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Sarcoma (SH Okuno, Section Editor)

First-Line Therapy for Metastatic Soft Tissue Sarcoma

Megan Meyer, MD[1]
Mahesh Seetharam, MD, FACP[2,*]

Address
[1]Internal Medicine, Mayo Clinic, 5777 E Mayo Blvd., Phoenix, AZ, 85054, USA
[*,2]Hematology and Oncology, Mayo Clinic, 5881 E Mayo Blvd., Phoenix, AZ, 85054, USA
Email: Seetharam.mahesh@mayo.edu

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Opinion statement

Soft tissue sarcomas are rare cancers with an expected incidence of about 14,000 new cases in 2018, and account for less than 1% of all cancers. It includes in excess of 75 heterogeneous subtypes with varying biology, molecular aberrations, and variable response to treatment. Because of the rarity of these tumors and the many different subtypes, there is no large-scale data to guide treatment, and hence the need for a multidisciplinary individualized approach to treatment, preferably at a high-volume tertiary referral center. For localized disease, surgery with or without radiation is the preferred treatment. In metastatic disease, the longest track record is with use of anthracyclines, either alone or in combination with ifosfamide, but the median overall survival even with combination was just over a year. There have been recent advances in understanding the heterogeneity of these tumors and the need for an individualized approach. With that new knowledge, recent approvals of trabectedin, eribulin, and pazopanib have been limited to some select histologic subtypes with improved outcomes. More recently, immunotherapy has been tested in select histotypes of sarcoma with encouraging activity and has led to further evaluation in combination with immunotherapeutic agents, as well as with chemotherapy and radiation treatments. Here, in this article, we summarize the data of the currently approved therapies in metastatic soft tissue sarcoma, with the principal focus on first-line therapies. We also review the recent encouraging data with PDGFR-targeted antibody (olaratumab) with doxorubicin which showed an impressive improvement in overall survival in phase II study. Molecular characterization of sarcoma subtypes will likely improve understanding of these very diverse tumors and improve target characterization. The ongoing efforts in better understanding these rare tumors hold the key to make a difference in the outcome of these patients.

Introduction

Soft tissue sarcomas are rare tumors of mesenchymal origin. They are as diverse as the tissues that arise from the mesenchyme and are comprised of greater than 75 distinct histopathological subtypes. These tumors are often difficult to diagnose and therapeutic options can be limited. According to the National Cancer Institute (NCI), the overall relative 5-year survival is approximately 50%. Sixteen percent of these malignancies are metastatic at the time of diagnosis and many will progress despite treatment. The treatment of metastatic disease is complex and often requires multidisciplinary approach including metastectomy, radioablation, systemic traditional chemotherapy, targeted therapies, or immunotherapy.

Metastatic disease

Localized soft tissue sarcomas can be cured with resection. However, according to the National Cancer Institute (NCI), 16% of patients present with metastatic disease and many will develop metastases following initial diagnosis of localized sarcoma. Metastasis usually occurs through hematologic spread and primarily involves the lung, but other possible sites include bone, liver, regional lymph nodes, intraperitoneal seeding, distant subcutaneous tissue, and brain. Only few subtypes travel lymphatically and these include epithelioid sarcoma, angiosarcoma, synovial sarcoma, and rhabdomyosarcoma. Retroperitoneal or visceral sarcomas have a tendency towards hepatic metastases. Myxoid/round cell sarcomas tend to cause spinal and paraspinous tissue metastases [1].

Median survival following metastatic disease is 12 to 15 months with only 20–25% 3-year survival rates. Positive prognostic factors included longer period of time to recurrence from primary resection, absence of liver metastasis, young age, good performance status, and low grade [2–4].

Pathophysiology

There is a variety of mutations which can lead to sarcomagenesis [5, 6]. In malignancies with simple genomics, they can arise from translocations, mutations, or gene amplifications. Others have complex genomics which include changes in chromosome number, unbalanced translocations, genetic deletions, and amplifications. Translocations are present in approximately one third of all sarcomas and represent clinical targets [7]. These translocations often occur in genes that effect transcription, leading to upregulation of proto-oncogenes or downregulation of tumor suppressor genes. Table 1 presents some of the most well-known translocation-targeted treatments for various sarcoma subtypes.

More rarely, point mutations can also represent clinical targets, such as the KIT/PDGFRA tyrosine kinase mutations in GIST. This has led to the treatment success of GIST with tyrosine kinase inhibitors. Lastly, complex karyotypes can be seen in sarcoma. These can arise from previously simple genomic malignancies with the aggregation of further mutations, or can appear de novo with complex genomics. Often times, the complex karyotypes are found in conjunction with deletions in tumor suppressor genes.

Table 1. Targeted therapies for sarcomas

Tumor	Translocation	Gene changes and targets	Drug
Alveolar soft parts sarcoma (ASPS)	T(X;17)(p11.2;q25)	ASPL-TFE3 VEGF receptor, MET, RET	Sunitinib and cediranib
Angiosarcoma		MYC amplification (esp. radiation induced) VEGF	TKIs, taxanes, and Doxil
Chondrosarcoma, myxoid	t(9;22)(q22–31;q11–12)	EWSR1-NR4A3	Hedgehog pathway inhibitors
Chordoma			TKIs EGFR inhibitors
Dermatofibrosarcoma Protuberans	T(17;22)(q22;q13)	COL1A1-PDGFB	Imatinib
Gastrointestinal stromal tumor		KIT/PDGFRA C-KIT, PDGFR-alpha Mutation	TKIs: imatinib, sunitinib, regorafenib
Inflammatory myofibroblastic tumor	2p23 re-arrangements	TMP3-ALK; TMP4-ALK	Crizotinib
Liposarcoma myxoid	t(12;16)(q13;p11) t(12;22)(q13;q12)	FUS-CHOP (FUS-DDIT3) EWSR1-CHOP (EWSR1-DDIT3)	Trabectedin
Perivascular epithelioid cell tumor	TFE3 gene re-arrangement	TSC2 mutation mTOR	Everolimus or temsirolimus
Pigmented villonodular synovitis	t(1,6)	COL6A3-M-CSF	Imatinib
Solitary fibrous tumor	Inversion 12q13	NAB2-STAT6 VEGF, PDGFR, RET	Sunitinib, bevacizumab + temozolomide

First-line therapies

Given the rarity of these malignancies, the majority of studies from which we base our recommendations include multiple types of sarcomas for accrual purposes. This means that the treatment guidelines and outcomes are skewed towards the most common sarcomas such as liposarcoma, leiomyosarcoma, and undifferentiated pleomorphic sarcoma. We will first review the major studies that guide our basic concepts prior to reviewing subtype-specific management. Table 2 lists some of the most influential studies and their outcomes.

In the 1970s, it was realized that some sarcomas would respond to single-agent doxorubicin with response rates of 10–25% [5]. There have been multiple studies showing good tolerability and efficacy of single-agent doxorubicin [5, 6]. The addition of ifosfamide to this regimen increased overall response rates by approximately 10% but is limited with the serious myelosuppression that occurs with combination treatment. In a phase III clinical trial, it has also reported to have no increase in

Table 2. First-line treatment trials in metastatic soft tissue sarcoma

Study	Agent	Patient #	OS (months)	PFS (months)	ORR %	SD %	PR %	CR %	Major adverse effects
Soft tissue sarcoma									
Judson et al. 2014 [8] (EORTC 62012)	Doxorubicin	228	12.8	4.6	14		30	1	Cytopenias, febrile neutropenia
	Doxorubicin + ifosfamide	227	14.3	7.4	26		56	4	
Judson et al. 2001 [9]	Doxorubicin	44	–	–	10		2	7	Myelosuppression, febrile neutropenia, alopecia, palmoplantar dysthesia
	Liposomal doxorubicin	50	–	–	9		2	8	
Tap et al. 2016 [10••]	Doxorubicin	67	14.7	4.1	11.9		–	–	Worsened neutropenia, mucositis, nausea, vomiting, and diarrhea in doxorubicin + olaratumab.
	Doxorubicin + olaratumab	66	26.5	6.6	18.2		–	–	
Hensley et al. 2002 [11]	Gemcitabine + docetaxel	34	–	5.6	53	20.6	44	8.8	Myelosuppression, febrile neutropenia
Maki et al. 2007 [12]	Gemcitabine	49	11.5	3	8	–	–	–	
	Gemcitabine + docetaxel	73	17.9	6.2	16	–	–	–	
Leiomyosarcoma									
Pautier et al. 2015 [13••]	Trabectedin + doxorubicin	108	–	–	–	27.7–52.5	36.1–59.6	0–3.3	Myelosuppression, ↑LFT, febrile neutropenia
Seddon et al.	Gemcitabine + docetaxel	44	17.9	7.1	–	36.6–52.5	25	–	
Gastrointestinal stromal tumor									
Demetri et al. 2002 [14]	Imatinib	140	–	–	–	27.9	53.7	–	Edema, diarrhea, fatigue
Angiosarcoma									
	Paclitaxel	30	8	4	–	–	10	–	

Table 2. (Continued)

Study	Agent	Patient #	OS (months)	PFS (months)	ORR %	SD %	PR %	CR %	Major adverse effects
Penel et al. 2008 [15]									23% with grades 3 and 4 toxicities
Dermatofibrosarcoma protuberans									
Rutkowski et al. 2010 [16]	Imatinib	24	–	20.4	–	83	4	–	
Pigmented villonodular synovitis/giant cell tumor of tendon sheath									
Gelderblom et al. 2018 [17]	Nilotinib	51	–	> 2.7	>	90%	–	–	–
Headache, dizziness, hepatic disorder, diarrhea									

OS, overall survival; *PFS*, progression-free survival; *ORR*, objective response rate; *SD*, stable disease; *PR*, partial response; *CR*, complete response

survival with the addition of ifosfamide. Overall survival (OS) was 14.3 months with combination therapy and 12.8 months with single-agent doxorubicin, $p = 0.076$ [8]. Ifosfamide had earlier been trialed as monotherapy as well, with a reported 19% response rate [18]. Although the combination did not show survival benefit, it improved response rates and progression-free survival. This may still make it relevant in borderline resectable tumors or symptomatic metastatic disease.

Due to the cardiotoxicity of doxorubicin, trials have evaluated the use of liposomal doxorubicin in sarcoma. Trials comparing doxorubicin to liposomal doxorubicin showed decreased rates of cardiac effects, myelosuppression, and alopecia but equivocal response rates [9, 19].

Now, there is promising evidence that doxorubicin + olaratumab may become a new standard of care pending results from the phase III trial. Olaratumab is a monoclonal antibody directed against platelet-derived growth factor alpha and early studies have generated a conditional approval from the FDA and EMA in late 2016. There has been a phase II trial in which the median OS was significantly improved compared to doxorubicin alone (26.5 months vs. 14.7 months, $p = 0.0003$). Progression-free survival (PFS) was also improved though not statistically so (6.6 months vs. 4.1 months, $p = 0.0615$) [10••]. The toxicity profile of olaratumab in combination with doxorubicin appears better tolerated than that of doxorubicin with ifosfamide though they have not been compared in a head to head trial.

Gemcitabine/docetaxel is another common chemotherapy agent that is often considered second line to doxorubicin/ifosfamide and could be considered first line in certain patients with pre-existing cardiac disease who may not tolerate anthracyclines. Response rates have been reported to be between 6 and 20% [20, 21]. These agents have been found to be particularly helpful in uterine leiomyosarcoma as will be discussed below. One randomized, phase II clinical trial showed improved response rates in combination therapy with gemcitabine and docetaxel vs. monotherapy with gemcitabine (16% vs. 8%, respectively). This increased response rate was at the consequence of increased adverse effects [12]. A randomized phase III trial of combination of gemcitabine and docetaxel vs. monotherapy with doxorubicin showed no significant difference in either OS or PFS at 24 weeks (46.3% vs. 46.6% alive at 24 weeks; PFS 23.3 weeks with doxorubicin vs. 23.7 weeks with gemcitabine/docetaxel) [22••].

Metastectomy

In unique cases with potentially resectable hepatic or pulmonary metastases, surgical removal or radiofrequency ablation has been used successfully to prolong patient's PFS and OS. Criteria used to determine candidacy include the absence of other sites of metastatic disease, absence of pleural effusion or lymph node involvement, controlled or potentially controllable primary site, and high likelihood that treatment of all disease is possible. Outcomes from pulmonary metastectomy have yielded 5-year survival rates between 34 and 40% [23, 24•, 25]. The evidence is more limited in terms of hepatic metastectomy and

radioablation, though there have been successful reported outcomes in metastatic leiomyosarcoma patients [26–28].

Unique treatments by sarcoma type

The clinical relevance of the previous studies is limited by the diversity of sarcomas included in the trials. It creates a mixed picture and oftentimes the power is too low for subgroup analyses to be performed. We will further discuss first-line treatments as it pertains to the most common sarcoma subtypes. Several subtypes, listed in the table below, have better response with targeted therapies than with traditional chemotherapy (Table 1).

Liposarcoma

Doxorubicin remains the first-line therapy for metastatic or advanced liposarcoma with response rates of approximately 20–25% based on mixed sarcoma studies [5, 20]. Trials comparing the efficacy of doxorubicin with ifosfamide consistently revealed improved PFS but no difference in OS [8]. This knowledge, paired with the significant increased toxicity of the combination regimen, is the reason that doxorubicin is generally recommended as a single agent for this malignancy. However, this is a subtype which can be further divided into four groups with varying response to chemotherapy. This includes pleomorphic, myxoid round cell, de-differentiated, and atypical lipomatous tumor/well-differentiated liposarcoma. While pleomorphic and myxoid round cell liposarcoma are particularly susceptible to chemotherapy, de-differentiated liposarcoma has a variable response and atypical lipomatous tumor or well-differentiated liposarcoma is less responsive to chemotherapy.

Two marine agents, trabectedin and eribulin, recently have been under study. Both of these have shown benefit over dacarbazine though they have not yet been compared in first-line therapy [29, 30, 31•]. Further trials will need to be performed to fully understand the use of these agents in liposarcoma. Other therapeutic targets include CDK4 and MDM2, though early clinical trials suggest response rates, are < 10% [32]. These newer agents may be particularly useful in the more chemo-resistant forms of liposarcoma, including de-differentiated liposarcoma.

Leiomyosarcoma

Leiomyosarcoma can arise from several locations, including the uterus, retroperitoneum, GI tract, and vasculature. Uterine leiomyosarcoma is more likely than the others to respond to chemotherapy such as doxorubicin, dacarbazine, and gemcitabine/docetaxel. As with other soft tissue sarcomas, the first-line treatment for leiomyosarcoma is considered gemcitabine/docetaxel or doxorubicin. Doxorubicin and trabectedin has also been evaluated as first-line therapy. The French Sarcoma Group phase II clinical trial revealed efficacy of this combination in both uterine and non-uterine leiomyosarcoma. Uterine leiomyosarcoma had a partial response (PR) rate of 59.6%, stable disease (SD) in 27.7%, and disease control in 87.2%. Non-uterine leiomyosarcoma had a complete response (CR) in 3.3%, PR in 36.1%, SD in 52.5%, and disease control in 91.8%. The toxicities were considered less than those of other combination options such as doxorubicin/ifosfamide or gemcitabine/docetaxel [13••].

A phase II trial with gemcitabine/docetaxel in leiomyosarcoma as first-line therapy reported an overall response rate of 77.5% with a 6 month PFS of 59.1% [33]. An earlier phase II trial had also found an overall response rate of 53%, including 3/34 patient with complete response. The regimen was found to be active in 50% of those with previous doxorubicin treatment [11].

Also important in the treatment of metastatic leiomyosarcoma is the use of metastectomy in select patients. In those who have completely resectable metastases whose first recurrence was prolonged (> 12 months), there is good evidence that resection is beneficial. This has been confirmed in both pulmonary and liver metastases [27, 28, 34, 35].

Gastrointestinal stromal tumors

GIST is a sarcoma that represents 1% of all GI malignancies and arises from the pacemaker cells of Cajal. The majority of these tumors (> 90%) are KIT or PDGFRA mutation positive. Because of these characteristic mutations, these tumors can respond to oral tyrosine kinase inhibitors. Approved treatments include imatinib, sunitinib, and regorafenib. Imatinib is currently the preferred initial treatment for the most common exon 11 mutation.

The efficacy of imatinib has significantly improved the outcomes of GIST patients. Results reported in several randomized phase II clinical trials suggest PR in 53.7–69% of patients and SD in an additional 18–28% [14, 36, 37]. PFS and OS are higher with longer treatment lengths and progression tends to occur rapidly after discontinuing these medications [36, 38]. Doses of 400 mg daily and 800 mg daily have been used. Side effects are higher with the increased dose and for the majority of GIST does not significantly impact outcomes [38]. The exception is the Kit exon 9 mutation which does benefit from the 800 mg dosing (PFS 17 vs. 6 months, $p = 0.017$) with a trend for improved survival [39]. The KIT exon 9 mutation is present in a sizable number of GIST patients and so it is considered standard of care to perform genetic analysis to determine dosage. In those who do not tolerate imatinib, or progress despite treatment, the next-line agents include sunitinib or regorafenib.

Of note, the KIT/PDGFRA negative tumors (7.5%) represent a unique clinical entity. These are found to have succinate dehydrogenase deficiency and do not respond as well to imatinib. Sunitinib or regorafenib has better response rates and is recommended first-line therapies in these cases [40•, 41].

Angiosarcoma

Angiosarcoma is a rare malignancy which has a tendency to metastasize early and carries a poor prognosis. Previous studies have shown the best response rates to taxanes. The phase II ANGIOTAX study enrolled 30 patients. After treatment with paclitaxel, PFS at 2 and 4 months was 74% and 45%, respectively. Median OS was 8 months [15]. Docetaxel has also been commonly used. In a trial with 9 patients, 2 patients had a CR, 3 with a PR [42].

Given the vascular nature of angiosarcoma, there has been significant interest in VEGF inhibitors such as bevacizumab. In a phase II trial, 32 patients were treated with two PRs, 11 patients with SD, and mean PFS at 26 weeks [43]. These new agents can be worthy options for elderly patients in whom chemotherapy may be intolerable or in those who have failed first-line therapy. While

there has been case reports of PRs with combination therapy a trial with docetaxel and bevacizumab failed to improve survival [15, 44–46].

Dermatofibrosarcoma protuberans

DFSP is a cutaneous sarcoma which only metastasizes in 5% of cases. However, when the cancer becomes locally advanced or metastatic, this subtype has historically not responded to chemotherapy. Recent phase II trials have shown promise for imatinib and this is now considered first-line therapy for tumors which cannot be adequately resected. Response rates have been reported to be > 50% with median OS > 3 years [16, 47].

Chordoma

Chordoma is a rare tumor which occurs along the axial spine and metastasizes in approximately 30% of patients. A phase II trial with 50 patients on imatinib showed a PFS of 9 months with 35/50 experiencing SD and 1/50 with PR. Other targeted therapies have also shown promise, including lapatinib, erlotinib, cetuximab + gefitinib, sorafenib, thalidomide, and GI-6301 [48].

Alveolar soft parts sarcoma

ASPS is a highly angiogenic soft tissue sarcoma that is typically resistant to chemotherapy. Sunitinib, a VEGF inhibitor, has shown promise in ASPS. For example, in a retrospective review of 15 patients with ASPS treated with sunitinib, 6 had a response per RECIST criteria, 8 had SD, and only one had progressive disease. Median OS was 56 months [49]. Similar results were confirmed in a Chinese study [50].

Cediranib is another similar medication which has had good results in a phase II clinical trial. A randomized phase II study by the Royal Marsden group was presented at the CTOS meeting in 2017. Forty-eight patients randomized to cediranib showed partial response rate of 21% at 24 weeks vs. 0% on placebo. The median PFS was 10.8 months vs. 3.7 months. OS at 1 year was 96% for cediranib group vs. 64.3% for placebo [51].

Malignant solitary fibrous tumor

Malignant solitary fibrous tumor is another clinical entity which has not responded well to traditional chemotherapy. However, there have been at least two more informative retrospective studies. One involved sunitinib. Out of the 31 patients who were assessable for RECIST response, 2 had PR, 16 had SD, and 13 had PD. Unfortunately, there was no control group to compare OS [52].

Another approach in this subtype has been temozolomide with bevacizumab. Temozolomide is an alkylating agent whose active metabolite resembles dacarbazine. This combination was used in 14 patients. Eleven or 79% of the patients treated had a Choi PR and 2 patients experienced SD [53].

Pazopanib, a tyrosine kinase inhibitor which impedes angiogenesis, as a treatment option, has been recently published in a 2018 retrospective study. Nine patients with recurrent or metastatic solitary fibrous tumors were treated with 50% having a response per Choi criteria. Stable disease occurred in 75–90% depending on criteria used with a PFS of 6.2 months [54•].

Pigmented villonodular synovitis/giant cell tumor of tendon sheath

Also known as diffuse-type giant cell tumor, the tyrosine kinase inhibitor nilotinib has shown promise in achieving SD. A recent trial published in 2018 with 51 patients eligible for assessment showed SD in 90% of the patients at 12 weeks. This response was believed to be related to suppression of the CSF1R tyrosine kinase protein [55]. There have also been case reports of responses to imatinib both as first-line treatment or following progression on nilotinib [56, 57].

Inflammatory myofibroblastic tumor

Approximately half of inflammatory myofibroblastic tumors express ALK mutations. In those with positive ALK mutations, there have been a series of case reports indicating that crizotinib, an ALK inhibitor, can induce partial or even CR in these tumors [17, 58, 59].

Perivascular epithelioid cell tumor

This is a family of tumors which include lymphangioleiomyomatosis, angiomyolipoma, and PEComa. In these malignancies, the mTOR pathway has been found to be significantly upregulated. Given the rarity of this tumor, randomized trials have not been able to be performed but there are multiple case reports in the literature of responses to mTOR inhibitors such as everolimus and temsirolimus [60–63].

Recent literature

In the SARC028 trial, pembrolizumab was evaluated in the treatment of soft tissue sarcoma. Unfortunately, the overall results were discouraging with a PR reported in 18%. Subtype analyses showed higher responses in undifferentiated pleomorphic sarcoma and de-differentiated liposarcoma so further research is still indicated [64•].

Tivozanib, a VEGF inhibitor, underwent a recent phase II study in a group of heavily pretreated patients. Results from that study showed a PR of 3.6% and SD in 54.5% with a median OS of 12.2 months [65].

Large treatment centers

Due to the complexity of sarcoma diagnosis and treatment, there has been a push for patients to be treated at large, high-volume treatment facilities. There are multiple benefits to this approach. The first benefit is at the time of diagnosis. There are currently greater than 70 distinct subtypes of sarcoma with rapidly changing diagnostic tools in pathology. This was shown in a study in which the initial pathologist's diagnosis was compared with pathologist who specializes in sarcoma. Approximately 24% of these tumors were considered to be a different histologic type from the first diagnosis and 3% a completely separate subtype. Overall, 40% had the pathology modified in some way after being analyzed by the specialized pathologist [66]. This misclassification could lead to treatment errors. For example, if the mass was initially thought to be benign and the patient underwent surgical resection by an unsuspecting surgeon, the outcomes were worse despite adequate radiation and chemotherapy [67].

Further benefit of referral to treatment facilities is the likelihood of having a patient enrolled in a clinical trial. Oftentimes, trial enrollment is in the patient's best interest given the poor response rates to the majority of first-line treatments. With the rarity of these tumors, it is near impossible for smaller treatment centers to have high enough accrual for these clinical trials. Even after treatment has been started, assessing response can be difficult as will be discussed in the next section.

Lastly, large treatment facilities are able to offer large multidisciplinary teams which are able to communicate with one another in the treatment of complex disease. For these reasons, every patient with sarcomatous disease should be considered for referral to a larger treatment center.

Response assessment

To complicate matters, our progress in the utilization of targeted agents and immunotherapy has challenged how we define response to treatment. The Response Evaluation Criteria in Solid Tumors (RECIST) was published in 2000, revised in 2009, and was meant to standardize documentation of response rates to cytotoxic chemotherapy. However, many tumors are kept stable in size rather than reaching a response per RECIST in the era of targeted agents and immunotherapy.

One striking example of this is in the treatment of GIST with imatinib. Per the RECIST criteria (requiring a 30% reduction in tumor size) very few of the study population demonstrated response despite a significantly lengthened PFS and OS. Because of this discrepancy, the Choi criteria were created in 2007 [68]. These criteria include a tumor density decrease of 15% and decreased tumor size by 10%. The criteria were validated as a prognostic indicator of response to treatment ($p = 0.0002$), whereas the RECIST criteria did not correlate with prognosis ($p = 0.74$) [69].

The Choi criteria for use in imatinib-treated GIST were the first tumor and treatment-specific response criteria. The success of the Choi criteria in prognosticating patient response led to further research into antiangiogenic treatment response in renal cell carcinoma, non-small cell lung cancer, and immunotherapy response in melanoma.

Practitioners involved in the treatment of sarcomas with newer agents should keep these factors in mind as they are assessing treatment response. It is also important to assess new data with an open mind given that the RECIST criteria may fail to accurately assess treatment response and prognosis.

Compliance with Ethical Standards

Conflict of Interest
Megan Meyer and Mahesh Seetharam declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

Publisher's Note

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

- • Of importance
- •• Of major importance

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