Surgery for Primary Cardiac Tumors in Children : Early and Late Results in a Multicenter European Congenital Heart Surgeons Association Study

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Circulation. 2012;126:22-30; originally published online May 24, 2012;
doi: 10.1161/CIRCULATIONAHA.111.037226
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0009-7322. Online ISSN: 1524-4539

Surgery for Primary Cardiac Tumors in Children

Early and Late Results in a Multicenter European Congenital Heart Surgeons Association Study

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Background—To evaluate indications and results of surgery for primary cardiac tumors in children.

Methods and Results—Eighty-nine patients aged ≤18 years undergoing surgery for cardiac tumor between 1990 and 2005 from 16 centers were included retrospectively (M/F=41/48; median age 4.3 months, range 1 day to 18 years). Sixty-three patients (68.5%) presented with symptoms. Surgery consisted of complete resection in 62 (69.7%) patients, partial resection in 21 (23.6%), and cardiac transplant in 4 (4.5%). Most frequent histotypes (93.2%) were benign (rhabdomyoma, myxoma, teratoma, fibroma, and hemangioma). Postoperative complications occurred in 29.9%. Early and late mortality were 4.5% each (mean follow-up, 6.3±4.4 years); major adverse events occurred in 28.2% of the patients; 90.7% of patients are in New York Heart Association class I. There were no statistically significant differences in survival, postoperative complications, or adverse events after complete and partial resection in benign tumors other than myxomas. Cardiac transplant was associated significantly with higher mortality rate (P=0.006). Overall mortality was associated to malignancy (P=0.0008), and adverse events during follow-up (P=0.005).

Conclusions—Surgery for primary cardiac tumors in children has good early and long-term outcomes, with low recurrence rate. Rhabdomyomas are the most frequent surgical histotypes. Malignant tumors negatively affect early and late survival. Heart transplant is indicated when conservative surgery is not feasible. Lack of recurrence after partial resection of benign cardiac tumors indicates that a less risky tumor debulking is effective for a subset of histotypes such as rhabdomyomas and fibromas. **(*Circulation*. 2012;126:22-30.)**

Key Words: cardiac surgery ■ cardiac tumors ■ congenital cardiac defects ■ outcomes ■ pediatrics

Primary cardiac tumors are a very rare disease in pediatric practice.[1–4] They are more frequently benign neoplasms arising primarily in the inner lining, the muscle layer or the surrounding pericardium of the heart.[2]

Clinical Perspective on p 30

The current literature is reporting mostly on surgical resection of primary cardiac tumors, particularly myxomas, in

Received April 13, 2011; accepted April 30, 2012.

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The online-only Data Supplement is available with this article at http://circ.ahajournals.org/lookup/suppl/doi:10.1161/CIRCULATIONAHA.111.037226/-/DC1.

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Circulation **is available at http://circ.ahajournals.org** **DOI: 10.1161/CIRCULATIONAHA.111.037226**

adults,[5,6] or single surgical case reports in pediatric patients.[7–9] There are only a few long-term retrospective analyses that include the whole spectrum of primary cardiac tumors in children.[10–12]

For this reason, we have embarked on a multicenter study within the European Congenital Heart Surgeons Association to evaluate indications and results after surgery for cardiac tumors in a large cohort of pediatric patients.

Materials and Methods

Patients who underwent surgery for primary cardiac tumor in the pediatric age (≤18 years of age), between January 1, 1990 and December 31, 2005 were included. Sixteen centers were enrolled in this study. Review of medical records was approved by each hospital's local committee on clinical investigation. Individual patients were not identified, and the need for patient consent was waived. Data were collected according to a common database; variables are described in online-only Data Supplement Table I.

Preoperative echocardiographic findings were defined as "hemodynamic impairment" in the presence of one of the following: right or left ventricular outflow tract obstruction, defined as significant when peak systolic pressure gradient was >50 mm Hg; mitral valve regurgitation (greater than mild), or stenosis (significant if transmitral velocity was >1.3 m/s); pericardial effusion causing tamponade.

Statistical analysis investigated the effects of various clinical variables on postoperative death and complications and onset of adverse events (such as cardiac/non–cardiac-related death, reoperation, recurrence of cardiac/noncardiac tumor, other, including tuberous sclerosis) at follow-up. Moreover, complications and adverse events were considered as risk factors for death. Log-rank test was used to test effect of clinical variables on survival. Because the precise chronology of adverse events was not always known, we included in analysis all complications and adverse events occurring during follow-up, and we applied Fisher's exact test to analyze the effects of clinical variables on complications and adverse events and the effects of complications and adverse events on overall death. For the same reason, freedom from adverse events (cardiac or noncardiac tumor recurrence, cardiac reoperation) was calculated at specific time points (1 and 10 years), including only patients with follow-up ≥1 year.

Finally, McNemar test was used to determine a significant difference of 3 major clinical variables (ie, presence of arrhythmia, congestive heart failure, and echocardiographic pathological findings) before and after surgical repair. Survival functions were constructed with Kaplan-Meier estimates.[13] Probability values <0.05 were considered statistically significant. Analyses were performed using SAS System, version 9.2.

Results

Early Outcomes

Eighty-nine patients were selected for this surgical series (M/F, 41/48; mean age at operation, 4.2 years; median age, 4.3 months; range 1 day to 18 years). Forty-six patients underwent operation at <4 months of age.

Surgery was advocated because of the presence of symptoms, ECG abnormalities, or echocardiographic impairment as defined above (Table 1).

At physical examination, a cardiac murmur was detected in 6.7% of the patients (6/89). Symptoms were present in 68.5% of patients (online-only Data Supplement Table II), comprising congestive heart failure in 22 (24.7%), arrhythmias in 12 (13.5%), neurological symptoms in 4 (4.5%, syncope and stroke from embolization in 2 patients each); other symptoms (such as chest pain, palpitations and respiratory distress, associated with pleural or pericardial effusions) were present in the remaining 17 symptomatic patients (online-only Data Supplement Table II).

Table 1. Indications for Surgery According to Tumor Histotype

Tumor Histotype (No. of Patients)	Presence of Symptoms	Abnormal ECG	Echocardiographic Hemodynamical Impairment
Rhabdomyoma (32)	23 (71.8)	9 (28.1)	26 (81.2)
Myxoma (18)	10 (55.5)	0 (0.0)	14 (77.7)
Teratoma (12)	7 (58.3)	3 (25.0)	4 (33.3)
Fibroma (9)	5 (55.5)	1 (11.1)	9 (100.0)
Hemangioma (8)	8 (100.0)	2 (25.0)	3 (37.5)
Sarcoma (5)	5 (100.0)	3 (60.0)	3 (60.0)
Other* (5)	3 (60.0)	0 (0.0)	4 (80.0)
Total (89)	61 (68.5)	18 (20.2)	63 (70.8)

All data shown are number of patients (% of tumor histotype).
*Other includes pseudotumor (3), papilloma (1), and malignant teratoma (1).

Overall, preoperative ECG showed a regular sinus rhythm in 71 patients (79.8%). Rhythm disturbances were present in 18 patients; the most common were ectopic multiple atrial and/or ventricular beats in 13 patients, followed by atrial flutter in 3, and paroxysmal supraventricular tachycardia in 2 (online-only Data Supplement Table II).

The cardiac mass was mainly detected by means of 2-dimensional echocardiography (92.0%). Prenatal echocardiographic diagnosis was available in 22.5%.

At echocardiographic evaluation, 63 patients (70.8%) presented with hemodynamic impairment that was caused by atrioventricular valve distortion in 20 patients (22.5%), left ventricular outflow tract obstruction in 18 (20.2%), right ventricular outflow tract obstruction in 11 (12.4%), and other findings in 14 (15.7%). Echocardiographic findings are listed in detail in online-only Data Supplement Table II.

To achieve a complete diagnosis, in addition to echocardiography, magnetic resonance imaging and computed tomography scan were necessary in 26 (29.2%) and 11 cases (12.4%), respectively.

Cardiac tumors were found as single masses in 65 patients (73.0%) and as multiple masses (2–4 masses) in 24 (27.0%). The mass was localized mostly in the ventricles (44 patients, 49.4%) and in the atria (29 patients, 32.6%), whereas it was extracardiac in 13 patients (14.6%); finally it was found in both atrial and ventricular cavities in 3 patients (3.4%; online-only Data Supplement Table II).

Pathological analysis revealed that rhabdomyoma was the most frequent tumor histotype (32 cases, 35.9%), followed by myxoma (18 cases, 20.2%), teratoma (12 cases, 13.5%), fibroma (9 cases, 10.1%), and hemangioma (8 cases, 9.0%). Most of primary cardiac tumors resulted in being histologically benign (93.2%). Malignant tumors were found in 6 patients (M/F, 4/2), who presented with congestive heart failure (4 cases), atrial flutter (1), and neurological symptoms (1). The tumor mass was >5 cm in diameter in the majority (4/6) of patients. At histology, the mass was consistent with a sarcoma in 5 patients and a malignant teratoma in 1.

Associated cardiac anomalies were present in 19 patients (21.3%; online-only Data Supplement Table III). Noncardiac

Table 2. Primary Surgical Procedures and Early and Late Death Rates According to Tumor Histotype

Histotype	No. of Patients	Complete Resection	Partial Resection	OHT	Other Surgery*	Early Death (Within 30 d From Operation)	Late Death (After 30 d From Operation)
Rhabdomyoma	32	15 (46.9)	14 (43.8)	1 (3.1)	2 (6.2)	1 (3.1)†	0 (0.0)
Myxoma	18	17 (94.4)	1 (5.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Teratoma	12	12 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (8.3)	0 (0.0)
Fibroma	9	5 (55.6)	1 (11.1)	3 (33.3)	0 (0.0)	0 (0.0)	2 (22.2)‡
Hemangioma	8	7 (87.5)	1 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Sarcoma§	5	2 (40.0)	3 (60.0)	0 (0.0)	0 (0.0)	1 (20.0)	2 (40.0)
Other‖	5	4 (80.0)	1 (20.0)	0 (0.0)	0 (0.0)	1 (20.0)¶	0 (0.0)
Total	89	62 (69.7)	21 (23.6)	4 (4.5)	2 (2.2)	4 (4.5)	4 (4.5)

All data are shown as number of patients (% of tumor histotype). OHT indicates orthotopic heart transplant.
*Other surgery includes cavopulmonary anastomosis (1), midline sternotomy and incisional biopsy (1).
†Postoperative brain hemorrhage.
‡Status post heart transplant.
§Two patients lost at follow up.
‖Other tumor histotypes include pseudotumor (3), papilloma (1), malignant teratoma (1).
¶Malignant teratoma.

anomalies were present in 15 patients (16.8%); tuberous sclerosis was the most common one (10 patients). The Carney complex was diagnosed in 2 patients only, who presented with multiple masses and who both had late recurrence at follow-up.

Surgery consisted in complete resection of the mass in 62 patients (69.7%), partial resection in 21 (23.6%) patients, and cardiac transplant in 4 (4.5%) patients (Table 2). In 1 patient with a large biventricular rhabdomyoma, a cavopulmonary anastomosis was performed as a staged univentricular palliation. One last patient was submitted to an incisional biopsy via midline sternotomy. Associated surgical maneuvers were performed in 34 patients (online-only Data Supplement Table IV).

Surgery required cardiopulmonary bypass in 85.4% of the patients (median cardiopulmonary bypass time, 74.5 minutes; mean, 86.6±69.3 minutes), with aortic cross-clamping in 76.4% (median time, 39 minutes; mean, 48.1±41.85 minutes).

Among patients with malignant tumors (6 cases), mean age at operation was 90.0±76.4 months (median, 8.8 years; range, 21 days to 16 years). Surgery consisted of partial resection in 4 patients and complete resection in 2.

Overall median intensive care unit stay was 3 days (range, 1–32 days), with a median mechanical intermittent positive-pressure ventilation of 18 hours (1–430 days). A longer hospitalization was observed after heart transplant (mean intensive care unit stay, 23.7±14.5 days; mean intermittent positive-pressure ventilation time, 120.0±86.5 hours).

Postoperative complications occurred in 26 patients (29.2%; Table 3).The most frequent were pericardial and/or pleural effusions requiring drainage (6 patients), low cardiac output syndrome (5 patients), and arrhythmias (4 patients). Complications are listed according to tumor histotype in Table 3.

Postoperative ECG showed sinus rhythm in 87.0%. Two-dimensional and Doppler echocardiographic study at discharge showed no major residual defects in 68.4%, a mild

Table 3. Postoperative Complications According to Tumor Histotype

Histotype	No. of Patients	LCO	Postoperative Arrhythmia	PNX	Pleural and/or Pericardial Effusion	Phrenic Nerve Injury	Other Complications*	Total
Rhabdomyoma	32	1	1	1	3	1	3	10 (31)
Myxoma	18	0	1	1	1	0	1	4 (22)
Teratoma	12	2	1	0	0	0	1	4 (33)
Fibroma	9	0	1	0	0	0	2	3 (33)
Hemangioma	8	0	0	0	1	0	1	2 (25)
Sarcoma	5	1	0	0	0	0	0	1 (20)
Other†	5	1	0	0	1	0	0	2 (40)
Total	89	5 (5.6)	4 (5.4)	2 (2.2)	6 (6.7)	1 (1.1)	8 (9.0)	26 (29.2)

All data are shown as number of patients (% of tumor histotype). LCO indicates low cardiac output syndrome; PNX, pneumothorax.
*Other complications include undetermined minor secondary complications (3), acute cardiac transplant rejection (1), multiorgan failure (1), superior vena cava thrombosis after heart transplant (1), respiratory insufficiency requiring long-term mechanical ventilation (1), and cerebral hemorrhage on previous brain surgery site (1).
†Other tumor histotypes include pseudotumor (3), papilloma (1), and malignant teratoma (1).

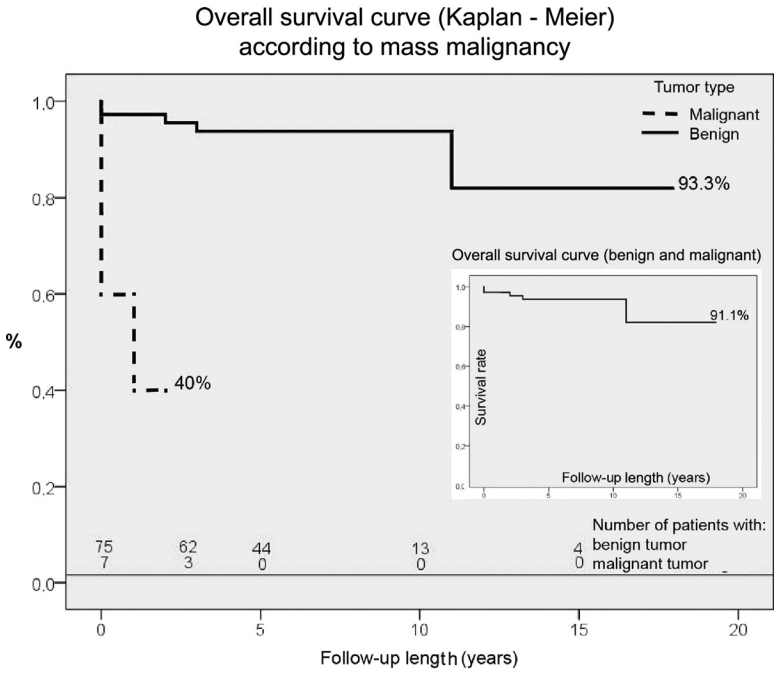

Figure 1. Survival curves according to Kaplan-Meier analysis: the survival estimate for surgical patients affected by a malignant tumor is significantly lower in comparison with patients with a benign tumor ($P=0.0008$). In the bottom line of the diagram, along the *x* axis (years if follow-up), we have listed the patients at risk for each period.

atrioventricular valve regurgitation in 19.0%, and trivial or mild aortic or pulmonary valve stenosis or regurgitation in the remaining patients.

Eighty-five of 89 patients (95.5%) were discharged from the hospital in good clinical condition. Four patients died within 30 days after surgery, accounting for an early mortality rate of 4.5%: 3 patients (2 with malignant neoplasms, 1 with a benign teratoma) died of postoperative low cardiac output syndrome; another patient with rhabdomyoma, who had previously undergone brain surgery, died late of massive intraparenchymal brain hemorrhage. Thus, operative mortality decreases to 2.4% in the benign subgroup.

Follow-Up

At a mean follow-up of 6.33±4.37 years (follow-up completeness, 91%; range, 0.3–18.6 years), 74 patients are alive and well, the majority of whom are in New York Heart Association class I. Among these, 59 patients (79.7%) show a functional capacity comparable to peers, whereas 11 patients (14.8%) affected by rhabdomyoma and tuberous sclerosis show an impaired neurological status. Sixty-two patients (83.7%) are medication free.

Late death occurred in 4 patients (4.5%; Table 2). In 1 patient, a malignant cerebral mass occurred 15 months after surgery for a malignant cardiac tumor; in another patient, a cerebral astrocytoma developed 3.1 years after cardiac transplant; a third patient died of severe pneumonia 2 years after surgery, complicating long-term mechanical ventilation for severe pulmonary fibrosis after resection of a sarcoma; a fourth patient died 11.3 years after heart transplant because of chronic cardiac rejection (graft vasculopathy).

At follow-up, global freedom from adverse events was 85.7% at 1 year (95% CI, 0.577–1.0), 76.3% at 10 years (95% CI, 0.654–0872).

Freedom from cardiac tumor recurrence was 94.9% at 10 years (95% CI, 0.892–1): a myxoma recurred in 2 patients with a late diagnosis of Carney complex; a benign teratoma was reoperated successfully 2 years after incomplete resection; finally, progressive growth of a partially resected sarcoma occurred in another patient.

Freedom from cardiac reoperation was 90.7% at 10 years (95% CI, 0.832–0.982): 8 patients needed a cardiac reoperation, which consisted in mitral valve plasty in 2, tricuspid valve plasty in 2, a redo heart transplant in 2, and a recurrent myxoma resection in 2.

Freedom from noncardiac tumor recurrence was 93.2% at 10 years (95% CI, 0.867–0.997): a brain tumor occurred in 2 patients (after heart transplant in 1 case), a cholesteatoma in one and an unspecified malignant mass in another. Seven patients had other adverse events (seizures related to tuberous sclerosis in 4 patients with a previous rhabdomyoma, and paroxysmal nocturnal hemoglobinuria, intestinal intussusception, and chronic heart rejection after transplant, one each).

Statistical Analysis

Survival curves according to Kaplan-Meier analysis are shown in Figure 1. The survival estimate for surgical patients affected by a malignant tumor is significantly lower in comparison with patients with a benign tumor (overall mortality is 60.0% versus 6.5%, respectively; $P=0.0008$; Table 4). In contrast, there is no statistical association between tumor malignancy and postoperative complications or follow-up adverse events.

Effects of clinical variables on outcomes are summarized in Table 4. Symptoms at presentation, arrhythmias, preoperative heart failure, and hemodynamic impairment are not significantly related to survival or a higher rate of postoperative complications or adverse events at follow-up. There is no significant difference in patients after complete or partial mass resection in terms of overall mortality and postoperative complications, whereas a significant incidence of adverse events at follow-up is detected (18.5% in complete versus

Table 4. Significance of Clinical Variables as Significant Risk Factors for Outcomes

Clinical Variables	Overall Mortality		Postoperative Complication	Adverse Events at Follow-Up
	Log-Rank Test	Fisher Exact Test	Fisher Exact Test	Fisher Exact Test
Malignancy	0.0008	…	0.409	0.086
Symptoms	0.171	…	0.189	0.600
ECG other than SR	0.881	…	0.094	0.370
CHF	0.299	…	0.050	0.743
Multiple mass	0.447	…	0.409	0.018
Hemodynamic impairment	0.971	…	0.147	0.693
Associated cardiac anomaly	0.402	…	0.203	0.208
Associated noncardiac anomaly	0.352	…	0.526	0.784
Total vs partial resection, benign	0.479	…	0.187	0.009
Orthotopic heart transplant	0.006	…	0.069	0.518
Associated surgical procedures	0.134	…	0.702	0.729
Age at operation <6 mo	0.211	…	0.717	0.694
Age at operation <12 mo	0.140	…	0.795	0.822
Postoperative complications for benign tumor	…	0.026	…	…
Adverse events during follow-up	…	0.005	…	…

CHF indicates congestive heart failure; SR, sinus rhythm.

43.7% in partial; Fisher's exact test $P=0.009$). Cardiac transplant is significantly associated with a higher overall mortality (25.0% versus 2.7%; $P=0.006$). Simultaneous surgical repair of associated cardiac anomalies does not increase either the surgical mortality risk or the incidence of postoperative complications or adverse events at follow-up. In addition, postoperative overall mortality is not influenced by the association with a noncardiac anomaly. Complicated postoperative course do have a negative effect on survival in patients with benign cardiac tumors (75% versus 27.8%; $P=0.026$), whereas occurrence of adverse events at follow-up negatively influence survival in all patients (100% versus 24.3%; $P=0.005$).

The effectiveness of surgery on improving patients' clinical conditions is demonstrated by McNemar test on variables such as presence of symptoms, hemodynamic impairment, and cardiac rhythm abnormalities (Table 5). In fact, 18 patients presented with arrhythmia before operation, but only 6 showed persistence of arrhythmias after surgery ($P=0.0075$). Likewise, 17 patients presented with congestive heart failure before operation, but only 1 patient among these 17 was showing persisting congestive heart failure postoperatively and during follow-up ($P=0.033$). Finally, 48 patients had

Table 5. Effects of Surgery on Patients' Clinical Conditions Evaluated by McNemar Test

	Postoperative		Total	McNemar *P* Value
ECG rhythm	SR	No SR		
Preoperative				
SR	65	2	67	0.0075
No SR	12	6	18	
Total	77	8	85	
CHF	No	Yes		
Preoperative				0.033
No	52	6	58	
Yes	16	1	17	
Total	68	7	75	
Echo alteration	No	Yes		
Preoperative				<0.0001
No	18	4	22	
Yes	32	16	48	
Total	50	20	70	

The McNemar test was used to determine a statistical relation between 2 identical variables belonging to the same population, before and after an event, such as cardiac surgery. The total number of patients is <89 because of missing information. CHF indicates congestive heart failure; ECG, electrocardiogram; SR, sinus rhythm.

echocardiographic hemodynamic impairment before operation, whereas this impairment persisted in only 16 patients after operation and during the follow-up ($P<0.0001$).

Discussion

Primary cardiac tumors are rare, with an estimated prevalence of 0.0017 to 0.28 in autopsy series.[1–2] In the pediatric age, an incidence of cardiac tumors of ≈0.14% has been reported during fetal life[3]; furthermore, the review of the echocardiographic database at Boston Children's Hospital showed an incidence of ≈0.17% in children.[4]

Current literature on treatment for primary cardiac tumors in children mostly reports on single cases[7–9] or small series.[10–12] Thus, definitive statements on this matter are often inconclusive. For this reason, we have started a multicenter study within the European Congenital Heart Surgeons Association to collect data on a large scale and define the early and late results after surgery for primary cardiac tumors in the pediatric age. To the best of our knowledge, this is the largest multicenter retrospective surgical series ever reported.

Because some cardiac tumors may potentially regress, surgical treatment is usually indicated whenever symptoms are present. In this series, symptoms were present in most of the patients (68.5%), but not in all. Nonetheless, surgery was advocated even in absence of symptoms, whenever instrumental data (echocardiography or ECG) indicated a life-threatening condition (Table 1). Even anticipating that a potential regression might have occurred in some of these cases, surgery was considered as a prophylactic strategy to prevent mass-related potentially fatal complications (tumor embolization, severe valve regurgitation or stenosis, impinging atrioventricular valve orifice, ventricular arrhythmias).

Furthermore, as described elsewhere[10–12,14,15] surgery for cardiac tumors in pediatric age carries an acceptable mortality risk. In our series, overall operative mortality accounts for 4.5%; however, considering only the benign histotypes, only 2 of 83 died at operation (2.4%), confirming a low operative mortality rate. In addition, in children with benign cardiac tumors, there was no difference in terms of overall mortality and postoperative complications between complete and partial resection of the tumor other than myxoma, especially for those tumors that may spontaneously regress such as rhabdomyomas.[15–17] This is not in contrast with the significantly different incidence of adverse events at follow-up detected in these 2 groups ($P=0.009$); in fact, most histotypes undergoing partial surgical resection were rhabdomyomas, in which development of tuberous sclerosis may be a common adverse event. Moreover, there was no regrowth of tumor late after partial resection, confirming the efficacy of this type of treatment. In light of these data, partial resection with a less risky tumor debulking may be the safest surgical option for patients with benign cardiac tumors other than myxomas, especially when the mass involves the ventricular myocardium close to the coronary arteries. Finally, our experience demonstrates that surgery ameliorates patients' clinical conditions, as shown in Table 5.

Surgical resection is usually tailored on patient's characteristics. It requires cardiopulmonary bypass and aortic cross-clamp in most cases, especially when the mass is intracardiac. Gentle manipulation of the heart is suggested to avoid cardiac mass fragmentation and embolization (ie, myxomas). Because surgical approach (ie, transatrial, transventricular, transaortic) depends on the mass position, it is of paramount importance that its correct location is diagnosed preoperatively. A proper surgical exposure of the mass is essential to ensure a radical resection and to preserve the integrity of the surrounding cardiac structures, especially of the coronary vessels that may run close to the mass. Partial debulking has proven to be effective in most benign histotypes, whenever a more complete resection may damage surrounding tissues. Finally, associated procedures may be necessary, such as atrial patch closure after myxoma resection, and right ventricular patch reconstruction after fibroma resection.

Overall, 8 patients died in this series (9.0%); mortality was associated with the malignant nature of the mass (3 cases) or with onset of noncardiac events (4 cases), whereas only 1 death can be directly related to the operation (after extensive resection of an extracardiac teratoma). As previously reported by Uzun and coworkers,[2] survival after surgery in the long term is definitely related to the malignant nature of the tumor ($P=0.0008$), with a mortality rate of 33% for the malignant masses versus 4.1% for the benign masses (Figure 1). These patients with a malignant mass may actually benefit clinically from palliative surgery, such as a partial resection, associated with chemotherapy and radiotherapy.[18] However, prognosis in these patients is extremely poor even after surgery.

In our multicenter experience, cardiac transplant was considered as the only option in 4 patients with a large mass (mostly a fibroma) that was invading the left ventricular cavity and infiltrating the left ventricular myocardium (Table 2). Despite the low numerosity, our analysis demonstrated a reduced long-term survival ($P=0.006$) in comparison with conservative surgery, and a mild tendency to higher rate of occurrence of postoperative complications ($P=0.069$). Thus, according to current data on results after cardiac transplant in children,[19–21] we believe that a surgical resection should be attempted whenever possible to avoid the undesirable complications of cardiac transplant.

In the current literature on pediatric cardiac tumors, the incidence of preoperative symptoms described is as high as 60% of cases.[1,2,10,21,22] These data are confirmed in our surgical series, in which the majority of patients were symptomatic preoperatively (68.5%). However, presence of symptoms does not affect overall survival, incidence of postoperative complications, or adverse event at follow-up. Symptoms are not associated with any specific cardiac tumor histotype, apart from malignancy and hemangioma, in which symptoms were always present in our series (online-only Data Supplement Table II).

Finally, in contrast with what is actually reported,[22–24] myxomas were not associated with a greater incidence of neurological symptoms (only 1 patient among 18) in comparison with other histotypes, and they were often operated on in the absence of symptoms (≈50% of cases), because of their intracavitary growth, to prevent life-threatening complications.

Our analysis shows a relationship between tumor histotype and cardiac localization, ie, rhabdomyoma in the ventricles, myxoma in the atria, and teratoma mostly intrapericardial and extracardiac (Figure 2); despite this relationship, the association was not statistically significant. As far as the presence of symptoms, which has often been associated with the size of tumor or its localization,[2,3,11,21,22] we were not able to demonstrate a statistically significant association in our series.

Our study has stressed once more the crucial role of 2-dimensional and Doppler echocardiography in achieving a proper diagnosis of cardiac tumor and mass location.[25,26] Echocardiography was the only instrumental diagnostic tool in most of the patients, precise enough to avoid other diagnostic imaging techniques that might delay an otherwise emergency surgery. Thus, computed tomography and magnetic resonance imaging remain a second-level examination, which was required in about one-third of our patients, especially when a malignant mass was suspected, to achieve a better definition of its location and relationship with the surrounding structures.[26–28] In our series, tumor masses were multiple in one-forth of patients; they consisted mostly of rhabdomyomas, as reported elsewhere.[10,21,22,29] It is noteworthy that, in our study, the incidence of multiple myxomas is slightly higher (12.5%) than what has been reported in literature (10%),[5,30] and they were found only in patients with associated Carney complex, ie, an autosomal dominant disorder characterized by multiple cardiac and nervous neoplasms, cutaneous myxomas, and spotty pigmentation of the skin (lentigines and blue nevi).[31–34] Most cases are familial, and clinical presentation often occurs in teenagers or young adults. In our experience, multiple myxomas were more frequent probably because our patients were all <18 years. In addition, the rare finding of tumor recurrence in our series was associated with Carney complex.

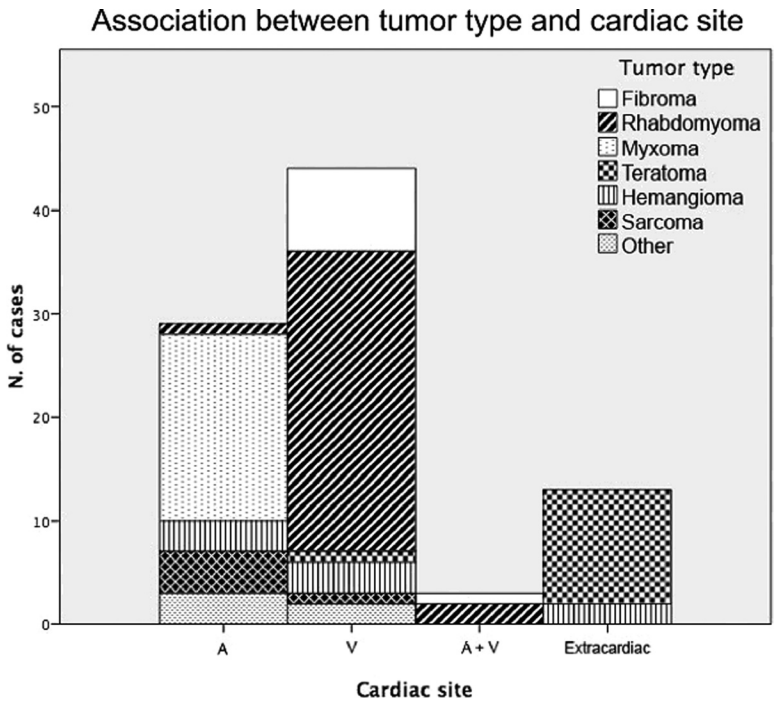

Figure 2. Bar chart showing association between cardiac tumor histotype and cardiac site (Fisher exact test $P<0.0001$).

Our study confirms the frequent association of tuberous sclerosis with rhabdomyomas.[35–38] In our experience, incidence of tuberous sclerosis is consistently lower (47.0%) than what commonly reported (80%–90%). This is probably due to the surgical nature of this series. As such, our series does not represent the whole population of pediatric patients with cardiac rhabdomyomas. Moreover, our data confirm the impaired late neurological status associated to tuberous sclerosis (88.0%).[39–41] Overall, these data and the documented regression of these tumors[42–44] may be important for the prenatal counseling.[45]

As previously emphasized, our series is a surgical one and does not reflect the characteristics of all pediatric cardiac tumors. Anyhow, the pathological examination of excised cardiac masses has revealed that rhabdomyoma is the most frequent tumor in the pediatric age, followed by myxoma, teratoma, fibroma, hemangioma, whereas the malignant tumors are very rare. These data differ substantially from what was reported in previous surgical series,[10–14,21] in which fibroma was considered the most common cardiac tumor requiring surgery. On the other hand, they confirm the prevalence and the age distribution of tumor histotypes in the general pediatric population.[1,2,11,46] In addition, the distribution of the various tumor histotypes depends on patient's age (Figure 3). In fact, the prevalence of rhabdomyomas, fibromas, and teratomas is higher in the first quartile of ages,

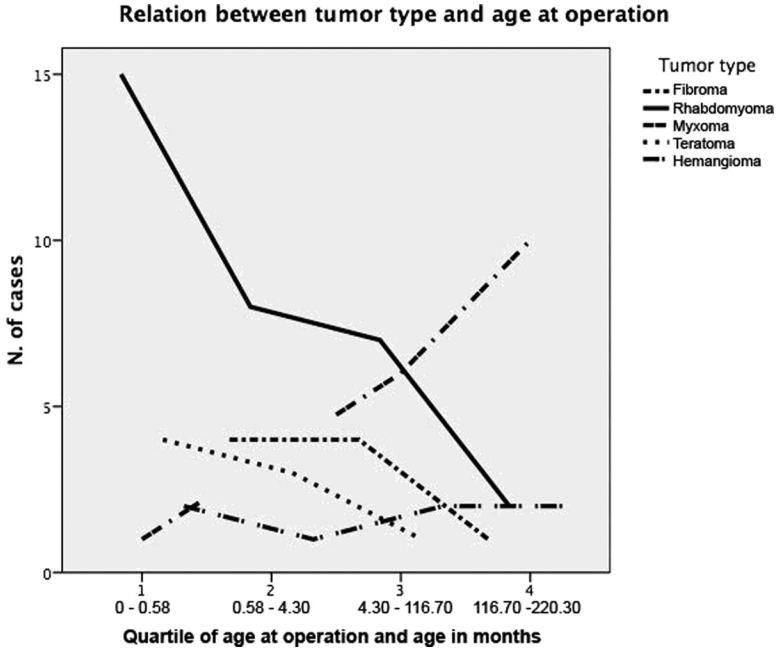

Figure 3. Relationship between tumor histotype and age at operation. It is evident that the need of surgery for rhabdomyomas decreases as age grows, whereas myxomas increase in frequency at older ages (ANOVA test applied to age in its original scale $P<0.0001$). The relation between tumor type and age at operation has been evaluated by means of ANOVA test, considering age as a continuous variable. Age is represented in quartiles in the figure to give a clearer visual display.

whereas myxomas are more frequent in older children, as also reported elsewhere.[2,10,21] This confirms on a large scale what has often been reported in previous case reports,[7,9,15,46,47] and it may support the acquired origin of myxomas[48] in comparison with other histotypes that are commonly described in neonates or even prenatally, and therefore may be considered congenital hamartomas (such as rhabdomyomas or fibromas).

Finally, prenatal echocardiography is nowadays an efficacious imaging diagnostic tool that allows the planning and optimizing of surgical and medical management in neonates with complex congenital heart disease.[49–50] In this surgical experience of primary cardiac tumors, prenatal diagnosis was achieved in 22.5% of cases, but it was not associated with significant differences in operative mortality or postoperative complications in comparison with patients without fetal diagnosis. This may be due to the fact that this surgical series includes patients of different ages, the majority of whom were referred because of symptoms rather than a fetal diagnosis.

Conclusions

Our study on a large cohort of pediatric patients confirms that surgical resection of primary cardiac tumors in children is indicated in presence of symptoms and hemodynamic impairment. Because tumor resection has a low mortality risk (especially in the setting of benign tumors), it may be indicated even in asymptomatic patients as a safe prophylactic therapy to avoid potentially lethal complications. In this surgical series, rhabdomyoma was the most frequent tumor, followed by myxoma, teratoma, fibroma, and hemangioma, whereas primary malignant cardiac tumors were very rare. Complete resection of the tumor, whenever possible, is the main goal of surgery. However, partial resection of benign cardiac tumors other than myxomas ensures optimal early and long-term results as well. Surgical repair of associated cardiac anomalies does not imply a higher risk of mortality or postoperative complications and adverse events at follow-up. Cardiac transplant should be considered only for unresectable cardiac masses that impair cardiac function, because of the increased mortality risk, postoperative complications, adverse events at follow-up, and the significant worsening of the quality of life. At a mean follow-up of >6 years, overall mortality rate is 8.9%. Mortality is mainly related to malignancy, associated diseases, postoperative complications, and adverse events during follow-up. Recurrence of a benign cardiac tumor is rare and usually related to Carney complex.

Disclosures

None.

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CLINICAL PERSPECTIVE

This study, which represents the largest surgical series ever reported, confirms on a large scale that primary cardiac tumor resection in children is indicated in presence of symptoms. In addition, because surgery is demonstrated to be a safe procedure in benign tumors, this study demonstrates that even in asymptomatic patients with instrumental signs of cardiac impairment, surgical resection, either complete or partial, is indicated as a safe prophylactic intervention to avoid potentially lethal complications. Complete resection of the tumor remains the main goal of surgery. However, partial resection or debulking procedures may be efficient enough to ensure optimal early and long-term results in benign tumors. Most importantly, cardiac transplant should be considered for unresectable cardiac masses only because of the increased risk of mortality, postoperative complications, adverse events at follow-up, and significant worsening of quality of life. In this surgical series, rhabdomyoma is the most frequent tumor, followed by myxoma, fibroma, hemangioma, and teratoma. This frequency reflects the current distribution of these diseases in the clinical setting. Overall mortality rate is mainly related to malignancy, associated diseases, postoperative complications, and adverse events during follow-up. Recurrence of a benign cardiac tumor is rare and is usually related to myxomas in patients with the Carney complex, suggesting a role for genetic counseling in these patients.