The impact of postoperative therapy on primary cardiac sarcoma

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ABSTRACT

Objective: Primary cardiac sarcomas (PCS) are extremely rare, portend a very poor prognosis, and have limited outcomes data to direct management. This study evaluated the impact of postoperative chemotherapy and/or radiotherapy on survival for PCS.

Methods: A retrospective chart review was conducted of 12 patients diagnosed with and who underwent resection for PCS at a single institution between 2000 and 2016. Data were collected on patient/tumor characteristics and analyzed with respect to treatment and outcome using Kaplan–Meier methods.

Results: Median age was 43 (range 21–73 years) with a 50:50 male-to-female ratio. The most common subtype was angiosarcoma (42%), and 25% presented with distant metastases (DMs). The initial treatment modality for all patients was surgery, with 58% having macroscopically positive (R2) margins. In total, 75% received postoperative chemotherapy and/or radiotherapy. Median progression-free survival (PFS) was 5.9 months, and median overall survival (OS) was 12.0 months. Achieving negative or microscopically positive margins (R0/R1) as compared with R2 resection significantly improved PFS (12.6 vs 2.7 months, $P = .008$) and OS (21.8 vs 7.2 months, $P = .006$). DM at presentation demonstrated a significantly shorter OS (7.0 vs 16.9 months, $P = .04$) and PFS (0.7 vs 7.9 months, $P = .003$) compared with localized disease. Patients given postoperative therapy had longer OS compared with surgery only, but this difference was not statistically significant (15.5 vs 2.6 months, $P = .12$).

Conclusions: Gross total surgical resection can significantly improve PFS and OS in PCS, but DM at diagnosis is an extremely poor prognostic sign. Postoperative therapy should be considered, although this study was likely underpowered to demonstrate a statistically significant benefit. (J Thorac Cardiovasc Surg 2018;156:2194–203)

CT axial image of a primary cardiac sarcoma case before and after trimodality therapy.

Central Message

Gross total resection in patients with primary cardiac sarcoma significantly improves PFS and OS; postoperative therapy should be considered to further improve outcomes.

Perspective

Primary cardiac sarcomas are rare tumors with few survivors at 1 year after diagnosis. There are limited data to guide management, especially in the postoperative setting. This study confirms the key role of gross total resection (R0/R1) in improving survival, with a statistical trend toward further prolongation of survival for those who receive postoperative radiation therapy and/or chemotherapy.

See Editorial Commentary page 2204.

Primary cardiac neoplasms are extremely rare, with an incidence ranging between 0.002% and 0.3%.^{1–4} Twenty-five percent of primary cardiac neoplasms are malignant, of which more than 75% are primary cardiac sarcomas

(PCS). The most common histologic subtypes include angiosarcoma, undifferentiated pleomorphic sarcoma, and leiomyosarcoma, and the tumors most frequently arise in the right atrium.^{5,6}

More than 29% of patients with PCS present with metastatic disease in part due to the location of the primary tumor site, where there is a very high risk of hematogenous dissemination from tumor emboli, but also most tumors

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Scanning this QR code will take you to a supplemental video for the article.

Abbreviations and Acronyms

CT	= computed tomography
DM	= distant metastasis
IORT	= intraoperative radiotherapy
LP	= local progression after R2 resection
LR	= local recurrence after R0/R1 resection
M1	= metastatic
MRI	= magnetic resonance imaging
OS	= overall survival
PCS	= primary cardiac sarcoma
PFS	= progression-free survival
R0	= complete resection with negative margins (no cancer cells at resection margin)
R1	= complete resection with microscopically positive margins (cancer cells at resection margin)
R2	= incomplete resection with macroscopic or gross residual cancer in operative bed
RT	= radiation therapy
STS	= soft-tissue sarcoma

are aggressive, infiltrative, and high grade.⁷⁻¹⁰ In addition, delay in diagnosis is common due to nonspecific clinical presentations including symptoms such as dyspnea, chest pain, arrhythmia, fever, and fatigue. As such, the prognosis of PCS is extremely poor, with reports of median overall survival (OS) of 5.8 to 28.8 months,^{7,11-16} with death attributed largely to locoregional progression of the primary tumor.¹⁷

Complete surgical resection of the primary site is important for potentially curative therapy. If surgery is not possible, fewer than 10% of patients survive at 1 year.⁵ In terms of postoperative therapy with chemotherapy and radiation therapy (RT), limited outcomes data exist to guide management despite the availability of several sizeable studies (95 patients⁷ and 124 patients⁸). Mixed results have been shown, with some data that show a survival benefit^{8,17} whereas others show no benefit.¹⁴ As a result, clinicians rely mainly on case reports and extrapolation from management strategies used for soft-tissue sarcomas (STS) in other sites, such as the extremities, where neoadjuvant chemotherapy and RT improve local control.¹⁴

The objective of this study was to provide more quantitative evidence available for clinicians who treat PCS by reviewing outcomes of patients treated during a 17-year period. The specific goal was to test the hypothesis that there is survival benefit to postoperative therapy for PCS. [Video 1](#) is a video slide show that summarizes the highlights from the manuscript.

THE IMPACT OF POST-OPERATIVE THERAPY ON PRIMARY CARDIAC SARCOMA

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VIDEO 1. Brief video summary of manuscript. Video available at: [https://www.jtcvs.org/article/S0022-5223\(18\)31514-9/fulltext](https://www.jtcvs.org/article/S0022-5223(18)31514-9/fulltext).

METHODS

Patient Selection

The study was approved by the Stanford University Research Compliance Office under protocol 39011. The surgical pathology and radiation treatment planning databases at Stanford Hospital & Clinics were searched to identify all patients who had a pathologic diagnosis of PCS and had undergone surgical resection for PCS from 2000 to 2016. The histologic subtypes in the search included angiosarcoma, liposarcoma, synovial sarcoma, epithelioid hemangioendothelioma, malignant fibrous histiocytoma (also known as undifferentiated pleomorphic sarcoma), malignant solitary fibrous tumor, fibrosarcoma, myxoid fibrosarcoma, rhabdomyosarcoma, and leiomyosarcoma. Patients who had metastatic tumors to the heart or benign cardiac tumors were excluded.

Data Collection

Stanford's institutional electronic medical records system was used to extract the following data from patients' records: demographics, clinical presentation, workup, tumor characteristics (including histologic subtype, grade, location, tumor-node-metastasis stage), treatment modalities and sequencing, response to treatment, and outcomes. All specimens were evaluated by STS pathologists at Stanford. Tumors were graded via the French Federation of Cancer Centers (Fédération Nationale des Centres de Lutte Contre le Cancer) system. Tumor-node-metastasis stage was based on the American Joint Committee on Cancer Seventh edition guidelines for STS. The classification system used to define treatment response was taken from Response Evaluation Criteria in Solid Tumors (RECIST) 1.1.¹⁸ Extent of surgical resection was defined as follows: R0 refers to a complete resection with negative margins; R1 refers to a complete resection with microscopically positive margins; and R2 refers to an incomplete resection with macroscopically positive margins (gross residual cancer in operative bed).

Statistical Analysis

Follow-up was calculated from the date of initial surgery up until the date of death or last follow-up. OS and progression-free survival (PFS) were determined with the Kaplan-Meier method. OS was defined as the time from initial surgery (all patients in this series underwent surgery as their first treatment modality) to death. Patients who were still alive at the time of the study were censored from OS analysis. PFS was defined as the time from initial surgery to the date of imaging evidence of local recurrence after R0/R1 resection (LR), local progression after R2 resection (LP), distant metastasis (DM), or death, whichever came first. LR was defined as new clinical evidence of disease after a period without evidence of disease. LP was defined as new clinical evidence of growth or spread of known disease. The log-rank test was used to compare survival between subgroups stratified by age, sex, stage, tumor size, site, nodal status,

TABLE 1. Patient, tumor, and treatment characteristics and outcomes

Case no./sex/age at diagnosis	Histologic subtype	Tumor site	TNM stage and FNCLCC grade	Resection margin	Surgical procedure
1/F/63	Epithelioid angiosarcoma	RA	IIB: T2bN0M0 G2	R0	En bloc resection of mass with RA, partial IVC/SVC/RV/TV → recon. of neo-RA with pericardium, RV, IVC, SVC, and TVR
2/M/33	Myxoid sarcoma	LA	IIA: T1bN0M0 G3	R1	Piecemeal resection of mass attached to left atrial septum + generation of tissue plane to remove mass from endocardium (appeared uninvolved)
3/F/73	Malignant solitary fibrous tumor	Pericardium	IIB: T2bN0M0 G2	R1	Resection of mass tethered to posterior right pericardium without involvement of other structures
4/M/35	Spindle cell sarcoma	RA	III: T2bN0M0 G3	R1	Piecemeal resection of mass attached by stalk to the atrial septum and patent foramen ovale → PFO closed
5/F/32	Epithelioid angiosarcoma	RA + pericardium	III: T2bN0M0 G3	R1	En bloc resection of mass with RA, TV, and AV groove → TVR
6/F/27	Myxosarcoma	LA	I: T2bN0M0 G1	R2	Resection of mass in posterior LA extending through the atrial septum and impacting the MV and pulmonary veins
7/F/21	Synovial sarcoma	RA	III: T2bN0M0 G3	R2	Piecemeal resection of mass that was adherent to SVC wall + debulking of portion that extended to innominate vein and pulmonary veins → PFO closure + R PA endarterectomy
8/M/45	Synovial sarcoma	Pericardium	III: T2bN0M0 G3	R2	Resected mass attached to the posterior pericardium by a thin stalk
9/F/55	Poorly differentiated angiosarcoma	RA + pericardium	III: T2bN1M0 G3	R2	Subtotal resection of mass along with RA free wall + partial pericardiectomy → recon. of RA free wall
10/M/39	Synovial sarcoma	LA	IV: T2bN0M1 G2 (met in clivus)	R2	En bloc resection of mass with LA dome, interatrial septum and partial RA free wall → recon. of LA dome, interatrial septum, LA and RA walls
11/M/53	Angiosarcoma	RA + pericardium	IV: T2bN0M1 G3	R2	En bloc resection of mass with RA and partial IVC/SVC/RV/TV → recon. of neo-RA + TVR
12/M/38	Angiosarcoma	Pericardium	IV: T2bN1M1 G3 (mets in liver and lung)	R2	Radical pericardiectomy for tumor involving entire surface of heart

TNM, Tumor–node–metastasis; FNCLCC, Fédération Nationale des Centres de Lutte Contre le Cancer (French Federation of Cancer Centers); LR, local recurrence after R0/R1 resection; LP, local progression after R2 resection; DM, distant metastases; F, female; RA, right atrium; R0, negative margin; IVC, inferior vena cava; SVC, superior vena cava; RV, right ventricle; TV, tricuspid valve; →, followed by; recon., reconstruction; TVR, tricuspid valve replacement; Gem-Tax, gemcitabine and docetaxel; Dox, doxorubicin; M, male; LA, left atrium; R1, microscopically positive margin; Dox-Ifos, doxorubicin and ifosfamide; N/A, not available; PFO, patent foramen ovale; CCRT, concurrent chemoradiation therapy; IMRT, intensity-modulated radiotherapy; VMAT, volumetric modulated arc radiotherapy; AV, aortic valve; R2, macroscopically positive margin; MV, mitral valve; IORT, intraoperative radiotherapy; R PA, right pulmonary artery; Ifex, ifosfamide; RT, radiation therapy; CK, CyberKnife; mets, metastases. *Alive at time of study. †RT doses are expressed as follows: “55.8 in 31” = 55.8 Gy in 31 fractions. ‡Case 11 died postoperative day 1 from tumor-related hemorrhage.

TABLE 1. Continued

Postoperative therapy	Response to postoperative therapy	LR, LP, DM (therapy given in response to progression)	Overall survival
Gem-Tax ×5 cycles → pazopanib	Remained in complete remission	DM 12.3 months in pericardium and liver (Dox ×2 cycles → dacarbazine)	21.8 mo
Dox-Ifos ×2 cycles	Remained in complete remission	LR at 48.9 mo (tumor debulking)	52.1 mo
None	N/A	Unknown	16.9 mo
Dox-Ifos ×1 cycle → CCRT (IMRT 45 in 25 [†] and Ifos) → Dox-Ifos ×4 cycles	Remained in complete remission	DM 25.2 months in left clavicular head and manubrium (radical resection → VMAT 45 in 25)	33.8* mo
Gem-Tax ×2 cycles → CCRT (Ifos + VMAT 55.8 in 31) → Gem-Tax	Partial response	Unknown	15.5 mo
None	N/A	LP at 0.7 mo (pericardial resection, pneumonectomy, IORT 7.5 in 1)	2.6 mo
Gem-Tax	Partial response	DM at 7.9 mo in brain (no treatment)	10.0 mo
Dox-Ifos ×6 cycles → CCRT (Ifos + VMAT 43.5 in 29) → Gem-Tax	Partial response	LP at 2.7 mo (tumor debulking and pericardiectomy), LP at 6.8 mo (high-dose Ifex), DM at 9.3 mo in pleura (no treatment)	14.0* mo
RT (IMRT 54 in 30) → Ifos ×4 cycles	Partial response	DM at 2.3 mo in L-spine, sacrum, clivus, skin on back (RT to base of skull)	7.3 mo
RT to clival met (CK 27 in 3), Dox-Ifos ×2 cycles → CCRT (Ifos + IMRT 45 in 25)	Partial response	DM at 0.7 mo in spine (no treatment)	7.2 mo
None	N/A	None	1 d [‡]
Dox-Ifos ×4 cycles → pazopanib	Partial response	DM 5.7 mo in brain (CK 22 in 1)	7.0 mo

histologic subtype, grade, types of treatment modality(ies), and resection margin status. All data were analyzed with SPSS software (version 19; IBM Corp, Armonk, NY) and GraphPad Prism (GraphPad Software, San Diego, Calif). Statistical significance was assumed at $P < .05$.

RESULTS

Patient and Tumor Characteristics

Table 1 summarizes 12 cases of PCS identified in the Stanford database with respect to patient and tumor characteristics. The mean age at diagnosis was 43 years (range 21–73 years). The male-to-female ratio was 50:50. The mean duration from symptom onset to diagnosis was 2.6 months (range 0.6–7.4 months). All patients presented with relatively nonspecific symptoms. The most common presenting symptoms included dyspnea (67%), chest pain (50%), and cough (33%). Other symptoms included left neck pain, back pain, orthopnea, palpitations, presyncope, syncope, dysphagia, poor appetite, unintentional weight loss, fatigue, and fever. All patients had thoracic and/or cardiac imaging. Chest radiographic findings consisted of pleural effusions, pulmonary edema, mediastinal widening, and tracheal deviation. Echocardiogram changes included a cardiac mass, partial mitral inflow/outflow obstruction, mitral/tricuspid regurgitation, left ventricular hypertrophy, dilated left atrium, pericardial effusion, and tamponade physiology. Computed tomography (CT) abnormalities were noted to be a cardiac mass, pericardial effusion, pleural effusion, and tracheal/esophageal deviation. Cardiac magnetic resonance imaging (MRI) demonstrated findings such as a cardiac mass, pericardial effusion, pericardial enhancement, and pleural effusion.

The most common preoperative diagnoses were cardiac myxoma (33% of patients) and intracardiac thrombus (17%). Other differential diagnoses included congestive heart failure, pericarditis, atrial pseudoaneurysm, pneumonia, and bronchitis.

The histologic subtypes included angiosarcoma (42%; of which 40% were epithelioid angiosarcoma), synovial sarcoma (25%), myxoid sarcoma (8%), myxosarcoma (8%), spindle cell sarcoma (8%), and solitary fibrous tumor (8%). The locations of the primary tumors were in the left atrium (25%), right atrium (25%), pericardium (25%), and both right atrium and pericardium (25%). Eight percent of patients presented with stage I, 25% with stage II, 42% with stage III, and 25% with stage IV disease. The majority of patients had grade 3 tumors (67%), followed by grade 2 (25%), and grade 1 (8%).

Treatment

Patient treatment characteristics are summarized in Table 1. All 12 patients underwent surgical intervention at the time of presentation. Three of these patients underwent surgery as the only treatment modality, whereas 4 patients had additional postoperative chemotherapy only, and 5 patients

received both postoperative chemotherapy and RT to the primary tumor site. Seven patients had an R2 resection (ie, gross residual disease), 4 had an R1 resection (ie, microscopically positive margins) and only 1 patient had an R0 resection (ie, negative margins). Details of the surgical procedure performed are shown in Table 1. It is important to note that the majority of the tumors were resected with an initial presumed diagnosis of a nonmalignant mass, and most procedures were performed at an outside center before referral to Stanford. These included cases 2, 4, and 6, whom all had a preoperative diagnosis of atrial myxoma and underwent piecemeal resections of the mass. Case 7 was initially planned to undergo an endovascular thrombectomy for a suspected intracardiac thrombus, but the mass was unable to be suctioned so a debulking procedure was performed instead. Case 8 required a median sternotomy, given difficult access for a pericardial window procedure, which led to incidental discovery of a posterior pericardial mass and resection. Case 12 underwent radical pericardiectomy for suspected infectious pericarditis and then biopsy of the tumor that was involving the entire surface of the heart.

Five patients (42%) received postoperative RT to the primary tumor site to improve local control. Intensity modulated radiotherapy or volumetric-modulated arc radiotherapy at doses of 43.5 to 55.8 Gy in 25 to 31 fractions were used. One patient (case 6) underwent intraoperative radiotherapy (IORT) with 7.5 Gy during a salvage resection for LP. An illustrative treatment plan example for postoperative RT (case 4) is shown in Figure 1. Acute radiation-associated side effects consisted of grade 1 fatigue, dermatitis, and esophagitis; grade 2 odynophagia and pleuritis; and grade 3 pneumonitis. Late effects of RT (>1 year) were not assessable due to death or follow-up at an outside institution. Nine patients (75%) received postoperative chemotherapy, with 4 patients (33%) receiving chemotherapy alone, 4 patients (33%) receiving concurrent chemoradiation therapy, and 1 patient (8%) receiving sequential RT and chemotherapy. Chemotherapy regimens included gemcitabine–docetaxel doublet, doxorubicin–ifosfamide doublet, and pazopanib. Chemotherapy-associated side effects included grade 1 weight loss, vomiting, and alopecia; grade 1 to 2 fatigue and nausea; grade 2 oral mucositis, gastroesophageal reflux disease, and back pain from infusion reaction; and grade 3 neutropenic fever, neutrophilia, thrombocytopenia, and encephalopathy.

Treatments for LR/LP included tumor debulking, pericardiectomy, and additional chemotherapy, and 1 case received IORT at the time of debulking surgery. Treatments for metastatic disease included resection, RT (including CyberKnife), and chemotherapy. Figure 2 is an illustrative example of a complete response seen in a patient (case 4) after surgical resection, postoperative concurrent chemoradiation therapy, followed by additional chemotherapy.

FIGURE 1. Illustrative example of postoperative RT treatment plan. Case 4, who had spindle cell sarcoma in the right atrium, received postoperative concurrent chemoradiation. RT, as displayed here, consisted of 45 Gy in 25 fractions via intensity-modulated radiotherapy. The gross tumor volume is highlighted in *red*, and clinical target volume (also the 45 Gy isodose line) in *blue*. Normal anatomic structures are displayed as follows: right atrium and pulmonary trunk in *yellow*; left atrium, ventricles, and aorta in *green*. Transverse (A), coronal (B), and sagittal (C) views are provided.

Outcomes

The median duration of follow-up was 12.0 months (range, 1 day to 52.1 months). Ten patients (83%) were deceased at the time of this retrospective study, and 2 are alive with disease. The median PFS was 5.9 months (range 1 day to 48.9 months). However, patients with stage I-III disease had a longer median PFS of 7.9 months. The median OS was 12.0 months (range 1 day to 52.1 months), but patients with stage I-III disease had a median OS of 16.9 months.

One of the 3 patients who presented with stage IV disease (case 11) died on postoperative day 1 due to refractory hemorrhage from the tumor surface. The other 2 patients with metastatic disease at the time of diagnosis (cases 10 and 12) developed additional sites of metastatic disease and had OS times of 7.2 months and 7.0 months despite having received, respectively, postoperative concurrent chemoradiation therapy and postoperative chemotherapy.

Nine of 12 patients presented with potentially curable disease (stage I-III). Two of these patients (cases 3 and 6) underwent surgical resection only. Case 3 had a resection with microscopically positive margins but died at 16.9 months of progressive disease. Case 6 had an initial resection with macroscopically positive margins and rapidly progressed within weeks requiring a second resection, which involved cardiac autotransplantation (ie, explantation of the heart for improved access to the tumor, followed by reimplantation) and IORT. The patient died on postoperative day 2 from congestive heart failure.

The remaining 7 patients (cases 1, 2, 4, 5, 7, 8, and 9) with potentially curable disease received postoperative therapy. One patient (case 1) had a margin-negative resection, received postoperative chemotherapy, and remained in complete remission until developing DM and passing away at 21.8 months. Three patients (cases 2, 4, and 5) underwent resections with microscopically positive margins.

FIGURE 2. Illustrative example of complete treatment response on computed tomography of the thorax. Case 4 had a right atrial primary cardiac sarcoma (A) and underwent an R1 surgical resection, Dox-Ifos for 1 cycle, concurrent chemoradiation therapy (intensity-modulated radiotherapy to the tumor site with Ifos), and Dox-Ifos for 4 cycles, which led to a complete response as demonstrated on imaging (B).

TABLE 2. Treatment and stage associated with outcomes

Treatment	No. patients	PFS (median)	P value	OS (median)	P value
Surgery only vs Surgery + postop therapy	3 9	0.7 mo 6.2 mo	.3467	2.6 mo 15.5 mo	.1188
<i>Subgroup 1: M0 and R0/R1</i>					
Surgery only vs Surgery + adjuvant therapy	1 4	12.6 mo 30.6 mo	.7741	16.9 mo 37.0 mo	.3508
<i>Subgroup 2: M1 and/or R2</i>					
Surgery only vs Surgery + postop therapy	2 5	0.4 mo 5.7 mo	.0574	1.3 mo 7.3 mo	.0082
R0/R1 resection vs R2 resection	5 7	12.6 mo 2.7 mo	.0083	21.8 mo 7.2 mo	.0062
Stage I-III vs stage IV	9 3	7.9 mo 0.7 mo	.0422	16.9 mo 7.0 mo	.0034

PFS, Progression-free survival; OS, overall survival; *postop*, postoperative; *M0*, nonmetastatic disease; *R0*, negative margin; *R1*, microscopically positive margin; *M1*, metastatic disease; *R2*, macroscopically positive margin.

Case 2 was in complete remission after postoperative therapy until developing LR 48.9 months after the date of surgery and passing away at 52.1 months. Case 4 was also in complete remission initially until developing DM in the left clavicular head and manubrium but is still alive with disease at 33.8 months. Case 5 had a partial response and died at 15.5 months. Finally, 3 patients (cases 7, 8, and 9) underwent resections with macroscopically positive margins. All 3 patients had partial responses and developed DM despite having received postoperative chemotherapy

and/or RT. Case 7 had an OS of 10.0 months, case 8 is still alive at 14.0 months, and case 9 had an OS of 7.3 months.

The median time to LR/LP was 2.7 months (range 0.7–48.9 months) and to DM was 7.9 months (range 0.7–25.2 months). All patients with LR/LP presented with worsening dyspnea and were confirmed with CT of the thorax or cardiac MRI. DM sites included the brain, bone, pleura, lung, liver, and skin.

Predictors of Outcomes

Factors associated with outcomes, including treatment characteristics and stage at presentation, are summarized in Table 2. Patients who had received postoperative therapy had a trend toward longer OS as compared with patients who underwent surgery only (median OS 15.5 vs 2.6 months, $P = .1188$, Figure 3). However, this did not reach statistical significance. Two subgroup analyses were conducted. The first subgroup comprised patients with non-metastatic (M0) disease who underwent R0/R1 resections. Adjuvant therapy (ie, therapy given to radiographically negative disease to prevent recurrence) compared with only surgery did not show a statistically significant difference in PFS (median 30.6 vs 12.6 months, $P = .7741$) or OS (median 37.0 vs 16.9 months, $P = .3508$). The second subgroup, made up of patients with metastatic (M1) disease and/or an R2 resection, had a trend toward improved PFS with postoperative therapy over surgery

FIGURE 3. Kaplan-Meier curve for overall survival, stratified by whether the patients received postoperative therapy or not. *Post-op*, Postoperative.

FIGURE 4. Kaplan–Meier curve for progression-free survival (A) and overall survival (B), stratified by type of surgical resection. *GTR*, Gross total resection; *R0*, negative margin; *R1*, microscopically positive margin; *R2*, macroscopically positive margin.

(median 5.7 vs 0.4 months, $P = .0574$). There was also a statistically significant OS benefit (median 7.3 vs 1.3 months, $P = .0082$). In terms of resection margins, patients who underwent a gross total resection (ie, R0 or R1) had a significantly longer PFS and OS compared with those with macroscopic residual disease (ie, R2) (median PFS 12.6 vs 2.7 months, $P = .0083$, Figure 4, A; median OS 21.8 vs 7.2 months, $P = .0062$, Figure 4, B). Patients with localized disease at presentation had a significantly longer PFS (median 7.9 vs 0.7 months, $P = .0422$, Figure 5, A) than patients with metastatic disease, as well as OS (median 16.9 months vs 7.0 months, $P = .0034$, Figure 5, B).

There were no statistically significant differences in PFS or OS when we compared patients by whether or not they received radiation or chemotherapy, nor when we stratified by age, sex, histologic subtype, tumor location, grade, size, or nodal status.

DISCUSSION

This study suggests a trend toward improved survival when postoperative therapy is incorporated into the

management plan for resected PCS. However, as most patients progressed within months after surgery, the greater predictors of outcome were the extent of surgical resection and absence of DM at diagnosis.

The rationale for studying the effects of postoperative therapy on PCS is that surgery alone has not been shown to be curative. This is similar for STS at other sites, with the exception of low-grade tumors that are widely resected with negative margins. Most other STS require postoperative therapy for tumor control.^{19,20} Although we did not find a statistically significant impact of postoperative therapy on PFS, those who did not receive postoperative therapy failed within weeks of surgery.

Our study shows that chemotherapy/RT delayed progression of disease, allowing patients to live up to 6 times longer compared with surgery alone. One of the reasons we could not demonstrate a statistically significant benefit on our hypothesis regarding postoperative therapy may have been that both patients with and without gross residual disease were included in the postoperative therapy group, thus masking the effect. However, a subgroup analysis of

FIGURE 5. Kaplan–Meier curves for progression-free survival (A) and overall survival (B), stratified by presence of metastatic disease at presentation. *M0*, Nonmetastatic disease; *M1*, metastatic disease.

patients with radiographic evidence of disease after surgery (ie, M1 disease and/or R2 resection) showed a trend toward PFS benefit with postoperative therapy, and a statistically significant OS benefit. Another subgroup analysis of patients with radiographically negative disease (ie, nonmetastatic [M0] disease with R0/R1 resection) showed PFS and OS to be more than 2 times longer with postoperative therapy compared with surgery only, although not statistically significant. These findings suggest that postoperative therapy may aid in improving survival outcomes, especially in patients with gross residual or metastatic disease, although the sample size of the subgroup analysis was very small and should be corroborated with larger cohorts in the future.

A significant finding of this study is that the extent of surgical resection is a key determinate in delaying progression of disease and improving OS. Those with a gross total section (R0/R1) fare much better than those with gross residual disease after surgery (R2). A meaningful statistical comparison could not be made in this study between R0 resections and R1 resections, as only 1 patient had negative margins. The literature on STS at other sites similarly demonstrate that those tumors are rarely controlled if complete resection is not possible.^{20,21} Literature on PCS also supports our surgical findings, and we concur with the idea that complete resection should be the primary objective at initial management.^{6-8,11,14,16,22}

Unfortunately, many cardiac tumors prove to be a challenge in gaining adequate exposure when using standard surgical techniques, due to anatomic location and/or proximity to vital structures. Specialized techniques are available that can increase the likelihood of complete resection, such as cardiac autotransplantation for left-sided cardiac tumors.²³ Neoadjuvant chemotherapy may also improve R0 resection rates and survival, as well as possibly act as a predictor of benefit from surgery based on tumor response.²⁴ Neoadjuvant therapy thus has been recommended for certain PCS cases, especially if right-sided.^{24,25} In cases in which a complete resection is unfeasible, a debulking procedure may temporarily help with symptom control, but rapid progression of disease is common (3 months in our series) and the main cause of death.^{7,11-16} In general, it is reasonable to refer complex cases to experienced centers, especially when specialized techniques are warranted. Multidisciplinary cardiac tumor teams are also crucial to providing optimal management for these patients.

Another statistical finding in our study involves the extent of disease at the time of diagnosis. That is, those with nonmetastatic disease have longer PFS and OS compared with those with metastatic disease. Poor outcomes for PCS have been attributed to the fact that most are high-grade, fast-growing, and a quarter of cases present with noncurable metastatic disease.⁷⁻¹⁰ Our series supports this finding,

given that no patient who presented with metastatic disease survived longer than 7 months.

The utility of postoperative chemotherapy for PCS is poorly defined due to limited data in the literature. However, recommendations may be extrapolated from treatment of STS in general. The doxorubicin–ifosfamide doublet was the most common regimen used in this study, as doxorubicin is the single most effective drug for STS. However, because of potential cardiac toxicity, there are dose limits on how much can be safely given. A meta-analysis of randomized-controlled trials in 2008 showed that postoperative doxorubicin and ifosfamide yielded a benefit in recurrence-free survival as well as OS in localized resectable STS.²⁶ When postoperative RT was used, it was delivered concurrently with ifosfamide due to its known radiosensitizing effects, allowing for lower doses of RT. The gemcitabine–docetaxel doublet is another effective regimen used for certain histologic subtypes and has been shown in a phase II trial to provide improved PFS and OS over gemcitabine alone in patients with metastatic STS.²⁷

Postoperative RT is known to improve local control for patients with microscopically margin-positive STS at other sites but rarely controls tumors with macroscopically positive margins after resection^{20,28} (Ganjoo and colleagues, unpublished data on undifferentiated pleomorphic sarcomas, 2017). High doses of RT are typically required in the postoperative setting for STS (approximately 60 Gy); however, this is unfeasible when treating the heart, where such doses exceed the dose tolerance of cardiac tissue.^{6,29} The radiation doses used in this series ranged from 43.5 to 55.8 Gy with highly conformal radiation techniques, including CT-based planning, reformatting preoperative CT/MRI scans to improve accuracy of recreating the target volume, contouring each section of the heart and large vessels to avoid high dose to the ventricle, tight target volume margins, 4D respiratory breathing techniques to reduce unwanted dose to moving structures, dose–volume histograms to evaluate the daily dose and volume each organ/vessel received, and image-guided RT to ensure alignment. We recognize the role of RT to the heart is controversial, given the potential for late cardiac injury; however, late effects of radiation to the heart and great vessels are usually not evident for many years after treatment, at which time most patients with PCS will have died of disease.³⁰ Acute cardiac toxicity from RT, which mainly presents in the form of transient pericarditis, was not noted in any cases of this series, likely due to the conformal nature of the delivered radiation.³⁰ We recommend, in the setting in which RT is a consideration, that highly conformal RT techniques be used to minimize the risk for cardiac injury.

Limitations of this study include its retrospective nature, nonuniformity of treatment regimens between patients, and a small sample size, which precludes definitive conclusions

on postoperative chemotherapy or RT. In addition, because of the small sample size, we did not find differences in survival when stratifying by tumor grade, size, location, or histologic subtype; however, the majority of our cases were grade 3 tumors (67%) and angiosarcoma histology (42%), both of which are prognostic features associated with very poor outcome.

In conclusion, patients with PCS undergoing complete surgical resection had 3 times longer OS than those who had macroscopically positive margins in the postoperative setting. Postoperative chemotherapy and RT trended toward improved OS, and within the subgroup of patients with R2 resection and/or M1 disease, had statistically significantly improved OS. For stage IV disease, there were no survivors greater than 7 months. Given the extremely rare nature of these tumors, multi-institutional collaboration should be considered, as this would allow for larger studies to better evaluate outcomes and develop treatment guidelines.

Conflict of Interest Statement

Authors have nothing to disclose with regard to commercial support.

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