JACC: CARDIOONCOLOGY VOL. 7, NO. 7, 2025

STATE-OF-THE-ART REVIEW

Sarcoma: Cardiovascular and Oncologic Considerations

JACC: CardioOncology State-of-the-Art Review

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ABSTRACT

Sarcomas are a heterogeneous group of connective tissue tumors that can occur at any anatomical site. This includes the heart and great vessels, where angiosarcoma, leiomyosarcoma, intimal sarcoma, and undifferentiated sarcomas are the dominant histologic subtypes. These presentations are as complex as treatment planning, which often requires a multimodality approach. For these tumors, as well as sarcomas in other sites, multiple treatments carry risks of cardiotoxicity. Crucially, treatment universally includes high cumulative doses of anthracyclines, requiring risk modification using dexrazoxane, infusional administration, or liposomal formulations. Furthermore, multiple other therapies for sarcoma are associated with cardiovascular side effects. This review highlights the unique aspects of care for cardiac sarcomas, cardiovascular considerations of systemic agents used to treat sarcoma, the pediatric sarcoma population, and how cardiac surveillance of sarcoma patients can be approached. (JACC CardioOncol. 2025;7:800-815) © 2025 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Sarcomas are a heterogenous group of rare neoplasms that originate from the body's connective tissue. They account for roughly 1% of new adult cancer cases per year and 15% of childhood malignancies.[1] With over 100 histological subtypes identified—categorized as either soft tissue (~80%) or bone (~20%)—each can be classified by a unique clinical and anatomical presentation, risk for metastatic spread, and biological behavior.[2] This diversity in disease creates significant challenges in diagnosis and treatment, and standardization of practice is difficult due to the barriers to generating high-quality prospective data to support evidence-based care for such rare tumors.

According to the 2024 American Cancer Society estimates, approximately 13,400 new cases of soft tissue sarcoma (STS) are diagnosed each year. The average age at diagnosis is 61 years, though this varies by subtype. The most common site for these tumors is the extremities, with the next most

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Saro Armenian, DO, MPH, Deputy Editor, served as Acting Editor-in-Chief for this paper.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received May 28, 2025; accepted September 8, 2025.

ISSN 2666-0873 https://doi.org/10.1016/j.jaccao.2025.09.005

HIGHLIGHTS

- Sarcomas can occur in the heart and great vessels, with different presentations based on their location.
- Treatments for sarcoma carry cardiovascular risks, especially high cumulative doses of anthracyclines, TKIs, and immunotherapies.
- Appropriate risk stratification and cardiac monitoring should be undertaken for all patients with sarcomas.

common sites including the trunk, retroperitoneum, and viscera, followed by the head and neck.[1] Treatment of STS is tailored by histology, grade, size, presence of metastasis, and location of the tumor. Multimodal strategies are often employed which combine surgery, radiation, and systemic therapy. The latter usually involves anthracyclines as monotherapy or in combinations, followed in sequence by other cytotoxic chemotherapies, targeted treatments, and immunotherapies.[1] The average age at diagnosis of primary malignant bone tumors (eg, osteosarcoma, Ewing sarcoma, chondrosarcoma) is approximately 35 to 40 years, though it spans a wide range. While Ewing sarcoma typically develops in children and adolescents, osteosarcoma is found more frequently in adolescents and young adults, and chondrosarcoma and chordomas present most commonly in adults >40 years of age.[3] Each histologic subtype has a different therapeutic approach due to variation in sensitivity to chemotherapy and radiation.[4]

Molecular profiling has revolutionized our understanding of cancer biology, including for sarcomas. For example, profiling by fluorescence in situ hybridization and next generation sequencing has become paramount for the diagnosis of Ewing sarcoma, synovial sarcoma, and gastrointestinal stromal tumor (GIST).[5] These molecular findings have improved clinical outcomes with the use of tyrosine kinase inhibitors (TKIs) in GIST and immunotherapy in undifferentiated pleomorphic sarcoma (UPS) and cutaneous angiosarcoma (AS).[6] Despite these efforts, treatment of advanced and metastatic sarcomas still strongly relies on old, cytotoxic chemotherapy regimens. Small advances have been made by capitalizing on differential sensitivities and toxicity profiles using medications like trabectedin, dacarbazine, and eribulin, but resistance to these drugs is inevitable.[7-9] New strategies with therapies including TKIs and immunotherapies remain at the forefront of drug development for patients with sarcomas.[6,10] However, until such time as these and other novel agents become widespread as first-line treatment options through rigorous clinical testing, medical oncologists treating sarcomas are limited to older and more toxic chemotherapies—mostly involving anthracyclines.

Although many side effects of sarcoma treatments can be mitigated with supportive therapies, cardiotoxicity, a well-known side effect of anthracycline-based sarcoma treatments (especially at higher cumulative doses), requires special attention. Regular cardiac assessments, incorporating echocardiography and biomarkers (troponins, B-type natriuretic peptide), are fundamental parts of patient monitoring and are recommended in patients undergoing therapy with anthracyclines and other drugs.[11] Beyond adverse effects of therapies, "cardiotoxicity" may result from the direct effects of tumors involving the heart and great vessels. This review focuses on the unique cardiovascular considerations of sarcomas, both due to the tumors themselves and the systemic treatments involved in their treatment. An emphasis on the use of anthracyclines in sarcomas is especially prudent because of the strong reliance on this class of drug. It also focuses on the risks of cardiotoxicity faced by pediatric populations and concludes with a description of survivorship considerations.

ABBREVIATIONS AND ACRONYMS

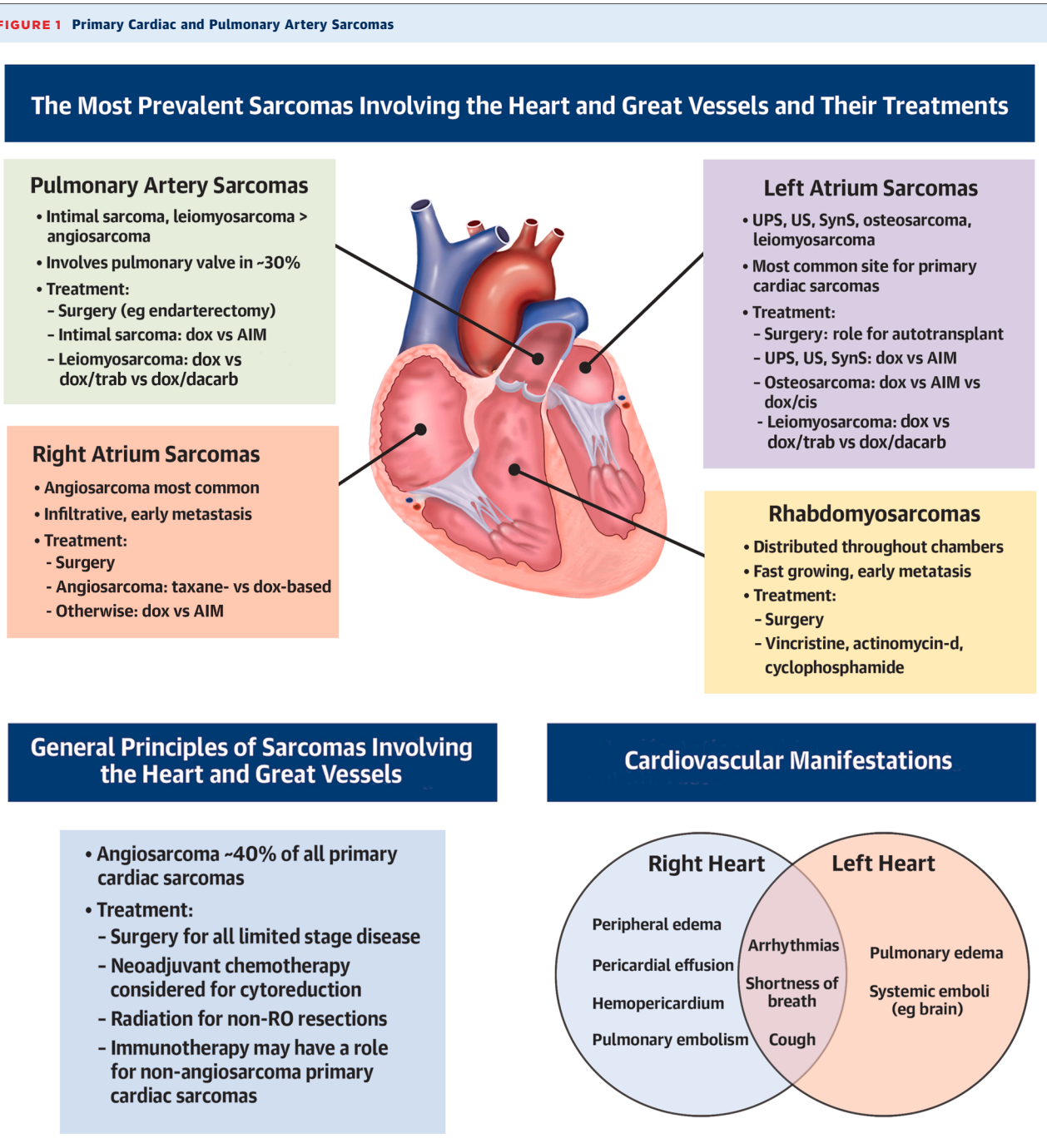
AS = angiosarcoma
BP = blood pressure
COG = Children's Oncology Group
CTRCD = cancer therapy-related cardiac dysfunction
DFS = disease-free survival
ECG = electrocardiogram
ESC = European Society of Cardiology
GIST = gastrointestinal stromal tumor
ICI = immune checkpoint inhibitor
LMS = leiomyosarcoma
LVEF = left ventricular ejection fraction
PAS = pulmonary artery sarcoma
PCS = primary cardiac sarcoma
RMS = rhabdomyosarcoma
STS = soft tissue sarcoma
TKI = tyrosine kinase inhibitor
UPS = undifferentiated pleomorphic sarcoma

SARCOMAS INVOLVING THE HEART AND GREAT VESSELS

Connective tissue neoplasms can arise anywhere in the body, including the heart and great vessels—sites that have unique implications for both prognosis and management. These are summarized in **Figure 1**. Only 10% to 15% of cardiac connective tissue tumors are malignant, yet even benign tumors can be associated with complications such as arrhythmias, valvular dysfunction, and embolic phenomena.[12] Still, the greatest risk to life is derived from true cancers, and approximately 60% of all cardiac malignancies are sarcomas.[13] Based on a SEER (Surveillance, Epidemiology, and End Results) database study, among 442 patients diagnosed between 1973 and 2015, the median survival of patients with primary cardiac sarcoma (PCS) was approximately 7 months, with 5-year survival of around 10%. This did not appear to change significantly over time, despite

JACC: CARDIOONCOLOGY, VOL. 7, NO. 7, 2025
DECEMBER 2025:800–815

FIGURE 1 Primary Cardiac and Pulmonary Artery Sarcomas



The most common tumors at each site are noted, with important clinical and treatment considerations. All tumors can occur at any site, but the most prevalent presentations and relevant therapies are highlighted. AIM = doxorubicin, ifosfamide, mesna; dox = doxorubicin; dox/cis = doxorubicin plus cisplatin; dox/dacarb = doxorubicin plus dacarbazine; dox/trab = doxorubicin plus trabectedin; IS = intimal sarcoma; LMS = leiomyosarcoma; OS = osteosarcoma; PCS = primary cardiac sarcoma(s); PV = pulmonic valve; SynS = synovial sarcoma; UPS = undifferentiated pleomorphic sarcoma; US = undifferentiated sarcoma(s); VAC = vincristine, actinomycin-d, cyclophosphamide.

advancements in the approach to care, and surgery and chemotherapy were both associated with improved overall survival.[14] By contrast, in a retrospective single-center review of 122 patients spanning 1998 to 2021, 5-year survival was 27.8% in a cohort with PCS, but all of these patients underwent surgery and thus were expected to have a better prognosis than the more general SEER analysis.[15] In both studies, PCS presented at a mean age of 45 to 47 years with a wide range, was evenly divided between men and women, and a plurality (approximately 40%) of cases were AS. Of the other sarcoma subtypes, each accounts for approximately 10% or less of PCS cases. These predominantly include UPS and related poorly differentiated subtypes, leiomyosarcoma (LMS,) rhabdomyosarcoma (RMS), and synovial sarcoma.[14,15]

PCS can occur in any chamber of the heart, but the atria are more commonly involved than the ventricles, and certain subtypes have predilections for different sites. AS, for instance, is most often found in the right atrium, whereas LMS, osteosarcoma, and UPS-like tumors occur more commonly in the left atrium.[12,15-18] Right heart sarcomas have been described as bulkier, more infiltrative, and tend to metastasize early in their course—probably owing to the prevalence of AS in this site.[19] Patients with right heart sarcomas may display signs of right heart failure (ie, peripheral edema, exercise intolerance), shortness of breath related to pericardial effusion or hemopericardium, pulmonary embolism, and supraventricular arrhythmias.[12] By contrast, left heart sarcomas present with left heart failure (ie, pulmonary edema, fatigue, and eventually peripheral edema) and systemic embolic complications such as stroke. These left-sided tumors pose unique surgical challenges and may demand advanced techniques such as autotransplantation.[19] They also necessitate brain imaging as part of the staging workup, as they tend to metastasize more frequently to this site as compared with other sarcomas.[18] RMS can present in any cardiac chamber and is mostly found in children.

The clinical presentation of pulmonary artery sarcomas (PAS) can be similar to PCS, due to shared features of cardiopulmonary obstruction and involvement of the pulmonic valve in about 30% of cases. Patients may also have constitutional symptoms, dyspnea, and cough.[20] In a combined analysis of 60 PAS patients from the literature and 8 PAS patients seen at a single center, all of whom underwent surgical intervention, median survival was 36.5 months for those undergoing treatment with curative intent compared with 11 months for those treated with palliative intent; 5-year survival was 49.2% vs 0%.[21] Those who underwent multimodality therapy tended to experience longer survival. Histologically, PAS is most commonly LMS and intimal sarcoma, but can also be AS or other subtypes. LMS and intimal sarcoma are also 2 of the most common sarcoma subtypes found in the venae cava and may cause distal edema, thrombosis, and organ dysfunction.[16,22]

Moreover, the clinical presentation of sarcomas of the heart and great vessels may vary depending on site and behavior, but there are common themes: vascular obstruction, propensity for thrombosis and embolization, arrhythmia, and even heart failure. Surgery is the cornerstone of management of PCS and sarcomas of the great vessels for those patients without distant disease.[12,15,21,23-25] For patients with PAS, procedures such as debulking and endarterectomy are used for hemodynamic and cardiopulmonary stabilization even in patients with unresectable, incurable disease.[21,26] Adjuvant therapy including systemic therapies and radiation are considered for patients for whom resection is deemed inadequate due to surgical limitations or who are at high risk of distant disease, and multimodality therapy appears to improve outcomes.[14,20,25,27]

Chemotherapy regimens are often tailored to specific anatomical and histological considerations. As with sarcomas originating in other sites, anthracycline-based therapy is used for these tumors, sometimes in combination with ifosfamide, dacarbazine, or trabectedin when a significant tumor response is desired.[7,21,26] Taxane-based therapy is an attractive option in AS.[28] Whether chemotherapy should be applied in the neo-/adjuvant setting is unclear, though R0 resection may be made more feasible by the early introduction of systemic therapies.[19] The same regimens used for STS are used in metastatic PCS with palliative intent. Finally, it appears that immunotherapies such as immune checkpoint inhibitors (ICIs) may have promising activity in PCS, especially in patients with non-AS PCS where median survival is significantly longer with ICI treatment than in patients with AS (24 vs 3 months).[29] This contrasts with evidence that cutaneous AS are quite sensitive to ICIs, but it aligns with the insensitivity of other visceral AS to ICIs.[30]

ANTHRACYCLINES IN SARCOMAS: TREATMENT AND TOXICITY

THE ROLES OF ANTHRACYCLINES IN THE TREATMENT OF SARCOMA. Anthracyclines have long been the cornerstone of systemic therapy for sarcomas. Several core principles apply to the prescription of

anthracyclines in sarcoma care: 1) efficacy is dose-dependent, and doses below 60 mg/m^2 every 3 weeks are not effective[31]; 2) the most important pharmacologic variable associated with efficacy is the peak concentration rather than the duration of exposure, and therefore high doses every 3 weeks are standard[32]; 3) combination chemotherapy regimens yield better response rates, and disease-free survival (DFS) compared with anthracycline monotherapy[33,34]; and 4) among anthracyclines, doxorubicin continues to be the most widely utilized in the treatment of sarcomas, though epirubicin has also been studied and used primarily in Europe.[35]

Doxorubicin 75 mg/m^2 every 3 weeks for 6 cycles is the foundation of systemic treatment in the first-line setting for patients with advanced STS.[1,36] Several randomized phase III trials compared combination regimens (mostly with high-dose ifosfamide or analogues) with single-agent doxorubicin and demonstrated an improved response rate (roughly 5% to 10% vs 25% to 30%) with combinations without significantly improving overall survival.[33,34] Thus, the use of single-agent doxorubicin vs combination with high-dose ifosfamide as standard of care in the first-line setting remains a matter of debate in the sarcoma community. Overall survival is a difficult endpoint to assess in the first-line setting since it is impacted by later lines and by the natural history of the different STS types included in these trials, leading to heterogeneous populations. In advanced LMS, combination therapy has become more widely accepted based on the LMS-04 trial (Study Comparing Efficacy of Doxorubicin With Trabectedin Followed by Trabectedin Versus Doxorubicine in Patients With Leiomyosarcoma), which showed that the addition of trabectedin to doxorubicin improved overall survival over doxorubicin alone (33.1 vs 23.8 months).[7] An alternative combination strategy for STS, including LMS, is doxorubicin with dacarbazine, though the evidence for this approach is primarily based on retrospective data.[8]

The use of adjuvant chemotherapy in the treatment of STS remains controversial, although its inclusion of high doses of anthracyclines is universal when applied. According to a landmark meta-analysis, the greatest overall survival benefit is observed in patients receiving both doxorubicin and ifosfamide.[37] Sarcoma experts recommend perioperative chemotherapy with doxorubicin and ifosfamide in patients with a high risk of recurrence, either defined using nomograms or using prognostic factors including age, pathologic grade, size, resection margins, and STS type.[38,39] An international randomized phase III trial compared neoadjuvant subtype-specific chemotherapy vs 3 cycles of anthracycline-ifosfamide in patients with localized high-risk STS in 5 select subtypes. Anthracycline-ifosfamide resulted in significantly better overall survival (76% vs 66% at 60 months; $P = 0.018$), making this a standard-of-care regimen for 3 to 6 cycles depending on the center.[40]

The treatment of bone sarcomas is more universally accepted. Frontline systemic treatment for osteosarcoma is a combination of doxorubicin and cisplatin, to which methotrexate is added in younger patients.[41,42] In the localized setting, these aggressive combinations have improved overall survival from <20% in the 1970s with surgery alone to 70% to 80% in more recent years.[43] Ewing sarcoma is a chemosensitive disease, with anthracycline-based combination regimens achieving objective response rates of approximately 70%. In the localized setting, 3-year DFS reaches 60% to 70%, whereas in the metastatic setting, a small subset of patients can achieve long-term remission, with 4-year DFS around 30%.[44,45] Maintaining a high-dose intensity of chemotherapy is paramount for the efficacy of these treatments.[46] A summary of anthracycline-based regimens used in bone and soft tissue sarcomas can be found in **Table 1**.

Rechallenge or prescription of anthracycline beyond the maximum cumulative recommended dose can be considered in expert centers after multidisciplinary discussion and careful assessment of the risks.[47-49] This approach is more appropriate when cardiac risk assessment and preventive strategies have been implemented before initiating anthracycline therapy, since patients with sarcoma are nearly universally planned to reach a maximum (or more) recommended lifetime dose of these important drugs.

CARDIOTOXICITY ASSOCIATED WITH ANTHRACYCLINES. The primary toxicity associated with anthracyclines is cardiomyocyte dysfunction leading to cardiomyopathy and heart failure, though other toxicities such arrhythmias are also associated with these agents and can occur independently of any other cardiotoxicity.[50,51] There is also emerging evidence that anthracyclines can lead to vascular toxicity and dysfunction potentiating atherosclerosis in survivors who have also received radiation.[52,53] Moreover, there is also a higher incidence of hypertension and metabolic abnormalities. Murine models have shown anthracyclines may promote atherosclerotic plaque development.[54]

Anthracycline-induced cardiotoxicity can be classified based on the time at which it occurs relative to

TABLE 1 Main Anthracycline-Containing Chemotherapy Regimens Used in the Treatment of Sarcomas

Sarcoma Type and Setting	Chemotherapy Regimen	Anthracycline Used	Schedule	No. of Cycles	Doxorubicin Equivalent Dose	References (PMID)
STS, advanced first-line	Doxorubicin	Doxorubicin	75 mg/m^2 q 3 wk	6	450 mg/m^2[a]	28882536
	Doxorubicin-ifosfamide	Doxorubicin	75 mg/m^2 q 3 wk	6	450 mg/m^2[a]	24618336
	Doxorubicin-dacarbazine	Doxorubicin	75 mg/m^2 q 3 wk	6	450 mg/m^2	32129883, 8315425
	Epirubicin	Epirubicin	120 mg/m^2 q 3 wk	6	480 mg/m^2	9862576
LMS, first-line	Doxorubicin-trabectedin	Doxorubicin	60 mg/m^2 q 3 wk	6	360 mg/m^2	39231341
STS, adjuvant and/or neoadjuvant	Doxorubicin-ifosfamide	Doxorubicin	75 mg/m^2 q 3 wk	3-6	225-450 mg/m^2[a]	18521899, 30690293
	Epirubicin-ifosfamide	Epirubicin	120 mg/m^2 q 3 wk	3-6	240-480 mg/m^2	32421444
Osteosarcoma, frontline, children	MAP	Doxorubicin	75 mg/m^2 q 5 wk*	6	450 mg/m^2[a]	25421877
Osteosarcoma, frontline, adults	Doxorubicin and cisplatin	Doxorubicin	75-90 mg/m^2 q 3 wk	6-8	Up to 600 mg/m^2	20213401
Ewing sarcoma and PNET	VDI/VDC	Doxorubicin	75 mg/m^2 q 3 wk	6	450 mg/m^2[a]	28710342
	VIDE	Doxorubicin	60 mg/m^2 q 3 wk	6	360 mg/m^2[a]	20547982
	VDC/IE	Doxorubicin	75 mg/m^2 q 4-6 wk	7	375 mg/m^2[a,b]	23091096

[a]Doses adjusted for age <1 year and/or body surface area <0.6 m^2 in pediatric populations depending on the trial and/or institutional standards. [b]Real-world practice varies, and some practitioners continue treatment to higher cumulative doses.

LMS = leiomyosarcoma; MAP = methotrexate-adriamycin-cisplatin; PMID = PubMed Indentifier; PNET = primitive neuroectodermal tumor; VDC = vincristine-doxorubicin-cyclophosphamide; VDI = vincristine-doxorubicin-ifosfamide; VIDE = vincristine-ifosfamide-doxorubicin-etoposide; VDC/IE = vincristine-doxorubicin-cyclophosphamide/ifosfamide-etoposide; STS = soft tissue sarcoma.

drug administration—acute (during or shortly after drug infusion), early-onset chronic progressive (within the first year of treatment), and late onset (more than 1 year after treatment).[55] Each of these toxicities has a unique phenotype. Acute toxicity is rare (<1%) and is thought to be stress-mediated and generally reversible with cessation of anthracyclines. Early-onset toxicity is the most common and presents as an asymptomatic decrease in left ventricular ejection fraction (LVEF), though overt heart failure is also possible. In 1 large cohort, 98% of cases of anthracycline-induced cardiotoxicity occurred in the first year after completion of chemotherapy.[56] In late-onset toxicity, patients demonstrate cardiac remodeling leading to a dilated cardiomyopathy and overt heart failure. In a large meta-analysis of 22,815 cancer patients treated with anthracyclines, LV dysfunction was identified in 6% with a median time to diagnosis of 9 years. Importantly, 18% of the total cohort had evidence of subclinical dysfunction.[57] This suggests a possible continuum starting with subclinical myocardial injury ultimately progressing over time to clinical heart failure.[55]

The pathophysiology of anthracycline-mediated cardiac dysfunction remains incompletely understood. Risk factors for developing anthracycline-induced cardiac dysfunction include cumulative anthracycline dose, time from exposure, age (<18 and >60 years), female sex, the use of concomitant systemic treatments, and radiation (especially directed to the mediastinum or left chest).[55,58] Toxicity is most likely to occur when anthracyclines accumulate in cardiac tissue at a rate the exceeds the ability of the cells to metabolize and clear the drug.[59,60] Postulated mechanisms of anthracycline cardiotoxicity include oxidative stress, increased apoptosis, and epigenetic changes. Anthracyclines generate reactive oxygen species and mobilize iron, which can damage mitochondria and the sarcoplasmic reticulum, leading to impaired calcium handling and dysregulated autophagy. This results in accumulation of intracellular toxins and premature cell death.[59,61] In addition, anthracyclines can impact DNA methylation and acetylation pathways, leading to impaired gene expression affecting the cell life cycle (**Table 2**).[62] Moreover, there are now data suggesting the immune system may also play a key role in the development of anthracycline cardiotoxicity. In particular, neutrophils appear to be involved in the regulation of ferropotosis and depletion of neutrophils from the myocardial microenvironment may help reduce the occurrence of anthracycline cardiotoxicity.[63,64]

Reports are relatively sparse for cardiovascular outcomes specific to sarcoma patients exposed to anthracyclines. In 1 retrospective study, (CTRCD) was reported in 31% of patients with sarcoma. However, estimates are highly variable and depend on the definition of toxicity (eg, ranging from echocardiographic evidence of LVEF changes to clinical heart failure).[65] For instance, data from the phase 3 ANNOUNCE trial (A Study of Doxorubicin Plus Olaratumab [LY3012207] in Participants With Advanced or Metastatic Soft Tissue Sarcoma) revealed that up to 48.8% of patients experienced either a >10% decrease in LVEF from baseline or an LVEF with an absolute value <50%.[66] LVEF deterioration was seen in 62 of 153 patients (40.5%) who received a

TABLE 2 Drugs Used in Sarcoma: Cardiac Toxicities and Mechanisms

Drug	Class/Target	Cardiac Toxicities	Proposed Mechanisms	References (PMID)
Anthracyclines (eg, doxorubicin, epirubicin)	Topoisomerase II inhibitors	Dose-dependent cardiomyopathy, HF, arrhythmias, pericarditis-myocarditis syndrome	Topoisomerase IIβ–mediated DNA damage, ROS generation, mitochondrial dysfunction, iron overload, myocyte apoptosis	39479333
Ifosfamide	Alkylating agent	Arrhythmias, hypotension, rare HF	Direct myocardial toxicity, acrolein-related endothelial injury, oxidative stress	14586140
Gemcitabine	Antimetabolite (pyrimidine analog)	Rare: myocardial ischemia, arrhythmias, pericarditis, cardiomyopathy	Endothelial injury, coronary vasospasm, microvascular thrombosis, possible immune-mediated effects	33096756
Paclitaxel	Microtubule stabilizer	Bradycardia, conduction abnormalities, hypotension, rare HF	Interference with microtubules in cardiomyocytes, autonomic dysregulation	20801127
Eribulin	Microtubule dynamics inhibitor	QTc prolongation	Disruption of microtubule-dependent signaling in cardiomyocytes; possible autonomic effects; off-target ion channel interactions	23143778
Trabectedin	DNA minor groove binder	Cardiomyopathy (especially in patients with anthracycline exposure), bradycardia, arrhythmias	Mitochondrial dysfunction, direct myocardial inflammation, DNA damage and impaired repair	33960681, 26371143
Pazopanib	Multi-TKI (VEGFR, PDGFR, KIT)	Hypertension, LVEF decline, QTc prolongation, arterial thromboembolism	VEGF inhibition → endothelial dysfunction, NO reduction, capillary rarefaction, increased afterload	37414756
Cabozantinib	Multi-TKI (VEGFR, MET, AXL)	Hypertension, LVEF decline, arterial thromboembolism	VEGF inhibition, cardiac remodeling	37414756, 30740760
Imatinib	TKI (BCR-ABL, PDGFR, KIT)	Fluid retention, rare HF	PDGFR-β inhibition impairing pericyte function and vascular integrity leading to increased vascular permeability and capillary leak; endoplasmic reticulum stress	17457301
Sunitinib	Multi-TKI (VEGFR, PDGFR, KIT, FLT3)	Hypertension, HF, QTc prolongation, arterial/venous thrombosis	VEGF inhibition, mitochondrial dysfunction, AMPK inhibition	37414756, 17457301
Regorafenib	Multi-TKI (VEGFR, PDGFR, RAF)	Hypertension, LVEF decline, cardiac ischemia	VEGF inhibition, off-target RAF inhibition, mitochondrial effects	23177515
Ripretinib	Broad KIT/PDGFRA switch-control TKI	Hypertension, rare reports of cardiac dysfunction, hypertriglyceridemia	Off-target KIT inhibition, vascular tone alterations	32511981
Avapritinib	Selective KIT/PDGFRA inhibitor	Rare cases of fluid retention, pericardial effusion	Unclear; may involve vascular endothelial effects or immune-mediated changes	32615108
Immune checkpoint inhibitors	Anti-PD-1/PD-L1/CTLA-4	Myocarditis, arrhythmias, pericarditis, HF, ischemia	T-cell–mediated autoimmune myocarditis	39547252, 34529770

AMPK = AMP activated protein kinase; AXL = a member of TAM family of receptor kinases; BCR-ABL = Breakpoint Cluster Region–Abelson murine leukemia viral oncogene homolog 1; CTLA-4 = cytotoxic T lymphocyte antigen 4; HF = heart failure; KIT = stem cell factor receptor; LVEF = left ventricular ejection fraction; MET = mesenchymal epithelial transition factor; NO = nitric oxide; PD-1 = programmed cell death protein 1; PDGFR = platelet derived growth factor; PD-L1 = programmed death ligand 1; PMID = PubMed Indentifier; RAF = rapidly accelerated fibrosarcoma; ROS = reactive oxygen species; TKI = tyrosine kinase inhibitor; VEGFR = vascular endothelial growth factor receptor.

cumulative dose <450 mg/m^2, 82 of 159 patients (51.6%) who received 450 to <600 mg/m^2, and 50 of 89 patients (56.2%) who received ≥600 mg/m^2. Cardiac dysfunctions grades 3 to 5 were observed in 2% of patients at <450 mg/m^2, 3% at 450 to <600 mg/m^2, and 1.1% at ≥600 mg/m^2.[47] A majority of patients seem to experience early adverse cardiac effects, and these are associated with higher mortality.[65,67,68] In cohorts of childhood cancer survivors, patients with STS had rates of heart failure and coronary diseases similar to those with other types of tumors.[53,69] Congestive heart failure grades 3 to 5 was reported in 1.6% of STS survivors, and the HR for developing congestive heart failure was 4.6 compared with the general population.

The relatively high incidence of CTRCD in sarcoma patients is likely related to the high cumulative doses this population receives—as compared with patients with other cancers. Predictors of risk for CTRCD in sarcoma patients are similar to other settings and include baseline diastolic blood pressure, female sex, left ventricular end-systolic diameter, and left ventricular mass.[68]

STRATEGIES TO PREVENT CARDIOTOXICITY. CTRCD from anthracyclines involves both anthracycline-specific strategies—such as continuous infusion,

dexrazoxane, and alternative formulations—and broader cardioprotective approaches, including other pharmacologic interventions (eg, statins, neurohormonal blockade) and nonpharmacologic lifestyle modifications (eg, smoking cessation, healthy diet, and regular exercise).

Two of the most efficient ways to prevent cardiac toxicity from anthracyclines in the treatment of sarcomas are by administration via continuous infusion and the addition of dexrazoxane. Several studies across cancer types have demonstrated that continuous infusion of doxorubicin over up to 96 hours rather than bolus administration reduces the risk of cardiotoxicity,[67,70] without reducing the efficacy of doxorubicin against sarcoma.[71-73] Dexrazoxane offers a more convenient cardioprotective approach since it can be administered in the outpatient setting.[74,75] Importantly, dexrazoxane does not reduce efficacy of doxorubicin in the treatment of sarcomas and is cost-effective.[76,77] Dexrazoxane is formally approved for patients who have received a cumulative dose of doxorubicin-equivalent higher than 300 mg/m^2.[50] However, for patients in whom high cumulative doses are anticipated (ie, sarcoma patients), prescription of dexrazoxane at the initiation of chemotherapy is recommended.[49,55,78]

Another strategy to reduce cardiotoxicity is to enhance drug delivery to the tumor while limiting exposure to cardiac tissue. Liposomal and pegylated liposomal doxorubicin offer this potential advantage through their favorable pharmacokinetic profiles.[79] These formulations are associated with higher rates of mucositis and hand-foot syndrome, which limit the maximum tolerated dose The single-arm data with these drugs imply inferior outcomes compared with those reported for other anthracyclines, but comparisons among trials is difficult—especially given variable methodologies, doses, and patient populations—and there are no randomized trials comparing the different formulations.[35,80,81] Liposomal doxorubicin is sometimes used in patients with prior exposure to anthracyclines beyond the maximum recommended lifetime dose, usually until progression or toxicity and with close cardiac monitoring.[82]

There have been no sarcoma-specific trials looking at early intervention with cardioprotective measures to prevent anthracycline CTRCD. Most trials have focused on patients treated for breast cancer who receive lower cumulative doses.[50] Sarcoma patients represent a unique subgroup of patients who receive high doses of anthracyclines and thus demand further investigation. Several randomized control trials have demonstrated that neurohormonal blockade with drugs such as beta-blockers and renin-angiotensin-aldosterone inhibitors may attenuate anthracycline-related decreases in LVEF, but does not reduce the incidence of clinically symptomatic heart failure, and therefore it is recommended specifically in patients at high risk of CTRCD.[50,55] Although clinical trial data are mixed, statins may also be cardioprotective in patients receiving anthracyclines and can be considered in high-risk cases.[83]

Nonpharmacologic interventions such as moderate daily exercise remain underutilized in preventing anthracycline-induced CTRCD, yet they are effective and should be encouraged before, during, and after treatment with anthracyclines.[84] In a murine model, exercise protected against acute and late cardiotoxicity—and induced cardiac repair when introduced after anthracycline exposure—which appeared to be associated with suppression of anthracycline-induced autophagosomes, preservation of normal mitochondria, and maintenance of pericytes.[85] Ongoing clinical trials are investigating novel cardioprotective pharmacologic strategies such as angiotensin receptor neprilysin inhibitors, sodium glucose co-transporter 2 inhibitors, and ranolazine, among others.[86]

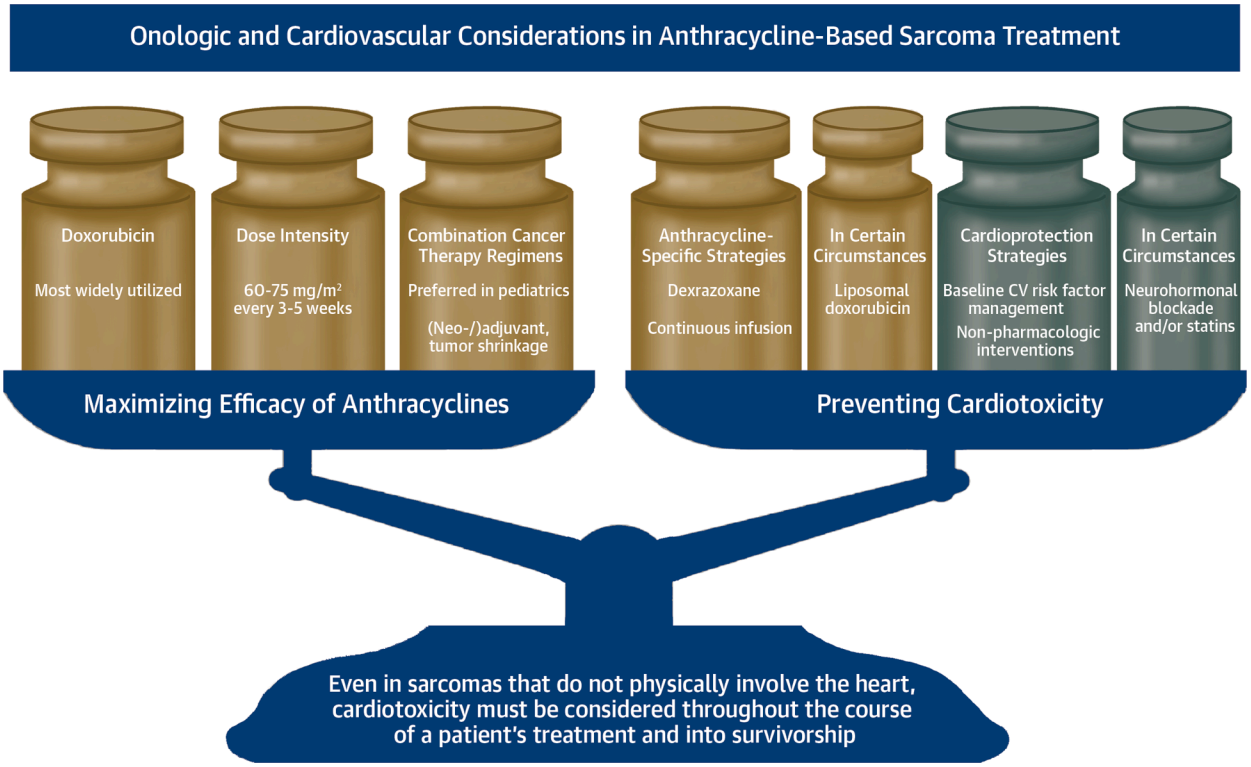
The applications, toxicities, and risk management approaches relevant to anthracyclines are summarized in the **Central Illustration**.

NON-ANTHRACYCLINE SARCOMA THERAPIES

Anthracyclines are the most well-studied sarcoma therapies with regards to cardiac toxicities, but many other drugs used to treat sarcomas have significant impacts on cardiovascular health (**Table 2**). Importantly, as anthracyclines are used most commonly in first-line treatment of advanced disease, patients who receive these other medications may be predisposed to cardiac dysfunction from prior anthracycline exposure.

TYROSINE KINASE INHIBITORS. The pivotal PALETTE (Pazopanib Versus Placebo in Patients With Soft Tissue Sarcoma Whose Disease Has Progressed During or Following Prior Therapy) trial conducted in 369 patients with metastatic STS, refractory to standard chemotherapy, showed that pazopanib improved median PFS as compared with placebo (4.6 months vs 1.6 months).[87] Its broad STS indication (excepting liposarcomas) has led to its frequent use as subsequent-line therapy in these patients. Pazopanib is an oral multi-targeted TKI that inhibits VEGFR1/2/3—and to a lesser degree, platelet derived growth factor (PDGFR) and stem cell factor receptor (KIT)—disrupting tumor angiogenesis and growth.[88] This

CENTRAL ILLUSTRATION **Prescription of Anthracycline Treatment for Patients With Sarcomas**



Lefler DS, et al. JACC CardioOncol. 2025;7(7):800–815.

This highlights common approaches to maximizing efficacy of anthracyclines and preventing toxicity in adult and pediatric practice. CV = cardiovascular.

class of drugs is most frequently associated with hypertension, but can rarely cause left ventricular systolic dysfunction, QTc prolongation, and arterial/venous thromboembolic events.[55] This is probably because vascular endothelial growth factor receptor (VEGFR) and other kinase blockade interfere with cardiac homeostasis, induce changes in the microvasculature of myocardial capillaries, and cause dysregulation of nitric oxide and endothelin.[89,90] In the PALETTE trial, pazopanib was associated with a higher incidence of all-grade (41% vs 7%) and grade 3 (7% vs 3%) hypertension compared with placebo.[87] Decreased LVEF and clinical heart failure attributed to pazopanib have been reported in the literature.[91] Like pazopanib, cabozantinib has also shown activity in both bone and soft tissue sarcomas due to its activity against VEGFR, mesenchymal epithelial transition factor (MET), and a member of TAM family of receptor kinases (AXL), with primary uses in Ewing sarcoma, osteosarcoma, and many STS subtypes.[92,93] It is also associated with hypertension and reports of decreased LVEF and cardiac dysfunction. In 1 prospective real-world study of cabozantinib in patients with renal cell cancer, one-third of patients had decreased LVEF on therapy, with 11% of patients experiencing a decline of >10%.[94]

GIST is characterized by gain-of-function mutations in the protooncogene tyrosine kinases KIT and PDGFRA. TKIs that inhibit KIT and PDGFRA are highly effective in the management of GIST. Imatinib is first-line therapy for unresectable, metastatic, or recurrent GIST with KIT/PDGFRA mutations. In the adjuvant setting, 3 years vs 1 year of post-resection imatinib has been shown to improve recurrence free survival in high-risk GIST, and treatment up to 5 years was shown to be safe, tolerable, and effective at preventing disease recurrence.[95,96] In these studies, imatinib was associated with peripheral edema in 40% to 50% of patients, but had no other significant cardiotoxic signals. Sunitinib, regorafenib, ripretinib, and avapritinib are also used in GIST. Sunitinib is associated with hypertension (~20%), left ventricular systolic dysfunction (2% to 8% and mostly reversible), QTc prolongation, and arterial/venous

thromboembolic events.[97] Meanwhile, regorafenib (with activity also against FGFR1) is associated with all-grade and grade 3 to 4 hypertension occurring in 49% and 24% of GIST patients, respectively.[98] In the INVICTUS trial (Phase 3 Study of DCC-2618 vs Placebo in Advanced GIST Patients Who Have Been Treated With Prior Anticancer Therapies), ripretinib caused all-grade and grade 3 hypertension in 9% and 4% of patients, respectively. Hypertriglyceridemia and heart failure were both seen in ~1% of patients.[99] Avapritinib may be associated with significant rates of edema (~30%) in GIST patients with PDGFRA D842V mutations, but hypertension is uncommon (estimated incidence <4%).[100] In summary, these TKIs have slightly different side-effect profiles based on varying activity against relevant kinases, but hypertension and decreased LVEF (albeit at low rates) are common features among them.

The 2022 European Society of Cardiology (ESC) cardio-oncology guidelines recommend baseline cardiovascular risk assessment including clinical examination, blood pressure (BP) measurement, and electrocardiogram (ECG) for QTc measurement in patients treated with TKIs.[55] Baseline echocardiography can be considered in high-risk patients, such as those with prior anthracycline exposure. According to these European guidelines, home BP monitoring is recommended daily during the first cycle, with dose escalations, and every 2 to 3 weeks thereafter. QTc monitoring should be considered with dose changes, when other QTc-prolonging drugs are used, or with electrolyte imbalances. BP should be carefully controlled, preferably with angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, followed by dihydropyridine calcium channel blockers.

ALTERNATIVE CYTOTOXIC CHEMOTHERAPIES. Trabectedin interferes with DNA repair by targeting the transcription-coupled nucleotide excision repair system and modulates the tumor environment. It is used in subsequent-line treatment for advanced STS—mostly in liposarcoma and LMS, where a phase III trial has shown it to be superior to dacarbazine in achieving disease control.[101,102] In this trial, the incidence of cardiac failure (5.0% vs 2.3%), cardiomyopathy (3.7% vs 2.3%), and heart failure (2.9% vs 0.6%) was higher with trabectedin.[101] When used as monotherapy or in combination with liposomal doxorubicin, age ≥65 years, a prior history of cardiovascular disease, LVEF less than the lower limit of normal, and prior exposure to high-dose anthracyclines (≥300 mg/m^2) are risk factors for trabectedin-associated cardiotoxicity.[103] Despite this, the combination of doxorubicin and trabectedin in the LMS-04 trial did not display increased risk of cardiac dysfunction in the combination arm, as compared with doxorubicin alone; however, both drugs were dosed at lower levels than as monotherapies.[7] Baseline echocardiographic assessment of LVEF and periodic surveillance every 2 to 3 months is recommended with trabectedin treatment.

Other commonly used cytotoxic chemotherapies include eribulin, gemcitabine, docetaxel, and ifosfamide. Eribulin is a non-taxane microtubule inhibitor and is generally associated with a low incidence of cardiotoxicity but can cause QTc prolongation. Baseline ECG with QTc measurement is recommended, and QTc monitoring should be considered with dose changes, when other QTc prolonging drugs are used, or with electrolyte imbalances.[55] Gemcitabine may be associated with a higher incidence of cardiac adverse effects including myocardial ischemia, pericardial disease, and supraventricular arrhythmias, based on observational pharmacovigilance data.[104] Docetaxel and ifosfamide are rarely associated with cardiovascular toxicities, and they are usually administered as part of combination regimens.

IMMUNE CHECKPOINT INHIBITORS. Small, open-label phase II studies have suggested that some patients with locally advanced, unresectable, or metastatic sarcoma who have received at least 1 previous line of systemic therapy may benefit from pembrolizumab or combination therapy with ipilimumab and nivolumab—particularly those with UPS and related sarcoma subtypes.[105,106] ICIs can be associated with cardiovascular toxicities including myocarditis, pericardial disease, heart failure, myocardial infarction, and cerebrovascular ischemia.[107] Myocarditis is the most dreaded complication of ICI therapy. While rare (~1% incidence), it can be associated with significant mortality (30% to 50%), and the risk is increased with dual ICI therapy.[107] It is recommended that all patients undergo a baseline ECG and troponin before ICI initiation, and a baseline echocardiogram may be considered in high-risk patients. In patients with suspected ICI myocarditis, discontinuation of ICI therapy and prompt initiation of high-dose steroids is recommended while a diagnosis is confirmed.[55] The safety of reinitiating ICI therapy in patients with ICI cardiotoxicity remains unclear.

THORACIC RADIATION. Thoracic radiation is not routinely used in all sarcoma patients. It may be used for local control, to shrink tumors to improve surgical outcomes, to prevent recurrence, or for palliative

care in patients with STS involving the chest wall, mediastinum, or intrathoracic organs. Thoracic radiation can be associated with significant long-term cardiotoxicity when the heart is in the radiation field.[108] This occurs decades after completion of radiation therapy and can include coronary artery disease, valvular heart disease, pericarditis/constriction, heart failure, and conduction system abnormalities. The risk of cardiotoxicity increases linearly with radiation dose and with greater anthracycline exposure.[109] In children treated with thoracic radiation, the Children's Oncology Group (COG) guidelines recommend an annual physical examination with assessment and modification of traditional cardiovascular risk factors. Screening echocardiography is recommended every 2 years with chest radiation doses ≥30 Gy or ≥15 Gy with >100 mg/m^2 anthracyclines; every 5 years with chest radiation doses of 15 to <30 Gy or <15 Gy with 100 to <250 mg/m^2 anthracyclines. Ischemic evaluation should be considered in asymptomatic patients exposed to high-dose chest radiation, starting 10 years after completion of radiation therapy.

PEDIATRIC SARCOMAS

Approximately 1,600 children and young adults <20 years of age are diagnosed with sarcomas in the United States each year.[110] These patients present unique challenges in care and require long-term monitoring for toxicity of therapies, given the potential for many decades of survival after treatment. The most common sarcomas in childhood are osteosarcoma, Ewing sarcoma, RMS, and non-RMS STS. PCSs are rare in children but can occur at any age, and the clinical presentation and management of these tumors in pediatric populations is parallel to those mentioned in the prior section in this review.[24,111] The treatment of many childhood sarcomas includes doxorubicin-based chemotherapy and radiation.[112-115] The standard chemotherapy regimens, including detailed doxorubicin dosing, utilized in North America for children with newly diagnosed sarcomas are included in **Table 1**. Importantly, doxorubicin is not commonly used in the upfront treatment of RMS in North America. Overall, approaches are similar between pediatric and adult populations, since there is significant overlap in disease biology and a limited ability to divide these populations in clinical trials due to the rarity of sarcomas.

The use of chemotherapy and radiation have led to significant improvements in survival in children with sarcomas.[114,115] A clear understanding of the acute, chronic, and late cardiac effects of sarcoma therapy is needed to effectively care for children during and after completion of sarcoma treatment. Survivors of childhood cancer are at substantial risk for cardiovascular disease, including an approximate 2% incidence of cardiomyopathy within 10 years.[116] Even decades after cancer diagnosis, childhood cancer survivors are at excess risk of late mortality—with heart disease being a leading cause of death in this population.[117] Among 10,724 patients surviving at least 5 years, the cumulative incidence of coronary artery disease, heart failure, valvular disease, and arrhythmia was 5.3%, 4.8%, 1.5%, and 1.3%, respectively, by age 45 years.[53] Among survivors of childhood cancer, specific factors that increase the risk of both cardiotoxicity and mortality include treatment with anthracyclines, higher cumulative anthracycline dose exposure, and radiotherapy involving the heart.[117] Importantly, patients <5 years of age are at higher risk of cardiotoxicity than older children and adolescents.[118]

Several strategies commonly are used to reduce the risk of cardiotoxicity during anthracycline-based therapy for childhood sarcomas. These largely match the efforts to limit cardiotoxicity in adults. The Children's Oncology Group (COG) Chemotherapy Standardization Task Force has sought to standardize dosing of chemotherapy, including anthracyclines, in infants and young children using dosing tables with body surface area dose banding that gradually transitions from weight-based to body surface area-based dosing,[119] and cumulative anthracycline doses are generally limited to a doxorubicin isotonic equivalent dose of 450 mg/m^2.[47,120] Many centers treating pediatric sarcomas administer doxorubicin as a short infusion to facilitate pretreatment with dexrazoxane, because continuous infusion has not shown a cardioprotective benefit in children (unlike adults), and pediatric trials have shown administration of dexrazoxane decreases the risk of serious cardiovascular complications.[77,112,121] Although there are variations in practice, and dexrazoxane use is off-label, it is often considered when the anticipated cumulative anthracycline dose is >250 mg/m^2, if there is prior or anticipated future radiotherapy including the myocardium, or there is an anticipated need for future anthracyclines, which is consistent with solid tumor chemotherapy guidelines used by the COG.[122]

Although there are variations in practice, echocardiograms are often obtained as part of routine monitoring at baseline and after cumulative doxorubicin doses of 150, 300, 375, and 450 mg/m^2. After completion of therapy for childhood sarcomas, ongoing monitoring for late cardiac complications is guided by risk factors. Long-term follow-up

guidelines recommend cardiac surveillance at intervals based on the cumulative anthracycline and radiation doses with potential impact to the heart.[108] Further studies of the role and timing of specific interventions for modifiable risk factors in childhood cancer survivors are warranted, given the association with increased risk for major cardiac events.[53]

SURVIVORSHIP: LIFE AFTER TREATMENT FOR SARCOMA

With improved screening, diagnosis, and treatments, an increasing number of sarcoma patients are being cured of their disease, joining the more than 20 million cancer survivors estimated to be living in the United States by the year 2030.[123] The 5-year survival across all patients with sarcomas is approximately 60% to 80%, but there is notable variation based on factors including histologic subtype, resectability, and stage.[124,125] Cancer survivors are at risk for various long-term health issues related to their treatments. Long-term and/or delayed cardiotoxicity from anthracycline exposure can have significant impact on the morbidity and mortality of cancer survivors. As previously suggested, multiple epidemiological studies of adult survivors of pediatric cancers exposed to anthracyclines have demonstrated increased rates of heart failure when compared with non-control patients.[126,127] Given these data, it is essential to continue to monitor cancer survivors, manage risk factors, and treat symptoms should they develop.

From initial sarcoma diagnosis to survivorship, a multidisciplinary approach involving cardio-oncology providers should be adopted to minimize cardiotoxicity and ensure long-term cardiovascular health.[128] The International Cardio-Oncology Society (IC-OS) and the Heart Failure Association of the European Society of Cardiology published pro forma categorizing patients as low, intermediate, and high risk for cardiotoxicity, and provided recommendations for monitoring and surveillance.[129] These were subsequently endorsed and included in the ESC cardio-oncology guidelines.[55]

Sarcoma survivors exposed to anthracyclines should be referred to a comprehensive survivorship clinic that includes cardio-oncology evaluations. For patients deemed to be at moderate or high risk for cardiac dysfunction, it is essential to pursue intensive control of risk factors including BP, lipid, and diabetes management. Long-term echocardiographic surveillance remains controversial. The ESC guidelines recommend echocardiograms every 2 to 5 years for patients categorized as at least moderate risk, though the duration of surveillance has not been addressed nor evaluated. Moreover, the clinical benefits and cost-effectiveness of this approach remain uncertain.[55]

CONCLUSIONS

Although the landscape of sarcomas is becoming clearer through scientific advancement, this heterogenous group of cancers remains difficult to study and treat. PCSs and tumors involving the great vessels pose challenges in management, which is reflected in the poorer prognosis of these tumors compared with other sites of sarcoma. However, multimodality therapy appears to be associated with the best outcomes in these complex patients, based on retrospective data. Even in sarcomas that do not physically involve the heart, cardiotoxicity must be considered throughout the course of a patient's treatment and into survivorship because of the near-universal use of high doses of anthracyclines. Other cytotoxic therapies contribute minimally to cardiac dysfunction, but TKIs and immunotherapies have unique cardiovascular side effect profiles that must be considered. In particular, the onset of hypertension (TKIs) and myocarditis (ICIs) must be closely monitored in the clinical setting to allow for early intervention. The community must be vigilant, especially in pediatric populations and those predisposed to cardiac disease due to comorbidities, and long-term monitoring is recommended.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

Dr Nassif Haddad was supported by the National Cancer Institute of the National Institutes of Health under Award Numbers P50CA272170, P30CA016672, and 5K12CA088084. Dr Crane is supported by funding from an Alex's Lemonade Stand Fund Center of Excellence in Childhood Cancer Drug Development grant. Dr Lefler has received honoraria for serving on advisory boards for Aadi Bioscience and SpringWorks Therapeutics; and for consulting for Physicians' Education Resource. Dr Nassif Haddad has received grant funding from Robert Winn Career Development Award 2024 and the BMS foundation; and honoraria from SpringWorks Therapeutics, Elsevier, and Sonata Therapeutics. Dr Nohria has received consulting fees from AstraZeneca and Takeda Oncology; and research support from Bristol Myers Squibb. Dr Agulnik has received consulting fees from Aadi Bioscience, Boehringer Ingelheim, and Deciphera; and research funding from Exelixis. Dr Fradley has received research funding from AstraZeneca; and honoraria from AstraZeneca, Janssen, Pfizer, and SpringWorks Therapeutics. Dr Crane has reported that she has no relationships relevant to the contents of this paper to disclose.

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REFERENCES

1. von Mehren M, Kane JM, Agulnik M, et al. Soft Tissue Sarcoma, Version 2.2022, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw*. 2022;20(7):815–833. https://doi.org/10.6004/jnccn.2022.0035

2. Grünewald TG, Alonso M, Avnet S, et al. Sarcoma treatment in the era of molecular medicine. *EMBO Mol Med*. 2020;12(11):e11131. https://doi.org/10.15252/emmm.201911131

3. Yang J, Lou S, Yao T. Trends in primary malignant bone cancer incidence and mortality in the United States, 2000–2017: a population-based study. *J Bone Oncol*. 2024;46:100607. https://doi.org/10.1016/j.jbo.2024.100607

4. Biermann JS, Hirbe A, Ahlawat S, et al. Bone Cancer, Version 2.2025, NCCN Clinical Practice Guidelines In Oncology. *J Natl Compr Canc Netw*. 2025;23(4):e250017. https://doi.org/10.6004/jnccn.2025.0017

5. Schaefer IM, Cote GM, Hornick JL. Contemporary sarcoma diagnosis, genetics, and genomics. *J Clin Oncol*. 2018;36(2):101–110. https://doi.org/10.1200/jco.2017.74.9374

6. Pollack SM, Ingham M, Spraker MB, Schwartz GK. Emerging targeted and immune-based therapies in sarcoma. *J Clin Oncol*. 2018;36(2):125–135. https://doi.org/10.1200/jco.2017.75.1610

7. Pautier P, Italiano A, Piperno-Neumann S, et al. Doxorubicin-trabectedin with trabectedin maintenance in leiomyosarcoma. *N Engl J Med*. 2024;391(9):789–799. https://doi.org/10.1056/NEJMoa2403394

8. D'Ambrosio L, Touati N, Blay JY, et al. Doxorubicin plus dacarbazine, doxorubicin plus ifosfamide, or doxorubicin alone as a first-line treatment for advanced leiomyosarcoma: a propensity score matching analysis from the European Organization for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group. *Cancer*. 2020;126(11):2637–2647. https://doi.org/10.1002/cncr.32795

9. Al Shihabi A, Tebon PJ, Nguyen HTL, et al. The landscape of drug sensitivity and resistance in sarcoma. *Cell Stem Cell*. 2024/10/03/ 2024;31(10):1524–1542.e4. https://doi.org/10.1016/j.stem.2024.08.010

10. D'Angelo SP, Araujo DM, Abdul Razak AR, et al. Afamitresgene autoleucel for advanced synovial sarcoma and myxoid round cell liposarcoma (SPEARHEAD-1): an international, open-label, phase 2 trial. *Lancet*. 2024;403(10435):1460–1471. https://doi.org/10.1016/s0140-6736(24)00319-2

11. Siontis BL, Leja M, Chugh R. Current clinical management of primary cardiac sarcoma. *Expert Rev Anticancer Ther*. 2020;20(1):45–51. https://doi.org/10.1080/14737140.2020.1711738

12. Tyebally S, Chen D, Bhattacharyya S, et al. Cardiac tumors: JACC CardioOncology state-of-the-art review. *JACC CardioOncol*. 2020;2(2):293–311. https://doi.org/10.1016/j.jaccao.2020.05.009

13. Antwi-Amoabeng D, Meghji Z, Thakkar S, et al. Survival differences in men and women with primary malignant cardiac tumor: an analysis using the Surveillance, Epidemiology and End Results (SEER) database from 1973 to 2015. *J Am Heart Assoc*. 2020;9(10):e014846. https://doi.org/10.1161/jaha.119.014846

14. Yin K, Luo R, Wei Y, et al. Survival outcomes in patients with primary cardiac sarcoma in the United States. *J Thorac Cardiovasc Surg*. 2021;162(1):107–115.e2. https://doi.org/10.1016/j.jtcvs.2019.12.109

15. Chan EY, Ali A, Zubair MM, et al. Primary cardiac sarcomas: treatment strategies. *J Thorac Cardiovasc Surg*. 2023;166(3):828–838.e2. https://doi.org/10.1016/j.jtcvs.2021.10.070

16. Burke AP, Virmani R. Sarcomas of the great vessels. a clinicopathologic study. *Cancer*. 1993;71(5):1761–1773. https://doi.org/10.1002/1097-0142(19930301)71:5<1761::aid-cncr2820710510>3.0.co;2-7

17. Stergioula A, Kokkali S, Pantelis E. Multimodality treatment of primary cardiac angiosarcoma: a systematic literature review. *Cancer Treat Rev*. 2023;120:102617. https://doi.org/10.1016/j.ctrv.2023.102617

18. Siontis BL, Zhao L, Leja M, et al. Primary cardiac sarcoma: a rare, aggressive malignancy with a high propensity for brain metastases. *Sarcoma*. 2019;2019:1960593. https://doi.org/10.1155/2019/1960593

19. Blackmon SH, Reardon MJ. Surgical treatment of primary cardiac sarcomas. *Tex Heart Inst J*. 2009;36(5):451–452.

20. Blackmon SH, Reardon MJ. Pulmonary artery sarcoma. *Methodist Debakey Cardiovasc J*. 2010;6(3):38–43. https://doi.org/10.14797/mdcj-6-3-38

21. Blackmon SH, Rice DC, Correa AM, et al. Management of primary pulmonary artery sarcomas. *Ann Thorac Surg*. 2009;87(3):977–984. https://doi.org/10.1016/j.athoracsur.2008.08.018

22. Shafique HS, Commander SJ, Blazer DG 3rd, Kim Y, Southerland KW, Williams ZF. Surgical outcomes of patients with inferior vena cava leiomyosarcoma. *J Vasc Surg Venous Lymphat Disord*. 2024;12(4):101885. https://doi.org/10.1016/j.jvsv.2024.101885

23. Bangolo A, Fwelo P, Iyer KM, et al. Primary cardiac sarcoma: clinical characteristics and prognostic factors over the past 2 decades. *Diseases*. 2023;11(2):74. https://doi.org/10.3390/diseases11020074

24. Butany J, Nair V, Naseemuddin A, Nair GM, Catton C, Yau T. Cardiac tumours: diagnosis and management. *Lancet Oncol*. 2005;6(4):219–228. https://doi.org/10.1016/s1470-2045(05)70093-0

25. Rusthoven CG, Liu AK, Bui MM, et al. Sarcomas of the aorta: a systematic review and pooled analysis of published reports. *Ann Vasc Surg*. 2014;28(2):515–525. https://doi.org/10.1016/j.avsg.2013.07.012

26. Assi T, Kattan J, Rassy E, et al. A comprehensive review on the diagnosis and management of intimal sarcoma of the pulmonary artery. *Crit Rev Oncol Hematol*. 2020;147:102889. https://doi.org/10.1016/j.critrevonc.2020.102889

27. Corradini S, von Bestenbostel R, Romano A, et al. MR-guided stereotactic body radiation therapy for primary cardiac sarcomas. *Radiation Oncol*. 2021;16(1):60. https://doi.org/10.1186/s13014-021-01791-9

28. Penel N, Bui BN, Bay JO, et al. Phase II trial of weekly paclitaxel for unresectable angiosarcoma: the ANGIOTAX Study. *J Clin Oncol*. 2008;26(32):5269–5274. https://doi.org/10.1200/jco.2008.17.3146

29. Nassar AH, El-Am E, Denu R, et al. Clinical outcomes among immunotherapy-treated patients with primary cardiac soft tissue sarcomas: a multicenter retrospective study. *JACC CardioOncol*. 2024;6(1):71–79. https://doi.org/10.1016/j.jaccao.2023.11.007

30. Diamond MS. Immune checkpoint inhibitors in cardiac sarcoma: reason to take heart? *JACC CardioOncol*. 2024;6(1):80–82. https://doi.org/10.1016/j.jaccao.2024.01.002

31. O'Bryan RM, Baker LH, Gottlieb JE, et al. Dose response evaluation of adriamycin in human neoplasia. *Cancer*. 1977;39(5):1940–1948. https://doi.org/10.1002/1097-0142(197705)39:5<1940::aid-cncr2820390505>3.0.co;2-0

32. El-Kareh AW, Secomb TW. Two-mechanism peak concentration model for cellular pharmacodynamics of doxorubicin. *Neoplasia*. 2005;7(7):705–713. https://doi.org/10.1593/neo.05118

33. Judson I, Verweij J, Gelderblom H, et al. 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(4):415–423. https://doi.org/10.1016/s1470-2045(14)70063-4

34. Tap WD, Papai Z, Van Tine BA, et al. Doxorubicin plus evofosfamide versus doxorubicin alone in locally advanced, unresectable or metastatic soft-tissue sarcoma (TH CR-406/SARC021): an international, multicentre, open-label, randomised phase 3 trial. *Lancet Oncol*. 2017;18(8):1089–1103. https://doi.org/10.1016/s1470-2045(17)30381-9

35. Tian Z, Yao W. Chemotherapeutic drugs for soft tissue sarcomas: a review. *Front Pharmacol*. 2023;14:1199292. https://doi.org/10.3389/fphar.2023.1199292

36. Gronchi A, Miah AB, Dei Tos AP, et al. Soft tissue and visceral sarcomas: ESMO-EURACAN-GENTURIS Clinical Practice Guidelines for diagnosis, treatment and follow-up(☆). *Ann Oncol*. 2021;32(11):1348–1365. https://doi.org/10.1016/j.annonc.2021.07.006

37. 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(3):573–581. https://doi.org/10.1002/cncr.23592

38. Pasquali S, Palmerini E, Quagliuolo V, et al. Neoadjuvant chemotherapy in high-risk soft tissue sarcomas: a Sarculator-based risk stratification analysis of the ISG-STS 1001 randomized trial. *Cancer*. 2022;128(1):85–93. https://doi.org/10.1002/cncr.33895

39. 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(12):2425–2432. https://doi.org/10.1093/annonc/mdu460

40. Gronchi A, Palmerini E, Quagliuolo V, et al. Neoadjuvant chemotherapy in high-risk soft tissue sarcomas: final results of a randomized trial from Italian (ISG), Spanish (GEIS), French (FSG), and Polish (PSG) Sarcoma Groups. *J Clin Oncol*. 2020;38(19):2178–2186. https://doi.org/10.1200/jco.19.03289

41. Marina NM, Smeland S, Bielack SS, et al. Comparison of MAPIE versus MAP in patients with a poor response to preoperative chemotherapy for newly diagnosed high-grade osteosarcoma (EURAMOS-1): an open-label, international, randomised controlled trial. *Lancet Oncol*. 2016;17(10):1396–1408. https://doi.org/10.1016/s1470-2045(16)30214-5

42. Whelan JS, Bielack SS, Marina N, et al. EURAMOS-1, an international randomised study for osteosarcoma: results from pre-randomisation treatment. *Ann Oncol*. 2015;26(2):407–414. https://doi.org/10.1093/annonc/mdu526

43. Smeland S, Bielack SS, Whelan J, et al. Survival and prognosis with osteosarcoma: outcomes in more than 2000 patients in the EURAMOS-1 (European and American Osteosarcoma Study) cohort. *Eur J Cancer*. 2019;109:36–50. https://doi.org/10.1016/j.ejca.2018.11.027

44. Brennan B, Kirton L, Marec-Bérard P, et al. Comparison of two chemotherapy regimens in patients with newly diagnosed Ewing sarcoma (EE2012): an open-label, randomised, phase 3 trial. *Lancet*. 2022;400(10362):1513–1521. https://doi.org/10.1016/s0140-6736(22)01790-1

45. Ladenstein R, Pötschger U, Le Deley MC, et al. Primary disseminated multifocal Ewing sarcoma: results of the Euro-EWING 99 trial. *J Clin Oncol*. 2010;28(20):3284–3291. https://doi.org/10.1200/jco.2009.22.9864

46. Cash T, Krailo MD, Buxton AB, et al. Long-term outcomes in patients with localized Ewing sarcoma treated with interval-compressed chemotherapy on Children's Oncology Group Study AEWS0031. *J Clin Oncol*. 2023;41(30):4724–4728. https://doi.org/10.1200/jco.23.00053

47. Jones RL, Wagner AJ, Kawai A, et al. Prospective evaluation of doxorubicin cardiotoxicity in patients with advanced soft-tissue sarcoma treated in the ANNOUNCE Phase III randomized trial. *Clin Cancer Res*. 2021;27(14):3861–3866. https://doi.org/10.1158/1078-0432.Ccr-20-4592

48. Tian Z, Yang Y, Yang Y, et al. High cumulative doxorubicin dose for advanced soft tissue sarcoma. *BMC Cancer*. 2020;20(1):1139. https://doi.org/10.1186/s12885-020-07663-x

49. Schuler MK, Gerdes S, West A, et al. Efficacy and safety of Dexrazoxane (DRZ) in sarcoma patients receiving high cumulative doses of anthracycline therapy - a retrospective study including 32 patients. *BMC Cancer*. 2016;16:619. https://doi.org/10.1186/s12885-016-2654-x

50. Camilli M, Cipolla CM, Dent S, Minotti G, Cardinale DM. Anthracycline cardiotoxicity in adult cancer patients: JACC: CardioOncology state-of-the-art review. *JACC CardioOncol*. 2024;6(5):655–677. https://doi.org/10.1016/j.jaccao.2024.07.016

51. Fradley MG, Beckie TM, Brown SA, et al. Recognition, prevention, and management of arrhythmias and autonomic disorders in cardio-oncology: a scientific statement from the American Heart Association. *Circulation*. 2021;144(3):e41–e55. https://doi.org/10.1161/cir.0000000000000986

52. Mulrooney DA, Ness KK, Huang S, et al. Pilot study of vascular health in survivors of osteosarcoma. *Pediatr Blood Cancer*. 2013;60(10):1703–1708. https://doi.org/10.1002/pbc.24610

53. Armstrong GT, Oeffinger KC, Chen Y, et al. Modifiable risk factors and major cardiac events among adult survivors of childhood cancer. *J Clin Oncol*. 2013;31(29):3673–3680. https://doi.org/10.1200/jco.2013.49.3205

54. Bosman M, Krüger D, Roth L, et al. Prior exposure to doxorubicin exacerbates atherosclerotic plaque formation in apolipoprotein-E-deficient mice on a high-fat diet. *Atherosclerosis*. 2025;403:119168. https://doi.org/10.1016/j.atherosclerosis.2025.119168

55. Lyon AR, López-Fernández T, Couch LS, et al. 2022 ESC guidelines on cardio-oncology developed in collaboration with the European Hematology Association (EHA), the European Society for Therapeutic Radiology and Oncology (ESTRO) and the International Cardio-Oncology Society (IC-OS). *Eur Heart J*. 2022;43(41):4229–4361. https://doi.org/10.1093/eurheartj/ehac244

56. Cardinale D, Colombo A, Bacchiani G, et al. Early detection of anthracycline cardiotoxicity and improvement with heart failure therapy. *Circulation*. 2015;131(22):1981–1988. https://doi.org/10.1161/circulationaha.114.013777

57. Lotrionte M, Biondi-Zoccai G, Abbate A, et al. Review and meta-analysis of incidence and clinical predictors of anthracycline cardiotoxicity. *Am J Cardiol*. 2013;112(12):1980–1984. https://doi.org/10.1016/j.amjcard.2013.08.026

58. Fabiani I, Chianca M, Cipolla CM, Cardinale DM. Anthracycline-induced cardiomyopathy: risk prediction, prevention and treatment. *Nat Rev Cardiol*. 2025;22(8):551–563. https://doi.org/10.1038/s41569-025-01126-1

59. Zhang S, Liu X, Bawa-Khalfe T, et al. Identification of the molecular basis of doxorubicin-induced cardiotoxicity. *Nat Med*. 2012;18(11):1639–1642. https://doi.org/10.1038/nm.2919

60. Salvatorelli E, Menna P, Chello M, Covino E, Minotti G. Low-dose anthracycline and risk of heart failure in a pharmacokinetic model of human myocardium exposure: analog specificity and role of secondary alcohol metabolites. *J Pharmacol Exp Ther*. 2018;364(2):323–331. https://doi.org/10.1124/jpet.117.246140

61. Sawicki KT, De Jesus A, Ardehali H. Iron metabolism in cardiovascular disease: physiology, mechanisms, and therapeutic targets. *Circ Res*. 2023;132(3):379–396. https://doi.org/10.1161/circresaha.122.321667

62. Boen HM, Cherubin M, Franssen C, et al. Circulating microRNA as biomarkers of anthracycline-induced cardiotoxicity: JACC: CardioOncology state-of-the-art review. *JACC CardioOncol*. 2024;6(2):183–199. https://doi.org/10.1016/j.jaccao.2023.12.009

63. Zhao P, Li Y, Xu X, et al. Neutrophil extracellular traps mediate cardiomyocyte ferroptosis via the Hippo-Yap pathway to exacerbate doxorubicin-induced cardiotoxicity. *Cell Mol Life Sci*. 2024;81(1):122. https://doi.org/10.1007/s00018-024-05169-4

64. Bhagat A, Shrestha P, Jeyabal P, Peng Z, Watowich SS, Kleinerman ES. Doxorubicin-induced cardiotoxicity is mediated by neutrophils through release of neutrophil elastase. *Front Oncol*. 2022;12:947604. https://doi.org/10.3389/fonc.2022.947604

65. Vitfell-Rasmussen J, Krarup-Hansen A, Vaage-Nilsen M, Kümler T, Zerahn B. Real-life incidence of cardiotoxicity and associated risk factors in sarcoma patients receiving doxorubicin. *Acta Oncol*. 2022;61(7):801–808. https://doi.org/10.1080/0284186x.2022.2082884

66. Tap WD, Wagner AJ, Schöffski P, et al. Effect of doxorubicin plus olaratumab vs doxorubicin plus placebo on survival in patients with advanced soft tissue sarcomas: the ANNOUNCE randomized clinical trial. *JAMA*. 2020;323(13):1266–1276. https://doi.org/10.1001/jama.2020.1707

67. Cranmer LD, Hess LM, Sugihara T, Muntz HG. Cardiac events among patients with sarcoma treated with doxorubicin by method of infusion: a real-world database study. *Cancer Rep (Hoboken)*. 2023;6(1):e1681. https://doi.org/10.1002/cnr2.1681

68. Shamai S, Rozenbaum Z, Merimsky O, et al. Cardio-toxicity among patients with sarcoma: a cardio-oncology registry. *BMC Cancer*. 2020;20(1):609. https://doi.org/10.1186/s12885-020-07104-9

69. Mulrooney DA, Yeazel MW, Kawashima T, et al. Cardiac outcomes in a cohort of adult survivors of childhood and adolescent cancer: retrospective analysis of the Childhood Cancer Survivor Study cohort. *BMJ*. 2009;339:b4606. https://doi.org/10.1136/bmj.b4606

70. van Dalen EC, van der Pal HJ, Kremer LC. Different dosage schedules for reducing cardiotoxicity in people with cancer receiving anthracycline chemotherapy. *Cochrane Database Syst Rev*. 2016;3(3):Cd005008. https://doi.org/10.1002/14651858.CD005008.pub4

71. Berrak SG, Ewer MS, Jaffe N, et al. Doxorubicin cardiotoxicity in children: reduced incidence of cardiac dysfunction associated with continuous-infusion schedules. *Oncol Rep*. 2001;8(3):611–614. https://doi.org/10.3892/or.8.3.611

72. Casper ES, Gaynor JJ, Hajdu SI, et al. A prospective randomized trial of adjuvant chemotherapy with bolus versus continuous infusion of doxorubicin in patients with high-grade extremity soft tissue sarcoma and an analysis of prognostic factors. *Cancer*. 1991;68(6):1221–1229. https://doi.org/10.1002/1097-0142(19910915)68:6<1221::aid-cncr2820680607>3.0.co;2-r

73. Zalupski M, Metch B, Balcerzak S, et al. Phase III comparison of doxorubicin and dacarbazine given by bolus versus infusion in patients with soft-tissue sarcomas: a Southwest Oncology Group study. *J Natl Cancer Inst*. 1991;83(13):926–932. https://doi.org/10.1093/jnci/83.13.926

74. de Baat EC, Mulder RL, Armenian S, et al. Dexrazoxane for preventing or reducing cardiotoxicity in adults and children with cancer receiving anthracyclines. *Cochrane Database Syst Rev*. 2022;9(9):Cd014638. https://doi.org/10.1002/14651858.CD014638.pub2

75. Upshaw JN, Parson SK, Buchsbaum RJ, et al. Dexrazoxane to prevent cardiotoxicity in adults treated with anthracyclines: JACC: CardioOncology controversies in cardio-oncology. *JACC CardioOncol*. 2024;6(2):322–324. https://doi.org/10.1016/j.jaccao.2024.02.004

76. Van Tine BA, Hirbe AC, Oppelt P, et al. Interim analysis of the phase ii study: noninferiority study of doxorubicin with upfront dexrazoxane plus olaratumab for advanced or metastatic soft-tissue sarcoma. *Clin Cancer Res*. 2021;27(14):3854–3860. https://doi.org/10.1158/1078-0432.Ccr-20-4621

77. Schwartz CL, Wexler LH, Krailo MD, et al. Intensified chemotherapy with dexrazoxane cardioprotection in newly diagnosed nonmetastatic osteosarcoma: a report from the Children's Oncology Group. *Pediatr Blood Cancer*. 2016;63(1):54–61. https://doi.org/10.1002/pbc.25753

78. Benjamin RS, Minotti G. Doxorubicin-dexrazoxane from day 1 for soft-tissue sarcomas: the road to cardioprotection. *Clin Cancer Res*. 2021;27(14):3809–3811. https://doi.org/10.1158/1078-0432.Ccr-21-1376

79. Mo Z, Deng Y, Bao Y, Liu J, Jiang Y. Evaluation of cardiotoxicity of anthracycline-containing chemotherapy regimens in patients with bone and soft tissue sarcomas: a study of the FDA adverse event reporting system joint single-center real-world experience. *Cancer Med*. 2023;12(24):21709–21724. https://doi.org/10.1002/cam4.6730

80. Chidiac T, Budd GT, Pelley R, et al. Phase II trial of liposomal doxorubicin (Doxil) in advanced soft tissue sarcomas. *Invest New Drugs*. 2000;18(3):253–259. https://doi.org/10.1023/a:1006429907449

81. Skubitz KM. Phase II trial of pegylated-liposomal doxorubicin (Doxil) in sarcoma. *Cancer Invest*. 2003;21(2):167–176. https://doi.org/10.1081/cnv-120016412

82. Alhaja M, Chen S, Chin AC, Schulte B, Legasto CS. Cardiac safety of pegylated liposomal doxorubicin after conventional doxorubicin exposure in patients with sarcoma and breast cancer. *Cureus*. Sep 2023;15(9):e44837. https://doi.org/10.7759/cureus.44837

83. Bhasin V, Vakilpour A, Scherrer-Crosbie M. Statins for the primary prevention of anthracycline cardiotoxicity: a comprehensive review. *Curr Oncol Rep*. 2024;26(10):1197–1204. https://doi.org/10.1007/s11912-024-01579-6

84. Wilson RL, Christopher CN, Yang EH, et al. Incorporating exercise training into cardio-oncology care: current evidence and opportunities: JACC: CardioOncology state-of-the-art review. *JACC CardioOncol*. 2023;5(5):553–569. https://doi.org/10.1016/j.jaccao.2023.08.008

85. Wang F, Chandra J, Kleinerman ES. Exercise intervention decreases acute and late doxorubicin-induced cardiotoxicity. *Cancer Med*. 2021;10(21):7572–7584. https://doi.org/10.1002/cam4.4283

86. Omland T, Heck SL, Gulati G. The role of cardioprotection in cancer therapy cardiotoxicity: JACC: CardioOncology state-of-the-art review. *JACC CardioOncol*. 2022;4(1):19–37. https://doi.org/10.1016/j.jaccao.2022.01.101

87. van der Graaf WT, Blay JY, Chawla SP, et al. Pazopanib for metastatic soft-tissue sarcoma (PALETTE): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet*. 2012;379(9829):1879–1886. https://doi.org/10.1016/s0140-6736(12)60651-5

88. Kumar R, Knick VB, Rudolph SK, et al. Pharmacokinetic-pharmacodynamic correlation from mouse to human with pazopanib, a multikinase angiogenesis inhibitor with potent antitumor and antiangiogenic activity. *Mol Cancer Ther*. 2007;6(7):2012–2021. https://doi.org/10.1158/1535-7163.Mct-07-0193

89. Force T, Krause DS, Van Etten RA. Molecular mechanisms of cardiotoxicity of tyrosine kinase inhibition. *Nat Rev Cancer*. 2007;7(5):332–344. https://doi.org/10.1038/nrc2106

90. Shyam Sunder S, Sharma UC, Pokharel S. Adverse effects of tyrosine kinase inhibitors in cancer therapy: pathophysiology, mechanisms and clinical management. *Signal Transduct Target Ther*. 2023;8(1):262. https://doi.org/10.1038/s41392-023-01469-6

91. Karaağaç M, Eryılmaz MK. Pazopanib-induced fatal heart failure in a patient with unresectable soft tissue sarcoma and review of literature. *J Oncol Pharm Pract*. 2020;26(3):768–774. https://doi.org/10.1177/1078155219875797

92. Italiano A, Mir O, Mathoulin-Pelissier S, et al. Cabozantinib in patients with advanced Ewing sarcoma or osteosarcoma (CABONE): a multicentre, single-arm, phase 2 trial. *Lancet Oncol*. 2020;21(3):446–455. https://doi.org/10.1016/s1470-2045(19)30825-3

93. Schöffski P, Blay JY, Ray-Coquard I. Cabozantinib as an emerging treatment for sarcoma. *Curr Opin Oncol*. 2020;32(4):321–331. https://doi.org/10.1097/cco.0000000000000644

94. Iacovelli R, Ciccarese C, Fornarini G, et al. Cabozantinib-related cardiotoxicity: a prospective analysis in a real-world cohort of metastatic renal cell carcinoma patients. *Br J Clin Pharmacol*. 2019;85(6):1283–1289. https://doi.org/10.1111/bcp.13895

95. Joensuu H, Eriksson M, Sundby Hall K, et al. One vs three years of adjuvant imatinib for operable gastrointestinal stromal tumor: a randomized trial. *JAMA*. 2012;307(12):1265–1272. https://doi.org/10.1001/jama.2012.347

96. Raut CP, Espat NJ, Maki RG, et al. Efficacy and tolerability of 5-year adjuvant imatinib treatment for patients with resected intermediate- or high-risk primary gastrointestinal stromal tumor: the PERSIST-5 clinical trial. *JAMA Oncol*. 2018;4(12):e184060. https://doi.org/10.1001/jamaoncol.2018.4060

97. Richards CJ, Je Y, Schutz FA, et al. Incidence and risk of congestive heart failure in patients with renal and nonrenal cell carcinoma treated with sunitinib. *J Clin Oncol*. 2011;29(25):3450–3456. https://doi.org/10.1200/jco.2010.34.4309

98. Demetri GD, Reichardt P, Kang YK, et al. Efficacy and safety of regorafenib for advanced gastrointestinal stromal tumours after failure of imatinib and sunitinib (GRID): an international, multicentre, randomised, placebo-controlled, phase 3 trial. *Lancet*. 2013;381(9863):295–302. https://doi.org/10.1016/s0140-6736(12)61857-1

99. Blay JY, Serrano C, Heinrich MC, et al. Ripretinib in patients with advanced gastrointestinal stromal tumours (INVICTUS): a double-blind, randomised, placebo-controlled, phase 3 trial. *Lancet Oncol*. 2020;21(7):923–934. https://doi.org/10.1016/s1470-2045(20)30168-6

100. Heinrich MC, Jones RL, von Mehren M, et al. Avapritinib in advanced PDGFRA D842V-mutant gastrointestinal stromal tumour (NAVIGATOR): a multicentre, open-label, phase 1 trial. *Lancet Oncol*. 2020;21(7):935–946. https://doi.org/10.1016/s1470-2045(20)30269-2

101. Demetri GD, von Mehren M, Jones RL, et al. Efficacy and safety of trabectedin or dacarbazine for metastatic liposarcoma or leiomyosarcoma after failure of conventional chemotherapy: results of a phase III randomized multicenter clinical trial. *J Clin Oncol*. 2016;34(8):786–793. https://doi.org/10.1200/jco.2015.62.4734

102. Grünwald V, Pink D, Egerer G, et al. Trabectedin for patients with advanced soft tissue sarcoma: a non-interventional, prospective, multicenter, phase IV trial. *Cancers (Basel)*. 2022;14(21):5234. https://doi.org/10.3390/cancers14215234

103. Jones RL, Herzog TJ, Patel SR, et al. Cardiac safety of trabectedin monotherapy or in combination with pegylated liposomal doxorubicin in patients with sarcomas and ovarian cancer. *Cancer Med*. 2021;10(11):3565–3574. https://doi.org/10.1002/cam4.3903

104. Hilmi M, Ederhy S, Waintraub X, et al. Cardiotoxicity associated with gemcitabine: literature review and a pharmacovigilance study. *Pharmaceuticals (Basel)*. 2020;13(10):325. https://doi.org/10.3390/ph13100325

105. Tawbi HA, Burgess M, Bolejack V, et al. Pembrolizumab in advanced soft-tissue sarcoma and bone sarcoma (SARC028): a multicentre, two-cohort, single-arm, open-label, phase 2 trial. *Lancet Oncol*. 2017;18(11):1493–1501. https://doi.org/10.1016/s1470-2045(17)30624-1

106. Mowery YM, Ballman KV, Hong AM, et al. Safety and efficacy of pembrolizumab, radiation therapy, and surgery versus radiation therapy and

surgery for stage III soft tissue sarcoma of the extremity (SU2C-SARC032): an open-label, randomised clinical trial. *Lancet*. 2024;404(10467):2053–2064. https://doi.org/10.1016/s0140-6736(24)01812-9

107. Dolladille C, Akroun J, Morice PM, et al. Cardiovascular immunotoxicities associated with immune checkpoint inhibitors: a safety meta-analysis. *Eur Heart J*. 2021;42(48):4964–4977. https://doi.org/10.1093/eurheartj/ehab618

108. Ehrhardt MJ, Leerink JM, Mulder RL, et al. Systematic review and updated recommendations for cardiomyopathy surveillance for survivors of childhood, adolescent, and young adult cancer from the International Late Effects of Childhood Cancer Guideline Harmonization Group. *Lancet Oncol*. 2023;24(3):e108–e120. https://doi.org/10.1016/s1470-2045(23)00012-8

109. Desai MY, Windecker S, Lancellotti P, et al. Prevention, diagnosis, and management of radiation-associated cardiac disease: JACC scientific expert panel. *J Am Coll Cardiol*. 2019;74(7):905–927. https://doi.org/10.1016/j.jacc.2019.07.006

110. Gurney JG, Young JG, Roffers SD, Smith MA, Bunin GR. Soft tissue sarcomas. In: Ries LAG, Smith MA, Gurney JG, eds. *Cancer Incidence and Survival among Children and Adolescents: United States SEER Program 1975–1995. NIH Pub No 99-4649*. National Cancer Institute, SEER Program; 1999:111–124.

111. Orlandi A, Ferlosio A, Roselli M, Chiariello L, Spagnoli LG. Cardiac sarcomas: an update. *J Thorac Oncol*. 2010;5(9):1483–1489. https://doi.org/10.1097/JTO.0b013e3181e59a91

112. Reed DR, Hayashi M, Wagner L, et al. Treatment pathway of bone sarcoma in children, adolescents, and young adults. *Cancer*. 2017;123(12):2206–2218. https://doi.org/10.1002/cncr.30589

113. Ferrari A, Orbach D, Sparber-Sauer M, et al. The treatment approach to pediatric non-rhabdomyosarcoma soft tissue sarcomas: a critical review from the INternational Soft Tissue SaRcoma ConsorTium. *Eur J Cancer*. 2022;169:10–19. https://doi.org/10.1016/j.ejca.2022.03.028

114. Ferrari A, Brennan B, Casanova M, et al. Pediatric non-rhabdomyosarcoma soft tissue sarcomas: standard of care and treatment recommendations from the European Paediatric Soft Tissue Sarcoma Study Group (EpSSG). *Cancer Manag Res*. 2022;14:2885–2902. https://doi.org/10.2147/cmar.S368381

115. Skapek SX, Ferrari A, Gupta AA, et al. Rhabdomyosarcoma. *Nat Rev Dis Primers*. 2019;5(1):1. https://doi.org/10.1038/s41572-018-0051-2

116. Petrykey K, Chen Y, Neupane A, et al. Predicting the 10-year risk of cardiomyopathy in long-term survivors of childhood cancer. *Ann Oncol*. 2025;36(10):1203–1211. https://doi.org/10.1016/j.annonc.2025.05.539

117. Dixon SB, Liu Q, Chow EJ, et al. Specific causes of excess late mortality and association with modifiable risk factors among survivors of childhood cancer: a report from the Childhood Cancer Survivor Study cohort. *Lancet*. 2023;401(10386):1447–1457. https://doi.org/10.1016/s0140-6736(22)02471-0

118. Chow EJ, Chen Y, Kremer LC, et al. Individual prediction of heart failure among childhood cancer survivors. *J Clin Oncol*. 2015;33(5):394–402. https://doi.org/10.1200/jco.2014.56.1373

119. Balis FM, Womer RB, Berg S, Winick N, Adamson PC, Fox E. Dosing anticancer drugs in infants: current approach and recommendations from the Children's Oncology Group's Chemotherapy Standardization Task Force. *Pediatr Blood Cancer*. 2017;64(11):e26636. https://doi.org/10.1002/pbc.26636

120. Vejpongsa P, Yeh ET. Prevention of anthracycline-induced cardiotoxicity: challenges and opportunities. *J Am Coll Cardiol*. 2014;64(9):938–945. https://doi.org/10.1016/j.jacc.2014.06.1167

121. Chow EJ, Aplenc R, Vrooman LM, et al. Late health outcomes after dexrazoxane treatment: a report from the Children's Oncology Group. *Cancer*. Feb 15 2022;128(4):788–796. https://doi.org/10.1002/cncr.33974

122. de Baat EC, van Dalen EC, Mulder RL, et al. Primary cardioprotection with dexrazoxane in patients with childhood cancer who are expected to receive anthracyclines: recommendations from the International Late Effects of Childhood Cancer Guideline Harmonization Group. *Lancet Child Adolesc Health*. 2022;6(12):885–894. https://doi.org/10.1016/s2352-4642(22)00239-5

123. Siegel RL, Giaquinto AN, Jemal A. Cancer statistics, 2024. *CA Cancer J Clin*. 2024;74(1):12–49. https://doi.org/10.3322/caac.21820

124. Spunt SL, Million L, Chi YY, et al. A risk-based treatment strategy for non-rhabdomyosarcoma soft-tissue sarcomas in patients younger than 30 years (ARST0332): a Children's Oncology Group prospective study. *Lancet Oncol*. 2020;21(1):145–161. https://doi.org/10.1016/s1470-2045(19)30672-2

125. Stiller CA, Botta L, Brewster DH, et al. Survival of adults with cancers of bone or soft tissue in Europe-Report from the EUROCARE-5 study. *Cancer Epidemiol*. 2018;56:146–153. https://doi.org/10.1016/j.canep.2018.08.010

126. Becktell K, Chen Y, Yasui Y, et al. Long-term outcomes among survivors of childhood osteosarcoma: a report from the Childhood Cancer Survivor Study (CCSS). *Pediatr Blood Cancer*. 2024;71(10):e31189. https://doi.org/10.1002/pbc.31189

127. Armstrong GT, Chen Y, Yasui Y, et al. Reduction in late mortality among 5-year survivors of childhood cancer. *N Engl J Med*. 2016;374(9):833–842. https://doi.org/10.1056/NEJMoa1510795

128. Fradley MG, Wilcox N, Frain I, et al. Developing a clinical cardio-oncology program and the building blocks for success: JACC: CardioOncology how to. *JACC CardioOncol*. 2023;5(5):707–710. https://doi.org/10.1016/j.jaccao.2023.06.002

129. Lyon AR, Dent S, Stanway S, et al. Baseline cardiovascular risk assessment in cancer patients scheduled to receive cardiotoxic cancer therapies: a position statement and new risk assessment tools from the Cardio-Oncology Study Group of the Heart Failure Association of the European Society of Cardiology in collaboration with the International Cardio-Oncology Society. *Eur J Heart Fail*. 2020;22(11):1945–1960. https://doi.org/10.1002/ejhf.1920

KEY WORDS **anthracyclines, cardiac tumors, chemotherapy complications, primary cardiac sarcoma, pulmonary artery sarcoma, sarcoma, tyrosine kinase inhibitors**