Title:

Pediatric Cardiac Tumors: A 45-year, Single Institution Review

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Abstract:

Background: Cardiac tumors in children are rare. Of cases reported in the literature, nearly all are benign and managed conservatively.

Methods: This is a retrospective, observational study of pediatric patients <18 years who presented for surgical evaluation of a cardiac tumor between 1969 and 2014 at a tertiary care children's hospital. Presentation, pathology, management, and outcomes were evaluated.

Results: Rhabdomyoma was the most common neoplasm (58%), and 17% of the tumors had malignant pathologies. While 42% of benign cardiac neoplasms require surgical intervention for significant hemodynamic concerns, 73% of malignant neoplasms underwent radical excision, if possible, followed by adjuvant chemotherapy. Despite a 37% mortality in patients with malignant pathology, an aggressive surgical approach can yield long-term survival in some patients. There were no deaths among patients with benign tumors and 17% had post-operative complications mostly related to mitral regurgitation.

Conclusion: Cardiac tumors in children are rare but can be managed aggressively with good outcomes. Benign tumors have an excellent survival with most complications related to tumor location. Malignant tumors have a high mortality rate, but surgery and adjuvant chemotherapy allow for prolonged survival in selected patients.

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Background

Cardiac neoplasms are rare in both the adult and pediatric populations. A retrospective review conducted in the late 1990's detected cardiac tumors in less than 0.5% of 30,000 children under evaluation for cardiac disease [1]. The majority of pediatric cardiac tumors are primary, originating in the heart itself, and benign. Of the 800 cases reported in the literature, 97% are benign neoplasms. While biopsy and histologic diagnosis are standard management with any neoplasm, they are rarely necessary in pediatric cardiac tumors [2].

A review of the literature revealed that many of these neoplasms, almost 40%, are detected incidentally through routine prenatal screening with fetal ultrasonography. Other common presentations include congestive heart failure, arrhythmia, or auscultated murmur detected from infancy all the way through adolescence. Echocardiography is the gold standard for diagnosis of a neoplasm in the heart [1].

Rhabdomyomas are by far the most common pediatric cardiac tumor [3]. Most are asymptomatic, regress over time, and do not require surgical intervention [4,5]. Rhabdomyomas have a high association with tuberous sclerosis complex (TSC), a genetic disorder defined by hamartomas found in multiple systems including the brain, skin, and heart [4,5,7-10]. Many cardiac rhabdomyomas found in children, especially those related to TSC, have multiple foci [3,4,11].

Large and multi-foci rhabdomyomas, in addition to other benign masses such as fibromas, can obstruct cardiac flow. As a result, these masses require surgical resection to restore normal hemodynamics [6,11]. Other benign tumors that may require surgical intervention include myxomas and teratomas. While these masses can be obstructive as well, they also have the potential to embolize, locally recur, or cause arrhythmias [6,12].

In children with rhabdomyomas secondary to TSC, long-term outcomes are generally dependent on the level of hamartomatous involvement of the nervous system [13]. Most malignant tumors reported in the literature are sarcomatous in nature and associated with poor outcomes [3]. In fact, some retrospective studies show 100% mortality in children with cardiac malignancies [3,6]. Nevertheless,

according to the literature, surgical resection of a malignant tumor should be attempted whenever possible [6]. Factors that may prohibit resection include tumor size, location, and extent of invasion.

Patients and Methods

This is a retrospective observation study of patients referred to the cardiothoracic surgical service for evaluation of a cardiac tumor at a large, tertiary children's hospital from 1969 to 2014. Surgical case logs and hospital medical records were reviewed for International Classification of Disease, Version 9, Clinical Modification codes (ICD-9-CM; 164.1, 212.7), and Current Procedural Terminology Codes (CPT; 32097, 33050, 33120, 33130, 39220) related to intra-cardiac and extra-cardiac tumors. Over this 45-year period, 35 patients who had surgical procedures were identified. Hospital medical records were reviewed for each patient. Of the 35 patients 5 were excluded, 2 patients operated on in the early 1970s had largely incomplete records and could not be further analyzed. Another patient with benign lipoma was older than 18 years at the time of surgery. Two patients with angiosarcoma who were operated on in their mid-20s and who subsequently died within 6 months of surgery were also excluded because of their age. Thirty-four patients where seen for surgical consultation and were not operated on which were identified by ICD-9-CM and CPT codes for outpatient consults in order to determine the overall denominator for patients presenting for surgical evaluation. These records were available back to 1985 and had limited clinical details. This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors. The Indiana University Institutional Review Board reviewed and approved this study.

Patient characteristics including age at presentation, age at surgery, gender, tumor pathology, clinical symptoms, and diagnostic imaging where collected. Congestive heart failure (CHF) pre-operatively was defined by symptoms of cough, dyspnea, edema, fatigue, or ascites that were unrelated to other etiologies. Incidental congenital heart lesions such as atrial septal defect (ASD), patent ductus arteriosis (PDA), and valve dysfunction (unrelated to the tumor) were noted. Pre-operative dysrhythmia was documented in the clinical history. Routine echocardiography (ECHO) was performed in all patients

and supplemental radiological evaluations including fetal ECHO, cardiac catheterization, computed tomography (CT), and magnetic resonance imaging (MRI) were reviewed.

Post-operative outcomes were described for all patients. Mortality at any time point was the primary outcome. Post-operative complications including valve dysfunction, arrhythmia, infections, and post-pericardiotomy syndrome were noted. Follow-up was determined by reviewing the most recent clinical documentation for each patient as well as all post-operative visits to determine the presence of complications or mortality. Five patients were considered to have incomplete follow-up because they had less than 5 years of known survival and had not been seen for 3 years. Follow-up surgery was evaluated but rarely occurred and is discussed separately.

Descriptive analysis and statistical comparisons were performed using Stata 12.1 (Stata Corp, College Station, TX). Proportions or median values with interquartile range (IQR) are reported. Bivariate comparisons using Fischer's exact and Ranksum testing were performed but in most cases were not statistically significant given the small sample size unless specifically noted. Potentially clinically significant differences between patients with malignant and benign pathologies are presented. Association between complications (regurgitation, infection, arrhythmia, post-pericardiotomy syndrome) and pre-operative factors (age, gender, number of surgical procedures, CHF, arrhythmia, and tumor location) for patients with benign tumors were assessed with bivariate logistic regression. Survival analysis was limited to patients with malignant pathology because no known deaths have occurred in patients with benign tumors.

Results

Sixty-four patients were evaluated for surgical excision of a cardiac tumor between 1969 and 2014. Eleven patients (17% of the total cohort) had malignant pathology with 8 (73% of malignant cohort) ultimately having a surgical intervention. Fifty-three patients (83% of the total cohort) had benign pathology with 22 (42% of the benign cohort) proceeding to surgical intervention.

Among patients with benign tumors the tumor pathology included: rhabdomyoma (37, 70%), myxoma (6, 11%), teratoma (4, 8%), and other pathology as delineated in Table 1. The 30 patients with benign pathology who did not have surgical intervention all had asymptomatic rhabdomyomas that were followed but never had a surgical intervention. Among the rhabdomyomas that required surgery (7 patients), 6 patients (86%) had tuber sclerosis complex. Most of these patients (6, 86%) had surgery before 3 months of age for symptomatic lesions. One patient with tuber sclerosis complex was identified around age 4 and subsequently had surgery. The tumor pathology for patients with malignant tumors was highly variable and is presented in Table 1. All patients presenting with malignant tumors were symptomatic except for one patient with a prenatally diagnosed teratoma (by prenatal ECHO), which was resected on the 2nd day of life. .

Among the 30 patients who required surgical intervention, the median age for patients with malignant tumors was 4.8 years (2.2,13.5) versus 1.9 years (0.1,8.0) for benign tumors. Patients with malignant tumors were 88% male compared to 60% in benign tumors. CHF symptoms were similar in both the malignant and benign tumor groups (38% and 32% respectively); and were not associated with right heart or pericardial tumors. Incidental heart lesions are delineated in Table 2 but occurred in 25% of patients with malignant tumors and 55% of benign tumors. Pre-operative rhythm issues such as ventricular tachycardia, atrial tachycardia, or bradycardia were noted in 13% of malignant tumors and 23% of benign tumors. Tumor location as assessed by ECHO is described in Table 2. Benign tumors more commonly had lesions in multiple locations and so direct comparisons were difficult. Left sided lesions were rare among malignant tumors (13%) versus benign (59%, p=0.04). Additional imaging was used in 63% of patients with malignant tumors and 32% of benign tumors and is specified in Table 2. Tumors were found on fetal ECHO in 7 patients (24% of operative cases) including 6 patients with benign tumors (4 rhabdomyomas, 1 teratoma, and 1 fibroma). Fetal ECHO was used in diagnosis of 55% (6/11) of all patients operated on by 1 year of age. Fetal ECHO initially diagnosed one patient with benign rhabdomyoma who was followed until 4 years of age, when he required surgery.

Thirty-eight cardiac surgical procedures were performed on 30 patients over this 45-year time period. Nineteen surgical procedures (63%) have been performed in the last 15 years. Twenty-seven patients (90%) required a single surgical resection. Complete surgical resection was the preferred approach for both benign and malignant tumors. Partial excision was used selectively for: 1) a rhabdomyoma causing right ventricular outflow tract obstruction (RVOTO) and was adherent to the interventicular septum, 2) biopsy and resection of a pericardial rhabdomyoma, 3) de-bulking of a osteosarcoma extending in the right atrium and inferior vena cava, and 4) an invasive leiomyosarcoma that invaded multiple structures in the chest. One patient with an extensive rhabdomyoma causing RVOTO required a planned staged procedure involving a Blalock-Taussig or bidirectional Glenn shunt until there was tumor regression. Subsequent shunt removal with tumor resection including ablation of the RVOTO resulted in adequate cardiac output but complicated by complete heart block and pacemaker dependence. Anther patient had recurrent myxomas and required 4 surgeries over 18 years to remove them as they became clinically significant. The same patient who initially had de-bulking of his right atrial osteosarcoma required 2 additional procedures for recurrence and metastasis.

Fresh autologous pericardium or 0.4mm thickness PTFE was used to replace cava, atrial free-wall and/or atrial septum that was resected with either benign or malignant tumors. In the rare occasions where ventricular free wall was resected, primary closure was accomplished without prosthetic material. Cryopreserved allograft tissue was used for one patient with an extensive malignant tumor that involved the left atrium and right pulmonary veins and inferior vena cava. To date we have not had to replace valve leaflet tissue. We would likely use gluteraldehyde autologous pericardium to replace leaflet tissue if replacement were necessary.

The outcomes for patients with benign tumors were good with no known deaths among these patients. Median follow-up for these patients was 5 years (2.7, 14.7) with a maximum follow-up in one patient of 26 years. As discussed, multiple procedures were planned in one patient and serial resections for recurrent myxomas in the other. One patient required extracorporeal membrane oxygenation post-operatively for low cardiac output after a resection of a large left ventricular fibroma but fully recovered.

Post-operative complications including mitral regurgitation (5 patients), arrhythmia (2), infection (1), and post-pericardiotomy syndrome (1) occurred in 32% (7/22). Pre-operative risk factors (including age, number of surgical procedures, gender, and CHF or arrhythmia at presentation) were not associated with the likelihood of developing a post-operative complication. Tumor location was only associated with a post-operative complication if the tumor was associated with the mitral valve. Of the three patients with mitral valve lesions all of them had post-operative mitral regurgitation. Two other patients with left sided lesions (one in the atria and one in the ventricle) also had mitral regurgitation post-operatively. No patient to date however has required mitral valve repair or replacement.

Overall mortality was 38% (3/8) among patients requiring surgery for malignant pathology. These three patients had highly aggressive tumors including leiomyosarcoma, osteosarcoma, and hepatoblastoma. Death occurred within the first 2 post-operative years. Figure 1 indicates the Kaplan-Meier survival curve for these patients. Survival was unrelated to age at surgery or CHF symptoms at presentation. Four patients with malignant tumors survived and were treated with adjuvant chemotherapy as shown in Table 3. Two of these patients have survived for more than 15 years.

Comment

Cardiac neoplasms are rare in both adults and children. The majority of tumors in adults are secondary, or arising from non-cardiac tissue, and either invading or metastasizing to the heart [14]. The majority of tumors in the pediatric population, however, are primary, arising from the heart itself. Of these primary tumors, rhabdomyoma is the most common pathology [3]. This single-institution, 45-year, retrospective review is congruent with the literature. Most (58%) of the patients in the study had a cardiac rhabdomyoma, often associated with tuberous sclerosis. Other observed, benign pathologies included fibroma, myxoma, and teratoma. All of these tumors were successfully resected with a 31% complication rate, mostly due to tumor location on or near the mitral valve resulting in post-operative regurgitation.

The literature recommends surgical intervention when a benign cardiac tumor compromises hemodynamics or is at significant risk for embolization [6]. Our institution followed suit and excised or

de-bulked less than half of its benign cases. Malignant tumors required a more aggressive approach. They were treated with radical excision, when possible, along with adjuvant chemotherapy or radiation. Patients with operable malignant tumors had a 38% mortality. All deceased patients in the study had malignant pathology; there were no deaths from benign pathology. Of note, aggressive surgical intervention in two cases of malignancy yielded long-term survivals greater than 15 years.

Patients with cardiac tumors present in a variety of ways. Common presentations in this study included CHF, arrhythmia, and auscultated murmur. Fetal ultrasound was able to detect a quarter of the surgical candidates and most children who were operated on before 1 year of age. Children with benign tumors tended to present at a younger age than those with malignant pathology. Post-operative mortality appears to be mostly associated with tumor pathology. The evaluation of pediatric cardiac tumors is focused on clinical symptoms of heart failure, dysfunction, or potential clinical impairment as well as non-invasive assessment of likely tumor pathology prior to surgery. ECHO has provided the most consistent assessment of anatomy and function. Cardiac catheterization has become less important with improvements in ECHO. Additional testing by CT and MRI are especially useful for malignant tumors to assess for metastasis and extension. As cardiac MRI continues to improve, this may prove to be a more useful modality.

A multitude of surgical approaches can be utilized in the management of pediatric cardiac neoplasms. In addition to complete tumor excision or de-bulking, surgeons may also find it necessary to reconstruct excised tissue as described above or even redirect flow around a non-resectable mass. These more involved surgical procedures have their additional risk, however. In this study, surgical procedures that required reconstruction seemed to be associated with more post-operative complications. Resections of tumors involving cardiac valves would also coincided with complications, particularly post-operative valvular insufficiency. In this series, however, mitral valve repair or replacement was not necessary and regurgitation improved with time.

Due to the rarity of pediatric cardiac tumors, single-institution studies often lack statistical power, limiting the conclusions that can be drawn. Additionally, as with all retrospective reviews, data is limited

to the signs, symptoms, and complications that were recorded in the medical records. Despite all this, our group found that aggressive surgical management of malignant cardiac tumors in combination with appropriate adjuvant chemotherapy can lead to long-term survival. We learned of potential predictors of outcome in this population including presentation with congestive heart failure, age, and type of surgical management. In the future, research on this topic could improve by utilizing a larger public or private databases to improve the conclusions that can be drawn.

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Tables:

Table 1: Cardiac tumor pathology by management type

Pathology	**Total, n (%)** (64 patients)	**Surgically-Managed, n (%)** (30 patients)
Benign Tumors		
Rhabdomyoma	37 (58%)	7 (23%)
Myxoma	6 (9%)	6 (20%)
Teratoma	4 (6%)	4 (13%)
Fibroma	4 (6%)	3 (10%)
Other (leiomyoma & neurogenic tumor)	2 (3%)	2 (7%)
Malignant Tumors		
Primary Cardiac Sarcomas	2 (3%)	2 (7%)
Secondary Tumors	9 (14%)	6 (20%)

Primary malignant cardiac sarcomas: leiomyosarcoma, & rhabdomyosarcoma
Secondary malignant tumors: teratoma (2), hepatoblastoma (2), osteosarcoma (2), Wilms tumor, pleuropulmonary blastoma ,& neuroblastoma

Table 2: Patient Characteristics among benign and malignant tumor pathology

	Benign Tumors (22 patients)	**Malignant Tumors** (8 patients)	*p*-value
Age at surgery (med, IQR)	1.9yr (0.1,8.0)	4.8yr (2.2,13.5)	0.41
Male Gender	60% (13)	88% (7)	0.21
CHF	32% (7)	38% (3)	1.0
Dysrhythmia	23% (5)	13% (1)	1.0
Incidental Heart Lesions	55% (12)	25% (2)	0.23
Fetal ECHO	29% (6)	13% (1)	0.64
Additional Imaging			0.12
Cardiac Catheterization	14% (3)	13% (1)	
CT Imaging	9% (2)	50% (4)	
MRI	9% (2)	26% (2)	
Anatomic Location			
Right Atrium	9% (2)	63% (5)	
Left Atrium	23% (5)	-	
Mitral Valve	14% (3)	-	
Right Ventricle	23% (5)	-	
Left Ventricle	32% (7)	13% (1)	
Pericardium	23% (5)	25% (2)	
Duration of follow-up	5yr (2.7,14.7)	2.9yr (0.5,10.5)	0.31
Mortality	-	38% (3)	-
Complications			
Mitral Regurgitation	23% (5)	-	-
Dysrhythmia	9% (2)	-	
Surgical Site Infection	5% (1)	-	
Post-pericardiotomy syndrome	5% (1)	-	

Age and follow-up duration are presented as median (IQR), all others presented as percent of total (n).
A single patient can have tumors in multiple anatomic locations.

Table 3: Adjuvant chemotherapeutic regimens used in patient that survived malignant tumors

Tumor	Adjuvant Chemotherapeutic Regimens
Rhabdomyosarcoma	3 rounds of vincristine, adriamycin/actinomycin-D, and cyclophosphamide
Teratoma	4 courses of bleomycin, cisplatin, and etoposide
Wilms tumor	6 weeks of vincristine and daunorubicin, followed by radiation, and a round of cytoxan & etoposide.
Pleuropulmonary blastoma	Initially treated with Ado-trastuzumab and intrapleural cisplatin. Had subsequent recurrence and has received an autologous stem cell transplant

Second teratoma required no adjuvant chemotherapy

Figure Legend:

Figure 1: Kaplan-Meier Survival curve for patients with malignant tumors.