



Surgical Outcomes of Malignant Primary Cardiac Tumor: A 20-Year Study at a Single Center

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Background: Malignant primary cardiac tumors are extremely rare, but have a poor prognosis. This study evaluated the surgical outcomes of patients with this disease.

Methods: Forty patients who underwent surgery for malignant primary cardiac tumors between January 1998 and December 2018 were enrolled. Participants were divided into 3 groups based on resection margins (R0, 14 patients; R1, 11 patients; and R2, 11 patients) and their surgical outcomes were compared. Heart transplantation was performed in 4 patients with unresectable tumors.

Results: Early mortality was reported in 2 cases (5%) due to postoperative bleeding and cerebral hemorrhage secondary to brain metastasis. The 1- and 2-year survival rates were 67.5% and 42.5%, respectively. The median survival time of the patients was 20.3 months (range, 9.2–37.6 months). The median survival time was 48.7, 20.3, and 4.8 months in patients with R0, R1, and R2 resections, respectively ($p=0.023$). Tumor recurrence occurred in 21 patients (61.7%), including 4 cases of local recurrence and 17 cases of distant metastasis. In patients who underwent heart transplantation, the median survival time was 29.5 months, with 3 cases of distant metastasis.

Conclusion: Although surgery for malignant primary cardiac tumors has a poor prognosis, complete resection of the tumor may improve surgical outcomes.

Keywords: Heart neoplasms, Sarcoma, Malignant tumor

Introduction

Malignant primary cardiac tumors are extremely rare, but lethal. The median overall survival of patients with cardiac sarcomas is 6 months. According to a prior study, patients who underwent surgery for cardiac sarcomas had a median survival of 12 months, whereas those who did not undergo surgery had a median survival of 1 month [1]. As suggested by previous research, complete surgical resection is the primary approach in treating malignant primary cardiac tumors [1-5]. However, complete resection is not always feasible, and deciding on an optimal treatment plan for these cases can be difficult. Heart transplants can be performed in patients with unresectable tumors, but their prognosis is unclear [6,7]. Because of their rarity, the management of malignant primary cardiac tumors and their subsequent outcomes are not well defined. This study re-

viewed the surgical outcomes of malignant primary cardiac tumors at a single center.

Methods

Patients who underwent surgical resection for malignant primary cardiac tumors at Asan Medical Center between January 1998 and December 2018 were enrolled in the study. Patients with tumors that had metastasized to the heart and those who underwent excisional biopsy were excluded from the study. We divided patients into 2 groups according to the operative period, the early group (1998–2008) and the late group (2009–2018). A retrospective review of medical records was performed to identify patients eligible for inclusion in the study, and their perioperative, operative, and follow-up data were obtained accordingly. This study was approved by the Institutional Review Board



of Asan Medical Center (2020–0616). Obtaining informed consent from the patients was not required owing to the retrospective nature of the study.

The primary outcome of interest was the survival rate among patients with different resection margin characteristics. Complete surgical resection was the surgical goal for malignant primary cardiac tumors. Complete resection (R0) was defined as a tumor-free margin with no microscopic tumor remnants in the primary tumor bed (R0), while R1 and R2 resection was defined by the presence of microscopic and macroscopic residual tumors in the resection margin, respectively. Heart transplant surgery was performed in 4 patients with unresectable cardiac tumors.

To evaluate differences in tumor invasiveness between the groups, 2 factors were analyzed: tumor size and the extent of tumor involvement. Tumor size was defined as the longest diameter on computed tomography imaging or magnetic resonance imaging. A scoring system was designed to represent the extent of tumor involvement, with the score assigned according to the number of structures that the tumor involved in the heart, including the right atrium, right ventricle, left atrium, left ventricle, mitral valve, tricuspid valve, pulmonary valve, aorta, pulmonary artery, and coronary artery.

Surgical technique

In most cases, median sternotomy with total cardiopulmonary bypass using bicaval venous and aortic cannulation was used. If standard central cannulation was deemed inappropriate because of factors such as extensive tumor invasion, peripheral cannulation through the femoral artery, femoral vein, internal jugular vein, or axillary artery was carried out. Right-sided mini-thoracotomy using the AESOP (Automated Endoscopic System for Optimal Positioning) was performed in 2 patients. The extent of surgical resection ranged from palliative debulking to complete gross resection. If a defect was detected after tumor resection, reconstruction was performed with a bovine pericardial patch, a Gore-Tex patch, or autologous pericardium. The aim of surgery was complete resection of the tumor mass. When the tumor invaded structures in the heart, such as a valve or a coronary artery, valve replacement, valvuloplasty, or coronary artery bypass grafting (CABG) was performed concomitantly. In cases where an extensive sarcoma involved the posterior wall of the left atrium, pulmonary vein inlets, and the mitral valve, autotransplantation was performed to achieve radical resection and precise reconstruction [8].

Statistical analysis

Continuous variables were reported as means±standard deviations or, for variables with an asymmetrical distribution, as median and interquartile ranges. The statistical analysis was performed using the Student t-test or the Mann-Whitney U-test. The Kruskal-Wallis test was used when comparing 3 groups. Categorical variables were presented as percentages and frequencies and were analyzed using the chi-square test or the Fisher exact test. Long-term survival was calculated and graphically presented using the Kaplan-Meier method. The log-rank and Breslow tests were used to confirm the statistical significance of differences in survival duration. A p-value <0.05 was considered to indicate statistical significance. Analyses were performed with IBM SPSS ver. 21.0 (IBM Corp., Armonk, NY, USA).

Results

Forty patients underwent surgical resection for malignant primary cardiac tumors, of whom 17 were men (42.5%). The mean age of the patients was 47.2 years (range, 16–78 years) (Table 1).

Operative data

Tumor excision was performed in 36 patients (R0 resection in 14 patients, R1 resection in 11, and R2 resection in 11) while 4 (10%) underwent heart transplantation. In all cases, surgery was performed under cardiopulmonary bypass (mean time, 130.7 minutes). Aortic cross-clamping was performed in 34 patients (mean time, 86.6 minutes). Concomitant tricuspid valvuloplasty and tricuspid valve replacement (TVR) were performed in 2 (5%) and 5 (12.5%) patients, respectively. Two of the patients who underwent TVR also underwent CABG. Mitral valvuloplasty and mitral valve replacement (MVR) were performed in 1 (2.5%) and 3 (7.5%) patients, respectively. In 1 patient, autotransplantation with MVR was performed owing to extensive tumor invasion of the left atrial posterior wall and mitral valve (Table 1).

Early outcomes

Early mortality was reported in 2 cases, both of whom had R2 resection margins and were in the early group. One patient died the day after surgery because of uncontrolled postoperative bleeding, while the other patient experienced a sudden alteration of mental status on postoperative day 10.

Table 1. Demographic and operative data

Characteristic	Total (n=40)	Early group (n=11)	Late group (n=29)	p-value
Age (yr)	47.2±17.6	48.46±20.17	46.76±16.95	0.790
Sex (male)	17 (42.5)	4 (36.4)	13 (44.8)	0.730
Diabetes mellitus	2 (5)	1 (9.1)	1 (3.4)	0.479
Hypertension	9 (22.5)	4 (36.4)	5 (17.2)	0.227
Chronic renal failure	0	0	0	
Creatinine (0.7–1.4 mg/dL)	0.78±0.31	0.95±0.52	0.71±0.15	0.109
Total bilirubin (0.2–1.2 mg/dL)	0.76±0.41	0.88±0.33	0.72±0.44	0.157
CPB time (min), n=40	130.7±69.9	118.82±73.39	139.62±69.08	0.308
ACC time (min), n=34	86.6±40.4	66.33±24.63	95.24±43.23	0.072
Concomitant procedure	13 (32.5)	1 (9.1)	12 (41.4)	0.068
TVR or TVP	7 (17.5)	0	7 (24.1)	0.159
PVR	2 (5)	0	2 (6.9)	<1
MVR or MVP	4 (10)	1 (9.1)	3 (10.3)	<1
CABG	2 (5)	0	2 (6.9)	<1
Resection margin				
R0	14 (35)	0	14 (48.3)	0.004
R1	11 (27.5)	2 (18.2)	9 (31)	0.694
R2	11 (27.5)	9 (81.8)	2 (6.9)	<0.001
Heart transplantation	4 (10)	0	4 (13.8)	0.560

Values are presented as mean±standard deviation or number (%).

CPB, cardiopulmonary bypass; ACC, aortic cross-clamp; TVR, tricuspid valve replacement; TVP, tricuspid valvuloplasty; PVR, pulmonary valve replacement; MVR, mitral valve replacement; MVP, mitral valvuloplasty; CABG, coronary artery bypass graft.

Table 2. Tumor pathology

Pathologic diagnosis	Total (n=40)	Early group (n=11)	Late group (n=29)	p-value
Sarcoma				
Angiosarcoma	16 (40)	3 (27.3)	13 (44.8)	0.473
Intimal sarcoma	6 (15)	0	6 (20.7)	0.162
Synovial sarcoma	5 (12.5)	3 (27.3)	2 (6.9)	0.117
Myxosarcoma	4 (10)	3 (27.3)	1 (3.4)	0.056
Ewing sarcoma	2 (5)	0	2 (6.9)	<1
Other sarcomas	5 (12.5)	1 (9.1)	4 (13.8)	<1
Other tumors	2 (5)	1 (9.1)	1 (3.4)	0.479

Values are presented as number (%).

The cause was determined to be brain metastasis with cerebral hemorrhage, and the patient died on postoperative day 15. Several postoperative complications were also reported. Postoperative bleeding severe enough to require surgical re-exploration occurred in 2 patients, while a persistent complete atrioventricular block necessitated the placement of a permanent pacemaker in another patient. Low cardiac output syndrome developed in 2 patients, one of whom needed extracorporeal membrane oxygenation for 4 days, while the other underwent surgical exploration, with sternal closure delayed for 4 days.

Tumor characteristics

Pathologic analysis was performed for all the resected

cardiac tumors to arrive at an accurate clinical diagnosis. All but 2 of the tumors were sarcomas. In patients with sarcomas, the most common histologic type was angiosarcoma (n=16, 40%) while the other types included intimal sarcoma (n=6, 15%), synovial sarcoma (n=5, 12.5%), myxosarcoma (n=4, 10%), and Ewing sarcoma/peripheral neuroectodermal tumor (n=2, 5%) [9]. Furthermore, cases of high-grade pleomorphic sarcoma (5%), rhabdomyosarcoma (2.5%), fibrosarcoma (2.5%), and leiomyosarcoma (2.5%) were also observed. The 2 patients with non-sarcoma tumors were diagnosed with malignant peripheral nerve sheath tumor [10] and pleomorphic malignant fibrous histiocytoma (Table 2).

The tumors were classified according to their anatomic location (i.e., the 4 chambers of the heart and the pericar-

Table 3. Location of the tumors

Characteristic	Total (n=40)	Early group (n=11)	Late group (n=29)	p-value
Location				
RA	16 (40)	3 (27.3)	13 (44.8)	0.473
RV	7 (17.5)	1 (9.1)	6 (20.7)	0.650
LA	12 (30)	6 (54.5)	6 (20.7)	0.056
LV	2 (5)	0	2 (6.9)	<1
Pericardium	3 (7.5)	1 (9.1)	2 (6.9)	<1
Attached part				
RA free wall	15 (37.5)	3 (27.3)	12 (41.4)	0.486
RV free wall	2 (5)	1 (9.1)	1 (3.4)	0.479
LA wall	4 (10)	1 (9.1)	3 (10.3)	<1
LV free wall	2 (5)	0	2 (6.9)	<1
Interatrial septum	7 (17.5)	3 (27.3)	4 (13.8)	0.369
Interventricular septum	3 (7.5)	0	3 (10.3)	0.548
Valve leaflet	2 (5)	2 (18.2)	0	0.071
Others (pericardium, 3; RVOT, 2)	5 (12.5)	1 (9.1)	4 (13.8)	<1

Values are presented as number (%).

RA, right atrium; RV, right ventricle; LA, left atrium; LV, left ventricle; RVOT, right ventricular outflow tract.

Table 4. Invasiveness of the tumors depending on the resection margins

Characteristic	R0 (n=14)	R1 (n=11)	R2 (n=11)	p-value
Tumor size (cm)	6.15±1.43	5.97±1.71	5.95±1.82	0.626
Score for the extent of tumor involvement	2.29±1.07	1.55±0.52	1.82±0.87	0.184

Values are presented as mean±standard deviation.

dium). Of the 16 right atrial tumors, only 1 was attached to the interatrial septum, while the rest were attached to the right atrial free wall. Of the left atrial tumors, the tumors were attached to the left atrial wall in 4 patients, the interatrial septum in 6 patients, and the mitral valve leaflet in 2 patients. In patients with right ventricular tumors, the right ventricular free wall was involved in 2 patients, the interventricular septum in 3 patients, and the right ventricular outflow tract in 2 patients. Left ventricular tumors were very rare, and were only present in 2 cases (Table 3).

We compared the invasiveness of the tumors among the 3 groups with different resection margin characteristics using tumor size and the scoring system for the extent of tumor involvement. The mean tumor size was 6.15, 5.97, and 5.95 cm for R0, R1, and R2 resections, respectively; the tumors were somewhat larger in R0 resections than in R2 resections, but this difference was not statistically significant ($p=0.626$). The extent of tumor involvement, as assessed using the scoring system, was also greater in R0 resections than in R2 resections, but the difference was not significantly different ($p=0.184$) (Table 4). Exceptionally, 3 patients with R2 resection margins had unresectable tumors. One tumor invaded the coronary sinus and crux cordis, and another was widely based in the interventricu-

lar septum and invaded the pulmonary valve annulus. The third case involved emergent right atrial rupture due to tumor erosion. The ventricular wall also had severe erosion, causing uncontrolled bleeding, and as a result the patient died the day after surgery.

Operative period: early (1998–2008) and late (2009–2018)

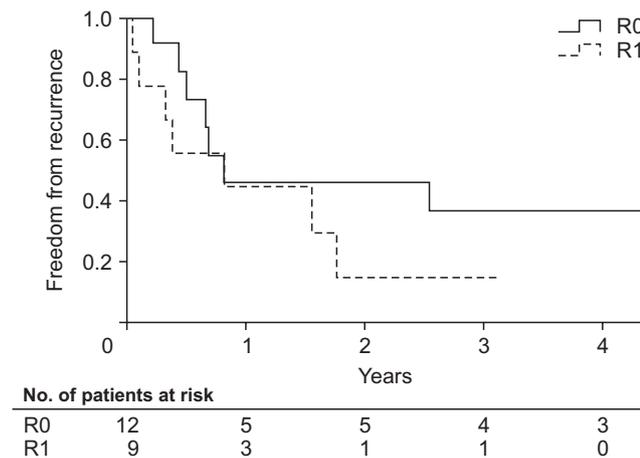
There was no significant differences in demographic characteristics between both groups. The only significant difference between these groups was the number of patients with R0 resections and R2 resections. The number of patients with R0 resections was higher in the late group ($p=0.004$), whereas the number of patients with R2 resections was higher in the early group ($p<0.001$). Concomitant surgery was performed in only 1 patient in the early group compared with 12 patients in the late group, but this difference was not statistically significant ($p=0.068$). Heart transplantation was only performed in 4 patients in the late group ($p=0.560$) (Table 1).

The pathological characteristics and location of tumors were not significantly different between these groups (Tables 2, 3). There was also no significant difference in tumor

Table 5. Invasiveness of the tumors depending on the operative period

Characteristic	Early group (n=11)	Late group (n=29)	p-value
Tumor size (cm)	6.13±2.08	5.97±1.58	0.819
Score for the extent of tumor involvement	1.91±0.83	2.03±0.98	0.835

Values are presented as mean±standard deviation.

**Fig. 1.** Freedom from recurrence (R0 and R1) (p=0.33).

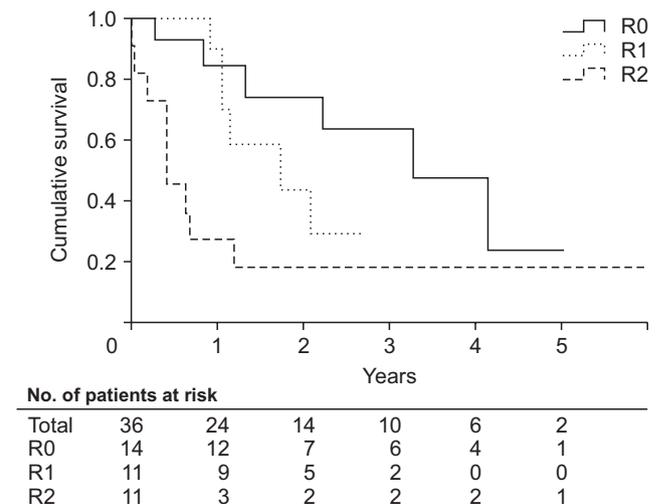
size and extent of involvement, assessed using the scoring system, between both groups (Table 5).

Chemotherapy and radiotherapy

Neoadjuvant chemotherapy and radiotherapy were administered in 3 (7.5%) and 2 (5%) patients, respectively. Only 1 patient received neoadjuvant chemoradiotherapy. Twenty-seven patients (67.5%) underwent postoperative chemotherapy, radiotherapy, or chemoradiotherapy; of them, 18 underwent chemotherapy, 2 underwent radiation therapy, and 7 underwent chemoradiotherapy.

Tumor recurrence

Postoperative tumor recurrence (either local recurrence or distant metastasis) was documented in 21 patients (61.7%) (Fig. 1). Six patients who were already diagnosed with distant metastasis before surgery were excluded (lung metastasis in 5 patients and bone metastasis in 1 patient). These patients underwent either urgent or emergent surgery owing to symptomatic causes such as atrial wall rupture or aggravation of dyspnea. The median interval until recurrence was 8.0 months. Local recurrence occurred in 4 patients, with the following distribution of recurrence sites: the left atrium in 2 patients, the left atrium and ventricle in 1 patient, and the right atrium in 1 patient. These patients

**Fig. 2.** Survival curves for the different types of resection margins (R0, R1, and R2). Patients who underwent complete surgical resection were observed to have an advantage in terms of survival (p=0.023) (R0 vs. R1, p=0.253; R0 vs. R2, p=0.015; R1 vs. R2, p=0.046).

underwent repeat surgery for mass excision, and 1 patient underwent concomitant MVR using the autotransplantation technique for radical tumor resection and reconstruction of the left atrium. Furthermore, 17 patients experienced distant metastasis, with the most common sites being the liver (n=6) and the lungs (n=4). Metastasis occurred in 3 patients who underwent heart transplantation surgery, with a median recurrence time of 12.6 months.

Survival

The 1- and 2-year survival rates were 67.5% and 42.5%, respectively. The median survival time was 20.3 months (range, 9.2–37.6 months). The median survival time was 48.7 months for patients with R0 resections, 20.3 months for those with R1 resections, and 4.8 months for those with R2 resections (p=0.023) (Fig. 2). A comparison of R0 and R2 resections showed a statistically significant difference in the survival time (p=0.015). In patients who underwent heart transplantation, the median survival time was 29.5 months, with no reports of early mortality.

Discussion

Malignant primary cardiac tumors are rare and have a poor prognosis. Although surgical resection is considered vital for the long-term survival of patients with this condition, the median survival time after surgical resection in this study was 20.3 months. These outcomes are similar to those reported by Ramlawi et al. [5], who reviewed the records of 95 patients who had undergone surgical resection of primary cardiac sarcomas between 1990 and 2015 and found that the median survival time was 20 months. Of the 95 patients in that study, 9 (9%) died within a month after surgery. Previous surgical series of primary cardiac sarcomas have emphasized the importance of complete tumor resection, and the Mayo Clinic also reported that performing complete surgical excision was associated with significant improvements in the median survival time, which was 17 months in patients who underwent complete surgical excision versus 6 months for patients in whom complete excision could not be accomplished [4]. Similarly, the current study determined that patients who underwent complete resection had a significantly better median survival time than those with incomplete resection. Thus, complete surgical resection should be attempted despite the technical challenges associated with the procedure [4,11].

In general, the more invasive the tumor, the harder it is to excise completely. In this respect, we could expect that patients with R2 resections had more invasive tumor characteristics before surgery than patients with R0 or R1 resections. As previously mentioned, there were 3 patients with unresectable tumors, but the others were not significantly different in either tumor size or the extent of tumor involvement. Meanwhile, it should be noted that 9 of the 11 patients with R2 resection margins underwent surgery before 2009. Furthermore, concomitant surgery was performed in more cases in the late group than in the early group, and heart transplantation was performed only in the late group. Consequently, it is possible that tumor resection was performed more aggressively in the late group. Because heart surgery became progressively more aggressive over the 20-year duration of the study, it is likely that the surgeons during the second half of this period were more active in attempting complete resection of the tumor as they gained more experience.

In our experience, achieving complete excision was difficult in several cases. In cases where a right atrial tumor spread to the right ventricle with invasion of the tricuspid valve and right coronary artery, TVR with CABG had to

be performed to achieve complete excision. Furthermore, for extensive left atrial tumors, which are already difficult to expose, autotransplantation was performed to achieve complete resection. Bakaeen et al. [12] adopted a strategy for aggressive surgical resection of cardiac sarcomas. Cardiac explantation with autotransplantation was performed in 8 cases (30%) owing to extensive left atrium involvement. Concomitant heart valve surgery (either repair or replacement surgery) and CABG was performed in 8 (30%) and 3 (11%) patients, respectively. In patients who underwent curative resection and survived, the median survival time was 23.5 months [12]. As previously mentioned, R0 resection yielded better survival rates than R1 resection in our study. Thus, aggressive surgical strategies should be used when feasible to achieve complete excision and improve surgical outcomes.

Because malignant primary cardiac tumors are often asymptomatic until they reach an advanced stages, many cases demonstrate extensive local invasion or distant metastasis even before surgery; unsurprisingly, rapid metastasis is often observed after the operation. Tumor metastasis was postoperatively diagnosed in 50% of the patients in our study, while 6 patients already had documented metastasis prior to surgery. The median duration until recurrence was 6 months after surgery. Truong et al. [13] reported that the mean interval between surgery for localized primary cardiac sarcoma and disease progression was 8.5 months (range, 0–34.5 months).

Heart transplantation is an uncommon method of treatment for unresectable and non-metastatic malignant primary cardiac tumors, and its role remains controversial. Li et al. [6] reviewed 46 patients who underwent heart transplantation for non-metastatic primary cardiac sarcoma. The overall median survival was 16 months (range, 2–112 months) with no mortality within 30 days after the surgery. Distant metastasis was reported in 24 patients, while local recurrence was documented in 3 patients [6]. At our institution, 4 patients with unresectable tumors underwent heart transplantation; none of them experienced early mortality and the mean survival time was 25.3 months (range, 4–39 months). However, metastasis occurred in 3 patients with a mean recurrence time of 14.3 months. Compared with patients with R1 or R2 resection margins, the median survival time was longer in patients who underwent heart transplantation, although not as long as those with R0 resection margins. Therefore, in view of the insufficiency of available heart donors, heart transplantation is unlikely to be established as the primary treatment for malignant primary cardiac tumors. However, once ad-

juvant therapies that are more effective in reducing the recurrence rate are established, transplantation may play a larger role in the management of malignant primary cardiac tumors [12,14].

Novel therapeutic approaches have been used to treat residual tumors or unresectable malignant cardiac tumors; an example is cryosurgery with brachytherapy using iodine-125 seed implantation, which can be used as an alternative treatment for patients with unresectable cardiac tumors. Cryotherapy can effectively control a localized tumor by inducing necrosis, while iodine-125 is a radioisotope that can destroy target cells by emitting radiation over short distances. This technique can be used to prevent or delay the growth, invasion, and eventual metastasis of residual tumor cells [15].

This study has several limitations: it is a retrospective study that enrolled a small number of participants and required a long follow-up period. During this period, advances in cardiac surgical techniques and better myocardial protection solutions changed our perspective and improved patient survival.

In conclusion, surgical treatments, including heart transplantation, for malignant primary cardiac tumors have a poor prognosis. The survival rate differed significantly depending on how much tumor tissue remained after resection. Therefore, aggressive surgical resection of primary cardiac tumors should be performed whenever possible.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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