Postoperative chemotherapy and radiation improve survival following cardiac sarcoma resection

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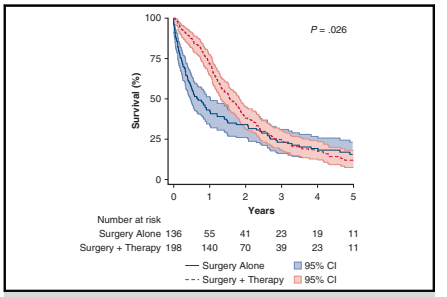
ABSTRACT

Objective: Cardiac sarcoma represents a rare and aggressive form of cancer with a paucity of data to produce outcome-driven evidence-based guidelines. Current surgical management consists of resection with postoperative therapy (chemotherapy, radiation, or both) offered on a selective, individualized basis. This study was designed to determine whether postoperative therapy was associated with improved overall survival after resection.

Methods: The National Cancer Database was used to identify patients with cardiac sarcoma between 2004 and 2015. Patient characteristics were stratified by treatment (surgical, nonsurgical, and none), and treatment was analyzed by stage. Overall survival, assessed with Kaplan–Meier methodology, was compared between patients who received postoperative therapy and those who did not following resection. Multivariable survival modeling using a Weibull model identified risk factors associated with survival while controlling for confounders.

Results: The study included 617 patients diagnosed with cardiac sarcoma. Only 24% (149/617) of patients were diagnosed with early-stage disease. Angiosarcoma represented 48% (298/617) of cases and was the most commonly identified histologic subtype. 60% (372/617) underwent surgical resection and 58% (216/372) of those patients were treated with postoperative therapy. Following surgery, median survival was more than doubled for patients treated with postoperative therapy (19 months vs 8 months, $P = .026$). However, 5-year overall survival was similar between the groups. Multivariable analysis confirmed an improvement in survival with postoperative therapy (hazard ratio, 0.68; 95% confidence interval, 0.51-0.91, $P = .009$).

Conclusions: Postoperative therapy is associated with better median survival following resection of cardiac sarcoma. However, at 5 years, the difference in overall survival is not statistically significant. (J Thorac Cardiovasc Surg 2021;161:110-9)



Survival after cardiac sarcoma resection stratified by the use of postoperative therapy.

CENTRAL MESSAGE

Postoperative therapy (chemotherapy, radiation, or both) is associated with improved median survival following resection of cardiac sarcoma. There is no improvement in overall survival at 5 years.

PERSPECTIVE

Our study investigates a rare group of tumors—cardiac sarcoma—with a dismal prognosis. Complete surgical resection remains the standard of care. Due to the rarity of these malignant tumors, the role of postoperative therapy (chemotherapy, radiation, or both) has not been well established. We show that postoperative therapy is associated with improved survival outcomes.

See Commentaries on pages 120 and 121.

Tumors of the heart are rare and commonly associated with morbid conditions such as valvular disease, heart failure, conduction defect, and embolism.[1,2] Rarer still are primary cardiac tumors, which have an estimated prevalence ranging from 0.001% to 0.03% and are thought to be as much as 30 times less common than metastatic tumors.[3,4]

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Abbreviations and Acronyms

AJCC = American Joint Committee on Cancer
CI = confidence interval
HR = hazard ratio
NCDB = National Cancer Database

Scanning this QR code will take you to the article title page to access supplementary information.

Cardiac sarcoma represents the most common malignant, primary tumor of the heart.[5] Initial presenting symptoms, including dyspnea, chest pain, palpitations, shortness of breath, and systemic symptoms such as fever, are nonspecific and associated with a broad differential diagnosis often resulting in delayed or prolonged evaluation and ultimately more advanced tumors at the time of diagnosis.[6] The prognosis and median overall survival for patients with these tumors is dismal and has been reported from 6 to 11 months.[7,8]

Complete wide surgical resection is the current standard treatment for cardiac sarcoma based on the results of small case series and retrospective studies suggesting a survival advantage after surgery.[9-13] However, negative margins are often difficult to achieve during these operations, and surgery is frequently performed for palliative purposes.[14]

The role of postoperative therapy, including chemotherapy, radiation, or both, for treatment of cardiac sarcomas has not been well established. A recent analysis of all mediastinal sarcomas including those of cardiac origin suggested survival advantages with the use of postoperative radiation but the results were less clear in regards to postoperative chemotherapy.[15] Several smaller studies have suggested possible survival benefits with the use of postoperative chemotherapy for cardiac sarcomas.[11,16-18]

The purpose of this study was to better determine trends in overall survival for a large retrospectively collected population of patients with cardiac sarcoma and more specifically to explore the association between postoperative therapy and overall survival.

METHODS

Data Sources

The National Cancer Database (NCDB) provided the data for this analysis. The NCDB is a collaboration between the American Cancer Society and the American College of Surgeons' Commission on Cancer. The NCDB was chosen for this project due to the depth and breadth of the data collection, which allows for analysis of rare diseases, as well as a robust reporting of overall survival data. The NCDB accounts for approximately 70% of new cancer diagnoses in the United States. Data provided by the NCDB are deidentified and include patient characteristics, diagnoses, treatments, and outcomes while ensuring anonymity of patients, providers, and hospitals.

Population

The soft-tissue tumor participant user file for 2004 to 2015 was obtained from the NCDB. From these data, we identified all patients 18 years and older diagnosed with a primary cardiac tumor through the third edition International Classification of Disease for Oncology code 38.0. The study cohort was then further refined by only selecting tumors designated as sarcomas.

In our principal analysis, we stratified all patients with primary cardiac sarcoma by treatment (surgical, nonsurgical, and no treatment) for comparison. We then examined only patients who underwent surgical resection and stratified by the use of postoperative therapy. For the purposes of this analysis, postoperative therapy combines chemotherapy, radiation therapy, and chemoradiation therapy administered following resection into a single category. The subtle difference between postoperative therapy and adjuvant therapy is valuable to note. Postoperative therapy includes all adjuvant therapy but additionally includes therapy provided for patients with positive margins following resection and patients who may have initially been treated surgically without curative intent.

Outcomes

The primary outcome of the study was overall survival. Patients were followed for 5 years; those who could not be followed for 5 years were censored at last follow-up. While disease-free survival would have been preferred to overall survival, this information was not available in the NCDB. The objective of the study was to determine whether 5-year overall survival differed across treatment groups and whether postoperative therapy was associated with improved survival after tumor resection among patients who received surgery.

Covariates

Covariates in the analysis can be categorized as demographic or clinical. Demographic covariates included age (18-39, 40-49, 50-59, 60+ years), sex (male, female), race (white, black, Hispanic, other), no high school degree (21%+, 13%-20.9%, 7%-12.9%, 0%-6.9%, unknown), median income quartile ($0-$37,999; $38,000-$47,999; $48,000-$62,999, $63,000+, unknown), primary payer (private, government, not insured, unknown), geography (metro, non-metro), and hospital volume (averaged <1 case/year, averaged ≥1 cases/year). Clinical variables included Charlson comorbidity index (0, 1, 2, 3+), histology of tumor (angiosarcoma, leiomyosarcoma, rhabdomyosarcoma, other), tumor size (0-4.4 cm, 4.5-5.9 cm, 6.0-7.4 cm, 7.5+ cm, unknown), tumor grade (well differentiated, moderately differentiated, poorly differentiated, undifferentiated, unknown), American Joint Committee on Cancer (AJCC) stage (stage I, stage II, stage III, stage IV), and treatment (surgery alone, surgery + postoperative therapy [including chemotherapy, radiation therapy, or both], nonsurgical, none). Tumor margins (R0, R1 or R2, unknown) were included for patients who received surgery.

Additional covariates were explored and are provided in supplemental materials. These include clinical stage (stage I, stage II, stage III, stage IV, unknown), clinical T stage (cT1, cT2, unknown), clinical N stage (cN0, cN1, unknown), clinical M stage (cM0, cM1, unknown), pathologic stage (stage I, stage II, stage III, stage IV, unknown), pathologic T stage (pT1, pT2, unknown), pathologic N stage (pN0, pN1, unknown), pathologic M stage (pM0, pM1, unknown) and the French sarcoma grading system (grade 1, grade 2, grade 3, unknown).

A missing-indicator method was used to create an "unknown" category for each covariate that was found to have missing data.

All AJCC staging was based on the 7th edition. The NCDB provides staging data with the "NCDB Analytic Stage Group" variable. Pathologic staging was used preferentially; clinical staging was used for patients without pathologic stage data. Substage groups were collapsed into general stages. This variable was used to assign AJCC stage for this study.

Several demographic covariates, including no high school degree, median income quartile, and population area, were measured at the patient's zip code level using results from American Community Survey data. Since these covariates were not patient-level characteristics, they were not included in multivariable modeling.

Covariates used in multivariable modeling were limited due to sample size to avoid overfitting the model. Certain covariates were not included to avoid collinearity. Ultimately, the covariates chosen for the model included surgical treatment, age, sex, race, Charlson comorbidity index, margins, histology, grade, AJCC stage, and hospital volume. To avoid bias, covariates were chosen by "expert opinion" based on perceived covariate impact on outcome. To do this, the authors convened before creating the model to agree on the limited covariates to be used.

Statistical Analysis

The primary goals of this study were to compare the characteristics and survival outcomes of patients with cardiac sarcoma by treatment strategy and then to determine whether the use of postoperative therapy following surgical resection was associated with improved survival.

Patient and tumor characteristics were stratified by treatment type (surgery, non-surgical, no treatment) and compared using analysis of variance tests. Kaplan–Meier analysis was then used to compare 5-year overall survival for the treatments. Treatment strategies were then stratified by AJCC stage and compared using analysis of variance tests. Kaplan–Meier curves were employed to show 5-year survival of patients with cardiac sarcoma based on AJCC stage.

The study cohort was then limited to patients who underwent surgical resection. Characteristics of patients who underwent surgery alone were compared with characteristics of patients who underwent surgery with postoperative therapy using χ^2 tests. A Weibull hazard model was then used to estimate overall survival while adjusting for potential confounding variables. We opted for a parametric survival model due to concerns that proportional hazards assumptions had been violated. To determine which specific distribution to use, we first fit the model to a generalized gamma survival model. This model contains several other models as special cases: lognormal, gamma, and Weibull depending on the value of the kappa coefficient. In our fitting of the generalized gamma model, the estimated kappa coefficient was near 1 and was not significantly different from one in χ^2 post-estimation tests. Kaplan–Meier curves were then used to show trends in 5-year survival between the surgery alone and surgery + postoperative therapy cohorts. As a robustness check for endogeneity, we fit survival models using inverse probability weighted estimators to control for both the probability of receiving surgery alone and the probability of censoring. We used these models to compute the average treatment effect at 1, 2, 3, and 4 years following diagnosis.

Finally, the role of surgical resection for patients with stage IV disease was investigated with the use of Kaplan–Meier analysis.

The software used to perform the statistical analysis was Stata (version 10.1; StataCorp, College Station, Tex). Statistical significance was defined by P value $< .05$.

RESULTS

Cardiac sarcoma was diagnosed in 617 patients from 2004 to 2015. The average age of these patients was 51 years (range 8-90 years). Patients were most commonly male (52%) and white (67%). The 3 most common histology types were angiosarcoma (48%), leiomyosarcoma (6%), and spindle cell sarcoma (6%); a large number of tumors were classified as sarcoma not otherwise specified (18%). Figure E1 shows trends in 5-year overall survival stratified by the 3 most commonly specified histologies. For all patients diagnosed with primary cardiac sarcoma, the median survival was 11 months and the 5-year overall survival rate was 9.5%.

Numbers of patients stratified by treatment strategy were as follows: 372 (60.3%) were treated surgically, 150 (24.3%) were treated with nonsurgical management (chemotherapy and/or radiation), and 95 (15.4%) were not provided any treatment modality. Characteristics of patients stratified by these treatment strategies are shown in Table 1. Additional characteristics not included in statistical analyses are shown in Table E1. Patients treated surgically had the lowest average comorbidity burden ($P = .0035$), the greatest median income quartiles ($P = .02$), the lowest rates of angiosarcoma ($P = .0045$), the most tumors less than 4.5 cm ($P = .0376$), and were most commonly AJCC stage I ($P < .0001$). Patients offered nonsurgical treatment were the youngest ($P < .0001$), commonly had greater comorbidity burden ($P = .0035$), and had a greater rate of metastatic disease ($P < .0001$). Notably, patients who did not receive treatment were the oldest ($P < .0001$) and had the lowest rates of private insurance ($P = .0051$). While tumor size and grade were found to be significantly different between the treatment strategies, the high and varying rates of missing data categorized as "unknown" made these findings difficult to interpret. Figure 1 shows the Kaplan–Meier analysis of 5-year overall survival stratified by treatments. Patients treated with surgery had a median survival of 16 months and a 5-year overall survival rate of 13.3%; patients treated with nonsurgical therapy had a median survival of 11 months and a 5-year overall survival rate of 2.4%; patients with no treatment had a median survival of 1 month and a 5-year overall survival rate of 5% ($P < .0001$).

Table 2 shows differences in treatment strategy by AJCC stage. Of patients undergoing surgical resection without additional therapy, 34% of patients had stage I or stage II disease, 22.4% had stage III disease, and only 7.1% had stage IV disease ($P < .0001$). Patients who underwent resection followed by adjuvant therapy were more evenly distributed across stage: stage I 14.4%, stage II 14.4%, stage III 24.1%, and stage IV 19.9% ($P = .0051$). The use of nonsurgical treatment without surgical resection was most commonly reserved for patients with stage IV disease (54.7%, $P < .0001$).

Unsurprisingly, more than 45% of patients who did not receive any treatment also did not have recorded staging data ($P < .0001$). The Kaplan–Meier analysis in Figure 2 shows significant differences in survival between stages ($P < .0001$) and Figure E2 provides confidence intervals. Stage I disease had a median survival of 23 months and a

TABLE 1. Patient and tumor characteristics stratified by treatment

Variable	Surgical treatment (n = 372)	Nonsurgical treatment (n = 150)	No treatment (n = 95)	*P* value
Age, %	50.6 y	46.3 y	60.4 y	< .0001
18-39	28.2	37.3	14.7	
40-49	20.7	18.7	10.5	
50-59	18.3	21.3	14.7	
60+	32.8	22.7	60.0	
Sex, %				.6694
Male	51.3	55.3	50.5	
Female	48.7	44.7	49.5	
Race, %				.5162
White	69.6	63.3	61.1	
Black	11.3	19.3	15.8	
Hispanic	15.3	11.3	16.8	
Other	3.8	6.0	6.3	
Charlson comorbidity index, %				.0035
Charlson 0	68.5	6.0	61.1	
Charlson 1	22.6	78.7	28.4	
Charlson 2	6.7	19.3	9.5	
Charlson 3+	2.2	1.3	1.1	
No high school degree, %				.2512
21+	16.1	18.0	18.9	
13-20.9	19.4	20.0	21.1	
7-12.9	32.3	33.3	36.8	
0-6.9	30.4	25.3	21.1	
Unknown	1.9	3.3	2.1	
Median income quartiles, %				.02
$0-$37,999	13.2	19.3	15.8	
$38,000-$47,999	21.5	21.3	30.5	
$48,000-$62,999	27.2	26.7	22.1	
$63,000+	36.3	28.0	29.5	
Unknown	1.9	4.7	2.1	
Insurance, %				.0051
Private	61.0	60.0	36.8	
Government	30.4	30.7	52.6	
Not insured	5.9	2.7	8.4	
Unknown	2.7	6.7	2.1	
Population area, %				.2445
Metro	82.3	76.7	76.8	
Non-metro	17.7	23.3	23.2	
Histology, %				.0045
Angiosarcoma	37.6	66.7	61.1	
Leiomyosarcoma	7.5	2.7	4.2	
Spindle cell	6.7	7.3	2.1	
Other	48.2	23.3	32.6	
Tumor size, cm, %				.0376
0-4.4	19.9	12.7	13.7	
4.5-5.9	22.3	10.7	8.4	
6.0-7.4	16.9	18.7	10.5	
7.5+	21.2	20.7	25.3	
Unknown	19.6	37.3	42.1	
Grade, %				< .0001
Well differentiated	3.2	1.3	1.1	
Moderately differentiated	5.6	0.7	3.2	
Poorly differentiated	31.2	23.3	14.7	
Undifferentiated	31.5	19.3	18.9	
Unknown	28.5	55.3	62.1	
AJCC stage, %				< .0001
Stage 1	13.7	8.7	11.6	
Stage 2	17.2	3.3	5.3	
Stage 3	23.4	9.3	10.5	
Stage 4	14.8	54.7	27.4	
Stage unknown	30.9	24.0	45.3	
Hospital volume, %				.5389
Averaged <1 case/y	91.1	88.7	92.6	
Averaged ≥1 case/y	8.9	11.3	7.4	

AJCC, American Joint Committee on Cancer.

5-year overall survival rate of 21.3%. Stage II disease had a median survival of 22 months and a 5-year overall survival rate of 12.2%. Stage III disease had a median survival of 13 months and a 5-year overall survival rate of 17.6%. Stage IV disease had a median survival of 8 months and a

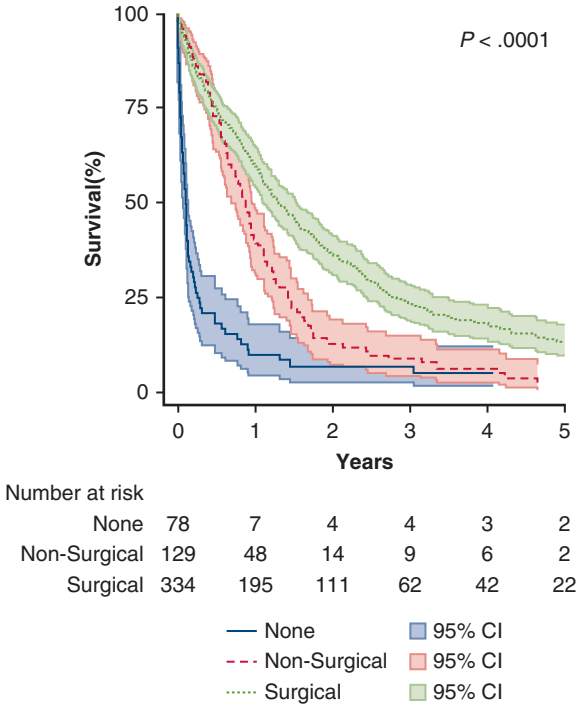


FIGURE 1. Kaplan–Meier analysis of cardiac sarcoma overall survival stratified by treatment approach: surgical, nonsurgical, none. Nonsurgical includes chemotherapy, radiation therapy, or both. Survival is best with surgical treatment and poorest with no treatment. *CI*, Confidence interval.

TABLE 2. Treatments stratified by AJCC stage

Treatment	AJCC staging					*P* value
	Stage I (n = 75)	Stage II (n = 74)	Stage III (n = 111)	Stage IV (n = 163)	Unknown (n = 194)	
Surgery alone, n (%)	20 (12.8)	33 (21.2)	35 (22.4)	12 (7.7)	56 (35.9)	<.0001
Surgery + adjuvant therapy, n (%)	31 (14.4)	31 (14.4)	52 (24.1)	43 (19.9)	59 (27.3)	.0069
Surgery + chemo, n	23	21	34	22	48	
Surgery + radiation, n	2	2	7	5	5	
Surgery + chemo + radiation, n	6	8	11	16	6	
Nonsurgical, n (%)	13 (8.7)	5 (3.3)	14 (9.3)	82 (54.7)	36 (24.0)	<.0001
Chemo alone, n	7	2	7	59	21	
Radiation alone, n	3	0	2	7	5	
Chemo + radiation, n	3	3	5	16	10	
No treatment, n (%)	11 (11.6)	5 (5.7)	10 (10.5)	26 (27.4)	43 (45.3)	< .0001

AJCC, American Joint Committee on Cancer.

5-year overall survival rate of 2.7%. Patients with "unknown" stage had median survival of 11 months and a 5-year overall survival rate of 3.5%, most similar to patients with stage IV disease. Interestingly, for patients with stage IV disease, 32% were found to have pulmonary metastases and those patients with pulmonary metastases were less likely than patients with other types of metastases to undergo surgical resection. More specifically, there was a 23% operative rate in patients with pulmonary metastases compared to a 39% operative rate for patients with nonpulmonary metastases ($P = .049$).

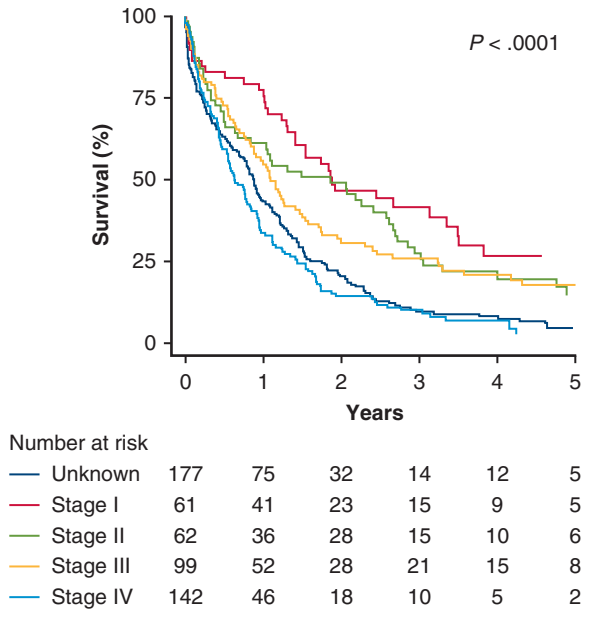


FIGURE 2. Kaplan–Meier analysis of cardiac sarcoma overall survival stratified by American Joint Committee on Cancer stage. Survival is significantly worse with increasing staging. Patients classified as unknown closely resemble patients categorized as stage IV. The confidence intervals for each stage are depicted in Figure E2.

The remainder of our analysis focused on patients who underwent surgical resection and was stratified by postoperative therapy. Characteristics of the patients in these groups are shown in Table 3. Patients treated with surgery alone were older ($P = .027$) and more likely to be female ($P = .011$). Surgery alone was also associated with greater comorbidity burden ($P = .019$), lower rates of private insurance ($P = .013$), more well-differentiated tumors ($P = .039$), fewer negative margins ($P = .014$), and fewer stage IV tumors ($P = .007$) compared with patients who were additionally treated with postoperative therapy. The 30-day mortality for surgery alone was 14% compared with 3% for those who received postoperative therapy. The 90-day mortality rates were 22% and 29%, respectively.

Multivariable Weibull hazard model results are shown in Table 4. Compared with surgery alone, surgery with postoperative therapy was associated with a significant survival advantage (hazard ratio [HR], 0.68, 95% confidence interval [CI], 0.51-0.91, $P = .009$). In addition, leiomyosarcomas (HR, 0.55; CI, 0.33-0.9, $P = .017$) and "other" sarcomas (HR, 0.72; CI, 0.53-0.97, $P = .033$) were associated with improved survival compared with angiosarcoma histology. Covariates associated with poorer survival included age 60+ years (HR, 1.80; CI, 1.27-2.55, $P = .001$) and stage IV or metastatic disease (HR, 3.08; CI, 1.77-5.37, $P < .001$). Kaplan–Meier survival curves for the surgery alone and surgery + therapy cohorts are depicted in Figure 3. Notably, the median survival for patients treated with postoperative therapy was more than twice the median survival of those who were treated with surgery alone (19 months compared with 8 months, $P = .026$) whereas 5-year survival rates were similar at 11.9% and 15.4%, respectively. Figure E3 similarly compares surgery + therapy and surgery alone but only for patients with disease stages I-III. Median survival remained significantly improved (23 months compared

TABLE 3. Patient and tumor characteristics stratified by the use of adjuvant therapy following surgical resection

Variable	Surgery alone (n = 156)	Surgery + adjuvant therapy (n = 216)	*P* value
Age, %	55.4 y	47.2 y	.027
18-39	22.4	32.4	
40-49	12.8	26.4	
50-59	20.5	16.7	
60+	44.2	24.5	
Sex, %			
Male	43.6	56.9	.011
Female	56.4	43.1	
Race, %			.698
White	69.2	69.9	
Black	10.9	11.6	
Hispanic	14.7	15.7	
Other	5.1	2.8	
Charlson comorbidity index, %			.019
Charlson 0	60.9	74.1	
Charlson 1	29.5	17.6	
Charlson 2	8.3	5.6	
Charlson 3+	1.3	2.8	
Insurance, %			.013
Private	51.3	68.1	
Government	38.5	24.5	
Not insured	7.1	5.1	
Unknown	3.2	2.3	
Histology, %			.371
Angiosarcoma	32.7	41.2	
Leiomyosarcoma	9.0	6.5	
Spindle cell	8.3	5.6	
Other	50.0	46.7	
Tumor size, %			.068
0-4.4 cm	15.4	23.1	
4.5-5.9 cm	28.2	18.1	
6.0-7.4 cm	18.6	15.7	
7.5+ cm	17.9	23.6	
Unknown	19.9	19.4	
Grade, %			.039
Well differentiated	5.1	1.9	
Moderately differentiated	9.0	3.2	
Poorly differentiated	32.1	30.6	
Undifferentiated	27.6	34.3	
Unknown	26.3	30.1	
Margins, %			.014
R0	28.8	22.7	
R1 or R2	29.5	44.4	
Unknown	41.7	32.9	
AJCC stage, %			.007
Stage 1	12.8	14.4	
Stage 2	21.2	14.4	
Stage 3	22.4	24.1	
Stage 4	7.7	19.9	
Stage unknown	35.9	27.3	
Hospital volume, %			.074
Averaged <1 case/y	94.2	88.9	
Averaged ≥1 case/y	5.8	11.1	

AJCC, American Joint Committee on Cancer.

with 9 months, $P = .047$) and the survival rates were 19.2% and 21.2%, respectively. Figure E4 depicts survivor, hazard, cumulative hazard, and density functions side by side. Results from the inverse probability weighted analysis in Table E2 show that after controlling for potential selection bias in the treatment effect, patients who received surgery plus additional therapy had significantly longer survival time up to 3 years following diagnosis, but this effect shrank and was no longer statistically significant after 4 years.

Lastly, Figure E5 compares the overall survival of treatment with and without surgical resection for patients with stage IV disease. Surgical resection trended toward improved survival compared with no resection ($P = .058$).

DISCUSSION

This study provides insight into the presentation and treatment outcomes of an extremely rare disease—cardiac sarcoma—using a national database with robust reporting of survival outcomes. The study also provides insight into the unanswered question as to whether postoperative therapy is warranted following resection of cardiac sarcoma.

In general, patients diagnosed with cardiac sarcoma in the United States tend to be more commonly male and white and can present in early or old age. This study corroborates a combination of several smaller reports that the median survival for patients with this disease is less than a year and that surgical resection does indeed provide a survival advantage and is warranted as the current standard of care for appropriate candidates based on a pragmatic and selective approach given high rates of mortality.[6-8,10,19-21]

The "appropriate candidate" can be difficult to define due to the rarity of the disease and the infrequency of treatment at any one institution or by any one surgeon. In the largest single-institution study of cardiac sarcomas, which included 95 patients operated on by a single surgeon, resection was offered after biopsy of all right-sided tumors without metastasis as well as for metastatic tumors with a nearly complete response to neoadjuvant therapy. Left-sided tumors were approached with caution if found

TABLE 4. Weibull model of survival

Variable	Hazard ratio	95% confidence interval Lower	Upper	*P* value
Surgical treatment				
Surgery alone	Reference			
Surgery + therapy	0.68	0.51	0.91	.009
Age, y				
18-39	Reference			
40-49	0.93	0.64	1.34	.686
50-59	1.05	0.71	1.55	.813
60+	1.80	1.27	2.55	.001
Sex				
Male	Reference			
Female	1.11	0.86	1.43	.43
Race				
White	Reference			
Black	1.07	0.71	1.62	.752
Hispanic	1.04	0.71	1.52	.854
Other	1.33	0.69	2.58	.392
Charlson comorbidity index				
Charlson 0	Reference			
Charlson 1	1.17	0.87	1.60	.294
Charlson 2	1.62	0.95	2.75	.076
Charlson 3+	1.55	0.70	3.41	.281
Margins				
R0 resection	Reference			
R1 or R2 resection	1.38	0.99	1.94	.058
Unknown	1.27	0.90	1.82	.174
Grade				
Well differentiated	Reference			
Moderately differentiated	0.86	0.28	2.64	.788
Poorly differentiated	2.06	0.78	5.47	.146
Undifferentiated	1.86	0.70	4.97	.214
Unknown	1.65	0.63	4.32	.31
Histology				
Angiosarcoma	Reference			
Leiomyosarcoma	0.55	0.33	0.90	.017
Spindle cell	0.90	0.51	1.56	.7
Other	0.72	0.53	0.97	.033
Stage				
Stage I	Reference			
Stage II	1.42	0.83	2.43	.202
Stage III	1.35	0.81	2.28	.252
Stage IV	3.08	1.77	5.37	<.001
Stage unknown	2.30	1.42	3.72	.001
Hospital volume				
Averaged <1 case/y	Reference			
Averaged ≥1 cases/y	1.21	0.77	1.91	.407

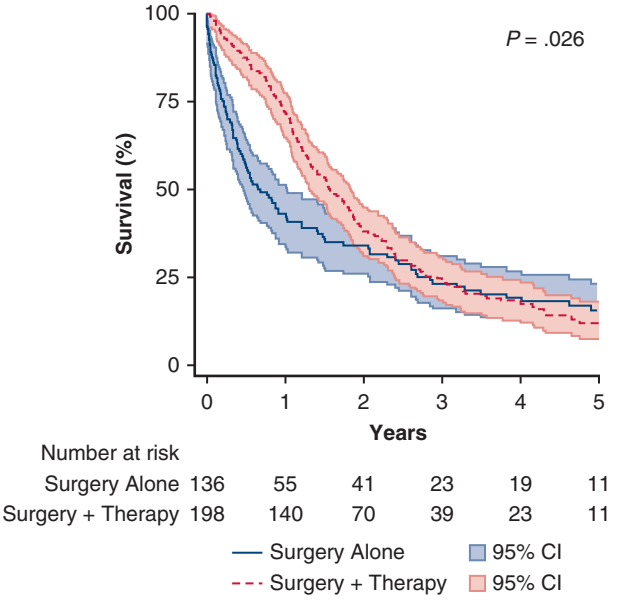


FIGURE 3. Kaplan–Meier analysis comparing overall survival following treatment of cardiac sarcoma with surgery alone compared with surgery combined with postoperative therapy. Median survival is significantly improved in the surgery combined with therapy cohort, whereas there is minimal difference in 5-year overall survival. Postoperative therapy included treatment with chemotherapy, radiation, or both after sarcoma resection. *CI*, Confidence interval.

to have extension into the pulmonary veins and an autotransplantation approach proved beneficial.[22]

In regards to surgical resection for stage IV or metastatic disease, our study correlates well with the suggestions from the aforementioned large, single institution experience. There may be a role for the resection of stage IV or metastatic disease reserved for patients in whom both the primary and metastatic disease processes can be controlled. However, our data do not help us to further identify the optimal candidate or account for healthy patient selection bias. The role of resection in metastatic disease merits further investigation.

With regard to postoperative therapy, our study demonstrates a survival advantage. Chemotherapy, radiation, or the combination of these therapies were combined in the analysis of postoperative therapy due to small treatment numbers. More clarification on the impact of each individual therapy is warranted. Furthermore, it would have been ideal to propensity score match the surgery alone and surgery with postoperative therapy cohorts but this was not statistically feasible. One might consider that if surgery alone was being performed for purely palliative purposes in sicker patients that this would account for the differences reported in our study and indeed the greater 30-day mortality rate amongst those undergoing surgery alone would add support to this notion. However, we found that postoperative therapy was more frequently used in patients with positive margins, stage IV/metastatic disease, and fewer well-differentiated tumors, which may indicate that the results of this study would have been even more pronounced with balanced cohorts. In addition, to account

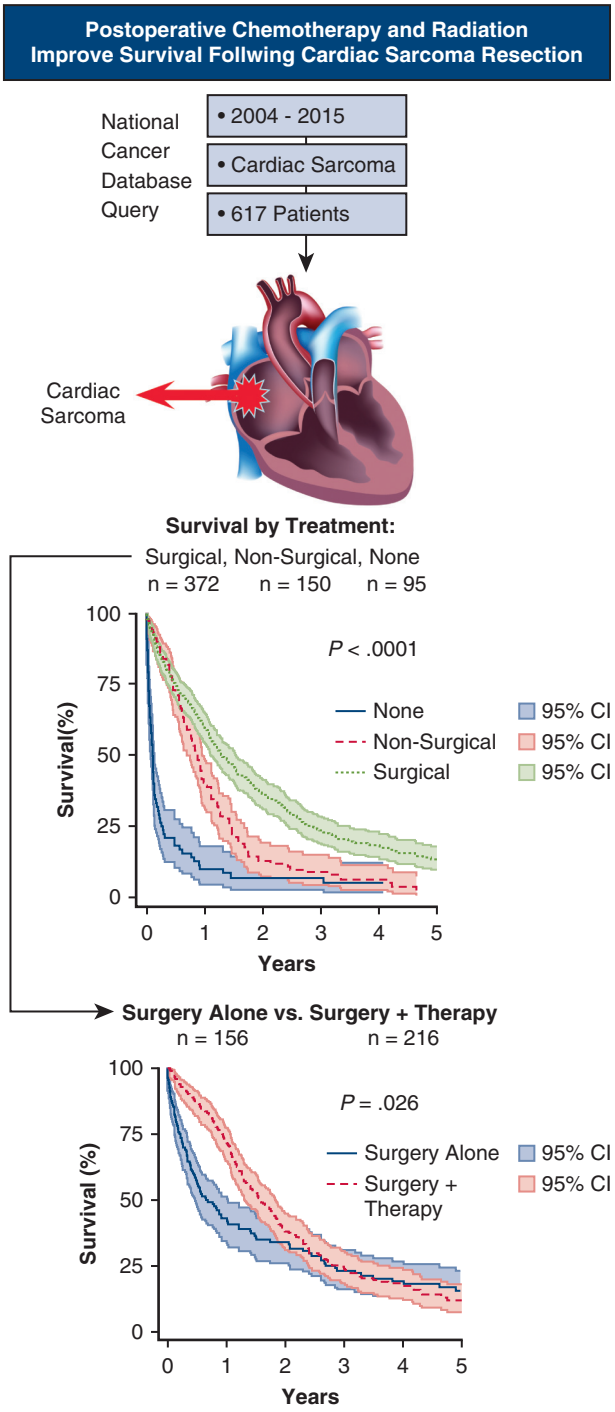
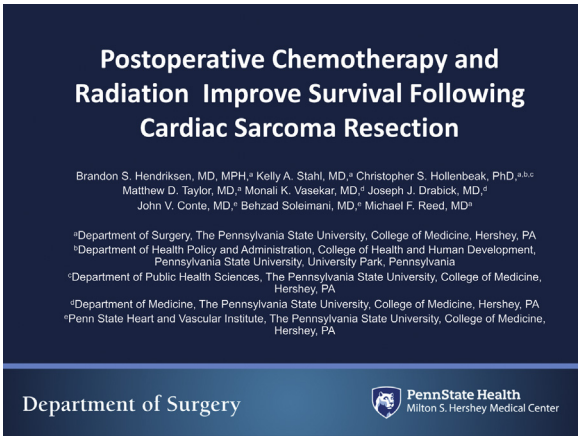


FIGURE 4. Cardiac sarcoma represents a rare and aggressive form of cancer with a paucity of data to produce outcome-driven, evidence-based, guidelines. Current surgical management consists of resection with postoperative therapy offered on a selective, individualized basis. This study was designed to determine whether postoperative therapy was associated with improved overall survival. Postoperative therapy included patients treated with chemotherapy, radiation, or both after tumor resection. *CI*, Confidence interval.



VIDEO 1. The importance and relevance of postoperative therapy on survival after cardiac sarcoma resection. Video available at: https://www.jtcvs.org/article/S0022-5223(19)32223-8/fulltext.

for selection and treatment biases associated with patients who have stage IV disease, we repeated our survival analysis in patients with disease stages I-III. The findings corroborated our initial results.

It should be noted that this analysis only investigates postoperative therapies. Several studies suggest positive results using neoadjuvant chemotherapy, resulting in improved R0 resection rates and better survival.[18,23] However, neoadjuvant therapy is unreliably reported for the cardiac sarcomas in this study and we cannot make further conclusions in regards to this treatment approach.

Another notable finding of this study is the high rate of positive margins following surgical resection. In fact, more operations had positive margins than negative margins. Our analysis on margins was limited, with approximately 40% of operations missing margin data. Despite the missing data, our multivariable model suggested a trend toward significance, with positive margins resulting in poorer survival, which echoes the findings of other studies.[12,15,18,24] Importantly, the question has arisen whether adjuvant therapy should be used with positive margins, negative margins, or both.[18] Unfortunately, due to the missing data regarding margin status, our study was unable to answer this critical question.

Until this study, there has been limited investigation into the impact of histologic sarcoma subtype on survival. Within the NCDB data, angiosarcoma, leiomyosarcoma, and spindle cell sarcoma represent the most common histologic subtypes besides sarcoma not otherwise specified, which accounted for 18% of all cases. The comparatively high prevalence of spindle cell sarcoma was surprising, given other reports of rarity in the literature.[25] Interestingly, our analysis suggests that

angiosarcoma is not only the most common subtype but that it is associated with significantly poorer survival. One possibility could be a histologic tumor predilection for location and/or invasion especially with angiosarcomas.[26] Ultimately, the driver behind the association with poorer survival is unclear and deserves further investigation.

Due to the rarity of cardiac sarcoma, there has been limited discussion, much less consensus, on the utility of using a staging system or grading system specific for cardiac sarcoma. In general, the AJCC suggests that use of the French Sarcoma grading system for sarcomas. Unfortunately, this grading system was not well reported for cardiac sarcoma in the NCDB. Other studies have found a strong correlation with pathologic grade and cardiac sarcoma outcome.[8,15] For our study, we had a relatively robust reporting of the AJCC 7th edition of Tumor, Node, Metastasis staging, from which we could draw several conclusions. First, there was utility in using the Tumor, Node, Metastasis system, as demonstrated by our Kaplan–Meier analysis of survival stratified by AJCC stage, which showed significant differences in survival by stage. Second, tumor size and node status as indicated by T-stage and N-stage, respectively, had relatively low impact on survival as evidenced by the results of our multivariable modeling. This may signify that these factors should have a limited role in dictating treatment for a given patient. Finally, stage IV, which is indicative of metastatic disease, is a major predictor of poorer survival in cardiac sarcoma. More in-depth discussion with regards to specific and uniform staging and grading criteria for cardiac sarcoma is needed.

There are a number of limitations to note. As with many analyses of other rare disease processes, our study was limited by lack of power due to small sample size. While to our knowledge, this study represents the largest collection of cardiac sarcoma cases, the overall case volume remains low, and may lead to type 2 errors. In addition to low power from sample size, the power of individual covariate analysis is limited by missing values in this dataset. Categorizing covariates as ''unknown'' and using the commonly used missing indicator method as we have done, is likely associated with some bias. In addition, the NCDB does not provide information about cardiac function, specific comorbidities, anatomic location of the tumor, presenting symptoms, imaging findings, reasons for treatment decisions, or operative reports. Selection bias is likely present in deciding which patients should receive postoperative therapy and difficult to account for with a database of this nature. Data specific to chemotherapeutic treatment are also missing. Drug and dosage information is not provided. Also, missing data regarding chemotherapy provided before the operation make analysis of neoadjuvant chemotherapy inappropriate. Finally, the NCDB is retrospective and data are compiled from hospitals with accreditation from the Commission on Cancer, likely resulting in inherent selection bias as these hospitals have a demonstrated commitment to the treatment of cancer. This resulting bias could exaggerate estimated effectiveness if present.

In conclusion, cardiac sarcoma is a rare disease with a difficult presentation and grim prognosis. Median overall survival is commonly less than 1 year. Complete surgical resection is the preferred treatment and can improve rates of survival but should be thoughtfully offered on a pragmatic and selective basis, given high mortality, high rate of incomplete resections, and limited survival for this biologically complicated cancer. Previously, there has been limited evidence about the benefit of postoperative therapy. Our study shows that postoperative therapy is associated with more than twice the median survival when compared to surgery alone. An overall summary of these findings is depicted in Figure 4 and discussed in Video 1. Future investigations should focus on the impact of chemotherapy and radiation therapy individually, specific chemotherapy drug and dosage recommendations, and the impact of neoadjuvant therapy on improved resections and overall survival.

Conflict of Interest Statement

Authors have nothing to disclose with regard to commercial support.

References

1. Hudzik B, Miszalski-Jamka K, Glowacki J, Lekston A, Gierlotka M, Zembala M, et al. Malignant tumors of the heart. *Cancer Epidemiol*. 2015;39:665-72.
2. Butany J, Nair V, Naseemuddin A, Nair GM, Catton C, Yau T. Cardiac tumours: diagnosis and management. *Lancet Oncol*. 2005;6:219-28.
3. Reynen K. Frequency of primary tumors of the heart. *Am J Cardiol*. 1996;77:107.
4. Abraham KP, Reddy V, Gattuso P. Neoplasms metastatic to the heart: review of 3314 consecutive autopsies. *Am J Cardiovasc Pathol*. 1990;3:195-8.
5. Silverman NA. Primary cardiac tumors. *Ann Surg*. 1980;191:127-38.
6. Putnam JB Jr, Sweeney MS, Colon R, Lanza LA, Frazier OH, Cooley DA. Primary cardiac sarcomas. *Ann Thorac Surg*. 1991;51:906-10.
7. Burke AP, Cowan D, Virmani R. Primary sarcomas of the heart. *Cancer*. 1992;69:387-95.
8. Hamidi M, Moody JS, Weigel TL, Kozak KR. Primary cardiac sarcoma. *Ann Thorac Surg*. 2010;90:176-81.
9. Shanmugam G. Primary cardiac sarcoma. *Eur J Cardiothorac Surg*. 2006;29:925-32.
10. Centofanti P, Di Rosa E, Deorsola L, Dato GM, Patanè F, La Torre M, et al. Primary cardiac tumors: early and late results of surgical treatment in 91 patients. *Ann Thorac Surg*. 1999;68:1236-41.
11. Mayer F, Aebert H, Rudert M, Königsrainer A, Horger M, Kanz L, et al. Primary malignant sarcomas of the heart and great vessels in adult patients—a single-center experience. *Oncologist*. 2007;12:1134-42.
12. Simpson L, Kumar SK, Okuno SH, Schaff HV, Porrata LF, Buckner JC, et al. Malignant primary cardiac tumors: review of a single institution experience. *Cancer*. 2008;112:2440-6.
13. Zhang PJ, Brooks JS, Goldblum JR, Yoder B, Seethala R, Pawel B, et al. Primary cardiac sarcomas: a clinicopathologic analysis of a series with follow-up information in 17 patients and emphasis on long-term survival. *Hum Pathol*. 2008;39:1385-95.
14. Yanagawa B, Mazine A, Chan EY, Barker CM, Gritti M, Reul RM, et al. Surgery for tumors of the heart. *Semin Thorac Cardiovasc Surg*. 2018;30:385-97.

15. Engelhardt KE, DeCamp MM, Yang AD, Bilimoria KY, Odell DD. Treatment approaches and outcomes for primary mediastinal sarcoma: analysis of 976 patients. *Ann Thorac Surg*. 2018;106:333-9.
16. Pessotto R, Silvestre G, Luciani GB, Anselmi M, Pasini F, Santini F, et al. Primary cardiac leiomyosarcoma: seven-year survival with combined surgical and adjuvant therapy. *Int J Cardiol*. 1997;60:91-4.
17. Antunes MJ, Vanderdonck KM, Andrade CM, Rebelo LS. Primary cardiac leiomyosarcomas. *Ann Thorac Surg*. 1991;51:999-1001.
18. Bakaeen FG, Jaroszewski DE, Rice DC, Walsh GL, Vaporciyan AA, Swisher SS, et al. Outcomes after surgical resection of cardiac sarcoma in the multimodality treatment era. *J Thorac Cardiovasc Surg*. 2009;137:1454-60.
19. Poole GV Jr, Meredith JW, Breyer RH, Mills SA. Surgical implications in malignant cardiac disease. *Ann Thorac Surg*. 1983;36:484-91.
20. Molina JE, Edwards JE, Ward HB. Primary cardiac tumors: experience at the University of Minnesota. *Thorac Cardiovasc Surg*. 1990;38(suppl 2): 183-91.
21. Murphy MC, Sweeney MS, Putnam JB Jr, Walker WE, Frazier OH, Ott DA, et al. Surgical treatment of cardiac tumors: a 25-year experience. *Ann Thorac Surg*. 1990;49:612-7; discussion 617-8.
22. Ramlawi B, Leja MJ, Abu Saleh WK, Al Jabbari O, Benjamin R, Ravi V, et al. Surgical treatment of primary cardiac sarcomas: review of a single-institution experience. *Ann Thorac Surg*. 2016;101:698-702.
23. Abu Saleh WK, Ramlawi B, Shapira OM, Al Jabbari O, Ravi V, Benjamin R, et al. Improved outcomes with the evolution of a neoadjuvant chemotherapy approach to right heart sarcoma. *Ann Thorac Surg*. 2017; 104:90-6.
24. Chen TW, Loong HH, Srikanthan A, Zer A, Barua R, Butany J, et al. Primary cardiac sarcomas: a multi-national retrospective review. *Cancer Med*. 2019;8: 104-10.
25. Muturi A, Kotecha V, Ruturi J, Muhinga M, Waweru W. High-grade spindle cell sarcoma of the heart: a case report and review of literature. *J Cardiothorac Surg*. 2015;10:46.
26. Patel SD, Peterson A, Bartczak A, Lee S, Chojnowski S, Gajewski P, et al. Primary cardiac angiosarcoma—a review. *Med Sci Monit*. 2014;20:103-9.

Key Words: cardiac sarcoma, postoperative therapy, chemotherapy, cardiac tumor, survival

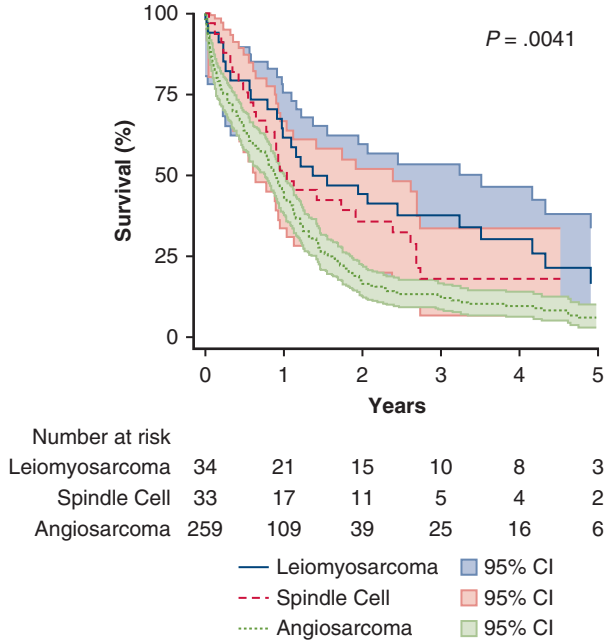


FIGURE E1. Kaplan–Meier analysis of 5-year overall survival for specific cardiac sarcoma histologies: angiosarcoma, leiomyosarcoma, and spindle cell sarcoma. Patients with angiosarcoma have significantly worse survival. *CI*, Confidence interval.

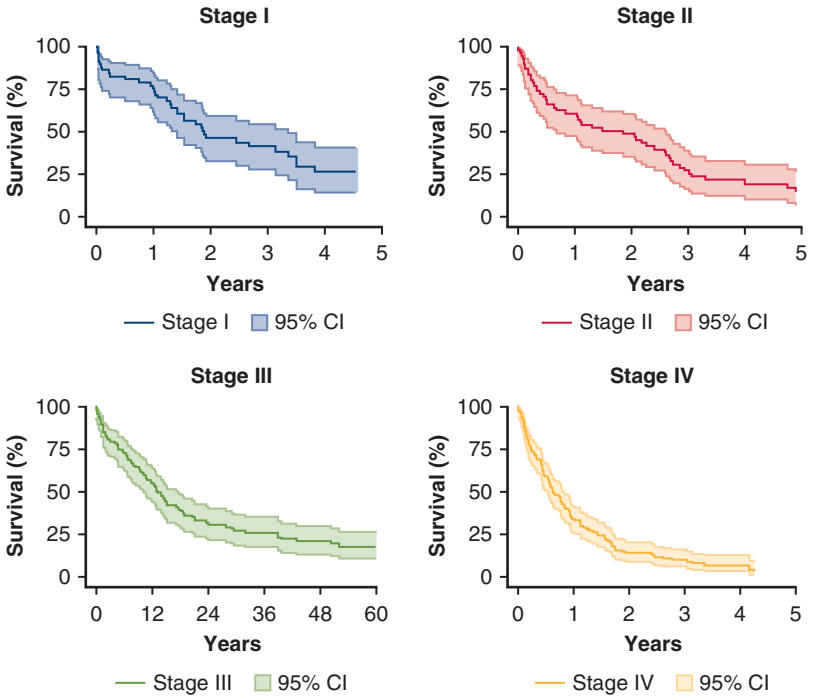


FIGURE E2. CIs provided for Kaplan–Meier curves depicting overall survival for individualized American Joint Committee on Cancer stages of cardiac sarcoma initially presented in Figure 2. *CI*, Confidence interval.

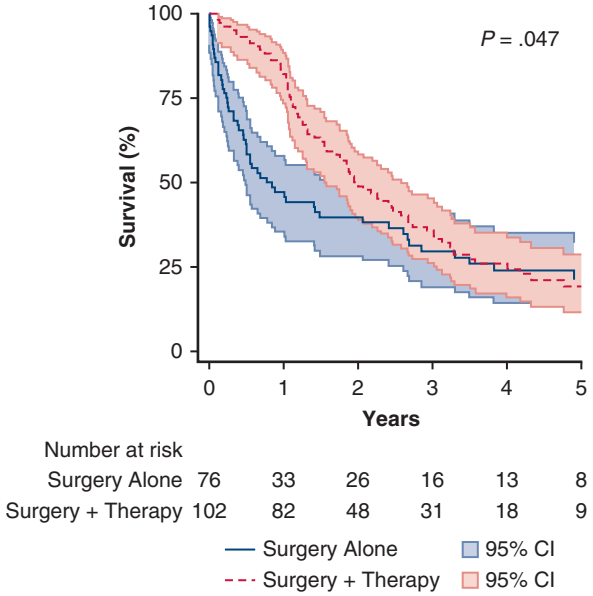


FIGURE E3. Kaplan–Meier analysis comparing overall survival following treatment of cardiac sarcoma with surgery alone compared with surgery combined with postoperative therapy for patients with disease stages I-III. The results are similar to the analysis in Figure 3, which included stage IV. Median survival is significantly improved in the surgery combined with therapy cohort, whereas there is minimal difference in 5-year overall survival. Postoperative therapy included treatment with chemotherapy, radiation, or both after sarcoma resection. *CI*, Confidence interval.

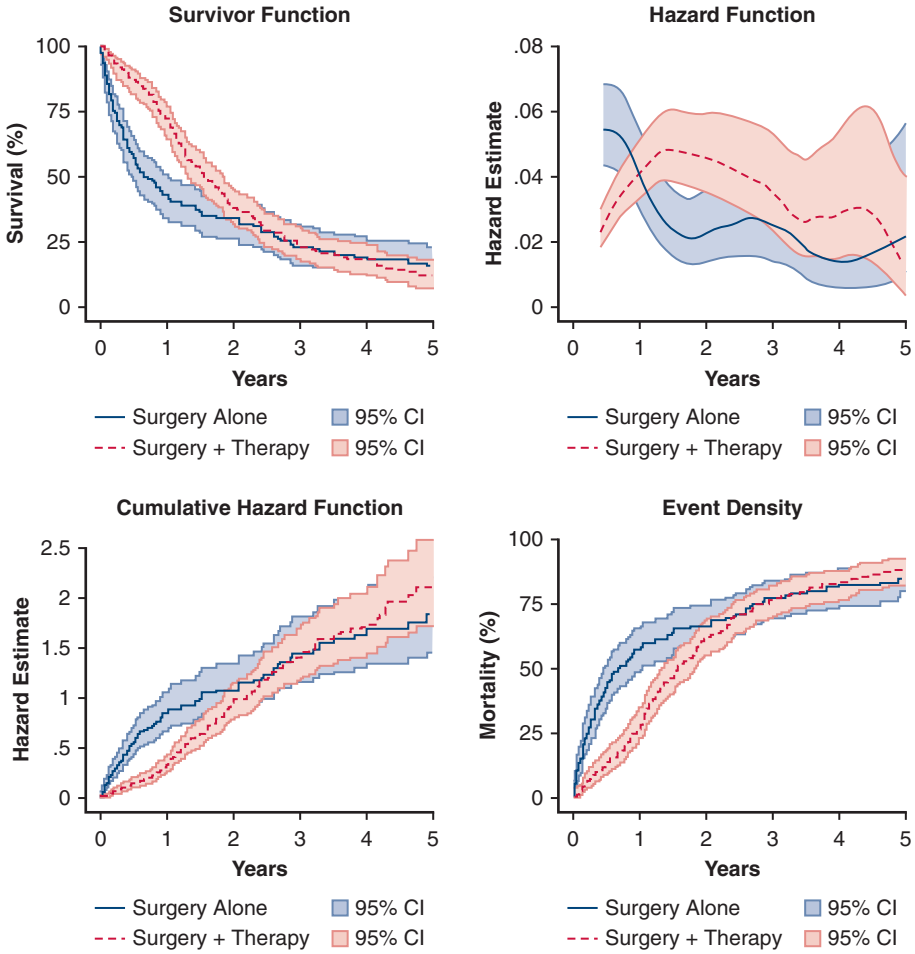


FIGURE E4. Survivor function, hazard function, cumulative hazard function, and event density shown side by side. Therapy refers to treatment with chemotherapy, radiation, or both after sarcoma resection. *CI*, Confidence interval.

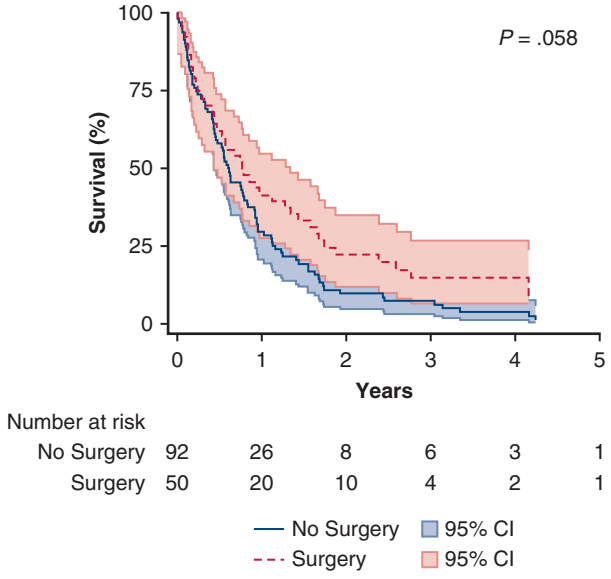


FIGURE E5. Kaplan–Meier analysis comparing overall survival for patients with stage IV cardiac sarcomas stratified by treatment with surgical resection ($P = .058$). *CI*, Confidence interval.

TABLE E1. Additional tumor staging characteristics by treatment

Variable	Surgical treatment (n = 372)	Nonsurgical treatment (n = 150)	No treatment (n = 95)	*P* value
Clinical stage, %				<.0001
Stage I	10.2	8.7	10.5	
Stage II	11.3	3.3	5.3	
Stage III	16.1	9.3	10.5	
Stage IV	13.2	50.7	26.3	
Unknown	49.2	28.0	47.4	
Clinical T stage, %				.1201
cT1	21.2	14.0	13.7	
cT2	29.0	38.0	26.3	
Unknown	49.7	48.0	60.0	
Clinical N stage, %				.0679
cN0	57.8	42.0	45.3	
cN1	3.8	16.7	11.6	
Unknown	38.4	41.3	43.2	
Clinical M stage, %				<.0001
cM0	83.1	48.0	62.1	
cM1	12.6	46.7	25.3	
Unknown	4.3	5.3	12.6	
Pathologic stage, %				<.0001
Stage I	8.6	1.3	1.1	
Stage II	12.9	0.7	1.1	
Stage III	16.9	0.7	0.0	
Stage IV	8.1	28.7	8.4	
Unknown	53.5	68.7	89.5	
Pathologic T stage, %				<.0001
cT1	22.3	1.3	4.2	
cT2	33.6	5.3	1.1	
Unknown	44.1	93.3	94.7	
Pathologic N stage, %				<.0001
cN0	34.9	4.7	45.3	
cN1	0.8	1.3	11.6	
Unknown	64.2	94.0	43.2	
Pathologic M stage, %				.8221
cM0	44.4	37.3	62.1	
cM1	6.5	20.0	25.3	
Unknown	49.2	42.7	12.6	
FNCLCC grade, %				.0528
Grade 1	0.8	0.7	1.1	
Grade 2	3.8	1.3	1.1	
Grade 3	9.9	7.3	4.2	
Unknown	85.5	90.7	93.7	

FNCLCC, French Sarcoma Grading System.

TABLE E2. Average survival time following cardiac sarcoma resection stratified by postoperative therapy after accounting for endogeneity

Years of follow-up	Average survival time, mo		*P* value
	Surgery alone	Surgery + therapy	
One year	4.15	6.93	<.0001
Two years	6.63	13.15	<.0001
Three years	10.22	16.18	<.0001
Four years	13.93	17.64	.187
Full sample	21.17	21.25	.982