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REVIEW

Basic Knowledge in Soft Tissue Sarcoma

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Abstract Sarcoma is rare and heterogenous with various subtypes having a different prognostic. Desmoid is a tumour with a local aggressiveness; GIST with KIT mutation responds massively to target treatment as IMATINIB, whereas soft tissue sarcoma and leiomyosarcoma are very aggressive with poor response to systemic therapies. Interventional radiology plays an important role in the diagnosis of sarcomas with image-guided percutaneous core needle biopsy being the most commonly used biopsy technique in the diagnosis of sarcomas. Biopsy access routes discussed with the surgeon, and skin access is tattooed. Surgery is a mainstay of sarcoma treatment; the resection can be large. Indeed, resection objective is R0 because quality of surgical margins impacts local control and survival. Radiotherapy is possible in neoadjuvant or in adjuvant treatment to improve local control rate. Recently radiotherapy enhancer injected percutaneously in soft tissue sarcoma has proven benefit in increasing the rate of R0 complete surgical resection. Several studies showed better local control rate linked with post-operative radiotherapy. In patients affected by oligometastatic disease, complete surgical resection of all metastatic sites is in fact considered the primary treatment because complete remission is critical for cure. The decision making to use local therapies is complex, depends upon diverse presentations and histologies, and should always be taken in a multidisciplinary discussion. Today, percutaneous image-guided treatments with ablation technologies (radiofrequency ablation, cryotherapy, microwaves ablation) provide high rate of durable local control for small-sized malignant deposit in many organs including lung, liver and bones. Sarcoma must be managed by multimodality treatment in expert reference centres. Such management has a considerable impact on the prognosis.

Keywords Sarcoma · Soft tissue sarcoma · Stromal tumor · Interventional oncology

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Soft Tissue Sarcoma	
Ten most important points of the cancer	1. Soft tissue sarcomas (STS) are rare and heterogeneous mesenchymal neoplasms, with more 70 histological subtypes
	2. Etiology of STS is unknown; however, there are several genetic syndromes and environmental risk factors well documented
	3. Depth, size and histopronostic grade are the most powerful prognostic factors
	4. Sarcoma management should be done in a referral centre
	5. Biopsy of STS needs expertise to avoid future recurrence on biopsy needle path
	6. Surgery is a mainstay of localized STS treatment (localized disease in 90% of cases at diagnosis). Initial quality of surgery impacts local control and survival
	7. Perioperative treatments (radiotherapy, chemotherapy, isolated limb perfusion) have to be discussed in MTB and could improve local control and risk of distant relapse in high-grade selected STS
	8. Oligometastatic forms can benefit from surgical or interventional radiology which improve local control and survival
	9. Metastatic treatment is palliative in the majority of cases, and chemotherapy with best supportive care is the mainstay of treatment
	10. With the exception of proof-of-concept therapies in rare sarcoma histotypes, the first line of chemotherapy contained anthracyclines. In last decade, targeted therapies have been increased to allow personalized treatment according to the histological subtypes
Five most important number of the cancer	1. Incidence is valued less than 6 cases for 100,000, which represented 1–2% of all adult cancer
	2. There were around 27,908 new cases per year in the European countries
	3. There are more than 70 sarcoma histological subtypes
	4. The 10-year relative survival rate for STS among patients > 20 years old was 70%, but approximately 50% among patients > 65 years old
	5. The overall median survival for patient with lung metastases was 15 months
Three major pivotal studies for the last 5 years	Improved sarcoma management in a national network of reference centres: analysis of NetSarc network on 13,454 patients treated between 2010 and 2014. Jean-Yves BLAY et al. JCO 2016
	Olaratumab and doxorubicin versus doxorubicin alone for treatment of STS: an open-label phase 1b and randomized phase 2 trial. W. Tap et al. Lancet oncol 2016
	Eribulin versus dacarbazine in previously treated patients with advanced liposarcoma or leiomyosarcoma: a randomized, open-label, multicentre, phase 3 trial. Schoffski P et al. Lancet 2016
Two messages about the cancer	STS are a rare cancer that requires management in a referral centre
	Focal treatment of oligometastatic patients is possible after tumour board discussion
One prediction for the 5 future years	The personalized treatment will develop during the next years. Indeed, an improvement of the bio-pathology knowledge of STS will allow the development of specific targeted therapy

Epidemiology

STS are rare and heterogeneous mesenchymal neoplams, with more 70 histological subtypes [1]. Sarcoma incidence is valued less than 6 cases for 100,000, which represented 1–2% of all adult cancer [1, 2]. The median age at diagnosis is 60 years old, with 2 incidence peaks, at 50 and 80 years old; 25% of diagnostic sarcomas are more than 75 years [3].

Predisposing Factors

Etiology of the majority of STS is unknown; however, there are several well-documented genetic syndromes and environmental risk factors.

In genetic predisposition syndromes, Li-Fraumeni syndrome is an autosomal disease associated with the loss of function of the TP53 tumour suppressor which induces many types of cancer such as STS [4]. The neurofibromatosis (NF1) or Von Recklinghausen disease is transmitted on the dominant autosomal mode and predisposed at central nervous system cancer but also to leukaemias and malignant tumours of nerve sheaths [4, 5]. Other syndromes of predisposition as the RB1 tumour suppressor gene mutation show an increase in the incidence of the occurrence of sarcomas [6].

Environmental factors are known to promote sarcoma as ionizing radiation to patients with a history of radiotherapy treatment or chemical exhibitors as the vinyl chloride [7–9].

Pathology

STS diagnosis is difficult and requires expert analysis. Sarcomas are classified by the "WHO histological classification" which is based on the identification of the cell line reached as well as its differentiation. Besides histopathology, it is completed by a molecular and genetic classification which is divided into five categories [4, 10]:

- STS with molecular translocations
- STS with activating mutations
- STS with inhibitory mutations
- STS with simple amplifications
- STS with complex genomic abnormalities

Each STS histotype had per se different outcomes. Desmoid tumour is local aggressive, whereas unknown pleomorphic sarcoma (UPS) or leiomyosarcoma is aggressive and undifferenced.

Diagnostic and Initial Work-Up

Due to its rarity and heterogeneity, patients with a mass in soft part have to be managed by a dedicated multidisciplinary tumour board (MTB) in expert reference centres as soon as a sarcoma diagnosis is suspected. Such management has a considerable impact on the prognosis as demonstrated recently in a study conducted in France within the clinical NETSARC of patients with STM support network [11].

Indeed, the diagnosis of sarcoma is complex; it requires a multidisciplinary approach with an expert pathologist in the field [12].

The exploration of tumours of soft tissues is carried out in three times:

- *Local exploration* All deep mass or superficial tumour with diameter > 5 cm needs specific exploration. For soft tissue, magnetic resonance imaging (MRI) is the main imaging in the extremity and computed tomography (CT) for retroperitoneal tumours.
- *Histological diagnosis* After local exploration pathological assessment is necessary to define the histological subtype, deep mass or superficial tumour > 5 cm needs biopsy which used relatively large bore (14G–16G) needles for adequate sampling. Needle path for sarcomas is of utmost importance due to high propensity of seeding of these tumours. Needle path must be discussed with surgeon so that this path is resected at the time of surgery if any. Consequently no non-resected compartment should be crossed. Of course an outer canula is highly recommended. Biopsy is interpreted by expert pathologist. Radiologist or surgeon performs biopsy after discussion access. Pathologic assessment distinguishes subtype, differentiation, necrosis, mitotic rate and genetic or molecular anomaly.
- *Staging* Tumour assessment includes exploration of the metastatic risk. STS often metastasize in lung which is explored by computed tomography. However, several subtypes like leiomyosarcoma metastasize everywhere. Highlighted sarcoma study showed prognostic factors which involved in disease-free survival (DFS) and overall survival (OS): in particular, size of tumour (more 5 or 10 cm), site (deep or superficial), histological grade and gender.

Approved/Recommended Treatments

Localized

- *Surgery* Surgery is the cornerstone of sarcoma treatment. The quality of initial resection influences outcomes in terms of local control and survival [13, 14]. The challenge is in between complete resection versus morbidity and functional results of the resection. This is why preoperative tumour size reduction by radiation therapy or isolated limb perfusion is important to consider. Positive microscopic resection margins significantly increase local relapse risk and impact free survival rate [15]. Surgery has to be managed in a reference centre with expert surgeons and specific MTB to optimize the initial take in charge which considerably influences outcomes of patients [16].
- Radiotherapy is possible in neoadjuvant or in adjuvant settings to improve local control rate. Several studies showed better local control rate linked with postoperative radiotherapy [17], but no improvement in overall survival (OS) has been demonstrated. ESMO recommendation favours adjuvant radiotherapy when tumours size is above 5 cm or deeply located or high grade and when R1 resection occurs [12]. In the context of neoadjuvant radiotherapy, NBTXR3 is a new class of radioenhancer and shows efficiency in localized sarcoma in a phase 1–2 study [18]. NBTXR3 follows by radiotherapy improved responses rate, with correct tolerance in comparison with radiotherapy alone.
- The role of perioperative chemotherapy remains controversial in both neoadjuvant and adjuvant settings. Adjuvant CT can be proposed as an option to the high-risk individual patient for a shared decision-making with the patient. Analysis by subgroups in meta-analysis revealed benefit preferentially to the soft tissue mass located in extremities and chest wall. If the

decision is made to use chemotherapy as upfront treatment, it may well be used preoperatively. A local benefit may be gained, facilitating surgery, in addition to the systemic one. Neoadjuvant chemotherapy with anthracyclines plus ifosfamide for at least three cycles can be viewed as an option in the high-risk individual patient [19, 20].

Meta-analysis	Studies numbers/patients	Local relapse rate	Distant relapse rate	Disease-free survival	Overall survival
Adjuvant chemotherapy for localized resectable soft tissue sarcoma of adults: meta-analysis of individual data	14/1568	0.73 (95% CI 0.56–0.94); (p = 0.016)	0.70 (95% CI 0.57–0.85); (p = 0.0001)	0.75 (95% CI 0.64–0.87); (p = 0.0001)	0.89 (95% CI 0.76–1.03); (p = 0.12)
A systematic meta-analysis of randomized controlled trials of adjuvant chemotherapy for localized resectable soft tissue sarcoma	18/1953	0.73 (95% CI 0.56–0.94); (p 0.02)	0.67 (95% CI 0.56–0.82); (p 0.0001)	0.67 (95% CI 0.56–0.82); (p 0.0001)	0.77 (95% CI 0.64–0.93); (p 0.01)
Adjuvant chemotherapy with doxorubicin, ifosfamide and lenograstim for resected soft tissue sarcoma (EORTC 62931): a multicentre randomized controlled trial	4/2145	–	–	–	0.86 (0.76–0.97) (p = 0.02)

- Isolated limb perfusion can be proposed in selected locally advanced marginally resectable STS of extremity. A meta-analysis for isolated limb perfusion of extremity STS demonstrated overall response rate of 73.3% with and complete response rate of 25.8% [21]. Such procedure required patient selection, due to complexity of surgery and rate of perioperative complications. Neoadjuvant chemotherapy with regional hyperthermia showed better overall survival versus chemotherapy alone [22]. It is a safe treatment for locally advanced tumours.

Oligometastatic Disease

In patients affected by oligometastatic disease, an intermediate stage between locally advanced disease defined by the presence of 1 of 5 metastases [23, 24], complete surgical resection of all metastatic sites is in fact considered the primary treatment because complete remission is critical for cure [19, 25]. Some arguments for using local treatment arise from retrospective analysis such as a study where among 281 oligometastatic sarcoma patients (1–5 metastases) suffered from pulmonary (71.5%), hepatic (10.6%) extra pulmonary and extrahepatic metastases (19.2%) at the onset of the oligometastatic diseases, 164 patients received local treatment, including surgery (77.9%) and RFA (16.4%) [26]. Patients who underwent loco-regional therapies exhibited a longer OS, even if this benefit can be attributed to a patient selection bias. Consequently, the decision-making to use local therapies is complex, depends upon diverse presentations and histologies and should always be taken in a multidisciplinary tumour board.

Most of the published data have been done on oligometastatic bone sarcomas [27]. Recently, studies have also reported favourable results in angiosarcomas [28], synovial sarcomas [29] and soft tissue sarcomas [30].

Metastatic Disease

In non-oligometastatic patients, treatment is palliative and chemotherapy is the mainstay of treatment. Doxorubicin alone remains the golden standard in these palliative situations. Recently, a relatively small phase 2 study tested the combination of doxorubicin with an antibody directed against platelet-derived growth factor receptor alpha (PDGFRA), olaratumab, and showed a statistically significant higher OS in comparison with doxorubicin alone. Olaratumab is available in some countries, but first the result of ANNOUNCE phase 3 trial does not show any benefit as phase 2 trial, and the final results are expected.

Multiagent chemotherapy with adequate-dose anthracyclines plus ifosfamide may be the treatment of choice, particularly when a tumour response is felt to be potentially advantageous and performance status is good, despite the lack of superiority of multiagent chemotherapy on doxorubicin alone in terms of overall survival in all randomized trials performed in the setting [19, 31]. The combination of doxorubicin plus dacarbazine is an option for multiagent, first-line chemotherapy of advanced leiomyosarcoma, in which the activity of ifosfamide is far less convincing in available retrospective evidence, or of solitary fibrous tumours.

While the first line is relatively standard in all sarcoma histotypes, the second line and beyond depend on histology.

Indeed, the response rates to chemotherapy agents vary with histological subtypes. Synovial sarcoma are usually responding to ifosfamide, trabectedin is used in lipoleiomyosarcoma (L-STS), gemcitabine and dacarbazine in leiomyosarcomas, pazopanib in non-liposarcoma, eribulin in liposarcoma, weekly taxanes in angiosarcoma.

What are the new treatment options, and their possible molecular drivers

Besides the proof of concepts and new paradigms already developed in mesenchymal neoplasms [imatinib in gastrointestinal stromal tumour (GIST) and dermato-fibrosarcoma protuberans, denosumab in giant cell tumour (GCT), anti-CSF1 (colony-stimulated factor 1) in pigmented villonodular synovitis (PVNS), mechanistic target of rapamycin (m-Tor) inhibitors in Pecoma, crizotinib in anaplasic lymphoma kinase (ALK) positive inflammatory myofibroblastic tumour (IMT)], new targeted therapies have been highlighted.

Regorafenib, an orally bioavailable multikinase inhibitor, inhibits vascular endothelial growth factor receptor 1 (VEGFR1), vascular endothelial growth factor receptor 2 (VEGFR2), and vascular endothelial growth factor receptor 3 (VEGFR3), and tumour cell signalling kinases [rearranged during transfection (RET), KIT, platelet derived growth factor receptor (PDGFR), and rapidly acceleraded fibrosarcoma (Raf)]. A phase 2 trial shows a improvement of progression-free survival versus placebo in non-adipocytic STS after anthracycline failure [32]. Overall toxicity and safety with regorafenib were as expected and were managed.

Selinexor, a selective inhibitor of the nuclear export protein XPO1, improves progression-free survival against placebo in phase 2 [33] in DD liposarcomas (dedifferenciated liposarcoma).

Epigenetic pathway is a promising therapeutic target as enhancer of zeste homogue 2 (EZH2) target [34]. Indeed, a phase 2 shows efficacity in epithelioid sarcoma, rhabdoid tumour and negative integrase interactor 1 (INI1) tumour [35].

The first results of immunotherapy are disappointing, but better selection seems necessary. Several studies are underway to define potentially population more immunosensitive as high tumour mutational load or immune cell infiltration. Associations with other molecules are also studied as talimogene laherparepvec (T-VEC), an ancolytic immunotherapy derived from HSV type-1, shows efficacity in association with pembrolizumab in phase 2 study. This trial enrolled metastatic sarcoma who failed at least one standard systemic therapy [36].

Two of the challenges in 2019 will be: (1) to treat the right patient in the right place at the right time with the right diagnosis, in molecular subsets of histological subgroups of rare STS, with the right treatment sequence with a right individual adapted schedule, in accordance with the patient's wishes and (2) to urgently individualize reproducible biomarkers of efficacy/resistance for any agents approved or used in all STS with the exception of proof-of-concept therapies described above.

Role of Interventional Radiology

Interventional radiology plays an important role in the diagnosis of sarcomas with image-guided percutaneous core needle biopsy being the most commonly used biopsy technique in the diagnosis of sarcomas. Large bore needle (14G) is used when possible and access route is discussed with the surgeon and skin access is tattooed.

Today, percutaneous image-guided treatments with ablation technologies (radiofrequency ablation, cryotherapy, microwaves ablation) provide high rate of durable local control for small size malignant deposit in many organs including lung, liver and bones. When compared with surgery, image-guided treatments provide a lower-morbidity option with excellent tolerance and preservation of long-term function with low damage to healthy parenchyma around the metastases.

A single-institution retrospective aimed at primary endpoint of time to untreatable progression (TTUP) defined as the time elapsed between the first thermal ablation and the re-initiation of systemic chemotherapy to treat disease progression in 30 metastatic leiomyosarcoma patients. They received 50 iterative thermal ablation treatments for 93 metastases (mean diameter 18.2 mm; range 3–45 mm) [6]. Metastases were recurrent or residual after completion of systemic treatment, or selective treatment of oligometastases progressive on systemic treatment. Metastases were visceral (40%), retroperitoneal (33%) or soft tissue (27%) locations. The median TTUP was 14.2 months (range 2.4–122.8), the local control rate was 89.4% at 3 years, and the median overall survival was 48.3 months.

For lung metastases, in a large series of 566 patients with 1037 lung metastases, the subgroup of sarcoma demonstrated a tumour control rate, OS and PFS at 5 years of 91.7%, 41.5% and 15.9%, respectively [37]. In the paediatric population, thermal ablation of osteosarcoma oligometastatic lung metastases recurring after previous surgery, in 11 children with 26 lung metastases measuring 2–16 mm (mean = 6.7 mm) [30], reported a 100% local control rate. Five patients remained in complete remission after median follow-up of 37.5 months, and five patients developed new metastases including 1 bone and 1 lung

metastases. Two of the 5 patients were retreated and are still in remission after subsequent treatment.

Liver metastases local treatments have been explored mostly for GIST tumours. Even if TKI have revolutionized GIST treatment, RFA appears helpful in providing effective local tumour control in liver metastases from GIST tumour. RFA can be used either at the time of best clinical response with patient maintained under TKI after the procedure, or to target a imatinib resistant foci in order to maintained imatinib [38]. In our experience, RFA delivered in patients while taking imatinib appeared safe; such combination may favour efficacy of thermal ablation through synergistic effects that have been described in preclinical model with sorafenib where volume of ablation is increased by concomitant targeted therapy [39].

For bone metastases from sarcomas, literature is scarce, because series often combined sarcomas and non-sarcomatous bone tumours. Thermal ablation performed in 89 oligometastatic patients with 122 bone metastases from various origin measuring ≤ 2 cm (39%), 2–3 cm (21%) and > 3 cm (39%) demonstrated a complete destruction rate of 67% at 1 year with 85% complete destruction in metastases ≤ 2 cm underlining the possible value of thermal ablation of bone metastases in a curative intent for disease control [40].

Suggested Reading (Websites, Guidelines, Publications, Cancer Society)

https://sarctrials.org/soft-tissue-sarcoma

https://www.essoweb.org/european-school-of-sts/

http://www.jnccn.org/content/16/5/536.abstract

https://www.esmo.org/Guidelines/Sarcoma-and-GIST/Soft-Tissue-and-Visceral-Sarcomas

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Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical Approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed Consent For this type of study, informed consent is not required.

Consent for Publication For this type of study, consent for publication is not required.

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