Current Problems in Cancer 43 (2019) 273–282

Contents lists available at ScienceDirect

Current Problems in Cancer

journal homepage: www.elsevier.com/locate/cpcancer

# Management of localized extremity and retroperitoneal soft tissue sarcoma

Sarah Abaricia[a], Brian Andrew Van Tine[a,b,*]

[a] Division of Oncology, Department of Internal Medicine, Washington University School of Medicine, St. Louis, Missouri
[b] Siteman Cancer Center, Washington University School of Medicine, St. Louis, Missouri

A B S T R A C T

The optimal management of localized soft tissue sarcomas of the extremities and retroperitoneum involves a high volume multidisciplinary team with expertise in sarcoma. In this review, we will highlight the importance of the sarcoma pathologist and imaging techniques prior to surgery and radiation. In addition, the data on neoadjuvant and adjuvant chemotherapy will be discussed. Finally, consideration is given to the importance of identifying genetic cancer predispositions, multidisciplinary management, long-term survivorship, and the current clinical trials for patients undergoing curative intent management.



A R T I C L E I N F O

*Keywords:* Soft tissue sarcoma; Surgery; Radiation; Extremity; Retroperitoneum

## Introduction

Sarcomas are a rare group of tumors that originate from mesenchymal cells. They can be broadly classified into 2 groups: soft tissue sarcomas (STS) and bone sarcomas. It is estimated

☆ BAVT reports Basic Science Grant Funding from Pfizer not relating to this work; Basic Science Grant Funding from Pfizer, Tracon and Merck; consulting fees from Epizyme, Lilly, CytRX, Janssen, Immune Design, Daiichi Sankyo, Plexxicon and Adaptimmune; and speaking fees from Caris, Janseen and Lilly outside the submitted work.

☆☆ SA reports consulting fees for Blueprint Medicines.

★ Research Support: None.

* Correspondence to: Brian A. Van Tine, Barnes and Jewish Hospital, Washington University in St. Louis, 3rd Floor Couch Biomedical Research Building Room 3302, Box 8076, 660 S. Euclid Ave., St. Louis, MO 63110.
*E-mail address:* bvantine@wustl.edu (B.A. Van Tine).

https://doi.org/10.1016/j.currproblcancer.2019.06.002
0147-0272/

that approximately 15,000 new cases of STS will be diagnosed in 2019.[1] STS can arise anywhere in the body, as it can develop from muscle, subcutaneous tissue, fat, nerves, and blood vessels. They arise most commonly in the extremities (upper extremities account for approximately 12% and the lower extremities account for approximately 28%) and the retroperitoneum, which accounts for about 16% of all cases.[2] The 3 most common types of soft tissue sarcomas found in the extremities and the retroperitoneum are liposarcomas (20%-25%), leiomyosarcomas (14%), and undifferentiated pleomorphic sarcomas (UPS) (14%).[2]

## Epidemiology

STS represents approximately 1% of cancers diagnosed in the US yearly.[1] The overall survival (OS) is highly dependent on the stage at which the STS is given at the time of diagnosis. When sarcomas are found early and are confined in one area (as opposed to metastatic, or when the disease has spread to distant regions); there are better outcomes. The overall 5-year survival rate with localized disease is 59%, with disease that has spread to regional lymph nodes 20%, and up to a 15% overall 5-year survival with distant metastatic disease.[3] STS is more common in men than women (4.2 per 100,000 persons vs 2.9) and is more common in Caucasians, African-Americans and Hispanics as opposed to Asian/Pacific Islanders and American Indian/Alaska Natives.[3] Diagnosis is most frequent in individuals ages 55-64 with a median age of 60.[3]

### *Genetic predispositions syndromes and causative environmental factors*

In the majority of STS diagnosed, the exact etiology cannot be identified. However, there are several genetic predisposition mutations that are associated with patients that develop sarcoma. With current methods available for germline genetic testing, identification of tumors with mutations that may also be germline can be vital information to these patients' families.

Li-Fraumeni syndrome is a genetic predisposition syndrome that greatly increases one's risk of developing certain types of cancers. Several cancers that are associated with this syndrome include osteosarcoma, STS, breast cancer, and adrenal carcinoma.[4] Li-Fraumeni is an autosomal dominant syndrome that is estimated to affect 400 people from 64 families in the United States, and is associated with the *CHEK2* and *TP53* genes.[4]

Neurofibromatosis, also known as von Recklinghausen disease, is another autosomal dominant genetic disorder that carries a high occurrence of tumors. Neurofibromatosis type 1, or NF1, is characterized by multiple neurofibromas and benign plexiforms that arise from peripheral nerves and have the potential for malignant transformation into a malignant peripheral nerve sheath tumors.[5] Neurofibromatosis type 2, NF2 and Schwannomatosis, are characterized by multiple benign tumors along cranial and peripheral nerves, meningiomas, and ependymomas that can cause pain, tinnitus, hearing loss, and facial nerve palsy.[5]

Gardner syndrome is associated with attenuated adenomatous polyposis (AAP) and familial adenomatous polyposis (FAP), which is characterized by multiple adenomas of the large bowel with almost certain potential for malignant transformation. This is also associated with abdominal desmoid tumors, and all abdominal desmoid patients need a screening colonoscopy for detection of FAP.[6]

Retinoblastoma is a genetic cancer affecting one or both eyes in children that is typically caused by mutations of the retinoblastoma tumor suppressor gene RB1.[7] These patients are also at high risk for developing secondary malignancies including bone sarcomas (osteosarcoma, Ewing's sarcoma, chondrosarcoma) as well as uterine leiomyosarcoma (LMS).[2] Surveillance with an annual whole-body MRI is recommended for these patients.

Gorlin syndrome, a rhabdoid tumor predisposition syndrome, is an autosomal dominant syndrome that is associated with childhood brain tumors and rhabdomyosarcomas. Typically, these mutations are associated with the Sonic Hedgehog pathway and Suppressor of fused.[8]

Certain environmental interactions can increase the risk of developing STS. Radiation exposure has been documented to cause STS, dating back to the 1920s for workers employed in a

factory painting dials on watches and clocks with radium luminous paint.[9] More commonly seen are radiation-induced sarcomas resulting from prior radiation therapy for a previous malignancy. Although these are fairly rare, varying from 0.09% to 0.11% of all cases of radiation therapy, these sarcomas tend to be aggressive and are associated with poorer prognosis.[10-12] Radiation-induced sarcomas account for less than 5% of all sarcomas and occur between 5 and 20 years after radiation exposure.[13]

Chemical exposure may also increase the risk for developing sarcoma. Chemicals such as vinyl chloride and arsenic have been associated with liver angiosarcoma. Other chemicals including dioxin, anabolic steroids, and herbicides containing phenoxyacetic acid at high levels all have been suggested to increase the risk of developing STS.[14-16]

### *Clinical presentation*

Presentation of STS is highly dependent on the location of the tumor and the structures it abuts or invades. One review was conducted examining 526 patients over a 2-year period, with the complaint of soft tissue swelling. It suggested that any patient exhibiting any of these 4 clinical features should be evaluated for possible malignancy: a mass or lump increasing in size, size >5 cm, pain, or location deep in the fascia.[17] STS is more common in men than women and approximately 40% of sarcomas arise in people over the age of 55.[18] In the retroperitoneum, patients typically present with an abdominal mass. Oftentimes, patients have no other complaints, as constitutional symptoms are uncommon. If symptoms are present, this is typically related to the tumor invading a regional structure or causing mass effect to surrounding organs that can cause pain, lower extremity swelling, loss of appetite, or weight loss.[3]

### *Imaging*

All enlarging masses should be carefully evaluated to rule out a soft tissue malignancy. Masses of the upper and lower extremities are more recognizable for growth than retroperitoneal masses due to the abdomen's ability to shift organs and accommodate a growing tumor. Both computed tomography scans (CT) and magnetic resonance imaging (MRI) are appropriate methods of imaging to evaluate a soft tissue tumor; however, for tumors involving the extremity, an MRI is the gold standard for imaging as this allows for a more detailed view of contents inside the tumor as well as surrounding structures.[19,20] A retrospective analysis evaluating MRI, CT, ultrasound, angiography, and plain film for preoperative planning revealed that MRI is superior to CT. The ultrasound lacked specificity and the angiography and plain film lacked the ability to stage tumors.[21] Staging for STS use the Enneking Staging System or The American Joint Committee on Cancer System (AJCC system), although the AJCC system is the preference by most orthopedic oncologists.[22]

### *Pathology*

Once a soft tissue mass has been imaged, a biopsy needs to be performed to determine histology. Multiple studies have been conducted to determine the best method of biopsy in regards to safety, invasiveness, cost effectiveness, while also yielding sufficient tissue for diagnosis. While open biopsy is considered to provide the highest probability to obtain sufficient tissue, this comes with a higher risk of infection postbiopsy, longer recovery time, and higher institutional costs. Percutaneous core needle biopsies have been proven to a safe, minimally invasive, and equally effective method in obtaining tissue and have become standard of care.[23-25] Fine needle aspiration (FNA) is generally not an adequate method for the diagnosis of sarcoma.[26,27]

STS pathology is a specialized area. It is essential that a pathologist with expertise in sarcoma, as well as access to ancillary molecular testing, review these specimens as studies have

shown discrepancies in the diagnoses between referral and tertiary centers. A retrospective review performed at one sarcoma center's pathology department compared secondarily reviewed vs primary reports.[28] There were 348 specimens evaluated from 286 patients with suspected or proven sarcoma over a 1-year period. Out of those specimens, 250 of those cases (71.8%) were diagnostic agreements or had minimal diagnostic discrepancies, 57 cases (16.4%) had major discrepancies, and 41 (11.8%) had minor discrepancies. Major discrepancies were defined as factors that could lead to a change in medical management including the diagnosis changing to a different malignancy, malignant diagnosis changed to a benign diagnosis, or a benign diagnosis changed to a malignant. These changes also included changes in grading from low grade (grade 1) to intermediate or high grade (2-3), which indicated a change in management. Of those major discrepancies, 10 cases were reclassified from benign to malignant and 13 were reclassified from malignant to benign. Overall, these 23 cases accounted for 23.5% of the discrepancies. In a peer review by the Southeastern Cancer Study Group, the subtype of sarcoma was felt to be incorrect in 27% of cases and 6% of cases were not felt to be sarcomas.[29] A histopathologic peer review completed by the Scandinavian Sarcoma Group indicated that 25% of the histologic types of sarcomas were reclassified and in 40% of the cases, the malignancy grade was changed.[30]

In regards to STS of the extremities and retroperitoneum, these malignancies will most often be a subtype of liposarcoma, LMS, or UPS, but many other subtypes of sarcoma are possible. Determining the type of malignancy is crucial in order to develop the appropriate treatment plan.

Liposarcoma is the most common type of STS and can be further divided into 5 subclasses: well-differentiated liposarcoma, de-differentiated liposarcoma, myxoid liposarcoma, round cell liposarcoma, and pleomorphic liposarcoma. Well-differentiated liposarcoma is considered to be a less aggressive tumor with surgery being the mainstay of treatment, but careful evaluation of these tumors needs to occur as these tumors can be mistaken for normal fatty tissue or lipomas.[31] De-differentiated liposarcoma is a high-grade malignancy with metastatic potential. Amplification of MDM2 and CDK4, through the use of a florescence in situ hybridization (FISH) test or genomic sequencing, can differentiate well/de-differentiated liposarcoma from benign lipomas or other malignancies.[32] Well/de-differentiated liposarcoma are found most commonly in the retroperitoneum or spermatic cord.[31] Myxoid liposarcoma represents a spectrum of disease with pure myxoid liposarcoma behaving indolently with low potential for metastasis while myxoid/round cell liposarcoma (defined as round cell percentage >5%) is aggressive with high chance of metastasis. More than 90% of myxoid liposarcoma are associated with a t(12:16)(q13;p11) translocation.[33,34] The myxoid liposarcoma subclass is more typically associated with tumors in the extremities. Pleomorphic liposarcoma is the least common type of liposarcoma making up approximately 5% of all cases with a complex karyotype. This is typically associated with a loss of tumor suppressor TP53 and RB and carries a poorer prognosis.[35]

LMS is the second most common type of soft tissue and has a cell of origin of smooth muscle lineage. The incidence of LMS depends on the subclass; while the risk of LMS increases with age and typically peaks in the seventh decade of life, uterine LMS can occur as early as the third decade but is more common in the perimenopausal population.[36] When attempting to determine pathology, these soft tissue malignancies are easily recognizable due to the presence of smooth muscle cells. In addition to the appearance, LMS will nearly always stain positive for smooth muscle actin as well as desmin.[37] Histologic grade, tumor size, and depth of the tumor are all used as prognostic factors and predictors for metastatic potential.[38]

UPS, previously known as malignant fibrous histiocytoma, is the third most common soft tissue sarcoma found in the extremities and retroperitoneum. This classification of sarcoma is described as a classification of exclusion. These STS need to be excluded from other histologies that have similar histologic features, such as dedifferentiated liposarcomas. These tumors tend to be large, deep, aggressive, and high-grade tumors. UPS carries a poor prognosis with a 5-year survival rate between 30% and 50%.[39] Molecular testing has revealed the most common mutations to be found in TP53, ATM, and PIK3CA.[39]

*Surgery*

Surgery is the cornerstone treatment for STS in the extremity and retroperitoneum. It is imperative that an experienced sarcoma surgeon who is familiar with these tumors treats the patient to ensure the greatest outcome possible. The goal of surgery is to achieve negative margins while salvaging the limb. A retrospective analysis was completed looking at 643 patients who underwent excision of their STS to determine the impact of surgical margins and clear margin widths. Outcomes looked at local recurrence-free survival, disease-specific survival, and metastatic-free survival. Negative margins were associated with better outcomes in all 3 of these areas regardless of adjuvant radiation.[40] This analysis implies that regardless of the width attained, if the margin is negative of disease ("no ink on tumor"), the outcomes are improved. In another larger analysis of 2084 patients with resected STS, surgical margins, tumor site, size, depth, histologic type, and grade were reviewed. In this analysis, 78% of patients had negative margins and 22% had positive margins. Having positive surgical margins approximately doubled the likelihood of local recurrence, increased the likelihood of developing distant metastatic disease, and increased the possibility of disease-related death. However, out of the 460 patients with positive margins, 72% did not experience a local recurrence.[41]

*Radiation*

Radiation has also become standard of care in the treatment of STS. In one prospective review of 43 patients with high-grade STS of the extremities, limb-sparing surgery with radiation was compared to amputation for local recurrence, disease-free survival (DFS), and OS. While there were 4 local recurrences in the limb-salvage surgery cohort compared to zero in the amputation cohort, there was no difference in the DFS (71% and 78% at 5-year) or the OS rate (83% and 88% at 5-year).[42]

There has been debate on whether neoadjuvant vs adjuvant radiation is superior. A randomized clinical trial evaluating preoperative verses postoperative radiation in STS of the limbs using external beam radiation was completed to determine if timing of radiation impacted wound-healing complications. There were 94 patients randomized to preoperative radiation and 96 patients to postoperative radiation; both cohorts were evaluated within 120 days of surgery. What this revealed was 35% of patients experienced wound healing complications in the preoperative cohort and 17% in the postoperative cohort.[43] The benefits of preoperative radiation include decreasing the treatment tumor volume, lower radiation doses, and decreasing vascularity of the tumor.[44] At this time, there are no radiation treatment guidelines for radiation as part of treatment for retroperitoneal sarcoma. There is a randomized phase 3 clinical trial underway, evaluating radiation therapy followed by surgery vs surgery alone in untreated nonmetastatic retroperitoneal soft tissue sarcomas sponsored by European Organization for Research and Treatment of Cancer (EORTC) (ClinicalTrial.gov NCT01344018).[45] The risks and benefits need to be discussed between the radiation oncologist and the surgeon in regards to timing of the radiation.

An abstract showing promising clinical experience using Uni-Directional LDR brachytherapy for treatment in patients with retroperitoneal sarcoma was presented at American Society of Radiation Oncology (ASTRO) in October of 2018. CivaSheet, a brachytherapy implant was placed in 6 patients at 4 different institutions during the surgical resection. The implant was tolerated extremely well with no documented evidence of complications or toxicities. At the median follow-up of 15 months, none of the patients had recurrence.[46]

*Neoadjuvant and adjuvant chemotherapy*

The decision of preoperative or postoperative chemotherapy needs to be made by an experienced medical oncologist and on an individualized patient basis. In 1993, results were published on a 3-armed phase III clinical trial in patients with STS evaluating regression rates, toxicity, and

OS using doxorubicin alone, ifosfamide and doxorubicin, and mitomycin with doxorubicin plus cisplatin.[47] In this study, 279 patients were enrolled and 262 patients were randomized; cohort A received doxorubicin 80 mg/m2, cohort B received ifosfamide 7.5 g/m2 plus doxorubicin 60 mg/m2, and cohort C received mitomycin 8 mg/m2 with doxorubicin 40 mg/m2 plus cisplatin 60 mg/m2. In cohort A, receiving doxorubicin alone, there was an objective regression in 20% of patients, there was a 34% objective regression in cohort B receiving doxorubicin and ifosfamide, and a 32% objective regression in cohort C receiving mitomycin with doxorubicin plus cisplatin. While cohort B had a higher response rate, this group also experienced more toxicities and myelosuppression than cohort A or C. There was also no significant improvement in OS.

Following this trial, there was a randomized clinical trial looking at adjuvant epirubicin with or without ifosfamide for adults with STS. Following a curative surgery, patients were randomized to chemotherapy or no chemotherapy with radiation being at the investigator's discretion. In the chemotherapy cohort, initially 26 patients received epirubicin 75 mg/m2 alone once every 21 days. After 1991, the chemotherapy cohort was changed so that these patients received epirubicin 25 mg/m2 on days 1-3 and ifosfamide 1,200 mg/m2 on days 1-5 every 4 weeks.[48] Unfortunately, this trial closed prematurely due to poor accrual. The results did indicate a statistically significant improvement in the 5-year DFS of patients who received adjuvant chemotherapy (69%) vs those who received no chemotherapy (44%) as well as the OS, 72% with patients who received adjuvant chemotherapy vs 47% without. While this study was never completed, this did hint at the possible improvement in outcomes with epirubicin-based chemotherapy.

A second European trial examining the use of adjuvant chemotherapy was performed using the 2 most active chemotherapy agents with a high dose-intensive regimen. Patients 18-65 years of age with grade 3-4 spindle-cell sarcomas were randomized to either receive epirubicin 60 mg/m2 days 1 and 2 and ifosfamide 1.8 gm/m2 days 1-5 or the control arm which received no chemotherapy.[49] There were 104 patients enrolled in the trial, 53 patients were in the chemotherapy arm of the trial and 51 patients were randomized to the control arm. Accrual of the trial was discontinued prematurely after interim analysis of DFS revealed a significant benefit for the chemotherapy arm. The overall DFS was 48 months in the chemotherapy cohort with a 41% relative risk reduction in disease relapse and an absolute improvement of 27% at 2 years and 13% at 4 years. The control arm exhibited only 16 months overall DFS.[49]

It was recognized that the basis on determining whether neoadjuvant or adjuvant chemotherapy was beneficial was based on clinical trials with smaller numbers of patients participating and follow-up was short term. Therefore, data from 2 phase III clinical trials were pooled by The EORTC-Soft Tissue Bone Sarcoma Group for patients with localized high-grade soft tissue sarcomas evaluating relapse-free survival and OS in patients who received adjuvant chemotherapy. The first study analyzed was EORTC 62771 which consisted of 468 patients using doxorubicin 50 mg/m2 on day 1, dacarbazine 400 mg/m2 given on days 1-3, cyclophosphamide 500 mg/m2 on day 1 and vincristine 1.5 mg/m2 on day 1 (CYVADIC); this regimen was given every 4 weeks for 8 cycles. The second trial analyzed was EORTC 62,931 which consisted of 351 patients given doxorubicin 75 mg/m2 and ifosfamide 5 g/m2 on day 1 given every 21 days for 5 cycles. The data compared relapse-free survival and OS in patients who received chemotherapy vs observation alone following a complete resection. A total of 819 patients were enrolled and followed for a mean of 8.2 years. What was observed was that although adjuvant chemotherapy improved relapse-free survival (hazard ratio [HR] 0.74), there was no improvement in OS. Subgroup analysis revealed that patients with marginal (R1) resections did seem to have an OS benefit with adjuvant chemotherapy (HR 0.64) while patients with R0 resections had no benefit (HR 1.07). However, it must be stressed that adjuvant chemotherapy is not used as a strategy to compensate for inadequate oncologic surgery. These results validate the importance of having the proper surgery completed with stringent follow-up regardless of the therapeutic regimen prescribed.[50]

The Italian Sarcoma Group in collaboration with the Spanish Sarcoma Group followed their high-dose adjuvant trial with a phase III randomized clinical trial for localized, high-risk, soft tissue sarcoma using the epirubicin-based chemotherapy with ifosfamide. There were 321 patients that were randomized into 2 arms; one of the arms received 3 neoadjuvant cycles of

epirubicin 120 mg/m2 plus ifosfamide 9 g/m2 and in the other arm, patients received the same 3 cycles of neoadjuvant chemotherapy with 2 additional cycles postoperatively. These patients were also able to receive radiation if it was indicated. The results from this trial revealed that 5 cycles were not superior to 3 cycles in terms of overall and progression-free survival and the treatment group who received 5 cycles experienced more adverse reactions.[51]

After the data resulted from the Italian Sarcoma Group and Spanish Sarcoma Group's phase III trial evaluating the benefit of 3 vs 5 cycles of epirubicin and ifosfamide, it was suggested that a histotype-tailored chemotherapy regimen might be superior to the standard of care, epirubicin, and ifosfamide. A large, international, open-label, randomized phase III clinical trial opened, enrolling patients from 32 hospitals across Italy, Spain, France, and Poland. This looked at adults with high-risk STS of the extremities or trunk wall who had one of the following histologies: high-grade myxoid liposarcoma, LMS, synovial sarcoma, malignant peripheral nerve sheath tumor, and UPS. A total of 287 patients were randomly assigned to receive 3 cycles of full-dose standard chemotherapy with epirubicin 60 mg/m2 given on days 1 and 2 plus ifosfamide 3 g/m2 given over days 1-3, or histologically tailored chemotherapy. For high-grade myxoid liposarcoma, these patient received trabectedin 1-3 mg/m2 given over 24 hours every 21 days. For LMS, they received gemcitabine 1800 mg/m2 and dacarbazine 500 mg/m2 on day 1 given every 14 days. Synovial sarcoma patients received high-dose ifosfamide 14 g/m2 given over 14 days with cycles being 28 days. Patients with malignant peripheral nerve sheath tumors received etoposide 150 mg/m2 and ifosfamide 3 g/m2, both given on days 1-3 every 21 days. Finally, for UPS, they received gemcitabine 900 mg/m2 on day's 1 and 8 plus docetaxel 75 mg/m2 on days 8, every 21 days. The trial was closed at the third futility analysis (median follow up of 12.3 months) after it was shown that the histotype-tailored chemotherapy had significantly worse projected DFS at 46 months (38% vs 62%).[52]

Most recently, the negative data from EORTC 62931 was reanalyzed according to predicted patient prognosis using the nomogram Sarculator.[53] Participants were grouped into 3 different categories according to the predicted percentage of OS: high (OS >66%), intermediate (OS >51% and <66%), and low (OS <51%).[53] Most patients were in the high OS group (58.6%) with fewer in the intermediate (23.5%) and low OS group (17.9%). Upon re-evaluation of the data, patients in the low-predicted OS group had significantly lower risk of recurrence and death with adjuvant chemotherapy (HR 0.46) while there was no effect in the intermediate and high OS groups. This study suggests that for patients with primary localized STS, the highest risk group with low-predicted OS may have substantial benefit with adjuvant chemotherapy. It reiterates that the determination to use adjuvant or neoadjuvant chemo needs to be assessed and individually interpreted for each patient.

### *Recent and ongoing clinical trials*

A neoadjuvant clinical trial through the Sarcoma Alliance for Research through Collaboration has proposed the addition of pembrolizumab, a PD-1 receptor antibody, with concurrent radiation followed by surgery and adjuvant pembrolizumab. This is a phase II randomized trial in which patients are randomized to receive either standard of care radiation with surgery verses standard of care radiation with concurrent pembrolizumab neoadjuvantly followed by surgery, plus adjuvant pembrolizumab for a year. This trial is available for patients with high-risk STS of the extremity with histology of UPS and dedifferentiated/pleomorphic liposarcoma. The hypothesis behind this trial is that while radiation and surgery treat the local primary, the addition of pembrolizumab will help to prevent distant metastatic spread. At this time, the trial is actively accruing (ClinicalTrial.gov NCT03092323).

The Radiation Therapy Oncology Group has an accruing neoadjuvant clinical trial, which uses the investigational agent AMG-232, a MDM2 inhibitor, with concurrent radiation. Patients with high-risk nonmetastatic STS in the extremity, body wall, or abdomen/pelvis/retroperitoneum who exhibit MDM2 amplification with wild type TP53, could be a candidate for this phase 1b clinical trial. In this trial, AMG-232 is given with concurrent radiation followed by surgical resection. The hypothesis is that in tumors with MDM2 amplification, the addition of an MDM2

inhibitor may sensitize the tumor to radiation by restoring wild type TP53 function (ClinicalTrial.gov NCT03217266).

M.D. Anderson Cancer Center has an available clinical trial for patients with surgically resectable UPS and dedifferentiated liposarcoma. In this phase II randomized trial, these 2 histologies are randomized either to receive ipilimumab plus nivolumab or nivolumab alone with or without radiation. The primary outcome is looking at pathologic response, which would be evaluated during the time of surgical excision (ClinicalTrial.gov NCT03307616).

A neoadjuvant clinical trial offered at Massachusetts General Hospital is a phase I/II trial of preoperative radiation comparing the use of intensity modulated proton therapy (IMPT) vs Photon (IMRT) with simultaneously integrated boost (SIB) for patients with retroperitoneal sarcomas and high-risk margins. Once the final therapeutic radiation dose is determined in the phase I trial, the phase II portion of the trial will evaluate if by using the combination of image guided IMPT or IMRT with SIB, the percentage of local recurrence will be reduced compared to conventional radiation dose and fractionation. In addition, it is hypothesized that by using protons, patients will experience less toxicity than with photons.[54]

### *Survivorship*

Ensuring that patients are set up with the appropriate surveillance follow-up is imperative. The surveillance schedule for STS of the extremities is based on the stage, in order to detect recurrences early. With stage 1 soft tissue sarcomas, it is recommended to have a history and physical every 3-6 months for 2-3 years, then annually with chest imaging, CT preferably, every 6-12 months.[55] An MRI of the primary site is also recommended. For tumors that are stage II/III, an MRI of the primary site is recommended in addition to having chest imaging and other sites with previous disease performed every 2-6 months for 2-3 years, then every 6 months for 2 years followed by annually.[55] Surveillance for patients with retroperitoneal/intra-abdominal soft tissue sarcomas include a CT of the chest, abdomen, and pelvis or an MRI every 3-6 months for 2-3 years, every 6 months for an additional 2 years, followed by annually.[55]

There are many potential long-term complications within the survivor population. First, the phantom pain from amputations can lead to long-term chronic symptoms. Second, within the sarcoma population that received anthracyclines, long-term follow-up must include screening for heart failure. In addition, the long-term effects of chemotherapy can result in diminished bone health, thyroid function and fertility. These need to be considered when putting in place a survivorship plan. Prospective studies on the late term effects of therapy in sarcoma patients are needed.

## Conclusions

The management of extremity and retroperitoneal STS is complex and best treated in conjunction with a high volume sarcoma center. A multidisciplinary approach involving surgeons, radiotherapists, medical oncologist, dedicated radiologists and pathologists are needed for optimal management of this highly complex and heterogeneous disease.

## References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. *CA Cancer J Clin*. 2019;69:7–34.
2. Hui JY. Epidemiology and etiology of sarcomas. *Surg Clin North Am*. 2016;96:901–914.
3. Niederhuber J, Armitage J, Doroshow J, Kastan M, Tepper J. *Abeloff's Clinical Oncology*. Elsevier, Philadelphia, PA (2020).
4. Li FP, Fraumeni Jr JF. Soft-tissue sarcomas, breast cancer, and other neoplasms. A familial syndrome? *Ann Intern Med*. 1969;71:747–752.
5. Korf BR. Neurofibromatosis. *Handb Clin Neurol*. 2013;111:333–340.
6. Roncucci L, Pedroni M, Mariani F. Attenuated adenomatous polyposis of the large bowel: present and future. *World J Gastroenterol*. 2017;23:4135–4139.

7. Soliman SE, Racher H, Zhang C, MacDonald H, Gallie BL. Genetics and molecular diagnostics in retinoblastoma–an update. *Asia Pac J Ophthalmol (Phila)*. 2017;6:197–207.
8. Foulkes WD, Kamihara J, Evans DGR. Cancer surveillance in Gorlin syndrome and rhabdoid tumor predisposition syndrome. *Clin Cancer Res*. 2017;23:e62–e67.
9. Martland HS, Brodkin HA, Martland Jr HS. Occupational beryllium poisoning in New Jersey with special reference to its incidence, diagnosis and compensation. *J Med Soc N J*. 1948;45:5–14.
10. Garg PK, Kumar A. Radiation induced sarcoma: everything comes with a price. *Urol Ann*. 2014;6:250–251.
11. Thijssens KM, van Ginkel RJ, Suurmeijer AJ. Radiation-induced sarcoma: a challenge for the surgeon. *Ann Surg Oncol*. 2005;12:237–245.
12. Murray EM, Werner D, Greeff EA, Taylor DA. Postradiation sarcomas: 20 cases and a literature review. *Int J Radiat Oncol Biol Phys*. 1999;45:951–961.
13. Brady MS, Gaynor JJ, Brennan MF. Radiation-associated sarcoma of bone and soft tissue. *Arch Surg*. 1992;127:1379–1385.
14. Thomas DM, Ballinger ML. Etiologic, environmental and inherited risk factors in sarcomas. *J Surg Oncol*. 2015;111:490–495.
15. Lahat G, Lazar A, Lev D. Sarcoma epidemiology and etiology: potential environmental and genetic factors. *Surg Clin North Am*. 2008;88:451–481.
16. Viel JF, Arveux P, Baverel J, Cahn JY. Soft-tissue sarcoma and non-Hodgkin's lymphoma clusters around a municipal solid waste incinerator with high dioxin emission levels. *Am J Epidemiol*. 2000;152:13–19.
17. Johnson CJ, Pynsent PB, Grimer RJ. Clinical features of soft tissue sarcomas. *Ann R Coll Surg Engl*. 2001;83:203–205.
18. Morrison BA. Soft tissue sarcomas of the extremities. *Proc (Bayl Univ Med Cent)*. 2003;16:285–290.
19. Miwa S, Otsuka T. Practical use of imaging technique for management of bone and soft tissue tumors. *J Orthop Sci*. 2017;22:391–400.
20. Gupta P, Potti TA, Wuertzer SD, Lenchik L, Pacholke DA. Spectrum of fat-containing soft-tissue masses at mr imaging: the common, the uncommon, the characteristic, and the sometimes confusing. *Radiographics*. 2016;36:753–766.
21. Roeren T, Gindele A, Grosspietsch C, Dueck M, Kauffmann GW. [imaging techniques in the preoperative diagnosis of soft tissue tumors. A comparison of MRT, CT, sonography, angiography and conventional X-rays]. *Radiologe*. 1992;32:591–596.
22. Steffner RJ, Jang ES. Staging of bone and soft-tissue sarcomas. *J Am Acad Orthop Surg*. 2018;26:e269–e278.
23. Pohlig F, Kirchhoff C, Lenze U. Percutaneous core needle biopsy versus open biopsy in diagnostics of bone and soft tissue sarcoma: a retrospective study. *Eur J Med Res*. 2012;17:29.
24. Skrzynski MC, Biermann JS, Montag A, Simon MA. Diagnostic accuracy and charge-savings of outpatient core needle biopsy compared with open biopsy of musculoskeletal tumors. *J Bone Joint Surg Am*. 1996;78:644–649.
25. Ray-Coquard I, Ranchere-Vince D, Thiesse P. Evaluation of core needle biopsy as a substitute to open biopsy in the diagnosis of soft-tissue masses. *Eur J Cancer*. 2003;39:2021–2025.
26. Singh HK, Kilpatrick SE, Silverman JF. Fine needle aspiration biopsy of soft tissue sarcomas: utility and diagnostic challenges. *Adv Anat Pathol*. 2004;11:24–37.
27. Akerman M. Fine-needle aspiration cytology of soft tissue sarcoma: benefits and limitations. *Sarcoma*. 1998;2:155–161.
28. Thway K, Wang J, Mubako T, Fisher C. Histopathological diagnostic discrepancies in soft tissue tumours referred to a specialist centre: reassessment in the era of ancillary molecular diagnosis. *Sarcoma*. 2014;2014.
29. Presant CA, Russell WO, Alexander RW, Fu YS. Soft-tissue and bone sarcoma histopathology peer review: the frequency of disagreement in diagnosis and the need for second pathology opinions. The southeastern cancer study group experience. *J Clin Oncol*. 1986;4:1658–1661.
30. Alvegard TA, Berg NO. Histopathology peer review of high-grade soft tissue sarcoma: the scandinavian sarcoma group experience. *J Clin Oncol*. 1989;7:1845–1851.
31. Kammerer-Jacquet SF, Thierry S, Cabillic F. Differential diagnosis of atypical lipomatous tumor/well-differentiated liposarcoma and dedifferentiated liposarcoma: Utility of p16 in combination with MDM2 and CDK4 immunohistochemistry. *Hum Pathol*. 2017;59:34–40.
32. Lee ATJ, Thway K, Huang PH, Jones RL. Clinical and molecular spectrum of liposarcoma. *J Clin Oncol*. 2018;36:151–159.
33. Trautmann M, Menzel J, Bertling C. FUS-DDIT3 fusion protein-driven IGF-IR signaling is a therapeutic target in myxoid liposarcoma. *Clin Cancer Res*. 2017;23:6227–6238.
34. Chowdhry V, Goldberg S, DeLaney TF. Myxoid liposarcoma: treatment outcomes from chemotherapy and radiation therapy. *Sarcoma*. 2018;2018.
35. Crago AM, Dickson MA. Liposarcoma: multimodality management and future targeted therapies. *Surg Oncol Clin N Am*. 2016;25:761–773.
36. Serrano C, George S. Leiomyosarcoma. *Hematol Oncol Clin North Am*. 2013;27:957–974.
37. Miettinen M. Smooth muscle tumors of soft tissue and non-uterine viscera: biology and prognosis. *Mod Pathol*. 2014;27(Suppl 1):S17–S29.
38. Coindre JM, Terrier P, Guillou L. Predictive value of grade for metastasis development in the main histologic types of adult soft tissue sarcomas: a study of 1240 patients from the french federation of cancer centers sarcoma group. *Cancer*. 2001;91:1914–1926.
39. Lewin J, Garg S, Lau BY. Identifying actionable variants using next generation sequencing in patients with a historical diagnosis of undifferentiated pleomorphic sarcoma. *Int J Cancer*. 2018;142:57–65.
40. Harati K, Goertz O, Pieper A, Daigeler A, Joneidi-Jafari H, Niggemann H, Stricker I, Lehnhardt M. Soft tissue sarcomas of the extremities: surgical margins can be close as long as the resected tumor has no ink on it. *Oncologist*. 2017;22:1400–1410.
41. Stojadinovic A, Leung DH, Hoos A, Jaques DP, Lewis JJ, Brennan MF. Analysis of the prognostic significance of microscopic margins in 2,084 localized primary adult soft tissue sarcomas. *Ann Surg*. 2002;235:424–434.
42. Rosenberg SA, Tepper J, Glatstein E. The treatment of soft-tissue sarcomas of the extremities: prospective random-

ized evaluations of (1) limb-sparing surgery plus radiation therapy compared with amputation and (2) the role of adjuvant chemotherapy. *Ann Surg*. 1982;196:305–315.
43. O'Sullivan B, Davis AM, Turcotte R. Preoperative versus postoperative radiotherapy in soft-tissue sarcoma of the limbs: a randomised trial. *Lancet*. 2002;359:2235–2241.
44. Shah C, Verma V, Takiar R. Radiation therapy in the management of soft tissue sarcoma: a clinician's guide to timing, techniques, and targets. *Am J Clin Oncol*. 2016;39:630–635.
45. Baldini EH, Wang D, Haas RL. Treatment guidelines for preoperative radiation therapy for retroperitoneal sarcoma: preliminary consensus of an international expert panel. *Int J Radiat Oncol Biol Phys*. 2015;92:602–612.
46. Howell KJ, Meyer JE, Rivard MJ. Initial clinical experience with uni-directional ldr brachytherapy in the treatment of retroperitoneal sarcoma. *Int J Radiat Oncol*. 2018;102:e256.
47. Edmonson JH, Ryan LM, Blum RH. Randomized comparison of doxorubicin alone versus ifosfamide plus doxorubicin or mitomycin, doxorubicin, and cisplatin against advanced soft tissue sarcomas. *J Clin Oncol*. 1993;11:1269–1275.
48. Petrioli R, Coratti A, Correale P, et al. Adjuvant epirubicin with or without ifosfamide for adult soft-tissue sarcoma. *Am J Clin Oncol*. 2002;25:468–473.
49. Frustaci S, Gherlinzoni F, De Paoli A, et al. 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.
50. Le Cesne A, Ouali M, Leahy MG, et al. Doxorubicin-based adjuvant chemotherapy in soft tissue sarcoma: pooled analysis of two STBSG-EORTC phase III clinical trials. *Ann Oncol*. 2014;25:2425–2432.
51. Palassini E, Ferrari S, Verderio P, et al. 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 espanol de investigacion en sarcomas randomized clinical trial: Three versus five cycles of full-dose epirubicin plus ifosfamide. *J Clin Oncol*. 2015;33:3628–3634.
52. Gronchi A, Ferrari S, Quagliuolo V, et al. Histotype-tailored neoadjuvant chemotherapy versus standard chemotherapy in patients with high-risk soft-tissue sarcomas (ISG-STS 1001): an international, open-label, randomised, controlled, phase 3, multicentre trial. *Lancet Oncol*. 2017;18:812–822.
53. Pasquali S, Pizzamiglio S, Touati N, et al. 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.
54. DeLaney TF, Chen YL, Baldini EH, et al. Phase 1 trial of preoperative image guided intensity modulated proton radiation therapy with simultaneously integrated boost to the high risk margin for retroperitoneal sarcomas. *Adv Radiat Oncol*. 2017;2:85–93.
55. von Mehren M, Randall RL, Benjamin RS, et al. Soft tissue sarcoma, version 2.2018, NCCN clinical practice guidelines in oncology. *J Natl Compr Canc Netw*. 2018;16:536–563.