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Diagnosis and treatment of soft-tissue sarcomas of the extremities and trunk

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- The relatively low incidence and often atypical clinical presentation of soft-tissue sarcomas (STS) impedes early and adequate diagnosis. Patients may report on recently enlarged soft-tissue swellings, infrequently complain of painful lesions, or even have no symptoms at all.
- A thorough diagnostic work-up is essential in order to distinguish between benign soft-tissue tumours and STSs. Patient history, clinical features and radiological findings all help in assessing the underlying pathology. 'Worrying' features such as recent increase in size, deep location relative to the fascia, a tumour exceeding 4 cm in size, and invasive growth patterns seen on imaging should prompt verification by biopsy.
- Even though acquisition of biopsy material may be incomplete, one should bear in mind some essential rules. Regardless of the biopsy technique applied, the most direct route to the lump in question should be identified, contamination of adjacent structures should be avoided and a sufficient amount of tissue acquired.
- Treatment of STS is best planned by a multidisciplinary team, involving experts from various medical specialities. The benchmark therapy consists of *en bloc* resection of the tumour, covered by a safety margin of healthy tissue. Depending on tumour histology, grade, local extent and anatomical stage, radiotherapy, chemotherapy and isolated hyperthermic limb perfusion may be employed.
- Due to the complexity of treatment, any soft-tissue swelling suspected of malignancy is best referred directly to a sarcoma centre, where therapeutic management is carefully planned by an experienced multidisciplinary team.

Keywords: soft-tissue sarcoma; diagnostic pathway; therapeutic management

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Soft-tissue swellings, lumps and bumps are frequently seen in routine clinical practice. However, with an estimated annual incidence of five cases per 100 000 people in Europe, soft-tissue sarcomas (STS) are relatively rare and are outnumbered by benign soft-tissue tumours a hundred times over.[1-3] Consequently, the majority of patients consulting their physician because of soft-tissue swellings will be diagnosed with a benign lesion. On the other hand, the early identification of patients with possible STS and prompt referral to a sarcoma centre is essential in order to avoid unnecessary delays in diagnosis and to ensure optimal multidisciplinary treatment.[4,5]

Contrary to most primary bone tumours, STSs mainly develop in the elderly population, with a peak incidence in the 6th decade of life.[6] Exceptions are rhabdomyosarcoma and synovial sarcoma, distinct histological subtypes mainly arising in children and young adults.[7] STSs are predominantly located in the lower limbs, followed by the upper limbs and trunk.[8] Further common locations include the head/neck region and retroperitoneal space.[9] As these STSs are usually seen by Ear-Nose-Throat physicians and Gastrointestinal surgeons, they will not be analysed in this article.

The following report will give an overview of the clinical, radiological and histological findings in patients with STS. Treatment options, outcomes and future perspectives will also be discussed.

Patient history and clinical examination

The diagnostic pathway should always start with a thorough documentation of the patient's history. Lumps that have not changed in size or shape over the years are most likely benign, whereas recently noticed, constantly-enlarging swellings should urge caution.[10] In cases of recently-emerged soft-tissue swellings, a preceding trauma is sometimes described.[11] Especially in elderly

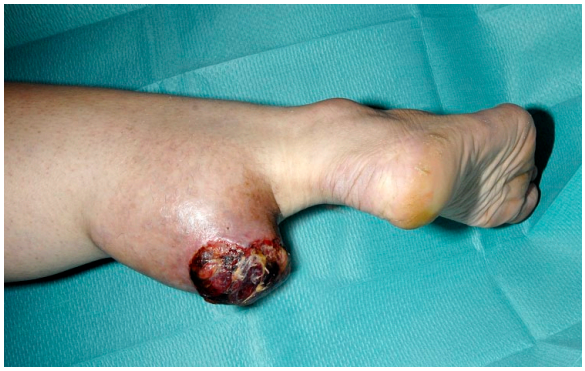

Fig. 1 Large, ulcerated tumour arising from a 30-year-old female patient's right calf, later confirmed as high-grade spindle cell sarcoma.

patients under anticoagulation therapy, this could be indicative of haematoma. On the other hand, lumps quickly increasing in size in the absence of bruising should prompt further investigation.[10]

Pain assessment is important in every physician–patient consultation. In cases of STS, however, pain is a rather poor discriminator between benign and malignant lesions.[10,12] Whilst traumatic soft-tissue swellings are usually painful, even quite large STSs may be indolent (Fig. 1). Malignant peripheral nerve sheath tumours (MPNSTs) developing in patients with neurofibromatosis type 1 are an exception, typically causing radicular pain, motor weakness or paraesthesiae.[13]

The inspection and palpation of the lump in question can reveal additional crucial information. Despite an often dramatic appearance, a reddened, hyperthermic and painful tumour is more often indicative of an ongoing inflammatory process than STS. Palpating and trying to move the lump can help assess its relation to surrounding structures. A tumour located within the subcutaneous tissues is easily moveable under the skin, whilst a mass attached to or located beneath the fascia appears to be fixed. As the majority of STSs are located deep to the fascia, every deeply-situated tumour should be considered malignant until proven otherwise.[14] However, 15% of STSs develop within the subcutaneous tissue.[14] For that reason, superficial lumps with additional worrying features also need to be further examined. In this respect, a simple rule of thumb is that every growing soft-tissue mass larger than a golf ball (equivalent to about 4 cm) that has been recently noticed should be suspected of being a sarcoma.[5,10,15]

Imaging

The chief objectives of imaging are to confirm clinical findings by detecting a soft-tissue mass, to estimate its size, tissue quality and relation to adjacent structures in detail,

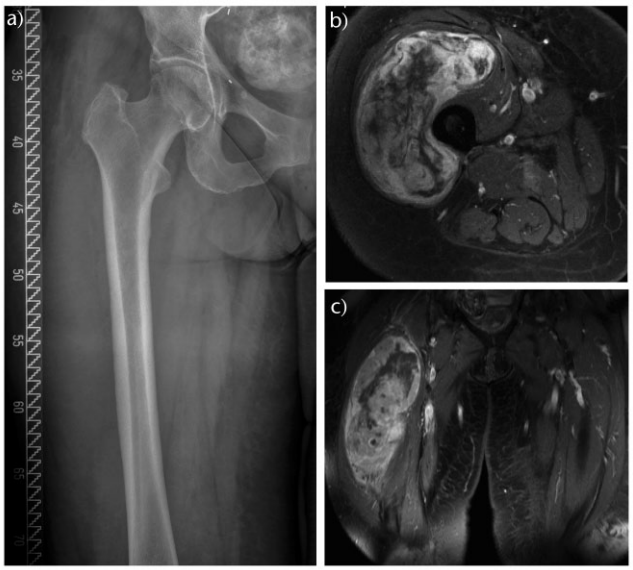

Fig. 2 Radiograph of the right hip of a 70-year-old female patient with a high-grade leiomyosarcoma showing moderate soft-tissue opacity (a). MRI scans of the same patient's leg, displaying a 25 cm × 11 cm × 9 cm partially-necrotic tumour with heterogeneous pathological contrast enhancement (b, c).

and to aid planning of the further course of action. Therefore, imaging should be carried out prior to any manipulation of the lesion, as biopsy-related artefacts may complicate image analysis.[16] More importantly, thorough imaging potentially reduces the danger of excising a tumour thought to be benign without adhering to oncological principles.

As a readily accessible and inexpensive imaging technique, ultrasound (US) is ideal for the initial evaluation of a soft-tissue mass.[17] The size of the lesion and its relation to the fascia can easily be estimated. Moreover, US can sometimes distinguish pseudotumours, such as haematomata, abscesses and cysts.[18] Assessment of the lesion's blood supply by using Doppler-US can be helpful and reveal additional information. Hypervascularity is indicative of malignancy, especially if the lesion is supplied via multiple peripheral vessels or contains large intratumoural vessels.[19]

Magnetic resonance imaging (MRI) is the method of choice to evaluate soft-tissue tumours and to distinguish benign from malignant lesions, especially if prior clinical findings and imaging were inconclusive.[20] Features indicative of malignancy include expansive and invasive growth, heterogeneous signalling on T1-weighted images and low signalling intensity on T2-weighted sequences (Figs 2 and 3).[21] Moreover, utilisation of static and dynamic gadolinium-based contrast-enhanced imaging is highly recommended to confirm the suspected pathology.[22]

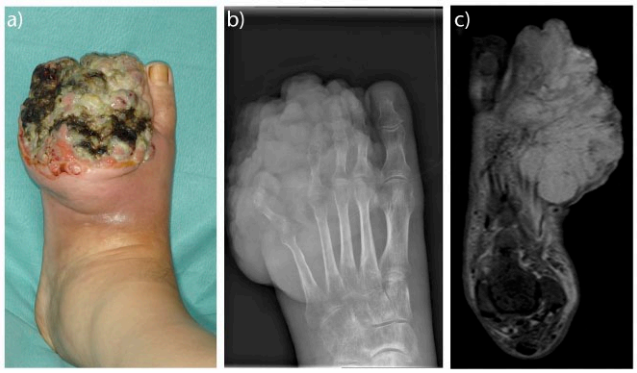

Fig. 3 Ulcerating, partially-necrotic tumour on the dorsum of the left foot of a 53-year-old male patient (a). Radiograph shows displacement of the 4th and 5th digit by the mass (b). MRI reveals the actual extent of the tumour, later confirmed as high-grade synovial sarcoma (c).

Whilst conventional radiographs are not adequate to assess soft-tissue masses, they may display calcified or ossified areas and bony involvement.[23] Particularly in children and young adults, the differential diagnosis of primary bone neoplasms with reactive soft-tissue swellings should be contemplated when osseous destruction is visible.[24] Due to overlapping features, however, even experienced radiologists are sometimes unable to distinguish between benign and malignant tumours. As an example, STSs frequently exhibit a peripheral or centripetal contrast-enhancement on MRI. However, this feature may also be seen in benign lesions with centrally-located ossification, calcification and haemorrhage (e.g. myofibromatosis).[25] Moreover, peri-tumoural oedema and ill-defined boundaries are seen both in STSs and benign tumours.[18] Consequently, imaging should always be interpreted in the context of clinical findings and should help decide whether a biopsy is necessary or not.

Biopsy

This is an essential part of the diagnostic pathway for soft-tissue tumours. In theory, acquisition of biopsy material seems uncomplicated. However, some essential rules must be considered prior to biopsy of a suspected STS. The ten simple rules listed in Table 1 aid planning a biopsy, choosing the optimal approach and obtaining sufficient tumour tissue to guide subsequent treatment (Table 1).[26] On the other hand, one must be aware of the lesion being dealt with and should consider which steps to initiate afterwards. In this case, a referral algorithm for soft-tissue lumps provides guidance (Fig. 4). As outlined above, any soft-tissue swelling larger than 4 cm or located in the deep tissues is highly indicative of a sarcoma. In case such a lesion is visible on MRI, immediate referral to a tumour centre should be initiated. For smaller lesions appearing suspect on MRI, a diagnostic biopsy may be suitable.

First, the most appropriate biopsy technique has to be decided (see rule I in Table 1), and if in doubt, this must be performed in consultation with the radiologist (minding rules II and III) and pathologist in charge (rule IV). A Tru-Cut™ (BD UK Limited) needle biopsy can be performed under local anaesthesia, hence being suitable for the outpatient setting.[27] As only a relatively small amount of tissue can be obtained, both surgeon and pathologist should be familiar with this method. Even if the skin incision is minimal when using the Tru-cut system, the entry point should be carefully planned. The needle must be directed straight down to the tumour, minimising contamination of surrounding structures (rules V and VI).

With open biopsy, sufficient and viable samples can be acquired (in compliance with rules VII and VIII), possibly enabling more precise tumour grading and sub-typing.[28] It should be noted that biopsy tracts are contaminated in up to one-third of open biopsies.[29] Therefore, liberal excision of the tract should be performed upon definitive surgery, which in turn depends on how careful and with how much foresight the biopsy has been planned (rules V and VI). However, this technique is more expensive than Tru-cut needle biopsy and necessitates hospital admission since it is performed under plexus or general anaesthesia. Another option is US- or CT-guided core needle biopsy, particularly in cases where a lesion is poorly accessible or comprises necrotic areas.[30,31] Consequently, Tru-cut biopsy

Table 1. Ten rules to aid planning and evaluation of biopsy

Rules		How to achieve?
I	Do not hurry	Take time and carefully plan your next steps
II	Do not contaminate neurovascular structures or joints	Plan your biopsy according to anatomy and eventual future surgery
III	Do adequate imaging before any operation	Arrange MRI (with contrast agent)
IV	Send biopsy specimen to a pathologist specialised in bone and soft tissues tumours	Check with your nearby pathology department whom to contact
V	Take the shortest way through one compartment only	Keeping in mind rules II, VI
VI	Plan your biopsy in view of eventual resections	Cut in longitudinal direction of the extremity
VII	Gain sufficient and representative tissue	Take samples from the peripheral area, not central necrotic regions
VIII	(If possible) store small fraction of tissue fresh frozen (-80°) for research purposes	Get in contact with the pathologist
XI	Operate as atraumatically as possible	Minimise incision or use CT-guided biopsy for deep lesions
X	Avoid any post-operative haematoma	Perform thorough haemostasis, use a drain (passed directly through skin incision) and apply compression dressing

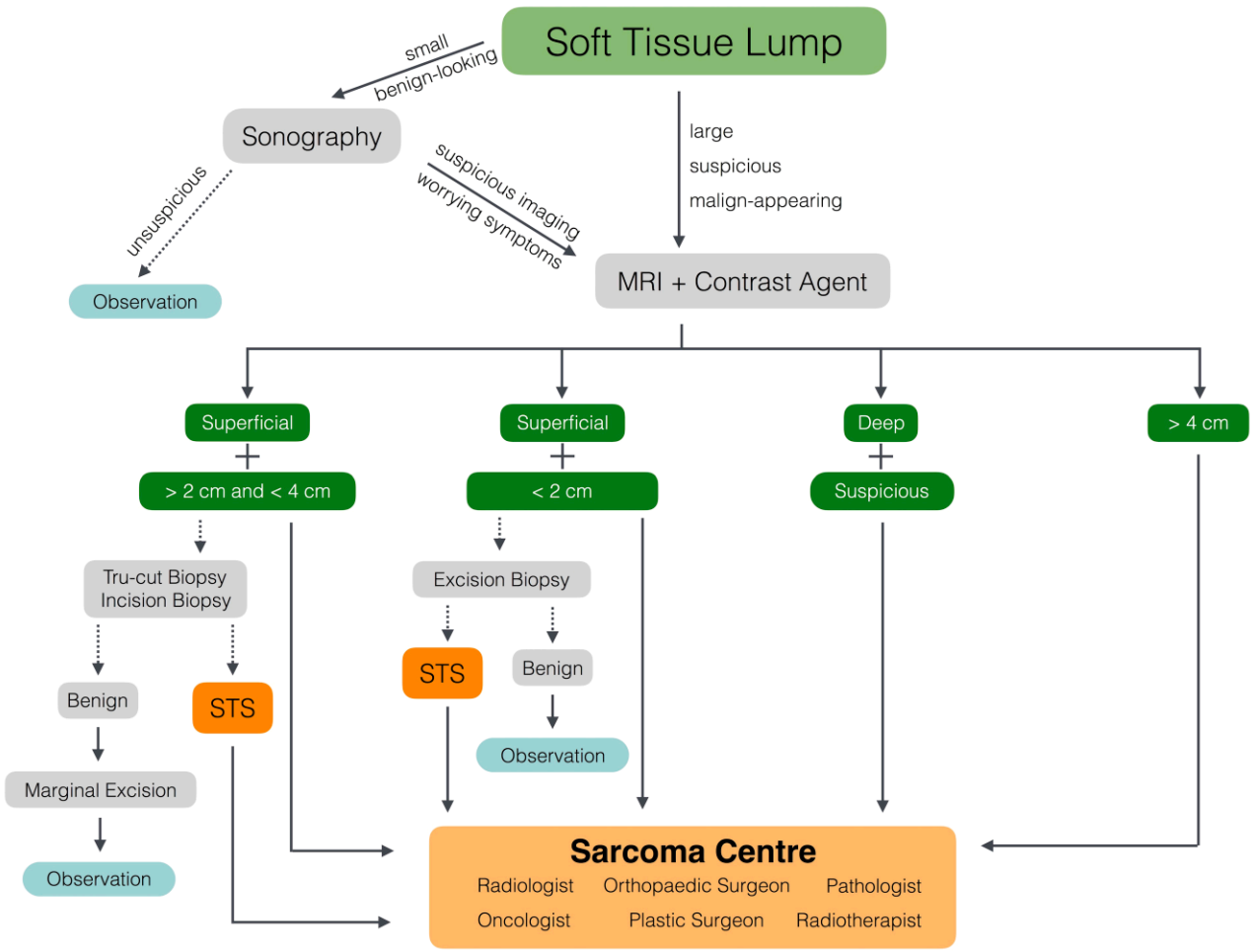

Fig. 4 Referral algorithm for soft-tissue lumps, as recommended by our department (STS, soft-tissue sarcoma).

is the method of choice for easily palpable and large tumours, whilst deeply located and/or small lesions may rather undergo incisional or image-guided biopsy. Moreover, for benign-appearing lesions smaller than 2 cm on MRI, an excision biopsy (i.e. removal of the entire lesion) may be carried out. Again, the same precautions as for Tru-cut and incisional biopsies must be taken.

Every biopsy inevitably entails opening of the tumour capsule, increasing the risk of bleeding and dispersal of malignant cells within the surgical wound. In open biopsy, a drain should therefore be inserted directly through the biopsy incision and not separately. Thorough wound closure and application of a compression dressing additionally forestalls the development of post-operative haematoma formation (bearing in mind rules IX and X).

Nevertheless, it has been demonstrated that the number of diagnostic errors and subsequent changes in treatment, as well as the risk for local recurrence (LR), are all elevated when biopsy of a musculoskeletal lesion has been carried out at institutions other than a tumour centre.[32,33] Therefore, direct referral to a specialist centre should best be initiated as soon as a malignant tumour is suspected (note solid arrows in Fig. 4).

Histology, grading and staging

The histological classification of STSs is an integral part of the diagnostic pathway. Personalised and targeted treatment approaches warrant precise sub-classification into one of more than 117 different soft-tissue tumours defined in the recent *WHO Classification of Bone and Soft Tissue Tumours*.[1]

The most common type is high-grade pleomorphic sarcoma, followed by liposarcoma – which itself comprises several sub-types – leiomyosarcoma, synovial sarcoma and MPNST.[34,35] For most STSs, histological grade is one of the most important prognostic factors in terms of LR-free, metastasis-free and disease-specific survival.[36] Distinct sub-types such as rhabdomyosarcoma and synovial sarcoma are high-grade by definition. For classification

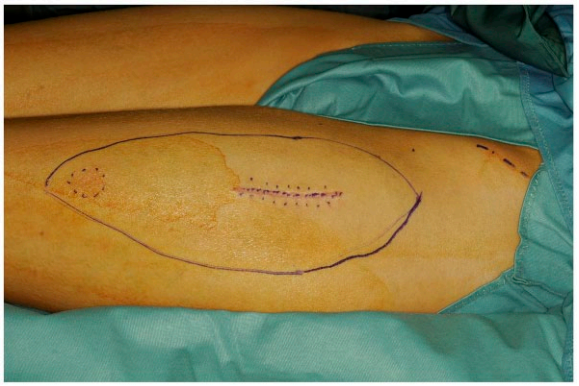

Fig. 5 Unplanned excision of a later histologically-verified alveolar soft-part sarcoma located in the left thigh of a 15-year-old female patient. Note the drain's exit point remote from the surgical wound.

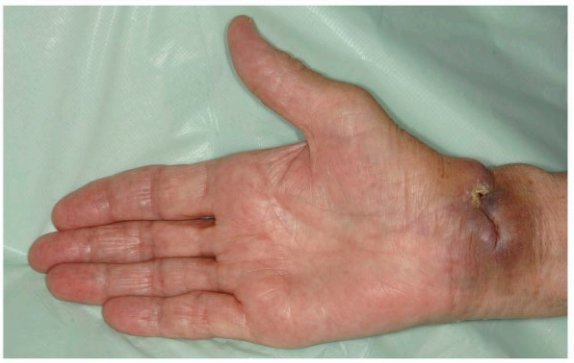

Fig. 6 Inappropriate resection of a tumour at the wrist of an 80-year-old female patient, thought to be a ganglion. Histology revealed a high-grade angiosarcoma. Consequently, a forearm amputation became necessary.

of other STS types the National Cancer Institute and the French Federation of Cancer Centres Sarcoma Group (FNCLCC) grading system are used.[37,38]

Recurrent genetic alterations are present in nearly half of STS sub-types; fusion between the SS18 gene and one of the SSX genes is pathognomonic for synovial sarcoma, whilst a PAX3-FOXO1A fusion gene is found in 80% of alveolar rhabdomyosarcomata.[39,40] In addition to conventional Haematoxylin-eosin stain and immunohistochemistry, molecular analysis with Fluorescence *in situ* hybridisation, Reverse transcription polymerase chain reaction and next generation sequencing is therefore indispensable.[41] Targetted therapies may be administered to patients based on specific genetic alterations.[42,43] However, the amount of biopsy material limits a rigorous diagnostic work-up.

Contrary to the four-part T-stage applied to most solid tumours, STSs are subdivided into two main categories only, depending on a size smaller (T1) or larger (T2) than 5 cm.[44,45] The location relative to the fascia – 'a' for superficial and 'b' for deep tumours (tumour grading according to the FNCLCC system) – and presence of lymph node or distant metastases, are taken into consideration for tumour stage according to the 7th version of the American Joint Committee on Cancer (AJCC) staging manual for STS.[44,45]

Unplanned excisions of STS

Quite frequently, patients first present to a tumour centre following an unintentional excision of a STS.[46-48] The cause for these colloquially termed 'whoops' (inadvertent)-procedures is most likely the rarity of STS, as a result of which many physicians simply do not include the possibility of sarcoma in their differential diagnosis.[49,50] A thorough diagnostic work-up notwithstanding, 'whoops'-procedures may be performed due to the often ambiguous presentation of STS. Further treatment planning of an inadvertently excised STSs can be difficult even for the experienced sarcoma specialist, as pre-operative imaging may be missing, suboptimal surgical approaches may have been chosen, healthy tissues may have been unnecessarily contaminated and resection margins may be unclear (Fig. 5).[51]

Therapeutic management following unplanned excision of STS depends on several factors; wait-and-see may be appropriate for marginally resected low-grade liposarcoma/atypical lipomatous tumours.[52,53] On the other hand, high-grade STSs undergoing unplanned excisions will most likely recur locally if left untreated.[54,55] Furthermore, limb-sparing procedures may not be feasible in cases where inappropriate surgical approaches lead to gross contamination of surrounding tissues (Fig. 6).

Nevertheless, any time delay from unplanned excision to definite surgery at a tumour centre eventually worsens prognosis.[56] Consequently, the most important step to take is urgent referral of these patients to a sarcoma centre, where further treatment will be planned and adequate re-resection or even amputation implemented.

Treatment

Treatment strategies for STSs are best planned by a multidisciplinary team including radiologists, pathologists, orthopaedic surgeons, plastic surgeons, medical oncologists, radiotherapists, thoracic surgeons and physiotherapists.[57] The standard treatment for high-grade STS is surgery, complemented by radiotherapy (RTX) and in selected cases chemotherapy (CTX).

Surgery

Over the last 30 years, amputation has progressively become less important and has been mostly replaced by

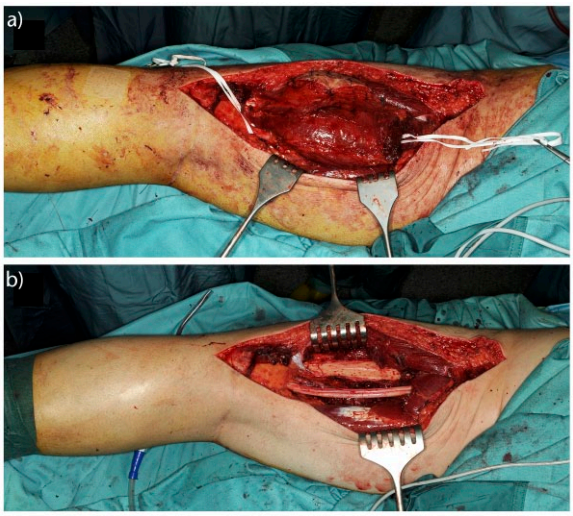

Fig. 7 Wide resection of a high-grade undifferentiated pleomorphic sarcoma arising in the dorsal aspect of the left thigh of a 50-year-old male patient (a). The sciatic nerve was dissected off the tumour and could be spared during *en bloc* resection (b).

limb-sparing procedures in the management of STS.[58] Nowadays, an extremity is only sacrificed if wide surgical tumour excision would result in severe functional impairment, due to the tumour's fixation to or infiltration of important anatomical structures, such as nerves, bone and vessels.[59]

Enneking et al[60] developed a surgical staging system for STSs, differentiating between radical, wide, marginal and intralesional resections. Intralesional resection implies that the tumour's capsule was opened upon surgery. Marginal surgery indicates that resection margins pass through a 'reactive zone' or 'pseudocapsule' surrounding the tumour. Wide resection is achieved by removing the tumour covered by a safety margin of healthy soft tissues (e.g. muscle, fascia). Radical surgery is defined as resection of an entire compartment containing the tumour. Besides this macroscopic surgical staging system, microscopic tumour margins are equally important.

However, in particular when it comes to 'clear' margins, definitions vary considerably.[58,61,62] According to the Union internationale contre le cancer (UICC) classification, wide microscopic margins (R0) are achieved when the tumour is covered by at least 1 mm of healthy tissue.[62] The R-classification, however, defines an R0-resection as microscopically-free tumour margins, irrespective of the thickness.[58] Moreover, a surgical margin built up with muscular fascia constitutes a more effective border against tumour cells than an equally thick layer of adipose tissue would do.[63-65] Therefore, an optimal margin both minimising the risk for local failure and preventing too radical resection is difficult to define precisely.

The benchmark procedure for STS is the wide *en bloc* resection of the tumour, with a reasonable safety margin.[57] As mentioned above, marginal resections may be suitable for atypical lipomatous tumours with a negligible risk of distant metastasis, even if they can recur locally.[52,53,57,66]

In order to avoid opening of the tumour capsule at surgery, major anatomical structures sometimes have to be sacrificed; the cortex of adjacent bones may be partially resected along with the specimen. Whenever possible, though, important anatomical structures such as large nerves and vessels should be spared if not directly invaded by the adjacent tumour (Fig. 7). In cases with extensive osseous involvement, total resection of the affected bone and consecutive reconstruction with a tumour prosthesis may be considered.[67] Moreover, principal veins encased by the tumour can be safely reconstructed with autologous vascular grafts following *en bloc* resection.[68] Large soft-tissue defects resulting from radical surgery may require usage of pedicled and free muscular flaps as well as split- or full-thickness skin grafts for wound closure.[69]

Isolated hyperthermic limb perfusion (ILP)

ILP with Tumour necrosis factor-alpha (TNFα) and melphalan may be applied in locally advanced STS, aiming at prevention of mutilating or ablative surgery. As TNFα selectively destroys vascular structures, the efficacy of ILP is not necessarily dependent on the tumour's histology but rather on its vasculature.[70] In a recent study, however, it was discovered that liposarcomata show the best response to ILP compared with other common histological sub-types.[71] The technique involves utilisation of a heart-lung-machine that is connected to major vessels via iliac and femoral access paths for the lower limb and transpectoral, axillary, brachial or cubital approaches for the upper limb. First, the limb is warmed to 39° ensuring optimal efficacy of the agents administered. Next, TNFα and melphalan are injected, followed by a wash-out phase with crystalloid and colloid solutions after 90 minutes. Six to ten weeks later, definite surgery may be performed. Average response rates of 72% have been reported, with complete remission achieved in 22% of patients.[72] Following ILP, limb-sparing procedures are feasible in over 80% of patients initially scheduled for amputation.[72] Notably, ILP-induced metabolic changes in the tumour already have prognostic implications; on MRI taken after ILP, tumours with a low maximum standardised uptake of 18F-Fluorodeoxyglucose significantly correlate with an improved metastasis-free survival.[73]

RTX

Radiation therapy can be administered in a neo-adjuvant setting, during surgery as intra-operative RTX or brachytherapy and in an adjuvant setting following resection.[74,75]

Depending on the treatment plan, patients may undergo irradiation of the tumour bed at several time points. Palliative RTX can be used to achieve local control in patients with inoperable tumours and/or distant metastases.

Irradiation of the operation field is strongly recommended in any high-grade (i.e. G2 and G3), deeply located tumour exceeding 5 cm in size following wide resection.[76] Based on the experience and personal preference of the multidisciplinary team, indication for RTX may be extended to high- and low-grade STSs smaller than 5 cm located beneath the fascia as well as any superficial tumour larger than 5 cm.[57]

Usually, external beam radiation therapy is applied in 1.8 to 2 Gray (Gy) fractions to the tumour bed and a surrounding safety gap, amounting to 50 Gy in total.[57] Additionally, the original tumour area is irradiated with a boost up to 66 Gy.

RTX is preferably administered post-operatively if major wound complications are anticipated.[77] On the other hand, RTX may be administered pre-operatively depending on the histological sub-type and resectability of the tumour;[78] in myxoid sarcomas and those supplied by a myxoid-like vasculature, for example, response rates to pre-operative RTX are as high as 80%.[79] However, neo-adjuvant and adjuvant RTX seem to be equally effective in terms of local disease control.[77]

CTX

The use of CTX in localised STSs of adult patients can prolong disease-free survival but is considered doubtful regarding overall survival benefits.[57,80] Neo-adjuvant CTX may be administered aiming at eliminating skip lesions or downsizing a locally advanced tumour in order to facilitate limb-sparing surgery.[81] Recent evidence suggests that the neo-adjuvant administration of epirubicin and ifosfamide improves likewise recurrence-free and overall survival in high-risk patients compared with histology-tailored regimens (e.g. gemcitabine and darcabazine in leiomyosarcoma).[82,83]

High risk patients (i.e. patients with deep, high-grade STSs of the extremities larger than 5 cm) may benefit from adjuvant CTX by deferring time to local or distant failure.[84,85] A typical regimen used in the adjuvant setting consists of anthracyclines and ifosfamide (AI-scheme).[86] Alternatively, CTX agents can be administered on the basis of histology, as gemcitabine and docetaxel for pleomorphic sarcoma and etoposide with ifosfamide for MPNST.[87,88] However, histology-driven approaches may be abandoned in future in view of the above-mentioned most recent findings.[82]

First-line treatment for advanced disease is based on anthracyclines (e.g. doxorubicin). The combination with ifosfamide may be chosen if the main goal is to palliate acute symptoms related to rapid metastatic growth.[89] Otherwise, single-agent CTX should be preferred, aiming at control of pulmonary metastases and prolongation of life.[57,89]

Apart from conventional chemotherapeutics, novel promising agents have been developed for STS over the past few years. Trabectedin is recommended as second-line treatment following failure of anthracycline-based CTX. Especially in (myxoid) liposarcoma and leiomyosarcoma, a prolongation in survival may be achieved.[90,91] In non-lipomatous STS refractory to conventional CTX, the tyrosine-kinase inhibitor pazopanib can be used, resulting in a slight prolongation of overall survival.[92]

Eribulin, a cytotoxic spindle-cell inhibitor, was the first agent showing a survival benefit in patients with advanced or metastatic liposarcoma.[93] Overall survival increased by 7.2 months under treatment with eribulin in comparison to dacarbacine. In April 2016, the European Medicines Agency approved eribulin as another second-line agent for advanced liposarcomas. Nonetheless, further multicentre trials are required to confirm the beneficial effects of novel agents in the treatment of STS.

Outcomes

Following wide resection of STSs at a sarcoma centre, the five-year LR rate ranges between 12% and 26%, depending on patient age, histological sub-type, tumour grade, anatomical location and the quality of surgical margins.[14,94] Whilst some LRs can be attributed to inadequate surgical margins or omission of adjuvant RTX, STSs sometimes recur even after an optimal primary treatment. In such cases, local failure results from a tumour's biological aggressiveness and is associated with a considerably worse prognosis.[95]

Grade 3 tumours metastasise in up to 60% of cases, as opposed to only 5% to 10% of grade 1 tumours.[96] Additionally, large tumour size and a deep location are associated with a higher risk for distant metastasis.[14] Patient prognosis is drastically reduced in cases with metastatic disease, with an expected two-year survival rate of 33% only.[97] Nevertheless, the median overall survival for patients with metastatic disease has improved over the last 20 years, due to reinforced multidisciplinary treatment approaches, development of the above-mentioned novel therapeutics and better understanding of disease dynamics.[97]

Future perspectives

The close cooperation between involved clinical specialities, from radiologists and pathologists diagnosing the tumour, through orthopaedic, plastic and thoracic surgeons performing surgical treatment, oncologists and radiotherapists responsible for (neo-) adjuvant CTX and

RTX to physiotherapists and psycho-oncologists supporting patients throughout treatment, has generally improved outcomes for patients with STS. Locally advanced STSs can be downsized by neo-adjuvant CTX alone or in combination with ILP and RTX in selected tumour types to make limb-salvage surgery possible.[98] Moreover, complex reconstructions – nowadays routinely performed following extensive tumour resection – improve patients' quality of life significantly. In the adjuvant and palliative setting, CTX can prolong disease-free survival, leads to tumour shrinkage and relieves metastasis-associated symptoms. Furthermore, recently developed agents prolong overall survival of STS patients with advanced disease.[93]

Additionally, modern analyses and technologies have found their way into management of STSs. The multi-state modelling enables prediction of outcome of patients with localised STSs.[99] With the Sarculator (Digital Forest SRL, Italy), the prognosis of patients with high-risk STSs of both the extremities and trunk undergoing peri-operative CTX can be calculated via an app.[100] Another app allowing estimation of the prognosis of patients with extremity-STS is the PERsonalised SARcoma Care (PERSARC) model that is being currently developed by sarcoma specialists.[101]

However, many questions remain to be answered, from the most appropriate width of surgical margins to the benefits of CTX in localised STS, to new treatment strategies in advanced disease. For some tumours, targeted agents, such as imatinib for gastrointestinal stromal tumours and pazopanib for non-lipomatous STS, seem to be more effective than conventional CTX.[92] The most recent discovery in this field is the human monoclonal antibody olaratumab, targeting platelet-derived growth factor receptor alpha.[102] The combination of doxorubicin with olaratumab improved median overall survival by 11.8 months in STS patients with metastatic disease in comparison with doxorubicin alone.[102]

The diagnosis of STS can be challenging. A thorough diagnostic workup is usually required to distinguish malignant from benign soft-tissue lesions. If performed only partially or inaccurately, misinterpretation of the underlying pathology at best delays ultimate diagnosis. Consequently, unplanned excisions may be performed, necessitating extensive re-resection and adjuvant therapy at tumour centres.

In order to avoid misdiagnoses, one should follow a standardised diagnostic approach, beginning with the patient history, clinical examination and appropriate imaging prior to conducting biopsy. The moment a STS is suspected – ideally prior to any invasive procedure – patients should be referred to the next sarcoma centre. Definitive treatment is best planned and performed by sarcoma specialists employing a multidisciplinary approach.

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