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## Multidisciplinary treatment of soft tissue sarcomas: An update

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### Abstract

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

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

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



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

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## INTRODUCTION

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

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

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

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

## LITERATURE SEARCH

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

## DIAGNOSIS

### *History and clinical examination*

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

### *Imaging*

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

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

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

### **Biopsy and molecular diagnosis**

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

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

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

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

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## **SOFT TISSUE SARCOMAS CLASIFICATION**

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

## TREATMENT

### Surgery

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

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

### Radiotherapy

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

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

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

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

### Chemotherapy

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

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

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

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

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

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

### Novel treatments

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

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

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



## CONCLUSION

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

## REFERENCES

- 1 **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**: 421-431 [PMID: 29209518 DOI: 10.1302/2058-5241.2.170005]
- 2 **Hoefkens F**, Dehandschutter C, Somville J, Meijnders P, Van Gestel D. Soft tissue sarcoma of the extremities: pending questions on surgery and radiotherapy. *Radiat Oncol* 2016; **11**: 136 [PMID: 27733179 DOI: 10.1186/s13014-016-0668-9]
- 3 **von Mehren M**, Randall RL, Benjamin RS, Boles S, Bui MM, Ganjoo KN, George S, Gonzalez RJ, Heslin MJ, Kane JM, Keedy V, Kim E, Koon H, Mayerson J, McCarter M, McGarry SV, Meyer C, Morris ZS, O'Donnell RJ, Pappo AS, Paz IB, Petersen IA, Pfeifer JD, Riedel RF, Ruo B, Schuetz S, Tap WD, Wayne JD, Bergman MA, Scavone JL. Soft Tissue Sarcoma, Version 2.2018, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw* 2018; **16**: 536-563 [PMID: 29752328 DOI: 10.6004/jnccn.2018.0025]
- 4 **Dasgupta R**, Fuchs J, Rodeberg D. Rhabdomyosarcoma. *Semin Pediatr Surg* 2016; **25**: 276-283 [PMID: 27955730 DOI: 10.1053/j.sempedsurg.2016.09.011]
- 5 **Rydholm A**, Gustafson P, Rööser B, Willén H, Akerman M, Herrlin K, Alvegård T. Limb-sparing surgery without radiotherapy based on anatomic location of soft tissue sarcoma. *J Clin Oncol* 1991; **9**: 1757-1765 [PMID: 1919628 DOI: 10.1200/JCO.1991.9.10.1757]
- 6 **Callegaro D**, Miceli R, Mariani L, Raut CP, Gronchi A. Soft tissue sarcoma nomograms and their incorporation into practice. *Cancer* 2017; **123**: 2802-2820 [PMID: 28493287 DOI: 10.1002/ncr.30721]
- 7 **Abellan JF**, Lamo de Espinosa JM, Duarte J, Patiño-García A, Martín-Algarra S, Martínez-Monge R, San-Julian M. Nonreferral of possible soft tissue sarcomas in adults: a dangerous omission in policy. *Sarcoma* 2009; **2009**: 827912 [PMID: 20066170 DOI: 10.1155/2009/827912]
- 8 **Bauer HC**, Trovik CS, Alvegård TA, Berlin O, Erlanson M, Gustafson P, Klepp R, Möller TR, Rydholm A, Saeter G, Wahlström O, Wiklund T. Monitoring referral and treatment in soft tissue sarcoma: study based on 1,851 patients from the Scandinavian Sarcoma Group Register. *Acta Orthop Scand* 2001; **72**: 150-159 [PMID: 11372946 DOI: 10.1080/000164701317323408]
- 9 **Beauchamp CP**. CORR Insights®: What is the Success of Repeat Surgical Treatment of a Local Recurrence After Initial Wide Resection of Soft Tissue Sarcomas? *Clin Orthop Relat Res* 2018; **476**: 1801-1802 [PMID: 29787395 DOI: 10.1097/01.blo.0000533636.35983.b7]
- 10 **Rath B**, Harges J, Tingart M, Braunschweig T, Eschweiler J, Miglioni F. [Resection margins in soft tissue sarcomas]. *Orthopade* 2019; **48**: 768-775 [PMID: 31463543 DOI: 10.1007/s00132-019-03795-6]
- 11 **de Matos CMM**, de Araújo Filho IT, Fernandes MV, Macedo Barbosa DJ, André AT, Antoniou G, De Mello RA, De Mello RA, Mountzios G, Tavares AA. Soft Tissue Sarcomas. De Mello RA, Mountzios G, Tavares AA. International Manual of Oncology Practice. Cham: Springer International Publishing, 2019: 775-799 [DOI: 10.1007/978-3-030-16245-0\_35]
- 12 **Ferrari A**, Dirksen U, Bielack S. Sarcomas of Soft Tissue and Bone. *Prog Tumor Res* 2016; **43**: 128-141 [PMID: 27595362 DOI: 10.1159/000447083]
- 13 **Baldini EH**, Goldberg J, Jenner C, Manola JB, Demetri GD, Fletcher CD, Singer S. Long-term outcomes after function-sparing surgery without radiotherapy for soft tissue sarcoma of the extremities and trunk. *J Clin Oncol* 1999; **17**: 3252-3259 [PMID: 10506627 DOI: 10.1200/JCO.1999.17.10.3252]
- 14 **Weitz J**, Antonescu CR, Brennan MF. Localized extremity soft tissue sarcoma: improved knowledge with unchanged survival over time. *J Clin Oncol* 2003; **21**: 2719-2725 [PMID: 12860950 DOI: 10.1200/JCO.2003.02.026]
- 15 **Röhrborn A**, Röher HD. [Surgical aspects in the multidisciplinary treatment of soft tissue sarcomas]. *Praxis (Bern 1994)* 1998; **87**: 1050-1060 [PMID: 9757788]
- 16 **Palassini E**, Ferrari S, Verderio P, De Paoli A, Martin Broto J, Quagliuolo V, Comandone A, Sangalli C, Palmerini E, Lopez-Pousa A, De Sanctis R, Bottelli S, Libertini M, Picci P, Casali PG, Gronchi A. Feasibility of Preoperative Chemotherapy With or Without Radiation Therapy in Localized Soft Tissue Sarcomas of Limbs and Superficial Trunk in the Italian Sarcoma Group/Grupo Español de Investigación en Sarcomas Randomized Clinical Trial: Three Versus Five Cycles of Full-Dose Epirubicin Plus Ifosfamide. *J Clin Oncol* 2015; **33**: 3628-3634 [PMID: 26351345 DOI: 10.1200/JCO.2015.62.9394]
- 17 **Calais G**. [Role of radiotherapy in soft tissue sarcoma]. *Cancer Radiother* 1997; **1**: 457-461 [PMID: 9587377]
- 18 **Haas RL**, Delaney TF, O'Sullivan B, Keus RB, Le Pechoux C, Olmi P, Poulsen JP, Seddon B, Wang D. Radiotherapy for management of extremity soft tissue sarcomas: why, when, and where? *Int J Radiat Oncol Biol Phys* 2012; **84**: 572-580 [PMID: 22520481 DOI: 10.1016/j.ijrobp.2012.01.062]
- 19 **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**: 1400-1405 [PMID: 26163048 DOI: 10.1016/j.ejso.2015.05.017]
- 20 **Jernigan EW**, Esther RJ. Soft tissue masses for the general orthopedic surgeon. *Orthop Clin North Am* 2015; **46**: 417-428, xi [PMID: 26043055 DOI: 10.1016/j.ocl.2015.02.009]
- 21 **Abbas JS**, Holyoke ED, Moore R, Karakousis CP. The surgical treatment and outcome of soft-tissue sarcoma. *Arch Surg* 1981; **116**: 765-769 [PMID: 7235973 DOI: 10.1001/archsurg.1981.01380180025006]
- 22 **Lakkaraju A**, Sinha R, Garikipati R, Edward S, Robinson P. Ultrasound for initial evaluation and triage of clinically suspicious soft-tissue masses. *Clin Radiol* 2009; **64**: 615-621 [PMID: 19414084 DOI: 10.1016/j.crad.2009.01.012]
- 23 **Yoon MA**, Chee CG, Chung HW, Song JS, Lee JS, Kim W, Lee MH, Lee SH, Shin MJ. Added value of

- diffusion-weighted imaging to conventional MRI for predicting fascial involvement of soft tissue sarcomas. *Eur Radiol* 2019; **29**: 1863-1873 [PMID: 30324391 DOI: 10.1007/s00330-018-5786-3]
- 24 **Hong JH**, Jee WH, Jung CK, Jung JY, Shin SH, Chung YG. Soft tissue sarcoma: adding diffusion-weighted imaging improves MR imaging evaluation of tumor margin infiltration. *Eur Radiol* 2019; **29**: 2589-2597 [PMID: 30413958 DOI: 10.1007/s00330-018-5817-0]
- 25 **Willeumier JJ**, Rueten-Budde AJ, Jeys LM, Laitinen M, Pollock R, Aston W, Dijkstra PD, Ferguson PC, Griffin AM, Wunder JS, Fiocco M, van de Sande MA. Individualised risk assessment for local recurrence and distant metastases in a retrospective transatlantic cohort of 687 patients with high-grade soft tissue sarcomas of the extremities: a multistate model. *BMJ Open* 2017; **7**: e012930 [PMID: 28196946 DOI: 10.1136/bmjopen-2016-012930]
- 26 **Crombé A**, Périer C, Kind M, De Senneville BD, Le Loarer F, Italiano A, Buy X, Saut O. T<sub>2</sub>-based MRI Delta-radiomics improve response prediction in soft-tissue sarcomas treated by neoadjuvant chemotherapy. *J Magn Reson Imaging* 2019; **50**: 497-510 [PMID: 30569552 DOI: 10.1002/jmri.26589]
- 27 **Peeken JC**, Spraker MB, Knebel C, Dapper H, Pfeiffer D, Devecka M, Thamer A, Shouman MA, Ott A, von Eisenhart-Rothe R, Nüsslin F, Mayr NA, Nyflot MJ, Combs SE. Tumor grading of soft tissue sarcomas using MRI-based radiomics. *EBioMedicine* 2019; **48**: 332-340 [PMID: 31522983 DOI: 10.1016/j.ebiom.2019.08.059]
- 28 **Zhang Y**, Zhu Y, Shi X, Tao J, Cui J, Dai Y, Zheng M, Wang S. Soft Tissue Sarcomas: Preoperative Predictive Histopathological Grading Based on Radiomics of MRI. *Acad Radiol* 2019; **26**: 1262-1268 [PMID: 30377057 DOI: 10.1016/j.acra.2018.09.025]
- 29 **Wang H**, Chen H, Duan S, Hao D, Liu J. Radiomics and Machine Learning With Multiparametric Preoperative MRI May Accurately Predict the Histopathological Grades of Soft Tissue Sarcomas. *J Magn Reson Imaging* 2020; **51**: 791-797 [PMID: 31486565 DOI: 10.1002/jmri.26901]
- 30 **Lehnhardt M**, Daigeler A, Homann HH, Schwaiberger V, Goertz O, Kuhnen C, Steinau HU. MFH revisited: outcome after surgical treatment of undifferentiated pleomorphic or not otherwise specified (NOS) sarcomas of the extremities -- an analysis of 140 patients. *Langenbecks Arch Surg* 2009; **394**: 313-320 [PMID: 18584203 DOI: 10.1007/s00423-008-0368-5]
- 31 **Lehnhardt M**, Hirche C, Daigeler A, Goertz O, Ring A, Hirsch T, Drücke D, Hauser J, Steinau HU. [Soft tissue sarcoma of the upper extremities. Analysis of factors relevant for prognosis in 160 patients]. *Chirurg* 2012; **83**: 143-152 [PMID: 21695557 DOI: 10.1007/s00104-011-2124-6]
- 32 **Siravegna G**, Marsoni S, Siena S, Bardelli A. Integrating liquid biopsies into the management of cancer. *Nat Rev Clin Oncol* 2017; **14**: 531-548 [PMID: 28252003 DOI: 10.1038/nrclinonc.2017.14]
- 33 **Eastley NC**, Ottolini B, Neumann R, Luo JL, Hastings RK, Khan I, Moore DA, Esler CP, Shaw JA, Royle NJ, Ashford RU. Circulating tumour-derived DNA in metastatic soft tissue sarcoma. *Oncotarget* 2018; **9**: 10549-10560 [PMID: 29535826 DOI: 10.18632/oncotarget.24278]
- 34 **Li X**, Seebacher NA, Hornicek FJ, Xiao T, Duan Z. Application of liquid biopsy in bone and soft tissue sarcomas: Present and future. *Cancer Lett* 2018; **439**: 66-77 [PMID: 30223067 DOI: 10.1016/j.canlet.2018.09.012]
- 35 **Darwanto A**, Hein AM, Strauss S, Kong Y, Sheridan A, Richards D, Lader E, Ngowe M, Pelletier T, Adams D, Ricker A, Patel N, Kühne A, Hughes S, Shiffman D, Zimmermann D, Te Kaat K, Rothmann T. Use of the QIAGEN GeneReader NGS system for detection of KRAS mutations, validated by the QIAGEN Therascreen PCR kit and alternative NGS platform. *BMC Cancer* 2017; **17**: 358 [PMID: 28532404 DOI: 10.1186/s12885-017-3328-z]
- 36 **Bridge JA**. The role of cytogenetics and molecular diagnostics in the diagnosis of soft-tissue tumors. *Mod Pathol* 2014; **27** Suppl 1: S80-S97 [PMID: 24384855 DOI: 10.1038/modpathol.2013.179]
- 37 **Roberts KG**, Odell AF, Byrnes EM, Baleato RM, Griffith R, Lyons AB, Ashman LK. Resistance to c-KIT kinase inhibitors conferred by V654A mutation. *Mol Cancer Ther* 2007; **6**: 1159-1166 [PMID: 17363509 DOI: 10.1158/1535-7163.MCT-06-0641]
- 38 **Jour G**, Scarborough JD, Jones RL, Loggers E, Pollack SM, Pritchard CC, Hoch BL. Molecular profiling of soft tissue sarcomas using next-generation sequencing: a pilot study toward precision therapeutics. *Hum Pathol* 2014; **45**: 1563-1571 [PMID: 24908143 DOI: 10.1016/j.humpath.2014.04.012]
- 39 **Rubin BP**, Fletcher CD, Inwards C, Montag AG, Peabody T, Qualman SJ, Rosenberg AE, Weiss S, Krausz T; College of American Pathologists. Protocol for the examination of specimens from patients with soft tissue tumors of intermediate malignant potential, malignant soft tissue tumors, and benign/locally aggressive and malignant bone tumors. *Arch Pathol Lab Med* 2006; **130**: 1616-1629 [PMID: 17076523]
- 40 **Cates JMM**. The AJCC 8th Edition Staging System for Soft Tissue Sarcoma of the Extremities or Trunk: A Cohort Study of the SEER Database. *J Natl Compr Canc Netw* 2018; **16**: 144-152 [PMID: 29439175 DOI: 10.6004/jnccn.2017.7042]
- 41 **Sampo M**, Tarkkanen M, Tukiainen E, Popov P, Gustafson P, Lundin M, Böhling T, Blomqvist C, Lundin J. A web-based prognostic tool for extremity and trunk wall soft tissue sarcomas and its external validation. *Br J Cancer* 2012; **106**: 1076-1082 [PMID: 22353813 DOI: 10.1038/bjc.2012.48]
- 42 **Daigeler A**, Harati K, Goertz O, Hirsch T, Steinau HU, Lehnhardt M. [Prognostic factors and surgical tactics in patients with locally recurrent soft tissue sarcomas]. *Handchir Mikrochir Plast Chir* 2015; **47**: 118-127 [PMID: 25897581 DOI: 10.1055/s-0034-1394425]
- 43 **Alamanda VK**, Crosby SN, Archer KR, Song Y, Schwartz HS, Holt GE. Predictors and clinical significance of local recurrence in extremity soft tissue sarcoma. *Acta Oncol* 2013; **52**: 793-802 [PMID: 22877243 DOI: 10.3109/0284186X.2012.711953]
- 44 **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**: 3003-3011 [PMID: 20645035 DOI: 10.1007/s11999-010-1471-9]
- 45 **Bonvalot S**, Rimareix F, Paumier A, Roberti E, Bouzaïene H, Le Péchoux C. [What is new in the local approach of limb sarcomas and desmoid tumours?]. *Cancer Radiother* 2010; **14**: 455-459 [PMID: 20797892 DOI: 10.1016/j.canrad.2010.06.016]
- 46 **Cates MM**, Cates JMM. Surgical resection margin classifications for high-grade pleomorphic soft tissue sarcomas of the extremity or trunk: definitions of adequate resection margins and recommendations for sampling margins from primary resection specimens. *Mod Pathol* 2019; **32**: 1421-1433 [PMID: 31053757 DOI: 10.1038/s41379-019-0278-9]
- 47 **Gundle KR**, Kafchinski L, Gupta S, Griffin AM, Dickson BC, Chung PW, Catton CN, O'Sullivan B, Wunder JS, Ferguson PC. Analysis of Margin Classification Systems for Assessing the Risk of Local Recurrence After Soft Tissue Sarcoma Resection. *J Clin Oncol* 2018; **36**: 704-709 [PMID: 29346043 DOI: 10.1200/JCO.2017.74.6941]

- 48 **Samkoe KS**, Sardar HS, Bates BD, Tselepidakis NN, Gunn JR, Hoffer-Hawlik KA, Feldwisch J, Pogue BW, Paulsen KD, Henderson ER. Preclinical imaging of epidermal growth factor receptor with ABY-029 in soft-tissue sarcoma for fluorescence-guided surgery and tumor detection. *J Surg Oncol* 2019; **119**: 1077-1086 [PMID: 30950072 DOI: 10.1002/jso.25468]
- 49 **Mahjoub A**, Morales-Restrepo A, Fourman MS, Mandell JB, Feiqi L, Hankins ML, Watters RJ, Weiss KR. Tumor Resection Guided by Intraoperative Indocyanine Green Dye Fluorescence Angiography Results in Negative Surgical Margins and Decreased Local Recurrence in an Orthotopic Mouse Model of Osteosarcoma. *Ann Surg Oncol* 2019; **26**: 894-898 [PMID: 30588559 DOI: 10.1245/s10434-018-07114-9]
- 50 **Whitley MJ**, Cardona DM, Lazarides AL, Spasojevic I, Ferrer JM, Cahill J, Lee CL, Snuderl M, Blazer DG, Hwang ES, Greenup RA, Mosca PJ, Mito JK, Cuneo KC, Larrier NA, O'Reilly EK, Riedel RF, Eward WC, Strasfeld DB, Fukumura D, Jain RK, Lee WD, Griffith LG, Bawendi MG, Kirsch DG, Brigman BE. A mouse-human phase I co-clinical trial of a protease-activated fluorescent probe for imaging cancer. *Sci Transl Med* 2016; **8**: 320ra4 [PMID: 26738797 DOI: 10.1126/scitranslmed.aad0293]
- 51 **Kim YB**, Shin KH, Seong J, Roh JK, Kim GE, Hahn SB, Suh CO. Clinical significance of margin status in postoperative radiotherapy for extremity and truncal soft-tissue sarcoma. *Int J Radiat Oncol Biol Phys* 2008; **70**: 139-144 [PMID: 17919843 DOI: 10.1016/j.ijrobp.2007.05.067]
- 52 **Alektiar KM**, Brennan MF, Singer S. Influence of site on the therapeutic ratio of adjuvant radiotherapy in soft-tissue sarcoma of the extremity. *Int J Radiat Oncol Biol Phys* 2005; **63**: 202-208 [PMID: 16111590 DOI: 10.1016/j.ijrobp.2005.01.011]
- 53 **DeLaney TF**. Optimizing radiation therapy and post-treatment function in the management of extremity soft tissue sarcoma. *Curr Treat Options Oncol* 2004; **5**: 463-476 [PMID: 15509480 DOI: 10.1007/s11864-004-0035-1]
- 54 **Folkert MR**, Singer S, Brennan MF, Kuk D, Qin LX, Kobayashi WK, Crago AM, Alektiar KM. Comparison of local recurrence with conventional and intensity-modulated radiation therapy for primary soft-tissue sarcomas of the extremity. *J Clin Oncol* 2014; **32**: 3236-3241 [PMID: 25185087 DOI: 10.1200/JCO.2013.53.9452]
- 55 **Wells S**, Ager B, Hitchcock YJ, Poppe MM. The radiation dose-response of non-retroperitoneal soft tissue sarcoma with positive margins: An NCDB analysis. *J Surg Oncol* 2019; **120**: 1476-1485 [PMID: 31710707 DOI: 10.1002/jso.25748]
- 56 **Zagars GK**, Ballo MT. Significance of dose in postoperative radiotherapy for soft tissue sarcoma. *Int J Radiat Oncol Biol Phys* 2003; **56**: 473-481 [PMID: 12738323 DOI: 10.1016/s0360-3016(02)04573-x]
- 57 **Dickie CI**, Parent AL, Griffin AM, Fung S, Chung PW, Catton CN, Ferguson PC, Wunder JS, Bell RS, Sharpe MB, O'Sullivan B. Bone fractures following external beam radiotherapy and limb-preservation surgery for lower extremity soft tissue sarcoma: relationship to irradiated bone length, volume, tumor location and dose. *Int J Radiat Oncol Biol Phys* 2009; **75**: 1119-1124 [PMID: 19362782 DOI: 10.1016/j.ijrobp.2008.12.006]
- 58 **Tsagozis P**, Brosjö O, Skorpil M. Preoperative radiotherapy of soft-tissue sarcomas: surgical and radiologic parameters associated with local control and survival. *Clin Sarcoma Res* 2018; **8**: 19 [PMID: 30323920 DOI: 10.1186/s13569-018-0106-x]
- 59 **Davis AM**, O'Sullivan B, Turcotte R, Bell R, Catton C, Chabot P, Wunder J, Hammond A, Benk V, Kandel R, Goddard K, Freeman C, Sadura A, Zee B, Day A, Tu D, Pater J; Canadian Sarcoma Group; NCI Canada Clinical Trial Group Randomized Trial. Late radiation morbidity following randomization to preoperative versus postoperative radiotherapy in extremity soft tissue sarcoma. *Radiother Oncol* 2005; **75**: 48-53 [PMID: 15948265 DOI: 10.1016/j.radonc.2004.12.020]
- 60 **Al-Absi E**, Farrokhyar F, Sharma R, Whelan K, Corbett T, Patel M, Ghert M. A systematic review and meta-analysis of oncologic outcomes of pre- versus postoperative radiation in localized resectable soft-tissue sarcoma. *Ann Surg Oncol* 2010; **17**: 1367-1374 [PMID: 20217260 DOI: 10.1245/s10434-009-0885-7]
- 61 **Hui AC**, Ngan SY, Wong K, Powell G, Choong PF. Preoperative radiotherapy for soft tissue sarcoma: the Peter MacCallum Cancer Centre experience. *Eur J Surg Oncol* 2006; **32**: 1159-1164 [PMID: 16765559 DOI: 10.1016/j.ejso.2006.04.003]
- 62 **Kuklo TR**, Temple HT, Owens BD, Juliano J, Islinger RB, Andejeski Y, Frassica DA, Berrey BH. Preoperative versus postoperative radiation therapy for soft-tissue sarcomas. *Am J Orthop (Belle Mead NJ)* 2005; **34**: 75-80 [PMID: 15789525]
- 63 **Wang D**, Zhang Q, Eisenberg BL, Kane JM, Li XA, Lucas D, Petersen IA, DeLaney TF, Freeman CR, Finkelstein SE, Hitchcock YJ, Bedi M, Singh AK, Dundas G, Kirsch DG. Significant Reduction of Late Toxicities in Patients With Extremity Sarcoma Treated With Image-Guided Radiation Therapy to a Reduced Target Volume: Results of Radiation Therapy Oncology Group RTOG-0630 Trial. *J Clin Oncol* 2015; **33**: 2231-2238 [PMID: 25667281 DOI: 10.1200/JCO.2014.58.5828]
- 64 **Tom MC**, Joshi N, Vicini F, Chang AJ, Hong TS, Showalter TN, Chao ST, Wolden S, Wu AJ, Martin D, Husain Z, Badiyan SN, Kolar M, Sherertz T, Mourtada F, Cohen GN, Shah C. The American Brachytherapy Society consensus statement on intraoperative radiation therapy. *Brachytherapy* 2019; **18**: 242-257 [PMID: 31084904 DOI: 10.1016/j.brachy.2019.01.015]
- 65 **Cahlon O**, Spierer M, Brennan MF, Singer S, Alektiar KM. Long-term outcomes in extremity soft tissue sarcoma after a pathologically negative re-resection and without radiotherapy. *Cancer* 2008; **112**: 2774-2779 [PMID: 18429001 DOI: 10.1002/cncr.23493]
- 66 **Clasby R**, Tilling K, Smith MA, Fletcher CD. Variable management of soft tissue sarcoma: regional audit with implications for specialist care. *Br J Surg* 1997; **84**: 1692-1696 [PMID: 9448617 DOI: 10.1002/bjs.1800841213]
- 67 **Manir KS**, Basu A, Choudhury KB, Basu S, Ghosh K, Gangopadhyay S. Interstitial brachytherapy in soft tissue sarcoma: a 5 years institutional experience with Cobalt 60-based high-dose-rate brachytherapy system. *J Contemp Brachytherapy* 2018; **10**: 431-438 [PMID: 30479620 DOI: 10.5114/jcb.2018.78994]
- 68 **Gimeno M**, San Julián M, Cambeiro M, Arbea L, Jablonska P, Moreno-Jiménez M, Amillo S, Aristu J, Lecanda F, Martínez-Monge R. Long-term results of Perioperative High Dose Rate Brachytherapy (PHDRB) and external beam radiation in adult patients with soft tissue sarcomas of the extremities and the superficial trunk: Final results of a prospective controlled study. *Radiother Oncol* 2019; **135**: 91-99 [PMID: 31015176 DOI: 10.1016/j.radonc.2019.02.011]
- 69 **Pohar S**, Haq R, Liu L, Koniarczyk M, Hahn S, Damron T, Aronowitz JN. Adjuvant high-dose-rate and low-dose-rate brachytherapy with external beam radiation in soft tissue sarcoma: a comparison of outcomes. *Brachytherapy* 2007; **6**: 53-57 [PMID: 17284387 DOI: 10.1016/j.brachy.2006.11.004]
- 70 **Klein J**, Ghasem A, Huntley S, Donaldson N, Keisch M, Conway S. Does an Algorithmic Approach to

- Using Brachytherapy and External Beam Radiation Result in Good Function, Local Control Rates, and Low Morbidity in Patients With Extremity Soft Tissue Sarcoma? *Clin Orthop Relat Res* 2018; **476**: 634-644 [PMID: 29443850 DOI: 10.1007/s11999-0000000000000079]
- 71 **Calvo FA**, Sole CV, Polo A, Cambeiro M, Montero A, Alvarez A, Cuervo M, Julian MS, Martinez-Monge R. Limb-sparing management with surgical resection, external-beam and intraoperative electron-beam radiation therapy boost for patients with primary soft tissue sarcoma of the extremity: a multicentric pooled analysis of long-term outcomes. *Strahlenther Onkol* 2014; **190**: 891-898 [PMID: 24715241 DOI: 10.1007/s00066-014-0640-2]
- 72 **Roeder F**, Krempien R. Intraoperative radiation therapy (IORT) in soft-tissue sarcoma. *Radiat Oncol* 2017; **12**: 20 [PMID: 28100249 DOI: 10.1186/s13014-016-0751-2]
- 73 **Frustaci S**, Gherlinzoni F, De Paoli A, Bonetti M, Azzarelli A, Comandone A, Olmi P, Buonadonna A, Pignatti G, Barbieri E, Apice G, Zmerly H, Serraino D, Picci P. Adjuvant chemotherapy for adult soft tissue sarcomas of the extremities and girdles: results of the Italian randomized cooperative trial. *J Clin Oncol* 2001; **19**: 1238-1247 [PMID: 11230464 DOI: 10.1200/JCO.2001.19.5.1238]
- 74 **Woll PJ**, Reichardt P, Le Cesne A, Bonvalot S, Azzarelli A, Hoekstra HJ, Leahy M, Van Coevorden F, Verweij J, Hogendoorn PC, Ouali M, Marreaud S, Bramwell VH, Hohenberger P; EORTC Soft Tissue and Bone Sarcoma Group and the NCIC Clinical Trials Group Sarcoma Disease Site Committee. Adjuvant chemotherapy with doxorubicin, ifosfamide, and lenograstim for resected soft-tissue sarcoma (EORTC 62931): a multicentre randomised controlled trial. *Lancet Oncol* 2012; **13**: 1045-1054 [PMID: 22954508 DOI: 10.1016/S1470-2045(12)70346-7]
- 75 **Judson I**, Verweij J, Gelderblom H, Hartmann JT, Schöffski P, Blay JY, Kerst JM, Sufliarsky J, Whelan J, Hohenberger P, Krarup-Hansen A, Alcindor T, Marreaud S, Litière S, Hermans C, Fisher C, Hogendoorn PC, dei Tos AP, van der Graaf WT; European Organisation and Treatment of Cancer Soft Tissue and Bone Sarcoma Group. Doxorubicin alone versus intensified doxorubicin plus ifosfamide for first-line treatment of advanced or metastatic soft-tissue sarcoma: a randomised controlled phase 3 trial. *Lancet Oncol* 2014; **15**: 415-423 [PMID: 24618336 DOI: 10.1016/S1470-2045(14)70063-4]
- 76 **Pervaiz N**, Colterjohn N, Farrokhyar F, Tozer R, Figueredo A, Ghert M. A systematic meta-analysis of randomized controlled trials of adjuvant chemotherapy for localized resectable soft-tissue sarcoma. *Cancer* 2008; **113**: 573-581 [PMID: 18521899 DOI: 10.1002/ncr.23592]
- 77 **Patrikidou A**, Domont J, Cioffi A, Le Cesne A. Treating soft tissue sarcomas with adjuvant chemotherapy. *Curr Treat Options Oncol* 2011; **12**: 21-31 [PMID: 21384115 DOI: 10.1007/s11864-011-0145-5]
- 78 **Fakhrai N**, Ebm C, Kostler WJ, Jantsch M, Abdolvahab F, Dominkus M, Pokrajac B, Kauer-Dorner D, Zielinski CC, Brodowicz T; Austrian Cooperative Soft Tissue Sarcoma Study Group. Intensified adjuvant IFADIC chemotherapy in combination with radiotherapy versus radiotherapy alone for soft tissue sarcoma: long-term follow-up of a prospective randomized feasibility trial. *Wien Klin Wochenschr* 2010; **122**: 614-619 [PMID: 20963638 DOI: 10.1007/s00508-010-1472-4]
- 79 **Sundby Hall K**, Bruland ØS, Bjerkehagen B, Zaikova O, Engellau J, Hagberg O, Hansson L, Hagberg H, Ahlström M, Knobel H, Papworth K, Zemmler M, Goplen D, Bauer HCF, Eriksson M. Adjuvant chemotherapy and postoperative radiotherapy in high-risk soft tissue sarcoma patients defined by biological risk factors-A Scandinavian Sarcoma Group study (SSG XX). *Eur J Cancer* 2018; **99**: 78-85 [PMID: 29929092 DOI: 10.1016/j.ejca.2018.05.011]
- 80 **Rothermundt C**, Fischer GF, Bauer S, Blay JY, Grünwald V, Italiano A, Kasper B, Kollár A, Lindner LH, Miah A, Sleijfer S, Stacchiotti S, Putora PM. Pre- and Postoperative Chemotherapy in Localized Extremity Soft Tissue Sarcoma: A European Organization for Research and Treatment of Cancer Expert Survey. *Oncologist* 2018; **23**: 461-467 [PMID: 29192019 DOI: 10.1634/theoncologist.2017-0391]
- 81 **Pasquali S**, Pizzamiglio S, Touati N, Litière S, Marreaud S, Kasper B, Gelderblom H, Stacchiotti S, Judson I, Dei Tos AP, Verderio P, Casali PG, Woll PJ, Gronchi A; EORTC – Soft Tissue and Bone Sarcoma Group. The impact of chemotherapy on survival of patients with extremity and trunk wall soft tissue sarcoma: revisiting the results of the EORTC-STBSG 62931 randomised trial. *Eur J Cancer* 2019; **109**: 51-60 [PMID: 30690293 DOI: 10.1016/j.ejca.2018.12.009]
- 82 **Grobmyer SR**, Maki RG, Demetri GD, Mazumdar M, Riedel E, Brennan MF, Singer S. Neo-adjuvant chemotherapy for primary high-grade extremity soft tissue sarcoma. *Ann Oncol* 2004; **15**: 1667-1672 [PMID: 15520069 DOI: 10.1093/annonc/mdh431]
- 83 **Zaidi MY**, Ethun CG, Tran TB, Poultsides G, Grignol VP, Howard JH, Bedi M, Mogal H, Tseng J, Roggin KK, Chouliaras K, Votanopoulos K, Krasnick B, Fields RC, Oskouei S, Reimer N, Monson D, Maithel SK, Cardona K. Assessing the Role of Neoadjuvant Chemotherapy in Primary High-Risk Truncal/Extremity Soft Tissue Sarcomas: An Analysis of the Multi-institutional U.S. Sarcoma Collaborative. *Ann Surg Oncol* 2019; **26**: 3542-3549 [PMID: 31342400 DOI: 10.1245/s10434-019-07639-7]
- 84 **Gortzak E**, Azzarelli A, Buesa J, Bramwell VH, van Coevorden F, van Geel AN, Ezzat A, Santoro A, Oosterhuis JW, van Glabbeke M, Kirkpatrick A, Verweij J; E. O.R.T.C. Soft Tissue Bone Sarcoma Group and the National Cancer Institute of Canada Clinical Trials Group/Canadian Sarcoma Group. A randomised phase II study on neo-adjuvant chemotherapy for 'high-risk' adult soft-tissue sarcoma. *Eur J Cancer* 2001; **37**: 1096-1103 [PMID: 11378339 DOI: 10.1016/s0959-8049(01)00083-1]
- 85 **Kraybill WG**, Harris J, Spiro IJ, Ettinger DS, DeLaney TF, Blum RH, Lucas DR, Harmon DC, Letson GD, Eisenberg B. Long-term results of a phase 2 study of neoadjuvant chemotherapy and radiotherapy in the management of high-risk, high-grade, soft tissue sarcomas of the extremities and body wall: Radiation Therapy Oncology Group Trial 9514. *Cancer* 2010; **116**: 4613-4621 [PMID: 20572040 DOI: 10.1002/ncr.25350]
- 86 **Mullen JT**, Kobayashi W, Wang JJ, Harmon DC, Choy E, Hornicek FJ, Rosenberg AE, Chen YL, Spiro IJ, DeLaney TF. Long-term follow-up of patients treated with neoadjuvant chemotherapy and radiotherapy for large, extremity soft tissue sarcomas. *Cancer* 2012; **118**: 3758-3765 [PMID: 22180344 DOI: 10.1002/ncr.26696]
- 87 **van der Graaf WT**, Blay JY, Chawla SP, Kim DW, Bui-Nguyen B, Casali PG, Schöffski P, Aglietta M, Staddon AP, Beppu Y, Le Cesne A, Gelderblom H, Judson IR, Araki N, Ouali M, Marreaud S, Hodge R, Dewji MR, Coens C, Demetri GD, Fletcher CD, Dei Tos AP, Hohenberger P; EORTC Soft Tissue and Bone Sarcoma Group; PALETTE study group. Pazopanib for metastatic soft-tissue sarcoma (PALETTE): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet* 2012; **379**: 1879-1886 [PMID: 22595799 DOI: 10.1016/S0140-6736(12)60651-5]
- 88 **Stacchiotti S**, Negri T, Zaffaroni N, Palassini E, Morosi C, Brici S, Conca E, Bozzi F, Cassinelli G,

- Gronchi A, Casali PG, Pilotti S. Sunitinib in advanced alveolar soft part sarcoma: evidence of a direct antitumor effect. *Ann Oncol* 2011; **22**: 1682-1690 [PMID: 21242589 DOI: 10.1093/annonc/mdq644]
- 89 **Cassier PA**, Gelderblom H, Stacchiotti S, Thomas D, Maki RG, Kroep JR, van der Graaf WT, Italiano A, Seddon B, Dòmont J, Bompas E, Wagner AJ, Blay JY. Efficacy of imatinib mesylate for the treatment of locally advanced and/or metastatic tenosynovial giant cell tumor/pigmented villonodular synovitis. *Cancer* 2012; **118**: 1649-1655 [PMID: 21823110 DOI: 10.1002/cncr.26409]
- 90 **Savina M**, Le Cesne A, Blay JY, Ray-Coquard I, Mir O, Toulmonde M, Cousin S, Terrier P, Ranchere-Vince D, Meeus P, Stoeckle E, Honoré C, Sargos P, Sunyach MP, Le Péchoux C, Giraud A, Bellera C, Le Loarer F, Italiano A. Patterns of care and outcomes of patients with METAstatic soft tissue SARcoma in a real-life setting: the METASARC observational study. *BMC Med* 2017; **15**: 78 [PMID: 28391775 DOI: 10.1186/s12916-017-0831-7]
- 91 **García-Del-Muro X**, López-Pousa A, Maurel J, Martín J, Martínez-Trufero J, Casado A, Gómez-España A, Fra J, Cruz J, Poveda A, Meana A, Pericay C, Cubedo R, Rubió J, De Juan A, Láinez N, Carrasco JA, de Andrés R, Buesa JM; Spanish Group for Research on Sarcomas. Randomized phase II study comparing gemcitabine plus dacarbazine versus dacarbazine alone in patients with previously treated soft tissue sarcoma: a Spanish Group for Research on Sarcomas study. *J Clin Oncol* 2011; **29**: 2528-2533 [PMID: 21606430 DOI: 10.1200/JCO.2010.33.6107]
- 92 **Seddon B**, Strauss SJ, Whelan J, Leahy M, Woll PJ, Cowie F, Rothermundt C, Wood Z, Benson C, Ali N, Marples M, Veal GJ, Jamieson D, Küver K, Tirabosco R, Forsyth S, Nash S, Dehbi HM, Beare S. Gemcitabine and docetaxel versus doxorubicin as first-line treatment in previously untreated advanced unresectable or metastatic soft-tissue sarcomas (GeDDiS): a randomised controlled phase 3 trial. *Lancet Oncol* 2017; **18**: 1397-1410 [PMID: 28882536 DOI: 10.1016/S1470-2045(17)30622-8]
- 93 **Teras J**, Mägi A, Teras M, Pata P, Teras RM, Randhawa N, Kalling K. Soft Tissue Cancer Management: Isolated Limb Infusion for Sarcoma. *Visc Med* 2019; **35**: 373-379 [PMID: 31934586 DOI: 10.1159/000495888]
- 94 **Stevenson MG**, Hoekstra HJ, Song W, Suurmeijer AJH, Been LB. Histopathological tumor response following neoadjuvant hyperthermic isolated limb perfusion in extremity soft tissue sarcomas: Evaluation of the EORTC-STBSG response score. *Eur J Surg Oncol* 2018; **44**: 1406-1411 [PMID: 29858098 DOI: 10.1016/j.ejso.2018.05.011]
- 95 **Assi T**, Cavalcanti A, Le Cesne A, Faron M, Honart JF, Hadji A, Camuzard O, Ibrahim T, LePéchoux C, Mir O, Dumont S, Terrier P, Adam J, Honoré C. Neoadjuvant isolated limb perfusion in newly diagnosed untreated patients with locally advanced soft tissue sarcomas of the extremities: the Gustave Roussy experience. *Clin Transl Oncol* 2019; **21**: 1135-1141 [PMID: 30656606 DOI: 10.1007/s12094-019-02034-w]
- 96 **Stevenson MG**, Seinen JM, Pras E, Brouwers AH, van Ginkel RJ, van Leeuwen BL, Suurmeijer AJH, Been LB, Hoekstra HJ. Hyperthermic isolated limb perfusion, preoperative radiotherapy, and surgery (PRS) a new limb saving treatment strategy for locally advanced sarcomas. *J Surg Oncol* 2018; **117**: 1447-1454 [PMID: 29484661 DOI: 10.1002/jso.25008]
- 97 **Salah S**, Lewin J, Amir E, Abdul Razak A. Tumor necrosis and clinical outcomes following neoadjuvant therapy in soft tissue sarcoma: A systematic review and meta-analysis. *Cancer Treat Rev* 2018; **69**: 1-10 [PMID: 29843049 DOI: 10.1016/j.ctrv.2018.05.007]
- 98 **Seinen JM**, Jutte PC, Been LB, Pras E, Hoekstra HJ. Fractures after multimodality treatment of soft tissue sarcomas with isolated limb perfusion and radiation; likely to occur and hard to heal. *Eur J Surg Oncol* 2018; **44**: 1398-1405 [PMID: 29789188 DOI: 10.1016/j.ejso.2018.04.012]
- 99 **Wiemann B**, Starnes CO. Coley's toxins, tumor necrosis factor and cancer research: a historical perspective. *Pharmacol Ther* 1994; **64**: 529-564 [PMID: 7724661 DOI: 10.1016/0163-7258(94)90023-x]
- 100 **Vormehr M**, Türeci Ö, Sahin U. Harnessing Tumor Mutations for Truly Individualized Cancer Vaccines. *Annu Rev Med* 2019; **70**: 395-407 [PMID: 30691374 DOI: 10.1146/annurev-med-042617-101816]
- 101 **Hartmaier RJ**, Charo J, Fabrizio D, Goldberg ME, Albacker LA, Pao W, Chmielecki J. Genomic analysis of 63,220 tumors reveals insights into tumor uniqueness and targeted cancer immunotherapy strategies. *Genome Med* 2017; **9**: 16 [PMID: 28231819 DOI: 10.1186/s13073-017-0408-2]
- 102 **Le Cesne A**, Cresta S, Maki RG, Blay JY, Verweij J, Poveda A, Casali PG, Balaña C, Schöffski P, Grosso F, Lardelli P, Nieto A, Alfaro V, Demetri GD. A retrospective analysis of antitumour activity with trabectedin in translocation-related sarcomas. *Eur J Cancer* 2012; **48**: 3036-3044 [PMID: 22749255 DOI: 10.1016/j.ejca.2012.05.012]
- 103 **Demetri GD**, Chawla SP, von Mehren M, Ritch P, Baker LH, Blay JY, Hande KR, Keohan ML, Samuels BL, Schuetz S, Lebedinsky C, Elsayed YA, Izquierdo MA, Gómez J, Park YC, Le Cesne A. Efficacy and safety of trabectedin in patients with advanced or metastatic liposarcoma or leiomyosarcoma after failure of prior anthracyclines and ifosfamide: results of a randomized phase II study of two different schedules. *J Clin Oncol* 2009; **27**: 4188-4196 [PMID: 19652065 DOI: 10.1200/JCO.2008.21.0088]
- 104 **D'Angelo SP**, Mahoney MR, Van Tine BA, Atkins J, Milhem MM, Jahagirdar BN, Antonescu CR, Horvath E, Tap WD, Schwartz GK, Streicher H. Nivolumab with or without ipilimumab treatment for metastatic sarcoma (Alliance A091401): two open-label, non-comparative, randomised, phase 2 trials. *Lancet Oncol* 2018; **19**: 416-426 [PMID: 29370992 DOI: 10.1016/S1470-2045(18)30006-8]
- 105 **Robbins PF**, Kassim SH, Tran TL, Crystal JS, Morgan RA, Feldman SA, Yang JC, Dudley ME, Wunderlich JR, Sherry RM, Kammula US, Hughes MS, Restifo NP, Raffeld M, Lee CC, Li YF, El-Gamil M, Rosenberg SA. A pilot trial using lymphocytes genetically engineered with an NY-ESO-1-reactive T-cell receptor: long-term follow-up and correlates with response. *Clin Cancer Res* 2015; **21**: 1019-1027 [PMID: 25538264 DOI: 10.1158/1078-0432.CCR-14-2708]
- 106 **Ahmadi M**, King JW, Xue SA, Voisine C, Holler A, Wright GP, Waxman J, Morris E, Stauss HJ. CD3 limits the efficacy of TCR gene therapy in vivo. *Blood* 2011; **118**: 3528-3537 [PMID: 21750319 DOI: 10.1182/blood-2011-04-346338]



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