World Journal of Clinical Oncology

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World J Clin Oncol 2020 April 24; 11(4): 180-189

DOI: 10.5306/wjco.v11.i4.180

ISSN 2218-4333 (online)

REVIEW

Multidisciplinary treatment of soft tissue sarcomas: An update

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Author contributions: Gómez J performed the literature review and analysis, and manuscript writing; Tsagozis P revised and edited the manuscript.

Conflict-of-interest statement: The authors declare no conflicts of interest.

Manuscript source: Invited manuscript

Received: December 28, 2019
Peer-review started: December 28, 2019
First decision: February 20, 2020
Revised: March 13, 2020
Accepted: March 22, 2020
Article in press: March 22, 2020
Published online: April 24, 2020

P-Reviewer: Bandyopadhyay SK, Yang L
S-Editor: Dou Y
L-Editor: A
E-Editor: Zhang YL

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Abstract

Standard treatment for soft tissue sarcoma, based on complete surgical resection with or without adjuvant radiotherapy and chemotherapy, has not substantially changed during the last several decades. Nevertheless, recent advances have contributed to considerable improvement in the management of these patients; for example, new magnetic resonance imaging sequences such as diffusion-weighted imaging and magnetic resonance imaging radiomics can better assess tumor extension and even estimate its grade. Detection of circulating genetic material (liquid biopsy) and next-generation sequencing are powerful techniques for genetic analysis, which will increase our understanding of the underlying molecular mechanisms and may reveal potential therapeutic targets. The role of chemotherapy in non-metastatic disease is still controversial, and there is a need to identify patients who really benefit from this treatment. Novel chemotherapeutic regimens have entered clinical praxis and can change the outcome of patients with metastatic disease. Advances in radiotherapy have helped decrease local adverse effects and sustain good local control of the disease. The following report provides an updated view of the diagnosis, treatment, and future perspectives on the management of patients with soft tissue sarcomas.

Key words: Soft tissue sarcomas; Multidisciplinary treatment; Surgery; Radiotherapy; Chemotherapy; Targeted therapy; Update treatment

Core tip: This report provides an updated view of the diagnosis, treatment, and future perspectives on the management of patients with soft tissue sarcomas. Recent advances include new magnetic resonance imaging sequences such as diffusion-weighted imaging and magnetic resonance imaging radiomics, which can better assess tumor extension and

estimate tumor grade. Detection of circulating genetic material (liquid biopsy) and next-generation sequencing are powerful techniques that may reveal potential therapeutic targets. Novel chemotherapeutic regimens have entered clinical praxis and can change the outcome of patients with metastatic disease. Advances in radiotherapy have helped decrease local adverse effects and sustain good local disease control.

Citation: Gómez J, Tsagozis P. Multidisciplinary treatment of soft tissue sarcomas: An update. *World J Clin Oncol* 2020; 11(4): 180-189
URL: https://www.wjgnet.com/2218-4333/full/v11/i4/180.htm
DOI: https://dx.doi.org/10.5306/wjco.v11.i4.180

INTRODUCTION

Soft tissue sarcomas (STS) are an uncommon aggressive group of tumors with an incidence of 5 cases per 100000 people per year (1% of adult solid neoplasms and 7% of pediatric solid neoplasms)[1-3]. There are more than 50 histologic subtypes of STS[2]. Rhabdomyosarcoma is the most common STS in children, whereas undifferentiated pleomorphic sarcoma is the most common in adults[4].

STS are predominantly located on the extremities and trunk, and some are found in the retroperitoneal area[5]. Patients with STS are at significant risk of local recurrence and lung metastasis[6]. Treatment of STS should be centralized in tertiary centers with devoted multidisciplinary teams comprising oncologists, orthopedic surgeons, radiologists and pathologists, and patients should be referred prior to any biopsy or excision[7,8].

The cornerstone of treatment of non-metastatic disease is complete resection of the tumor with a margin of normal tissue[9,10]. Amputation was common in the past, whereas current clinical practice entails limb-sparing resections in the majority of patients, without compromising survival[11,12]. Adjuvant radiotherapy and chemotherapy (for metastatic disease) may also have a role in the treatment of selected patients[13-18].

The aim of this report is to provide an overview of the diagnosis and treatment of extremity STS, with a focus on recent developments and future perspectives.

LITERATURE SEARCH

A systematic literature search was conducted using MEDLINE/PubMed, EMBASE, and Cochrane Library databases. We used the key words "soft tissue sarcoma" for the search. An advanced search was also made with "chemotherapy", "radiotherapy", "brachytherapy", "isolated hyperthermic limb perfusion", "multidisciplinary treatment/management", and "next-generation sequencing (NGS)". The exclusion criteria were non-published abstracts and expert opinions. A total of 226 studies about STS treatment were included for review. Of the studies with 45 results distinguished by "soft tissue sarcoma", 30 contained "surgery", 56 contained "chemotherapy" or "isolated hyperthermic limb perfusion", 42 contained "radiobrachytherapy", 34 contained "multidisciplinary treatment/management", and 19 contained "NGS".

DIAGNOSIS

History and clinical examination

The history of the patient gives important clues; for example, tumors that do not change for years are more likely to be benign. However, a mass larger than 5 cm with rapid growth, swelling, or causing neurological symptoms suggests a malignant tumor and further investigation is needed[19,20]. Pain is present in few STS and is a poor discriminator between malignant and benign tumors, although it can start after trauma[21]. About 80% of STS are deep-seated, but even a superficial tumor with troubling characteristics deserves further examination[20].

Imaging

Plain radiographic images may reveal a mass in the soft tissues and sometimes

calcification, but they are not sufficient for diagnosis. Ultrasound can identify a tumor and may show if it is superficial or deep, and doppler can evaluate tumor vascularization, but otherwise it has very limited use in diagnosis[22]. Magnetic resonance imaging (MRI) is the cornerstone of radiologic investigation, often distinguishing a benign from malignant tumor and showing its relationship with important anatomical structures.

New MRI sequences, such as diffusion-weighted imaging, can help to assess adjacent tissue infiltration. Yoon *et al*[23] reported an improved confidence level to predict fascial involvement with this sequence, and Hong *et al*[24] reported better specificity in assessing the tumor margin infiltration. Thus, diffusion-weighted imaging may help determine the extent of the resection, but additional data are needed. Furthermore, MRI findings may help define the histological grade, which is the strongest prognostic factor in STS[25]. Crombé *et al*[26] found that peritumoral enhancement, necrosis, or intratumoral heterogeneity at T2-weighted imaging were associated with tumor grade patient survival. In addition, MRI-based radiomics seems to differentiate between low- and high-grade STS more accurately[27-29]. Thus, MRI-based radiomics features in STS may correlate with histological findings and patient prognosis.

Biopsy and molecular diagnosis

Patients should be promptly referred to specialized centers where diagnosis is undertaken by multidisciplinary teams[19,20,30,31]. Well-defined guidelines should be adopted, minimizing time to surgery, wrong biopsy, and inadequate initial excision[7]. The goal is to increase awareness among general practitioners in recognizing the disease, to establish easy contact with sarcoma centers, and to minimize erroneous surgery (whoops excisions)[8].

Biopsy should preferably be performed by the surgeon who will also remove the tumor, minimizing contamination of surrounding structures[15]. A closed biopsy (fine needle aspiration or tru-cut) is usually sufficient, with an open biopsy required in some cases. The use of an ultrasound-guided-biopsy should be encouraged in cases where the tumor is heterogeneous or difficult to locate during physical examination[22]. In deep tumors or those with complicated localization, a computed tomography-guided biopsy can be performed.

In the last decade, the use of liquid biopsy has been studied as a new method for the diagnosis and staging of STS. It is based on the identification of circulating genetic material from fluids, including blood, urine, feces, saliva, or cerebrospinal fluid[32]. A study detected circulating cell-free DNA and circulating tumor-derived DNA in 4 of 11 metastatic STS patients (36%)[33]. A review of the four blood-based biosources, namely circulating tumor cells, cell-free DNA, exosomes, and metabolites, supported the view that they can improve our understanding of how STS metastasize, how tumor components reach the endovascular space, and in the future, also detect tumor evolution, reveal drug resistance mechanisms, and develop new strategies to prevent dissemination[34].

Next-generation sequencing (NGS) has improved STS diagnosis, genomic discovery, and understanding of the underlying molecular mechanisms through detection of gene deletions, insertions, copy number variants, and structural alterations in multiple STS genes, complementing traditional pathological diagnosis[35]. NGS can sequence, with minimal DNA, multiple genetic loci simultaneously, faster than traditional mutation detection systems and distinguishing morphologically similar STS[36]. Furthermore, it provides data that can be useful in the context of personalized medicine, assessing mutations with therapeutic response or resistance. For example, imatinib response in gastrointestinal stromal tumors depends on *c-KIT* gene mutations; although mutations in exon 11 usually respond to Imatinib, changes on exon 13 confer drug resistance[37]. Although experience with these procedures is still limited, NGS platforms will simplify the processing and interpretation of bioinformatics data and include genes related to diagnosis, prognosis, and treatment[38].

SOFT TISSUE SARCOMAS CLASIFICATION

STS grading and staging predict prognosis. Tumor grade is based on histological findings, while staging also considers the size and characteristics of each STS subtype. The most commonly used grade classification is the French Federation of Cancer Centers Sarcoma Group, due to its precise prognostic value[39]. The traditional tumor-node-metastasis staging system, on the other hand, used by the Joint American Commission on Cancer, directs the treatment based on the stage of the disease[40].

TREATMENT

Surgery

Inherent tumor-associated factors (tumor dimensions, histological type, grade) generally influence the overall survival (OS) of patients with STS. Web-based tools provide accurate prognosis regarding STS patients[41]. The most important parameter regarding local control is to achieve a free resection margin (R0)[9,31,42]. Since contaminated margins increase the risk of a local recurrence[9,42,43], careful preoperative planning is essential. The biopsy site must be excised en bloc with the tumor. Close margins are acceptable in an effort to preserve major neurovascular structures, when they are not invaded by the tumor, and drains must exit close to the surgical wound[44].

Several studies have described an appropriate margin as > 1 mm, including an anatomical barrier (capsule, tendon, fascia, cartilage, periosteum)[10,14,31,44,45]. A study showed that 5-mm margins without use of adjuvant radiotherapy or 1-mm margins with adjuvant radiotherapy were adequate[46]. Another study corroborated the view that limited resection achieved a negative margin, but < 1 mm may be adequate in the setting of modern multidisciplinary treatment[47]. Thus, radical resection of the whole compartment is currently considered not necessary, and amputation is generally reserved for cases when free margins cannot be achieved without loss of limb function[31]. As an attempt to increase accuracy of the surgical margin, the use of fluorescenceguided surgery has been studied in preclinical models and phase 1 trials, but the technique has not yet entered clinical praxis[48-50].

Radiotherapy

Radiation therapy (RT) improves local control of stages II and III of STS in association with limb-sparing surgery[51,52]. The extended dose of external beam RT (EBRT) is 50 Gy preoperatively and 60-76 postoperatively[53,54]. A recent study in 5726 patients compared the radiation dose-response of non-retroperitoneal STS and detected higher OS in patients treated with 69 Gy compared to 66 Gy[55]. Another report showed lower local recurrence on patients treated with 64-68 Gy compared with 60 Gy[56]. However, side effects, wound complications, and secondary fractures also increase with higher doses[57].

There is still controversy on the timing of RT: Preoperative RT involves a lower dose of radiation, and can simplify surgical resection by reducing tumor size or inducing the formation of a pseudo capsule, but is accompanied by surgical wound complications and infection[58]. On the other hand, postoperative RT entails a higher dose and a larger field of irradiation, with more fibrosis. Some authors thus recommend preoperative RT due to its lower dose and lower rates of late toxicities[59]. Furthermore, one study reported superior local control and OS in 1098 patients with preoperative RT (76% *vs* 67%)[60]. Other studies have also shown that postoperative RT seems to have more long-term side effects (edema, fibrosis, fracture) and a worse functional result[59,61,62].

New techniques such as intensity modulation RT, brachytherapy (BT), and intraoperative electron RT (IOERT) promise to reduce the side effects of the conventional EBRT with the same rates of local control[63,64]. Positive margins after surgery pose a treatment dilemma: Although re-resection should be considered whenever feasible[65], boost RT can be performed in patients, albeit with a high impact on functionality[18,66].

BT consists of administering postoperative radiotherapy through catheters placed in the surgical bed[67]. Similar local control rates are seen in low- and high-dose BT[68], but less toxicity is observed in the latter[69]. BT can be administered alone or in combination with EBRT when the treatment volume exceeds the treatment range of BT catheters or when BT is used in the setting of inadequate surgical margin[70]. IOERT involves the application of a single fraction of high-dose radiation after surgery. In the past, this technique was exclusive for specialized operating rooms with linear accelerators mounted. Nevertheless, development of mobile accelerators may spread the use of IOERT[71]. IOERT is usually used as a boost, preceded by EBRT. A dose of 10-18 Gy is applied once, followed by 50 Gy EBRT. The smaller treatment volumes and the possibility of excluding major nerves, vessels, and skin from the radiation field can reduce late complications and improve long-term functional outcome[72]. Although several studies have affirmed good local control of STS with IOERT, it is always administered in combination with EBRT, and its efficacy without the concomitant use of conventional RT is uncertain.

Chemotherapy

Neoadjuvant chemotherapy (NCT) and adjuvant chemotherapy (ACT) have been used in STS with inconclusive benefit. Although small series have reported an

improvement in local control and distant metastasis in high-risk patients[73], larger studies have shown no definitive benefit[74]. Doxorubicin alone or in combination with ifosfamide are the principle agents used in STS, albeit with low response rates even when used in combination[75]. However, other studies have failed to detect differences in relapse-free survival, time to local failure, time to distant failure, and OS compared with surgery and RT[76-78]. It appears that patients with certain prognostic factors associated with poor outcome may benefit more from chemotherapy[79].

Another study detected significant heterogenicity in the selection of patients and in the type and timing of chemotherapy received, restricting the beneficial effects of CT on high-risk patients[80]. In addition, a recent revision of the EORTC-62931 trial showed a significant reduction in the risk of death when ACT was used only in the group with low predicted survival[81]. A single-institution retrospective study in 74 patients treated with NCT containing doxorubicin and ifosfamide detected a benefit in disease-specific survival for patients with tumors > 10 cm[82]. In the same vein, a recent retrospective multi-institutional study showed that patients with extremity tumors of 10 cm or larger treated with NCT had superior survival, while no differences were found in smaller tumors[83]. On the other hand, a phase II randomized study on 134 patients with high-risk STS, comparing preoperative CT and surgery *vs* surgery alone, found no differences in survival[84]. Although other studies[85,86] have also demonstrated the efficacy of NCT combined with adjuvant radiotherapy, surgery, and ACT, OS rates do not differ from those shown in patients with high-risk STS treated with R0 surgery and radiotherapy, while significant short-term toxicities were described.

Tyrosine-kinase inhibitors have shown efficacy in STS. Pazopanib prolonged progression-free survival in patients with non-lipogenic STS in which anthracycline-based chemotherapy had failed[87]. Sunitinib is active against advanced alveolar soft part sarcoma[88]. Imatinib, a platelet-derived growth receptor antagonist, is active against dermatofibrosarcoma protuberans and metastatic tenosynovial giant cell tumor[89].

Unresectable and metastatic disease is a challenge because the benefits of systemic therapy beyond second-line are limited[90]. Despite the fact that gemcitabine in combination with docetaxel, vinorelbine, or dacarbazine has been shown to be active in these patients[91], they are probably not superior to single-agent doxorubicin. The GeDDiS trial failed to show superiority of gemcitabine and docetaxel against doxorubicin alone in 275 patients[92].

Isolated hyperthermic limb perfusion (IHLP) with tumor necrosis factor-alpha and melphalan is a form of extremity rather than whole-body chemotherapy[93]. IHLP seems to be more effective in liposarcoma than in other STS[94]. In a series of 41 patients with unresectable STS treated with IHLP, a local control rate of 98% and a 5-year OS of 63% was reported[95]. Another study reported a limb salvage rate of 91% at 32 mo of follow-up[96]. Finally, there is a higher probability of achieving ≥ 90% tumor necrosis compared to chemotherapy, radiotherapy, and the combination[97]. However, IHLP results in a high incidence of secondary fractures (15%-18%) with a low proportion of bone healing[11,98].

Novel treatments

Immunogenic targets and immunomodulatory therapies aim to improve or re-activate immune responses against STS using monoclonal antibodies, cellular therapies, or vaccines[99]. Furthermore, NGS techniques detect specific tumor mutations and altered antigens[100], contributing to the development of targeted cancer therapies, such as monoclonal antibodies and cytotoxic lymphocytes modified to express antigen-specific receptors (T-cell receptor and chimeric antigen receptor)[101]. In this setting, trabectedin has been shown to be active in STS, especially in myxoid liposarcoma[102,103].

A phase II study evaluated the combination of ipilimumab (anti-cytotoxic T-lymphocyte-associated protein 4) and nivolumab (anti-programmed cell death protein 1) against isolated nivolumab in patients with metastatic STS and bone sarcomas. Although no objective response was observed with bone sarcomas, metastatic STS patients had a 16% response in the combination group (5% on monotherapy) and an increase in progression-free survival (4.1 *vs* 1.7) and OS (14.3 mo *vs* 10.7 mo)[104].

Cell therapies use modified T cells and natural killer cells to treat tumors recognizing specific antigens. New York Esophageal Squamous Cell Carcinoma-1 is an antigen detected in 80% of synovial sarcoma[105]. The development of specific T-cell receptors that recognize New York Esophageal Squamous Cell Carcinoma-1 has shown a clinical response in these patients. Nevertheless, more studies are needed to understand the side effects of the administration of genetically modified cells[106].

CONCLUSION

Curative treatment of localized STS continues to be based on surgery with or without radiotherapy depending on the type of tumor, location, and margins. Chemotherapy in non-metastatic disease appears to play a role in patients with a worse prognosis. Modern powerful molecular analysis has provided an understanding of the molecular biology of STS and led to the development of novel specific drugs, and recent advances in biological therapies promise to open new doors to patient treatment.

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