Curr. Treat. Options in Oncol. (2019) 20: 54
DOI 10.1007/s11864-019-0656-z

Skin Cancer (T Ito, Section Editor)

Diagnosis and Management of Subcutaneous Soft Tissue Sarcoma

Makoto Endo, MD, PhD.[*]
Nokitaka Setsu, MD, PhD.
Toshifumi Fujiwara, MD, PhD.
Takeaki Ishii, MD.
Makoto Nakagawa, MD, PhD.
Kenichiro Yahiro, MD.
Atsushi Kimura, MD.
Eijiro Shimada, MD.
Yasuharu Nakashima, MD, PhD.
Yoshihiro Matsumoto, MD, PhD.

Address
[*]Department of Orthopaedic Surgery, Kyushu University, 3-1-1 Maidashi, Higashi-ku, Fukuoka, 812-8582, Japan
Email: makendo@ortho.med.kyushu-u.ac.jp

Published online: 25 May 2019

This article is part of the Topical Collection on *Skin Cancer*

Keywords Sarcoma · Soft tissue sarcoma · Soft tissue tumor · Superficial soft tissue sarcoma · Subcutaneous soft tissue sarcoma · Subcutaneous soft tissue tumor

Opinion statement

The proper diagnosis and treatment planning for subcutaneous soft tissue sarcoma is very important. Soft tissue tumors can occur anywhere in the body, but if they occur subcutaneously, patients can easily notice a subcutaneous soft tissue mass. Therefore, it is possible to determine through recording, the growth speed of the mass, which is often difficult to obtain with deep-situated soft tissue masses. Palpation can also provide information about the firmness and mobility of the mass. Thus, history taking and physical examinations are informative for subcutaneous soft tissue tumors, compared to tumors that occur deeply. Because subcutaneous soft tissue tumors are easily recognized, they are often resected, without sufficient imaging analyses or thorough treatment planning. An operation performed based on such an inadequate preoperative plan is called a "whoops surgery." In the case of "whoops surgeries," subsequent radical surgery is required to remove additional areas, including hematomas that result from the initial surgery, that

require a wider range of resection and soft tissue reconstruction. Therefore, as with deep-seated soft tissue tumors, it is important to conduct careful imaging examinations and make appropriate preoperative plans for subcutaneous soft tissue tumors. Subcutaneous soft tissue sarcomas often show an invasive pattern, and such tumors require a more careful assessment to prevent local recurrence after surgery. During surgery, it is necessary to remove the entire infiltration area along the fascia. Sometimes, an adequately wide excision is necessary, which is considered the minimum necessary procedure to eradicate the lesion. As noted above, clinicians who see patients with subcutaneous soft tissue tumors are encouraged to have sufficient knowledge and experience regarding the diagnosis and treatment. This article is intended for all doctors who deal with subcutaneous soft tissue tumors and focuses on essential points regarding their diagnosis and management.

Introduction

Subcutaneous soft tissue sarcoma (STS) accounts for approximately one third of all STSs of the extremities and trunk wall [1]. The annual incidence of subcutaneous STS has been reported to occur at a rate of 0.4 per 100,000 individuals [1]. Compared with deep-situated STS, which occurs in deeper soft tissue than the fascia, subcutaneous STSs are almost half the size at diagnosis, more common in the lower legs and feet, more often myxofibrosarcoma, and of a lower grade of malignancy [1]. Although the resection of subcutaneous STS is easier than the resection of deeper ones, unplanned excision causes serious problems such as a wide range of contaminations that require reoperation with soft tissue reconstruction [2••]. Therefore, clinicians, especially surgeons, who treat subcutaneous STS should have sufficient knowledge and experience regarding their diagnosis and treatment.

Diagnosis

History taking and physical examination

A thorough documentation of the patient's medical history is generally the first step and plays an important role in diagnosis. A soft tissue mass that has not changed in size or shape over time is rarely malignant; and for such a mass, there is no need to rush examinations [3]. In contrast, a mass that has recently or gradually enlarged should be evaluated rapidly. It is generally difficult to distinguish between benign and malignant soft tissue tumors based on pain, although the presence of pain is sometimes useful for the diagnosis of hemangiomas [4], synovial sarcomas [5], and nerve sheath tumors, such as schwannomas and malignant peripheral nerve sheath tumors (MPNSTs) [6]. The past medical history and family history are particularly useful for the diagnosis of neurofibromatosis type 1, which results in neurofibroma and MPNST [7, 8], and neurofibromatosis type 2 and schwannomatosis, which result in multifocal schwannomas [9].

The inspection of the mass provides information about skin color, size, and shape of the mass [10]. Through palpation, firmness, mobility, local heat, and size and shape of the mass are evaluable. If a mass is soft to elastic-soft, hemangiomas or lipogenic tumors, including lipomas and atypical lipomatous tumors, are suspected [11], whereas an elastic hard mass has a potential to be

malignant [12]. Mobility provides useful information about tumor infiltration, especially for subcutaneous soft tissue tumors. A tumor that is located strictly within the subcutaneous tissue is movable under the skin and above the fascia; however, a mass appears fixed when it invades the skin or the fascia.

The simple "golf ball rule," which states that every growing soft tissue mass larger than a golf ball (equivalent to about 4.3 cm) should be suspected of being a sarcoma [13, 14••], is easily applicable to subcutaneous soft tissue tumors. If a new soft tissue lump is bigger than a golf ball and growing, the possibility of STS should be considered. Both size larger than a golf ball and increasing in size are strong predictors of sarcoma, with a positive predictive value of 78.5% [14••].

Imaging studies

Imaging studies are very important for assessing tumor nature and spread [15]. Ultrasound (US) is an inexpensive and easily accessible test that provides information on the size of the subcutaneous tumor and its anatomical relationship with the fascia [15]. Subcutaneous tumors, hematomas, and cystic diseases, including epidermal cyst and ganglion, can be distinguished using Doppler, which detects blood supply inside the mass [16]. Abundant blood flow inside the mass suggests that the mass is a true tumor. In such a case, it is strongly recommended to perform a magnetic resonance imaging (MRI) examination [17]. MRI examinations can confirm the size and spread of the tumor more clearly than US, and evaluate the nature of the tumor, to some extent. The signal intensities inside the tumor in T1-weighted and T2-weighted images allow a discrimination of fatty, myxoid, and fibrous tumors. MRI is useful for locally invasive tumors, such as subcutaneous myxofibrosarcomas, which frequently invade and develop along the fascia. For appropriate preoperative planning, it is essential to accurately determine the spread of the tumor. By using a contrast agent that contains gadolinium, it is possible to evaluate the blood flow inside the tumor more clearly than through US. For lesions with calcification, X-ray is also useful, and the detection of phleboliths leads to the diagnosis of hemangioma. Furthermore, intratumoral calcification is observed in tumoral calcinoses [18], ossifying fibromyxoid tumors [19], and synovial sarcomas [5], and so on.

Biopsy

A histological examination is extremely important for the diagnosis of soft tissue tumors, and each histological diagnosis has characteristic clinicopathological features. In cases of a clearly benign soft tissue tumor, the lesions are often not resected, but rather followed by routine imaging examinations. However, in cases with the possibility of malignancy, biopsies and pathological examinations are mandatory [20, 21••]. Biopsy methods include aspiration cytology, needle biopsy, incision biopsy, and excisional biopsy [22]. Each biopsy method has its strengths and limitations. It is necessary to select an appropriate biopsy method, biopsy route, and intratumoral zone of sampling in each case, because soft tissue tumors vary in their location, size, intratumoral necrosis, and anatomical relation with important organs, nerves, and blood vessels. Particularly with respect to the biopsy route, consultation with an expert surgeon, prior to biopsy, should be considered, since the contaminated biopsy route should be removed during radical surgery for malignancy [23].

In soft tissue tumors, it is often difficult to estimate their histology from image findings. A biopsy should be considered in tumors with a maximum diameter of more than around 5 cm or tumors that show potentially malignant findings. Soft tumor masses that are unnecessary for biopsy are ganglion cyst with jelly-like content, as confirmed by puncture, obvious epidermal cysts, hemangiomas, and lipomas, as confirmed by imaging [24]. Hemangiomas and schwannomas are relatively common soft tissue tumors, but both have a variety of image findings and often require differentiation from malignant tumors. If there is a possibility of malignancy or a progressive course during follow-up, a biopsy should be done promptly, and the diagnosis should be confirmed. Depending on the tumor localization and size, it is necessary to select an appropriate biopsy method.

Fine-needle aspiration cytology

Fine-needle aspiration cytology is performed using a specialized suction needle. The advantage of puncture aspiration cytology is that the possibility of tumor cell dissemination is low, because it usually uses a 21- to 23-gauge needle. The procedure can be performed in an outpatient clinic, and the test results can be obtained quickly. On the other hand, for soft tissue tumors, it is difficult to determine the histology only with fine-needle aspiration cytology, and the agreement rate of histological malignancies is reported to range from 33 to 89% [22, 25–28]. For a precise cytological diagnosis, a skilled cytologist is required, and the clinician must know that the correct diagnosis rate depends largely on the experience and knowledge of the cytologist.

Needle biopsy (core-needle biopsy)

For a soft tissue tumor biopsy, a needle of 14 to 16 gauge is usually used. Needle biopsy can be performed under local anesthesia at an outpatient clinic. Although it is sometimes difficult to determine the histological diagnosis because the obtained tissue piece is small, the correct diagnosis rate reaches to 46 to 98% for soft tissue tumors [22, 29–33]. Even if the histology is not confirmed, this method is useful for distinguishing between tumor and non-tumor lesions and estimating histologic malignancies, such as through discriminating between spindle cell sarcoma and small round cell sarcoma. Needle biopsy should be the first choice if the tumor is large enough to insert a needle without tumor penetration. Attention should be paid to avoid seeding tumor cells into deep normal tissue by penetrating the tumor.

Incisional biopsy

Incisional biopsy is a method of incising the skin and sampling a part of the tumor tissue as a small block. It is possible to obtain a small block of tumor that is sufficient for pathological diagnosis. The correct diagnosis rate is reported to be as high as 82 to 100% [22, 33, 34]. For translocation-related sarcomas, including synovial and extraskeletal Ewing's sarcomas, a detection of the fusion gene is extremely useful for pathological diagnosis. Therefore, it is desirable to collect and preserve frozen samples for future genetic testing. There are some possible disadvantages, including the requirement of an operating room and the risk of contamination by the tumor cells, which are higher than the risks associated with needle biopsies.

Excisional biopsy

Excisional biopsy is a method of resecting the entire tumor for diagnosis and treatment. The indications of excisional biopsy are a superficial soft tissue tumor, a maximum diameter of approximately 2 to 3 cm or less, and a strong suspicion of benign tumor [35•]. If the biopsy result is a malignant tumor, an extensive additional resection is required [2••]. Therefore, the excisional biopsy should be applied after careful considerations.

For STS, the site of the biopsy and hematoma are highly suspected to be contaminated by tumor cells, so it is necessary to minimize tumor contamination through biopsies [36]. Especially in incisional biopsy, the skin incision should be minimal, and the hemostasis should be performed thoroughly after sampling. If postoperative bleeding is a concern, indwelling a drain should be considered. When installing the drain, it should be in the vicinity of the incisional wound and on the extension line of the incision, so as not to enlarge the tumor contamination.

Especially in the limbs, incisions are made along the underlying muscles, in the direction of the long axis of the limb. A transverse incision may increase the amount of muscles that require resection during radical surgery. A transverse incision should be avoided because it will cause a significant decrease in postoperative limb function.

Major differential histological diagnoses

In an analysis of 367 superficial STSs, the French Sarcoma Group reported that the common histological diagnoses were unclassified sarcoma (24%), leiomyosarcoma (22%), dermatofibrosarcoma protuberans (DFSP) (17%), angiosarcoma (14%), and myxofibrosarcoma (9%) [37]. In another report of superficial non-small round cell STS, the most frequent histology was malignant fibrous histiocytoma (25%), followed by liposarcoma (19%), DFSP (16%), MPNST (9%), leiomyosarcoma (8%), and myxofibrosarcoma (4%) [38]. Although rare, synovial sarcoma, clear cell sarcoma, extraskeletal Ewing sarcoma, epithelioid sarcoma, and extraskeletal osteosarcoma have been also reported [1, 37–40]. In the papers published before 2002, malignant fibrous histiocytoma (MFH) was the most common histology accounting for 46–48% in subcutaneous STSs [1, 39], however, MFH was reclassified to UPS, myxofibrosarcoma, and so on with the revision of World Health Organization (WHO) Classification of Tumours of Soft Tissue and Bone [41, 42]. Some clinical information, including family history of neurofibromatosis type 1, overlying skin pigmentation, skin elevation, and image findings may facilitate the differential diagnosis; however, a histological confirmation is necessary in almost all cases. The major histological diagnoses for subcutaneous STS are summarized in Table 1.

Treatment

Choice of treatment

Regardless of the histological diagnosis, the mainstay treatment is surgical removal, if the patient has no distant metastases. The role of adjuvant chemotherapy and/or radiotherapy is limited for subcutaneous STS [43•, 44].

Table 1. Major histological diagnoses of subcutaneous soft tissue sarcoma

Histology	Frequency	Character
UPS/US*	24–25%	> Almost all UPSs are classified as high grade in histology. > Cellular pleomorphism are commonly observed. > Most of UPS had been called MFH.
Leiomyosarcoma	8–22%	> Most of subcutaneous leiomyosarcoma is thought to originate in smooth muscle of blood vessel in subcutis. > Myogenic markers are positive in immunohistochemistry.
DFSP**	16–17%	> DFSP is graded intermediate (rarely metastasizing) according to WHO classification. > DFSP is also characterized by locally aggressive growth. > Local recurrence is common unless the tumor is widely excised. > COL1A1-PDGFB fusion gene is detected.
Liposarcoma	6–19%	> Liposarcoma includes dedifferentiated-type and myxoid-type. > Most of subcutaneous lipogenic tumor is benign lipoma. > Myxoid liposarcoma has either FUS-DDIT3 or EWSR1-DDIT3 fusion gene.
Angiosarcoma	2–14%	> Angiosarcoma commonly presents as a painful enlarging mass. > Angiosarcoma is high-grade sarcoma with a high mortality.
Myxofibrosarcoma	4–9%	> Myxofibrosarcoma is one of the representative examples of invasive soft tissue sarcoma. > Myxofibrosarcoma often spreads along the fascia. > Myxofibrosarcoma had been called myxoid MFH.
MPNST***	1–9%	> About half MPNSTs are related to neurofibromatosis type 1 (NF1). > MPNSTs usually occur in patients aged 20–50 years.
Synovial sarcoma	2–6%	> More than half of patients are teenagers and young adults. > Synovial sarcoma occasionally accompanies calcification and/or cystic change. > SS18-SSX1 or SS18-SSX2 or SS18-SSX4 fusion gene is accompanied.
Clear cell sarcoma	1–3%	> Clear cell sarcoma affect your adults, with peak incidence in the third and fourth decades. > EWSR1-ATF1 or EWSR1-CREB1 fusion gene is commonly seen.

*Undifferentiated pleomorphic sarcoma/unclassified sarcoma
**Dermatofibrosarcoma protuberans
***Malignant peripheral nerve sheath tumor

Planning of surgical resection

The surgeon should consider the histological diagnosis, the local spread of the tumor, the growth rate of the tumor, and the patient's general condition before determining the resection area and reconstruction method. MRI with enhancement is the most useful diagnostic imaging method for assessing the affected region of locally invasive tumors. It is of top priority to secure a sufficiently-wide margin and achieve a negative margin microscopically (R0 resection) [45].

In the preoperative plan for radical surgery, the resected area is in principle set to acquire a microscopically negative margin based on image findings, especially contrast MRI scans. Since STS occurs in all parts of the body, the anatomical condition varies greatly from case to case. In order to achieve the targeted resection margin, the surgeons need to carefully decide which healthy

tissue in the surroundings should be removed. For most STSs, it is reasonable to plan to excise the tumor that is within a muscle with 1 to 2 cm of muscle or fat. If there are durable barriers, such as thick fascia and periosteal layers, fewer tissues may be removed. However, in the planning of highly invasive STSs, such as locally invasive myxofibrosarcoma, a margin of 3 cm or more is potentially required. Even if the biopsy pathological diagnosis is low-grade, there is the possibility of increasing the risk of local recurrence, so the temptation to reduce the extent of resection should be avoided. The histological grade reflects the metastatic potential of the tumor rather than its local aggressiveness.

Currently, limb-sparing surgery is the mainstay surgical treatment for most STSs. The limb preservation rate has exceeded 90% in recent years, with improvements in imaging, techniques for limb reconstruction, and perioperative radiotherapy and/or chemotherapy, even though perioperative radiotherapy and/or chemotherapy is rarely applied to subcutaneous STS. Amputations are limited to cases where the tumor involves important blood vessels and nerves and they cannot be saved; however, such cases are rare among subcutaneous STSs. The amputation rate has been reported to be only 0.2% in subcutaneous STSs [46•]. In surgical planning for radical surgery, tumor resection with a macroscopically positive margin (R2 excision) is not tolerated for any reason. After determining the range of resection, reconstructive surgery should be adjusted to deal with tissue defects. To facilitate reconstruction surgery, the surgeons should not compromise or reduce the extent of resection.

Precautions on resection

An important aspect of surgery for subcutaneous STS is adherence to the planned surgical margin to be excised. The surgical margin adopts the smallest margin among all resected planes of specimen, so cutting into the planned resection area is prohibited, even only in part. Notably, since subcutaneous and muscle tissue may contract, deform, or move during surgery, it is necessary to carefully perform surgery while frequently confirming the resected surface. In addition, it is prudent to suture the fascia to the skin and subcutaneous fat so that these tissues do not come off, as subcutaneous tissues tend to detach from the fascia and expose the biopsy route or even the tumor itself.

Reconstruction after resection of tumor

In the analysis of 457 patients with superficial STS, the wounds were primarily closed in 58% of the patients, needed a rotation flap in 20% of the patients, required split-thickness skin grafting in 15% of the patients, and required free tissue transfer in 5% of the patients [46•]. The overall complication rate was 12%, and was significantly higher for patients who received free tissue transplants, 43% of whom developed complications that included infections, flap failures and dehiscences [46•]. Generally speaking, superficial STS rarely requires an advanced reconstructive procedure and almost never results in amputation [39].

Surgical margins

The surgical margins for STS resections are most commonly evaluated with R classification. The R classification is based on both the macroscopic and

microscopic evaluation of the surgical margins. The margins are classified either as grossly positive (R2), microscopically positive (R1), or microscopically negative (R0).

The resected STS specimen can easily deform. The surrounding connective tissues, especially muscle fibers, are often shortened due to formalin fixation and reduction of tension. Special attention is required to evaluate the surgical margin of subcutaneous STS. To avoid misunderstandings, the surgical margin of the resected specimen should be examined and documented by both the surgeon and the pathologist [20]. Applying ink to the surgical resection surface is recommended to accurately assess the surgical margin [47]. Temporarily stabilizing the soft tissue using pins, rubber plates, or other devices as needed is useful to avoid changing the shape of the resected specimen.

It is widely accepted that surgical margins are related to the risk of local recurrence [48–57]. In one study, the 5-year local recurrence rates were 6%, 17%, and 38%, for margins that were R0, R1, and R2, respectively [50]. In another paper, the 5-year local recurrence rates were reported to be 9.5% and 36.7% for R0 and R1 margins, respectively [49]. These papers concluded that the risk of local recurrence can be estimated using the R classification. Both macroscopic and microscopically positive surgical margins have been found to reduce local recurrence free survival in limb STSs. However, the impact of surgical margin on overall or disease-specific survival rate is more or less controversial [51–54, 58–61]. It is difficult to drive a strong conclusion based on the literature, and further research is needed in this field.

If the surgical margins turn out positive (affected by the tumor cells), additional wide resection should be considered to achieve an R0 margin, according to the National Comprehensive Cancer Network (NCCN) [20] and ESMO-EURACAN clinical practice guidelines [21••]. If resection with an R0 margin is impossible or harmful, radiotherapy to the surgical field is an option. In a randomized prospective study of adjuvant radiotherapy for STS in limbs, local recurrence was significantly decreased with adjuvant radiotherapy [62, 63]. The Scandinavian sarcoma group reported that adjuvant radiotherapy reduced the local recurrence of STS, regardless of the surgical margin status [64]. Although postoperative radiotherapy improves local control, it should be noted that postoperative radiotherapy cannot reduce the local recurrence rate to a level that is comparable to that of patients with negative margins, when radiotherapy is applied to patients with positive margins.

Invasive soft tissue sarcoma

Certain STSs show highly invasive growth patterns, which can be revealed by a tail-like sign on MRI (Fig. 1). A representative example of invasive STS is myxofibrosarcoma, which tends to spread along the fascia. The risk of myxofibrosarcoma local recurrence is very high and has been estimated to be about 20 to 30% [65–67]. Haglund et al. found that the local recurrence of myxofibrosarcoma occurred in 11 (31%) of 36 patients [66]. In this cohort, local recurrence was observed in seven of 27 patients (26%) with negative margins and four of nine patients (44%) with positive margins, which indicates a high local

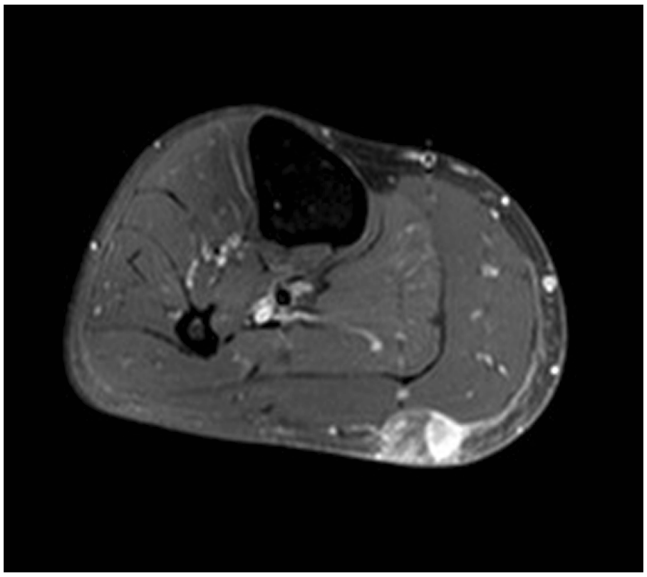

Fig. 1. Myxofibrosarcoma in the subcutis of the lower leg. Contrast-enhanced MRI shows the tail-like sign extending anteriorly from the tumor along with the fascia

recurrence rate, even with negative surgical margin. Notably, among patients with negative microscopic margins, 6 (40%) of 15 patients with a margin less than 1 cm developed local recurrence, while six patients with margins of 1 cm or greater did not show local recurrence. In another study of myxofibrosarcoma, Kikuta et al. described a group of patients who were treated with surgery, in whom the surgical margins were intended to be more than 3 cm [67]. Despite the intention of achieving adequate margins in all patients, a histologically positive margin after surgery was evident in 28% of the patients. Iwata et al. investigated the effect of invasive growth on the outcome of patients with undifferentiated pleomorphic sarcomas and myxofibrosarcomas [68]. Their surgical protocol involved tumor resection, with 2–3 cm margins from the edge of the tumor's spread on MRI. Nonetheless, the surgical margins were microscopically positive in 43 of 89 patients (48%), despite the attempt to remove a wide margin, with a 5-year local recurrence-free survival rate of 81%. These results highlight the difficulty of achieving a microscopically negative margin for invasive STS. In order to obtain a microscopically negative surgical margin, surgical planning, with a margin of 3 cm or more, is potentially required on the MRI image for each case of invasive STS. The ideal extent of resection for such tumors is unknown and remains unestablished. The use of intraoperative frozen sections, especially frozen sections of the fascia, may be useful; however, their usefulness remains controversial.

Treatment plans after unplanned excision (whoops surgery)

Unplanned excision is defined as a surgical resection without proper preoperative evaluation and surgical planning to achieve a microscopically negative margin [69]. The greatest problem of unplanned resection

is contamination by tumor cells and tumor spread to surrounding tissues [70]. Macroscopic residual tumors often present after unplanned resection. It is therefore not surprising that unplanned excision is associated with increased risk of local recurrence, unless accompanied by subsequent tumor bed resection [71]. In re-resection surgeries after unplanned resections, the goal is to completely resect the surgical bed, including areas of the skin incision, drain hole, postoperative hematoma, and so on [72]. Lateral or oblique incisions during unplanned resection may result in contamination of multiple or adjacent compartments, which will lead to a much wider area of resection that is need to achieve microscopically negative margins. In such cases, the reconstruction of soft tissues by flap is often required.

Survival

The American Joint Committee on Cancer (AJCC) TNM classification of bone and soft tissue sarcomas has revised and published its eighth edition [73]. In the eighth edition, the notation of tumor depth (superficial or deep from the superficial fascia) has been eliminated. This does not necessarily mean that both superficial and deep STS show the same prognoses. It is widely accepted that superficial STS shows better prognosis that deep STS. The 5-year overall survival rate is variable but has been reported to range from 75 to 95.3% [1, 37, 38, 74–76].

Summary

When subcutaneous soft tissue tumors are encountered, it is necessary to remember that medical histories and physical examination findings are important for estimating the possibility of malignancy. The possibility of malignancy should be considered for masses larger than golf balls (equivalent to about 4.3 cm) and those that tend to increase in size. In peripheral nerve sheath tumors, a family history of neurofibromatosis and the presence or absence of Tinel's sign may aid the accurate diagnosis, and MRI is an essential imaging evaluation method that can give a qualitative assessment of the tumor and assess the spread of the tumor, especially for tumors that show locally invasive growth patterns.

Subcutaneous soft tissue tumors often require a biopsy for a definitive diagnosis. Care should be taken to minimize contamination by tumor cells during biopsy. For small subcutaneous masses, such as those less than 2 cm, a resection biopsy is also indicated, but should only be performed by a surgeon who is familiar with soft tissue tumors.

With regard to treatment, a sufficient surgical excision range is crucial for avoiding local recurrence. For tumors with invasive growth patterns, resection with a safer resection margin, of greater than 3 cm margin for some situations, is recommended. During resection, R0 resection (microscopic stump negative) should be the goal. If necessary, the surgeon should consider reconstruction of soft tissues, such as flaps and skin grafts.

Subcutaneous soft tissue tumors have a generally good prognosis if properly treated, and clinicians who treat subcutaneous soft tissue tumors must have sufficient knowledge and experience.

Funding Information

This work was supported in part by Grants-in-Aid for Young Scientists (18K16627) from the Japan Society for the Promotion of Science and a Grant from Japan Orthopaedics and Traumatology Research Foundation Inc. (no. 332).

Compliance with Ethical Standards

Conflict of Interest

Makoto Endo has received compensation from Taisho Toyama Pharmaceutical Co., Ltd., Daiichi Sankyo, Eli Lilly and Company, Eisai, and Novartis for service as a consultant or a speaker.
Nokitaka Setsu declares that he has no conflict of interest.
Toshifumi Fujiwara declares that he has no conflict of interest.
Takeaki Ishii declares that he has no conflict of interest.
Makoto Nakagawa declares that he has no conflict of interest.
Kenichiro Yahiro declares that he has no conflict of interest.
Atsushi Kimura declares that he has no conflict of interest.
Eijiro Shimada declares that he has no conflict of interest.
Yasuharu Nakashima has received research funding from Kyocera and Eisai, and has received speaker's honoraria from Zimmer Biomet, Chugai Pharmaceutical, Mitsubishi Tanabe Pharma, Janssen Pharmaceuticals, Eisai, AbbVie, Bristol-Myers Squibb, Astellas, Hisamitsu Pharmaceutical Co., Inc., and Taisho Toyama Pharmaceutical Co., Ltd.
Yoshihiro Matsumoto declares that he has no conflict of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1. Rydholm A, Gustafson P, Rooser B, Willen H, Berg NO. Subcutaneous sarcoma. A population-based study of 129 patients. J Bone Joint Surg (Br). 1991;73(4):662–7.
2.•• Pretell-Mazzini J, Barton MD Jr, Conway SA, Temple HT. Unplanned excision of soft-tissue sarcomas: current concepts for management and prognosis. J Bone Joint Surg Am. 2015;97(7):597–603. https://doi.org/10.2106/JBJS.N.00649
Current concept review of unplanned resection of soft tissue sarcomas. This review paper focuses on management and prognosis of soft tissue sarcomas after unplanned resection.
3. Smolle MA, Andreou D, Tunn PU, Szkandera J, Liegl-Atzwanger B, Leithner A. Diagnosis and treatment of soft-tissue sarcomas of the extremities and trunk. EFORT Open Rev. 2017;2(10):421–31. https://doi.org/10.1302/2058-5241.2.170005.
4. Crawford EA, Slotcavage RL, King JJ, Lackman RD, Ogilvie CM. Ethanol sclerotherapy reduces pain in symptomatic musculoskeletal hemangiomas. Clin Orthop Relat Res. 2009;467(11):2955–61. https://doi.org/10.1007/s11999-009-0919-2.
5. Setsu N, Kohashi K, Fushimi F, Endo M, Yamamoto H, Takahashi Y, et al. Prognostic impact of the activation status of the Akt/mTOR pathway in synovial sarcoma. Cancer. 2013;119(19):3504–13. https://doi.org/10.1002/cncr.28255.
6. Endo M, Yamamoto H, Harimaya K, Kohashi K, Ishii T, Setsu N, et al. Conventional spindle cell-type malignant peripheral nerve sheath tumor arising in a sporadic schwannoma. Hum Pathol. 2013;44(12):2845–8. https://doi.org/10.1016/j.humpath.2013.05.021.
7. Endo M, Kobayashi C, Setsu N, Takahashi Y, Kohashi K, Yamamoto H, et al. Prognostic significance of p14ARF, p15INK4b, and p16INK4a inactivation in malignant peripheral nerve sheath tumors. Clin Cancer Res. 2011;17(11):3771–82. https://doi.org/10.1158/1078-0432.CCR-10-2393.

8. Endo M, Yamamoto H, Setsu N, Kohashi K, Takahashi Y, Ishii T, et al. Prognostic significance of AKT/mTOR and MAPK pathways and antitumor effect of mTOR inhibitor in NF1-related and sporadic malignant peripheral nerve sheath tumors. Clin Cancer Res. 2013;19(2):450–61. https://doi.org/10.1158/1078-0432.CCR-12-1067.
9. Widemann BC, Acosta MT, Ammoun S, Belzberg AJ, Bernards A, Blakeley J, et al. CTF meeting 2012: Translation of the basic understanding of the biology and genetics of NF1, NF2, and schwannomatosis toward the development of effective therapies. Am J Med Genet A. 2014;164A(3):563–78. https://doi.org/10.1002/ajmg.a.36312.
10. Rochwerger A, Mattei JC. Management of soft tissue tumors of the musculoskeletal system. Orthop Traumatol Surg Res. 2018;104(1S):S9–S17. https://doi.org/10.1016/j.otsr.2017.05.031.
11. Hogg ME, Wayne JD. Atypical lipomatous tumor/well-differentiated liposarcoma: what is it? Surg Oncol Clin N Am. 2012;21(2):333–40. https://doi.org/10.1016/j.soc.2011.12.007.
12. Endo M, Oda Y, Harimaya K, Tamiya S, Yamamoto H, Kohashi K, et al. Low-grade dedifferentiated liposarcoma of the neck: magnetic resonance imaging and pathological correlation. J Orthop Sci. 2010;15(1):148–52. https://doi.org/10.1007/s00776-009-1407-y.
13. Grimer RJ. Size matters for sarcomas! Ann R Coll Surg Engl. 2006;88(6):519–24. https://doi.org/10.1308/003588406X130651.
14.•• Nandra R, Forsberg J, Grimer R. If your lump is bigger than a golf ball and growing, think sarcoma. Eur J Surg Oncol. 2015;41(10):1400–5. https://doi.org/10.1016/j.ejso.2015.05.017
Take-home message of this paper is that the patients should be referred to a tertiary center if the tumor's size is greater than 4.3 cm (golf ball) and increasing in size.
15. Morel M, Taieb S, Penel N, Mortier L, Vanseymortier L, Robin YM, et al. Imaging of the most frequent superficial soft-tissue sarcomas. Skelet Radiol. 2011;40(3):271–84. https://doi.org/10.1007/s00256-009-0855-y.
16. Gruber L, Gruber H, Luger AK, Glodny B, Henninger B, Loizides A. Diagnostic hierarchy of radiological features in soft tissue tumours and proposition of a simple diagnostic algorithm to estimate malignant potential of an unknown mass. Eur J Radiol. 2017;95:102–10. https://doi.org/10.1016/j.ejrad.2017.07.020.
17. Chung WJ, Chung HW, Shin MJ, Lee SH, Lee MH, Lee JS, et al. MRI to differentiate benign from malignant soft-tissue tumours of the extremities: a simplified systematic imaging approach using depth, size and heterogeneity of signal intensity. Br J Radiol. 2012;85(1018):e831–6. https://doi.org/10.1259/bjr/27487871.
18. Tiwari V, Goyal A, Nagar M, Santoshi JA. Hyperphosphataemic tumoral calcinosis. Lancet. 2019;393(10167):168. https://doi.org/10.1016/S0140-6736(18)33045-9.
19. Endo M, Kohashi K, Yamamoto H, Ishii T, Yoshida T, Matsunobu T, et al. Ossifying fibromyxoid tumor presenting EP400-PHF1 fusion gene. Hum Pathol. 2013;44(11):2603–8. https://doi.org/10.1016/j.humpath.2013.04.003.
20. NCCN clinical practice guidelines in oncology soft tissue sarcoma version 2.2019. 2019.
21.•• Casali PG, Abecassis N, Bauer S, Biagini R, Bielack S, Bonvalot S, et al. Soft tissue and visceral sarcomas: ESMO-EURACAN Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2018;29:iv51–67. https://doi.org/10.1093/annonc/mdy096.
Clinical practice guidelines for diagnosis, treatment and follow-up of soft tissue sarcomas, which was established by European Society for Medical Oncology and European network for Rare adult solid Cancer.
22. Kasraeian S, Allison DC, Ahlmann ER, Fedenko AN, Menendez LR. A comparison of fine-needle aspiration, core biopsy, and surgical biopsy in the diagnosis of extremity soft tissue masses. Clin Orthop Relat Res. 2010;468(11):2992–3002. https://doi.org/10.1007/s11999-010-1401-x.
23. Mankin HJ, Lange TA, Spanier SS. The hazards of biopsy in patients with malignant primary bone and soft-tissue tumors. J Bone Joint Surg Am. 1982;64(8):1121–7.
24. Rimondi E, Mavrogenis AF, Errani C, Calabro T, Bazzocchi A, Facchini G, et al. Biopsy is not necessary for the diagnosis of soft tissue hemangiomas. Radiol Med. 2018;123(7):538–44. https://doi.org/10.1007/s11547-018-0862-y.
25. Jones C, Liu K, Hirschowitz S, Klipfel N, Layfield LJ. Concordance of histopathologic and cytologic grading in musculoskeletal sarcomas: can grades obtained from analysis of the fine-needle aspirates serve as the basis for therapeutic decisions? Cancer. 2002;96(2):83–91.
26. Agrawal P, Srinivasan R, Rajwanshi A, Gupta N, Dey P, Kakkar N, et al. Fine needle aspiration cytology of pediatric soft tissue tumors highlighting challenges in diagnosis of benign lesions and unusual malignant tumours. Cytopathology. 2019;30:301–8. https://doi.org/10.1111/cyt.12685.
27. Akerman M, Rydholm A, Persson BM. Aspiration cytology of soft-tissue tumors. The 10-year experience at an orthopedic oncology center. Acta Orthop Scand. 1985;56(5):407–12.
28. Kumar S, Chowdhury N. Accuracy, limitations and pitfalls in the diagnosis of soft tissue tumors by fine needle aspiration cytology. Indian J Pathol Microbiol. 2007;50(1):42–5.
29. Colletti SM, Tranesh GA, Whetsell CR, Chambers LN, Nassar A. High diagnostic accuracy of core needle biopsy of soft tissue tumors: an institutional experience. Diagn Cytopathol. 2016;44(4):291–8. https://doi.org/10.1002/dc.23440.
30. Zornoza J, Bernardino ME, Ordonez NG, Thomas JL, Cohen MA. Percutaneous needle biopsy of soft tissue

tumors guided by ultrasound and computed tomography. Skelet Radiol. 1982;9(1):33–6.
31. Yao L, Nelson SD, Seeger LL, Eckardt JJ, Eilber FR. Primary musculoskeletal neoplasms: effectiveness of core-needle biopsy. Radiology. 1999;212(3):682–6. https://doi.org/10.1148/radiology.212.3.r99se19682.
32. Adams SC, Potter BK, Pitcher DJ, Temple HT. Office-based core needle biopsy of bone and soft tissue malignancies: an accurate alternative to open biopsy with infrequent complications. Clin Orthop Relat Res. 2010;468(10):2774–80. https://doi.org/10.1007/s11999-010-1422-5.
33. Pohlig F, Kirchhoff C, Lenze U, Schauwecker J, Burgkart R, Rechl H, et al. Percutaneous core needle biopsy versus open biopsy in diagnostics of bone and soft tissue sarcoma: a retrospective study. Eur J Med Res. 2012;17:29. https://doi.org/10.1186/2047-783X-17-29.
34. Clayer M. Open incisional biopsy is a safe and accurate technique for soft tissue tumours. ANZ J Surg. 2010;80(11):786–8. https://doi.org/10.1111/j.1445-2197.2010.05340.x.
35.• Khoo M, Pressney I, Hargunani R, Saifuddin A. Small, superficial, indeterminate soft-tissue lesions as suspected sarcomas: is primary excision biopsy suitable? Skelet Radiol. 2017;46(7):919–24. https://doi.org/10.1007/s00256-017-2635-4
This paper suggests that primary excision biopsy of small, superficial soft-tissue masses might be a safe practice, but only in the setting of a specialist sarcoma service.
36. Mankin HJ, Lange TA, Spanier SS. THE CLASSIC: The hazards of biopsy in patients with malignant primary bone and soft-tissue tumors. The Journal of Bone and Joint Surgery, 1982;64:1121–1127. Clin Orthop Relat Res. 2006;450:4–10. https://doi.org/10.1097/01.blo.0000229299.36969.b5.
37. Salas S, Stoeckle E, Collin F, Bui B, Terrier P, Guillou L, et al. Superficial soft tissue sarcomas (S-STS): a study of 367 patients from the French Sarcoma Group (FSG) database. Eur J Cancer. 2009;45(12):2091–102. https://doi.org/10.1016/j.ejca.2009.03.006.
38. Tsukushi S, Nishida Y, Shido Y, Wasa J, Ishiguro N. Clinicopathological prognostic factors of superficial non-small round cell soft tissue sarcomas. J Surg Oncol. 2012;105(7):668–72. https://doi.org/10.1002/jso.23025.
39. Gibbs CP, Peabody TD, Mundt AJ, Montag AG, Simon MA. Oncological outcomes of operative treatment of subcutaneous soft-tissue sarcomas of the extremities. J Bone Joint Surg Am. 1997;79(6):888–97.
40. Di Giannatale A, Frezza AM, Le Deley MC, Marec-Berard P, Benson C, Blay JY, et al. Primary cutaneous and subcutaneous Ewing sarcoma. Pediatr Blood Cancer. 2015;62(9):1555–61. https://doi.org/10.1002/pbc.25535.
41. Fletcher CD, Unni KK, Mertens F, editors. WHO classification of tumours of soft tissue and bone. 3rd ed. Lyon: IARC; 2002.
42. Fletcher CD, Bridge JA, Hogendoorn PC, Mertens F, editors. WHO classification of tumours of soft tissue and bone. 4th ed. Lyon: IARC; 2013.
43.• Tsagozis P, Bauer HC, Styring E, Trovik CS, Zaikova O, Brosjo O. Prognostic factors and follow-up strategy for superficial soft-tissue sarcomas: Analysis of 622 surgically treated patients from the scandinavian sarcoma group register. J Surg Oncol. 2015;111(8):951–6. https://doi.org/10.1002/jso.23927 The Scandinavian Sarcoma Group organized prognostic analysis of patients with superficial soft tissue sarcoma (SSTS) treated with surgery. The largest number of patients (n=) were included in this study. In conclusions, SSTS had a favorable prognosis and adequate surgical margins were important for local control.
44. Austin JL, Temple WJ, Puloski S, Schachar NS, Oddone Paolucci E, Kurien E, et al. Outcomes of surgical treatment alone in patients with superficial soft tissue sarcoma regardless of size or grade. J Surg Oncol. 2016;113(1):108–13. https://doi.org/10.1002/jso.24091.
45. Endo M, Lin PP. Surgical margins in the management of extremity soft tissue sarcoma. Chin Clin Oncol. 2018;7(4):37. https://doi.org/10.21037/cco.2018.08.10.
46.• Eward WC, Lazarides AL, Griffin AM, O'Donnell PW, Sternheim A, O'Neill A, et al. Superficial soft-tissue sarcomas rarely require advanced soft-tissue reconstruction following resection. Plast Reconstr Surg Glob Open. 2017;5(11):e1553. https://doi.org/10.1097/GOX.0000000000001553
The authors investigated 457 patients with superficial soft tissue sarcoma, and found that the majority of patients had complete excisions with negative margins and primary closure. Only one patient required an amputation (0.2% of the patients).
47. Docquier PL, Paul L, Cartiaux O, Lecouvet F, Dufrane D, Delloye C, et al. Formalin fixation could interfere with the clinical assessment of the tumor-free margin in tumor surgery: magnetic resonance imaging-based study. Oncology. 2010;78(2):115–24. https://doi.org/10.1159/000306140.
48. Trovik CS, Bauer HC, Alvegard TA, Anderson H, Blomqvist C, Berlin O, et al. Surgical margins, local recurrence and metastasis in soft tissue sarcomas: 559 surgically-treated patients from the Scandinavian Sarcoma Group Register. Eur J Cancer. 2000;36(6):710–6.
49. Kainhofer V, Smolle MA, Szkandera J, Liegl-Atzwanger B, Maurer-Ertl W, Gerger A, et al. The width of resection margins influences local recurrence in soft tissue sarcoma patients. Eur J Surg Oncol. 2016;42(6):899–906. https://doi.org/10.1016/j.ejso.2016.03.026.
50. Gundle KR, Kafchinski L, Gupta S, Griffin AM, Dickson BC, Chung PW, 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):704–9. https://doi.org/10.1200/JCO.2017.74.6941.
51. Dickinson IC, Whitwell DJ, Battistuta D, Thompson B, Strobel N, Duggal A, et al. Surgical margin and its influence on survival in soft tissue sarcoma. ANZ J Surg. 2006;76(3):104–9. https://doi.org/10.1111/j.1445-2197.2006.03615.x.

52. Novais EN, Demiralp B, Alderete J, Larson MC, Rose PS, Sim FH. Do surgical margin and local recurrence influence survival in soft tissue sarcomas? Clin Orthop Relat Res. 2010;468(11):3003–11. https://doi.org/10.1007/s11999-010-1471-9.
53. Vraa S, Keller J, Nielsen OS, Jurik AG, Jensen OM. Soft-tissue sarcoma of the thigh: surgical margin influences local recurrence but not survival in 152 patients. Acta Orthop Scand. 2001;72(1):72–7. https://doi.org/10.1080/000164701753606734.
54. Gronchi A, Miceli R, Fiore M, Collini P, Lozza L, Grosso F, et al. Extremity soft tissue sarcoma: adding to the prognostic meaning of local failure. Ann Surg Oncol. 2007;14(5):1583–90. https://doi.org/10.1245/s10434-006-9325-0.
55. Potter BK, Hwang PF, Forsberg JA, Hampton CB, Graybill JC, Peoples GE, et al. Impact of margin status and local recurrence on soft-tissue sarcoma outcomes. J Bone Joint Surg Am. 2013;95(20):e151. https://doi.org/10.2106/JBJS.L.01149.
56. Ahmad R, Jacobson A, Hornicek F, Haynes AB, Choy E, Cote G, et al. The width of the surgical margin does not influence outcomes in extremity and truncal soft tissue sarcoma treated with radiotherapy. Oncologist. 2016;21(10):1269–76. https://doi.org/10.1634/theoncologist.2015-0534.
57. Tang YW, Lai CS. The significance of close but negative excision margin for treatment of soft-tissue sarcoma. Ann Plast Surg. 2012;69(6):633–6. https://doi.org/10.1097/SAP.0b013e3182756afe.
58. Heslin MJ, Woodruff J, Brennan MF. Prognostic significance of a positive microscopic margin in high-risk extremity soft tissue sarcoma: implications for management. J Clin Oncol. 1996;14(2):473–8. https://doi.org/10.1200/JCO.1996.14.2.473.
59. Stojadinovic A, Leung DH, Hoos A, Jaques DP, Lewis JJ, Brennan MF. Analysis of the prognostic significance of microscopic margins in 2,084 localized primary adult soft tissue sarcomas. Ann Surg. 2002;235(3):424–34.
60. Tanabe KK, Pollock RE, Ellis LM, Murphy A, Sherman N, Romsdahl MM. Influence of surgical margins on outcome in patients with preoperatively irradiated extremity soft tissue sarcomas. Cancer. 1994;73(6):1652–9.
61. Bonvalot S, Levy A, Terrier P, Tzanis D, Bellefqih S, Le Cesne A, et al. Primary extremity soft tissue sarcomas: does local control impact survival? Ann Surg Oncol. 2017;24(1):194–201. https://doi.org/10.1245/s10434-016-5462-2.
62. Yang JC, Chang AE, Baker AR, Sindelar WF, Danforth DN, Topalian SL, et al. Randomized prospective study of the benefit of adjuvant radiation therapy in the treatment of soft tissue sarcomas of the extremity. J Clin Oncol. 1998;16(1):197–203. https://doi.org/10.1200/JCO.1998.16.1.197.
63. Alektiar KM, Velasco J, Zelefsky MJ, Woodruff JM, Lewis JJ, Brennan MF. Adjuvant radiotherapy for margin-positive high-grade soft tissue sarcoma of the extremity. Int J Radiat Oncol Biol Phys. 2000;48(4):1051–8.
64. Jebsen NL, Trovik CS, Bauer HC, Rydholm A, Monge OR, Hall KS, et al. Radiotherapy to improve local control regardless of surgical margin and malignancy grade in extremity and trunk wall soft tissue sarcoma: a Scandinavian sarcoma group study. Int J Radiat Oncol Biol Phys. 2008;71(4):1196–203. https://doi.org/10.1016/j.ijrobp.2007.11.023.
65. Ghazala CG, Agni NR, Ragbir M, Dildey P, Lee D, Rankin KS, et al. Myxofibrosarcoma of the extremity and trunk: a multidisciplinary approach leads to good local rates of local control. Bone Joint J. 2016;98-B(12):1682–8. https://doi.org/10.1302/0301-620X.98B12.37568.
66. Haglund KE, Raut CP, Nascimento AF, Wang Q, George S, Baldini EH. Recurrence patterns and survival for patients with intermediate- and high-grade myxofibrosarcoma. Int J Radiat Oncol Biol Phys. 2012;82(1):361–7. https://doi.org/10.1016/j.ijrobp.2010.08.042.
67. Kikuta K, Kubota D, Yoshida A, Suzuki Y, Morioka H, Toyama Y, et al. An analysis of factors related to recurrence of myxofibrosarcoma. Jpn J Clin Oncol. 2013;43(11):1093–104. https://doi.org/10.1093/jjco/hyt119.
68. Iwata S, Yonemoto T, Araki A, Ikebe D, Kamoda H, Hagiwara Y, et al. Impact of infiltrative growth on the outcome of patients with undifferentiated pleomorphic sarcoma and myxofibrosarcoma. J Surg Oncol. 2014;110(6):707–11. https://doi.org/10.1002/jso.23708.
69. Noria S, Davis A, Kandel R, Levesque J, O'Sullivan B, Wunder J, et al. Residual disease following unplanned excision of soft-tissue sarcoma of an extremity. J Bone Joint Surg Am. 1996;78(5):650–5.
70. Randall RL, Bruckner JD, Papenhausen MD, Thurman T, Conrad EU 3rd. Errors in diagnosis and margin determination of soft-tissue sarcomas initially treated at non-tertiary centers. Orthopedics. 2004;27(2):209–12.
71. Giuliano AE, Eilber FR. The rationale for planned reoperation after unplanned total excision of soft-tissue sarcomas. J Clin Oncol. 1985;3(10):1344–8. https://doi.org/10.1200/JCO.1985.3.10.1344.
72. Morii T, Yabe H, Morioka H, Anazawa U, Suzuki Y, Toyama Y. Clinical significance of additional wide resection for unplanned resection of high grade soft tissue sarcoma. Open Orthop J. 2008;2:126–9. https://doi.org/10.2174/1874325000802010126.
73. Tanaka K, Ozaki T. New TNM classification (AJCC eighth edition) of bone and soft tissue sarcomas: JCOG Bone and Soft Tissue Tumor Study Group. Jpn J Clin Oncol. 2019;49(2):103–7. https://doi.org/10.1093/jjco/hyy157.
74. Brooks AD, Heslin MJ, Leung DH, Lewis JJ, Brennan MF. Superficial extremity soft tissue sarcoma: an analysis of prognostic factors. Ann Surg Oncol. 1998;5(1):41–7.

75. Cany L, Stoeckle E, Coindre JM, Kantor G, Bonichon F, Bui BN. Prognostic factors in superficial adult soft tissue sarcomas: analysis of a series of 105 patients. J Surg Oncol. 1999;71(1):4–9.
76. Francescutti V, Sanghera SS, Cheney RT, Miller A, Salerno K, Burke R, et al. Homogenous good outcome in a heterogeneous group of tumors: an institutional series of outcomes of superficial soft tissue sarcomas. Sarcoma. 2015;2015:325049. https://doi.org/10.1155/2015/325049.

Publisher's Note