liposomal), gemcitabine in combination with docetaxel and pazopanib (IIIB).

Alveolar sarcoma has a high sensitivity to tyrosine kinase inhibitors, including sunitinib and pazopanib. The recommended regimens are sunitinib 50 mg continuous oral dose for 4 weeks and a 2-week pause and pazopanib 800 mg continuous oral dose (IIIB).[100]

The *solitary fibrous tumor* is an STS that has low sensitivity to conventional chemotherapy. In cases of advanced disease, for which surgery is not possible, or metastatic disease, the combination of temozolomide and bevacizumab should be considered, especially for a parameningeal location. The drugs that can be considered are sunitinib,[104] pazopanib,[105] and the combination of temozolomide and bevacizumab[106] (IIIB).

Finally, search for NTRK fusion 1, 2, or 3 might be indicated in refractory cases, because larotrectinib is efficacious[107] in these cases of sarcomas with NTRK fusion. The dosage is 100 mg twice daily in a continuous manner.

3.17 | Final recommendations

- In light of the possibility of complex treatment plans for patients with advanced disease, which can include, in addition to systemic treatment, strategies that are combined with RT or metastasectomy, among others, the evaluation of cases of advanced sarcomas by multidisciplinary groups is recommended (IIIA).
- Systemic treatment options that are applicable to most STSs, including anthracyclines and alkylating agents (especially ifosfamide), were defined several decades ago. In randomized studies, the use of multidrug regimens, despite the possibility of a higher response rate in certain situations, at the expense of greater toxicity, did not result in gains in overall survival compared with doxorubicin alone. However, the use of such regimens as doxorubicin/ifosfamide and gemcitabine/docetaxel can be considered in patients who need symptom control, the perspective of surgical salvage, or, in the case of gemcitabine-based combinations, in those who are not candidates for anthracyclines (IIIB).

  For subsequent lines of chemotherapy, in patients who have failed anthracyclines, such alternatives as gemcitabine, dacarbazine, pazopanib, eribulin, and trabectedin, which have been evaluated in randomized studies, should be considered.

  Note: Studies that evaluated eribulin and trabectedin included only leiomyosarcomas and liposarcomas. The survival gains with eribulin were restricted to patients with liposarcomas, whereas trabectedin, which seems to have better results, is not approved for use in Brazil (IIIC).
- Ifosfamide is particularly active in patients with synovial sarcoma and is an alternative as a first-line treatment and for rescue (IBI).

ACKNOWLEDGMENTS

The authors their colleagues from Brazilian medical societies who helped to do this consensus with their expertise that greatly assisted this study and SSO (society of Surgical Oncology) for providing all the support to publish this manuscript after its presentation at second BSSO/BSRT/BSOC Oncology Week.

AUTHOR CONTRIBUTIONS

All authors contributed to the conception, acquisition of data, drafting and revising of the manuscript. Everyone approved of the final version of the manuscript

ORCID

Ranyell M. S. S. B. Spencer http://orcid.org/0000-0002-4497-5964
Samir A. Hanna http://orcid.org/0000-0002-1976-0662
Raphael L. C. de Araujo http://orcid.org/0000-0002-7834-5944

REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. *CA Cancer J Clin*. 2018;68(1):7-30.
2. Casali PG, Abecassis N, Aro HT, et al. Soft tissue and visceral sarcomas: ESMO-EURACAN Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2018;29(suppl 4):iv268-iv269.
3. Riechelmann RP, Weschenfelder RF, Costa FP, et al. Guidelines for the management of neuroendocrine tumours by the Brazilian gastrointestinal tumour group. *Ecancermedicalscience*. 2017;11:716.
4. Riechelmann R, Coutinho AK, Weschenfelder RF, et al. Guideline for the management of bile duct cancers by the brazilian gastrointestinal tumor group. *Arq Gastroenterol*. 2016;53(1):5-9.
5. Burningham Z, Hashibe M, Spector L, Schiffman JD. The epidemiology of sarcoma. *Clin Sarcoma Res*. 2012;2(1):14.
6. Engels EA, Biggar RJ, Marshall VA, et al. Detection and quantification of Kaposi's sarcoma-associated herpesvirus to predict AIDS-associated Kaposi's sarcoma. *AIDS*. 2003;17(12):1847-1851.
7. Pereira ESP, Moraes ET, Siqueira DM, Santos MAS. Stewart-Treves syndrome. *An Bras Dermatol*. 2015;90(3 suppl 1):229-231.
8. Olivier M, Goldgar DE, Sodha N, et al. Li-Fraumeni and related syndromes: correlation between tumor type, family structure, and TP53 genotype. *Cancer Res*. 2003;63(20):6643-6650.
9. Achatz MI, Zambetti GP. The inherited p53 mutation in the Brazilian population. *Cold Spring Harb Perspect Med*. 2016;6(12):a026195.
10. van Houdt WJ, Wei IH, Kuk D, et al. Yield of colonoscopy in identification of newly diagnosed desmoid-type fibromatosis with underlying familial adenomatous polyposis. *Ann Surg Oncol*. 2019;26(3):765-771.
11. Brems H, Beert E, de Ravel T, Legius E. Mechanisms in the pathogenesis of malignant tumours in neurofibromatosis type 1. *Lancet Oncol*. 2009;10(5):508-515.

12. Kleihues P, Schäuble B, zur Hausen A, Estève J, Ohgaki H. Tumors associated with p53 germline mutations: a synopsis of 91 families. *Am J Pathol*. 1997;150(1):1-13.
13. Rubino C, Shamsaldin A, Lê MG, et al. Radiation dose and risk of soft tissue and bone sarcoma after breast cancer treatment. *Breast Cancer Res Treat*. 2005;89(3):277-288.
14. Virtanen A, Pukkala E, Auvinen A. Incidence of bone and soft tissue sarcoma after radiotherapy: a cohort study of 295,712 Finnish cancer patients. *Int J Cancer*. 2006;118(4):1017-1021.
15. Hoppin JA, Tolbert PE, Herrick RF, et al. Occupational chlorophenol exposure and soft tissue sarcoma risk among men aged 30–60 years. *Am J Epidemiol*. 1998;148(7):693-703.
16. Hoppin JA, Tolbert PE, Flanders WD, et al. Occupational risk factors for sarcoma subtypes. *Epidemiology*. 1999;10(3):300-306.
17. Beaman FD, Motamedi K, Lenchik L, et al. ACR Appropriateness Criteria ® soft-tissue masses. *J Am Coll Radiol*. 2018;15(5):S189-S197.
18. Kransdorf MJ, Murphey MD. Radiologic evaluation of soft-tissue masses. *Am J Roentgenol*. 2000;175(3):575-587.
19. Gartner L, Pearce CJ, Saifuddin A. The role of the plain radiograph in the characterization of soft tissue tumours. *Skeletal Radiol*. 2009;38(6):549-558.
20. Pollock R, Sandhu R, De La Hoz Polo M, Bhumbra R, Saifuddin A, Dick E. Surgical considerations when reporting MRI studies of soft tissue sarcoma of the limbs. *Skeletal Radiol*. 2017;46(12):1667-1678.
21. Christie-Large M, James SLJ, Tiessen L, Davies AM, Grimer RJ. Imaging strategy for detecting lung metastases at presentation in patients with soft tissue sarcomas. *Eur J Cancer*. 2008;44(13):1841-1845.
22. Thompson MJ, Ross J, Domson G, Foster W. Screening and surveillance CT abdomen/pelvis for metastases in patients with soft-tissue sarcoma of the extremity. *Bone Joint Res*. 2015;4(3):45-49.
23. Steffner RJ, Jang ES. Staging of bone and soft-tissue sarcomas. *J Am Acad Orthop Surg*. 2018;26(13):e269-e278.
24. von Mehren M, Randall RL, Benjamin RS, et al. Soft tissue sarcoma, version 2.2018: clinical practice guidelines in oncology. *J Natl Compr Canc Netw*. 2018;16(5):536-563.
25. Amin MB, Edge S, Greene F, et al., eds. *AJCC Cancer Staging Manual*. 8th ed. Springer International Publishing: American Joint Commission on Cancer; 2017. https://www.springer.com/gp/book/9783319406176
26. Eary JF, O'Sullivan F, Powitan Y, et al. Sarcoma tumor FDG uptake measured by PET and patient outcome: a retrospective analysis. *Eur J Nucl Med Mol Imaging*. 2002;29(9):1149-1154.
27. Dietel M, Bubendorf L, Dingemans AMC, et al. Diagnostic procedures for non-small-cell lung cancer (NSCLC): recommendations of the European Expert Group. *Thorax*. 2016;71(2):177-184.
28. Bass BP, Engel KB, Greytak SR, Moore HM. A review of preanalytical factors affecting molecular, protein, and morphological analysis of formalin-fixed, paraffin-embedded (FFPE) tissue: how well do you know your FFPE specimen? *Arch Pathol Lab Med*. 2014;138(11):1520-1530.
29. Fletcher CDM, Bridge JA, Hogendoorn PCW, Mertens F, eds. *WHO Classification of Soft Tissue and Bone Tumors*. 4th ed. Geneva, Switzerland: WHO Press; 2013.
30. Trojani M, Contesso G, Coindre JM, et al. Soft-tissue sarcomas of adults; study of pathological prognostic variables and definition of a histopathological grading system. *Int J Cancer*. 1984;33:37-42.
31. Ray-Coquard I, Montesco MC, Coindre JM, et al. Sarcoma: concordance between initial diagnosis and centralized expert review in a population based study within three European regions. *Ann Oncol*. 2012;23:2442-2449.
32. Recommendations for the reporting of soft tissue sarcomas. Association of Directors of Anatomic and Surgical Pathology. *Mod Pathol*. 1998;11(12):1257-1261.
33. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Soft tissue sarcoma version 3.
34. Neuville A, Chibon F, Coindre J-M. Grading of soft tissue sarcomas: from histological to molecular assessment. *Pathology*. 2014;46(2):113-120.
35. Fong Y, Coit DG, Woodruff JM, Brennan MF. Lymph node metastasis from soft tissue sarcoma in adults. Analysis of data from a prospective database of 1772 sarcoma patients. *Ann Surg*. 2017;217(1):72-77.
36. Mazeron JJ, Suit HD. Lymph nodes as sites of metastases from sarcomas of soft tissue. *Cancer*. 1987;60(8):1800-1808.
37. Vraa S, Keller J, Nielsen OS, Sneppen O, Jurik AG, Jensen OM. Prognostic factors in soft tissue sarcomas: the Aarhus experience. *Eur J Cancer*. 1998;34(12):1876-1882.
38. Callegaro D, Miceli R, Mariani L. Soft tissue sarcoma nomograms and their incorporation into practice. *Cancer*. 2017;123(15):2802-2820.
39. Kattan MW, Leung DH, Brennan MF. Postoperative nomogram for 12-year sarcoma-specific death. *J Clin Oncol*. 2002;20(3):791-796. 1.
40. Mariani L, Miceli R, Kattan MW, et al. Validation and adaptation of a nomogram for predicting the survival of patients with extremity soft tissue sarcoma using a three-grade system. *Cancer*. 2005;103(2):402-408.
41. Cai L, Mirimanoff RO, Mouhsine E, et al. Prognostic factors in adult soft tissue sarcoma treated with surgery combined with radiotherapy: a retrospective single-center study on 164 patients. *Rare Tumors*. 2013;5(4):e55.
42. Gundle KR, Kafchinski L, Gupta S, et al. Analysis of margin classification systems for assessing the risk of local recurrence after soft tissue sarcoma resection. *J Clin Oncol*. 2018;36(7):704-709.
43. Gronchi A, Lo Vullo S, Colombo C, et al. Extremity soft tissue sarcoma in a series of patients treated at a single institution: Local control directly impacts survival. *Ann Surg*. 2010;251:506-511.
44. Dagan R, Indelicato DJ, McGee L, et al. The significance of a marginal excision after preoperative radiation therapy for soft tissue sarcoma of the extremity. *Cancer*. 2012;118:3199-3207.
45. O'Sullivan B, Davis AM, Turcotte R, et al. Preoperative versus postoperative radiotherapy in soft-tissue sarcoma of the limbs: a randomized trial. *Lancet*. 2002;359:2235-2241.
46. Frustaci S, Gherlinzoni F, De Paoli A, et al. Adjuvant chemotherapy for adult soft tissue sarcomas of the extremities and girdles: results of the Italian randomized cooperative trial. *J Clin Oncol*. 2001;19:1238-1247.
47. Mussi CE, Daolio P, Cimino M. Atypical lipomatous tumors: should they be treated like other sarcoma or not? Surgical consideration from a bi-institutional experience. *Ann Surg Oncol*. 2014;21(13):4090-4097.
48. Cordeiro PG, Neves RI, Hidalgo DA. The role of free tissue transfer following oncologic resection in the lower extremity. *Ann Plast Surg*. 1994;33:9-16.
49. Bridgham K, El Abiad JM, Lu ZA, et al. Outcomes of Lower Extremity Soft-Tissue Sarcoma Reconstruction: A 20-Year Experience. *J Am Col of Surg*. 2018;227(4):S209.
50. Chao AH, Chang DW, Shuaib SW, Hanasono MM. The effect of neoadjuvant versus adjuvant irradiation on microvascular free flap reconstruction in sarcoma patients. *Plast Reconstr Surg*. 2012;129:675-682.
51. Azadgoli B, Carre AL, Perrault DP, Wong AK. Complex reconstruction of the lower extremity following sarcoma resection: a literature review. *Plast Aesthet Res*. 2018;5:3.
52. López JF, Hietanen KE, Kaartinen IS, et al. Primary flap reconstruction of tissue defects after sarcoma surgery enables curative treatment with acceptable functional results: a 7-year review. *BMC Surg*. 2015;15:71.

53. Zaretski A, Amir A, Meller I, et al. Free fibula long bone reconstruction in orthopedic oncology: a surgical algorithm for reconstructive options. *Plast Reconstr Surg*. 2004;113:1989-2000.
54. Yan TQ, Zhou WH, Guo W. Endoprosthetic reconstruction for large extremity soft-tissue sarcoma with juxta-articular bone involvement: functional and survival outcome. *J Surg Res*. 2013;187(1):142-149.
55. Moore J, Isler M, Barry J, Mottard S. Major wound complication risk factors following soft tissue sarcoma resection. *Eur J Surg Oncol*. 2014;40(12):1671-1676.
56. Kennedy S, Mayo Z, Gao Y, Miller BJ. What are the results of surgical treatment of postoperative wound complications in soft tissue sarcoma? A retrospective, multi-center case series. *Iowa Orthop J*. 2018;38:131-136.
57. Duncan C, Ramsey RA, Jones JK. Identification of infectious species after resection of soft-tissue sarcomas. *J of Surg Oncol*. 2019;119(7):836-842.
58. Yang JC, Chang AE, Baker AR, et al. Randomized prospective study of the benefit of adjuvant radiation therapy in the treatment of soft tissue sarco- mas of the extremity. *J Clin Oncol*. 1998;16:197-203.
59. Beane JD, Yang JC, White D, Steinberg SM, Rosenberg SA, Rudloff U. Efficacy of adjuvant radiation therapy in the treatment of soft tissue sarcoma of the extremity: 20-year follow- up of a randomized prospective trial. *Ann Surg Oncol*. 2014;21:2484-2489.
60. Cahlon O, Brennan MF, Jia X, Qin LX, Singer S, Alektiar KM. A postoperative nomogram for local recurrence risk in extremity soft tissue sarcomas after limb-sparing surgery without adjuvant radiation. *Ann Surg*. 2012;255:343-347.
61. Issels RD, Lindner LH, Verweij J, et al. Neo-adjuvant chemotherapy alone or with regional hyperthermia for localised high-risk soft-tissue sarcoma: a randomised phase 3 multicentre study. *Lancet Oncol*. 2010;11:561-570.
62. Neuwirth MG, Song Y, Sinnamon AJ, Fraker DL, Zager JS, Karakousis GC. Isolated limb perfusion and infusion for extremity soft tissue sarcoma: a contemporary systematic review and meta-analysis. *Ann Surg Oncol*. 2017;24(13):3803-3810.
63. Rosenberg SA, Tepper J, Glatstein E, et al. Prospective randomized evaluations of (1) limb-sparing surgery plus radiation therapy compared with amputation and (2) the role of adjuvant chemotherapy. *Ann Surg*. 1982;196(3):305-314.
64. Baldini EH, Raut C. Radiation therapy for extremity soft tissue sarcoma: in the absence of a clear survival benefit, why do we give it? *Ann Surg Oncol*. 2014;21:2463-2465.
65. Pisters PW, Harrison LB, Leung DH, Woodruff JM, Casper ES, Brennan MF. Long-term results of a prospective randomized trial of adjuvant brachytherapy in soft tissue sarcoma. *J Clin Oncol*. 1996;14:859-868.
66. Pisters PW, O'Sullivan B, Maki RG. Evidence-based recommendations for local therapy for soft tissue sarcomas. *J Clin Oncol*. 2007;25(8):1003-1008.
67. O'Sullivan B, Griffin AM, Dickie CI, et al. Phase 2 study of preoperative image-guided intensity-modulated radiation therapy to reduce wound and combined modality morbidities in lower extremity soft tissue sarcoma. *Cancer*. 2013;119(10):1878-1884.
68. Baldini EH, Lapidus MR, Wang Q, et al. Predictors for major wound complications following preoperative radiotherapy and surgery for soft-tissue sarcoma of the extremities and trunk: importance of tumor proximity to skin surface. *Ann Surg Oncol*. 2013;20:1494-1499.
69. Al Yami A, Griffin AM, Ferguson PC, et al. Positive surgical margins in soft tissue sarcoma treated with preoperative radiation: is a postoperative boost necessary? *Int J Radiat Oncol Biol Phys*. 2010;77(4):1191-1197.
70. Pan E, Goldberg SI, Chen YL, et al. Role of post-operative radiation boost for soft tissue sarcomas with positive margins following pre-operative radiation and surgery. *J Surg Oncol*. 2014;110(7):817-822.
71. Adjuvant chemotherapy for localised resectable soft tissue sarcoma of adults: meta-analysis of individual data. Sarcoma Meta-analysis Collaboration. *Lancet*. 1997;350(9092):1647-1654.
72. Pervaiz N, Colterjohn N, Farrokhyar F, Tozer R, Figueredo A, Ghert M. A systematic meta-analysis of randomized controlled trials of adjuvant chemotherapy for localized resectable soft-tissue sarcoma. *Cancer*. 2008;113(3):573-581.
73. Frustaci S, De Paoli A, Bidoli E, et al. Ifosfamide in the adjuvant therapy of soft tissue sarcomas. *Oncology*. 2003;65(suppl 2):80-84.
74. Woll PJ, Reichardt P, Le Cesne A, et al. Adjuvant chemotherapy with doxorubicin, ifosfamide, and lenograstim for resected soft-tissue sarcoma (EORTC 62931): a multicentre randomised controlled trial. *Lancet Oncol*. 2012;13(10):1045-1054.
75. Gronchi A, Ferrari S, Quagliuolo V, et al. Histotype-tailored neoadjuvant chemotherapy versus standard chemotherapy in patients with high-risk soft-tissue sarcomas (ISG-STS 1001): an international, open-label, randomised, controlled, phase 3, multicentre trial. *Lancet Oncol*. 2017;18(6):812-822.
76. Dangoor A, Seddon B, Gerrand C, Grimer R, Whelan J, Judson I. UK guidelines for the management of soft tissue sarcomas. *Clin Sarcoma Res*. 2016;6:20.
77. Choi H, Varma DG, Fornage BD, Kim EE, Johnston DA. Soft-tissue sarcoma: MR imaging vs sonography for detection of local recurrence after surgery. *AJR Am J Roentgenol*. 1991;157:353-358.
78. Pastorino U, Buyse M, Friedel G, et al. Long-term results of lung metastasectomy: prognostic analyses based on 5206 cases. *J Thorac Cardiovasc Surg*. 1997;113(1):37-49.
79. Billingsley KG, Burt ME, Jara E, et al. Pulmonary metastases from soft tissue sarcoma: analysis of patterns of diseases and post metastasis survival. *Ann Surg*. 1999;229(5):602-610.
80. Ohnstad HO, Bruland ØS, Taksdal I, et al. Response to preoperative chemotherapy in patients undergoing resection of pulmonary metastasis from soft tissue sarcoma—a predictor of outcome? *Acta Oncol*. 2014;53:1180-1886.
81. Chudgar NP, Brennan MF, Munhoz RR, et al. Pulmonary metastasectomy with therapeutic intent for soft-tissue sarcoma. *J Thorac Cardiovasc Surg*. 2017;154(1):319.e1-330.e1.
82. Pastorino U, Veronesi G, Landoni C, et al. Fluorodeoxyglucose positron emission tomograph improves preoperative staging of resectable lung metastasis. *J Thorac Cardiovasc Surg*. 2003;126:1906-1910.
83. McCormack P. Surgical resection of pulmonary metastases. *Semin Surg Oncol*. 1990;6(5):297-302.
84. Quiros RM, Scott WJ. Surgical treatment of metastatic disease to the lung. *Semin Oncol*. 2008;35(2):134-146.
85. Lo Faso F, Solaini L, Lembo R, et al. Thoracoscopic lung metastasectomies: a 10-year, single-center experience. *Surg Endosc*. 2013;27:1938-1944.
86. Gossot D, Radu C, Girard P, et al. Resection of pulmonary metastases from sarcoma: can some patients benefit from a less invasive approach? *Ann Thorac Surg*. 2009;87(1):238-243.
87. Chao C, Goldberg M. Surgical treatment of metastatic pulmonary soft-tissue sarcoma. *Oncology*. 2000;14(6):835-841.
88. Pogrebniak HW, Roth JA, Steinberg SM, Rosenberg SA, Pass HI. Reoperative pulmonary resection in patients with metastatic soft tissue sarcoma. *Ann Thorac Surg*. 1991;52(2):197-203.
89. Casson AG, Putnam JB, Natarajan G, et al. Efficacy of pulmonary metastasectomy for recurrent soft tissue sarcoma. *Journal of surgical oncology*. 1991;47(1):1-4.
90. Hartsell WF, Scott CB, Bruner DW, et al. Randomized trial of short- versus long-course radiotherapy for palliation of painful bone metastases. *J Natl Cancer Inst*. 2005;97(11):798-804.

91. Brown PD, Jaeckle K, Ballman KV, et al. Effect of radiosurgery alone vs radiosurgery with whole brain radiation therapy on cognitive function in patients with 1 to 3 brain metastases: a randomized clinical trial. *JAMA*. 2016;316(4):401-409.
92. Mahajan A, Ahmed S, McAleer MF, et al. Post-operative stereotactic radiosurgery versus observation for completely resected brain metastases: a single-centre, randomised, controlled, phase 3 trial. *Lancet Oncol*. 2017;18(8):1040-1048.
93. Steenland E, Leer J, van Houwelingen H, et al. The effect of a single fraction compared to multiple fractions on painful bone metastases: a global analysis of the Dutch Bone Metastasis Study. *Radiother Oncol*. 1999;52(2):101-109.
94. Lorigan P, Verweij J, Papai Z, et al. Phase II study of capecitabine plus trastuzumab in human epidermal growth factor receptor 2 overexpressing metastatic breast cancer pretreated with anthracyclines or taxanes. *J Clin Oncol*. 2007;25(21):3144-3150.
95. Judson I, Radford JA, Harris M, et al. Randomised phase II trial of pegylated liposomal doxorubicin (DOXIL/CAELYX) versus doxorubicin in the treatment of advanced or metastatic soft tissue sarcoma: a study by the EORTC Soft Tissue and Bone Sarcoma Group. *EUR J Cancer*. 2001;37(7):870-877.
96. Judson I, Verweij J, Gelderblom H, et al. Doxorubicin alone versus intensified doxorubicin plus ifosfamide for first-line treatment of advanced or metastatic soft-tissue sarcoma: a randomised controlled phase 3 trial. *Lancet Oncol*. 2014;15(4):415-423.
97. Da Silva FR, Lima AVJ, Albuquerque EWRP, et al. Complete remission of recurrent retroperitoneal liposarcoma after the administration of gemcitabine and docetaxel as first-line adjuvant chemotherapy: a case report. *Case Rep Oncol*. 2018;11:341-346.
98. García-Del-Muro X, López-Pousa A, Maurel J, et al. Randomized phase II study comparing gemcitabine plus dacarbazine versus dacarbazine alone in patients with previously treated soft tissue sarcoma: a Spanish Group for Research on Sarcomas study. *J Clin Oncol*. 2011;29(18):2528-2533.
99. Dileo P, Morgan JA, Zahrieh D, et al. Gemcitabine and vinorelbine combination chemotherapy for patients with advanced soft tissue sarcomas: results of a phase II trial. *Cancer*. 2007;109(9):1863-1869.
100. van der Graaf WT, Blay JY, Chawla SP, et al. PALETTE study group: Pazopanib for metastatic soft-tissue sarcoma (PALETTE): a randomized, double-blind, placebo-controlled phase 3 trial. *Lancet*. 2012;379(9829):1879-1886.
101. Demetri GD, Schöffski P, Grignani G, et al. Activity of eribulin in patients with advanced liposarcoma demonstrated in a subgroup analysis from a randomized phase iii study of eribulin versus dacarbazine. *J Clin Oncol*. 2017;35(30):3433-3439.
102. Demetri GD, von Mehren M, Jones RL, et al. Efficacy and safety of trabectedin or dacarbazine for metastatic liposarcoma or leiomyosarcoma after failure of conventional chemotherapy: results of a phase III randomized multicenter clinical trial. *J Clin Oncol*. 2016;34(8):786-793.
103. Tawbi HA, Burgess M, Bolejack V, et al. Pembrolizumab in advanced soft-tissue sarcoma and bone sarcoma (SARC028): a multicentre, two-cohort, single-arm, open label, phase 2 trial. *Lancet Oncol*. 2017;18(11):1493-1501.
104. Stacchiotti S, Negri T, Libertini M, et al. Sunitinib malate in solitary fibrous tumor (SFT). *Ann Oncol*. 2012;23:3171-3179.
105. Maruzzo M, Martin-Liberal J, Messiou C, et al. Pazopanib as first line treatment for solitary fibrous tumours: the Royal Marsden Hospital experience. *Clin Sarcoma Res*. 2015;2(5):5.
106. Park MS, Patel SR, Ludwig JA, et al. Activity of temozolomide and bevacizumab in the treatment of locally advanced, recurrent, and metastatic hemangiopericytoma and malignant solitary fibrous tumor. *Cancer*. 2011;117(21):4939-4947.
107. Miettinen M, Felisiak-Golabek A, Luiña Contreras A, et al. New fusion sarcomas: histopathology and clinical significance of selected entities. *Hum Pathol*. 2019;86:57-65.

How to cite this article: Spencer RMSSB, de Camargo VP, Silva MLG, et al. Brazilian consensus on the diagnosis and treatment of extremities soft tissue sarcomas. *J Surg Oncol*. 2020;121:743–758. https://doi.org/10.1002/jso.25847