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Surgery for Primary Cardiac Tumors in Children: Early and Late Results in a Multi-Center European Congenital Heart Surgeons Association (ECHSA) Study

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Massimo A. Padalino, MD, PhD[1]; Vladimiro L. Vida, MD, PhD[1]; Giovanna Boccuzzo, PhD[2]; Marco Tonello, MD[1]; George E Sarris, MD, PhD[3]; Hakan Berggren, MD[4]; Juan V. Comas, MD[5]; Duccio Di Carlo, MD[6]; Roberto M. Di Donato, MD[6]; Tjark Ebels, MD[7]; Viktor Hraska, MD[8]; Jeffrey Jacobs, MD[9]; J. William Gaynor, MD[10]; Dominique Metras, MD[11]; Rene Pretre, MD[12]; Marco Pozzi, MD[13]; Jean Rubay, MD[14]; Heikki Sairanen, MD[15]; Christian Schreiber, MD[16]; Bohdan Maruszewsky, MD[17]; Cristina Basso, MD, PhD[18]; Giovanni Stellin, MD[1]

[1]Pediatric & Congenital Cardiac Surgery Unit, Dept of Cardiac, Thoracic & Vascular Sciences, [18]Dept of Medico-diagnostical Sciences & Special Therapies, Univ of Padova Med School; [2]Dept of Statistical Science, Univ of Padova, Italy; [3]Dept of Congenital Heart Surgery, Mitera Children's & Hygeia Hosptls, Marousi - Athens, Greece; [4]Children's Heart Ctr, The Queen Silvia Children's Hosptl, Goteborg, Sweden; [5]Pediatric Heart Inst, Hosptl Univ Madrid, Spain; [6] DMCCP, Ospedale Pediatrico Bambino Gesù, Roma, Italy; [7]Pediatric & Cardiothoracic Surgery, Univ Med Ctr, Groningen, The Netherlands; [8]German Pediatric Heart Ctr, Asklepios Clinic, Sankt Augustin, Germany; [9]The Congenital Heart Inst of Florida, St. Petersburg, FL; [10]Division of Pediatric Cardiothoracic Surgery, The Children's Hosptl of Philadelphia, Philadelphia, PA; [11]Dept of Cardiothoracic Surgery, Hosptl de la Timone, Marseille, France; [12]Pediatric & Congenital Cardiac Surgery, Univ Children's Hosptl, Zurich, Switzerland; [13]Pediatric & Congenital Cardiac Surgery, Ancona, Italy; [14]Service de Chirurgie Cardivasculaire et Thoracique, Univ Catholique de Louvain, Clinique Univ Saint-Luc, Bruxelles, Belgium; [15]Hosptl for Children & Adolescents, Univ of Helsinki, Helsinki, Finland; [16]German Heart Ctr, Clinic of Cardiovascular Surgery, Munich, Germany; [17]Children's Memorial Hlth Inst, Dept of Cardiothoracic Surgery, Warsaw, Poland

Correspondence:

Massimo A. Padalino, MD, PhD

UOC Cardiochirurgia Pediatrica e Cardiopatie Congenite

Department of Cardiac, Thoracic and Vascular Sciences

University of Padova Medical School, Centro "Vincenzo Gallucci"

Via Giustiniani 2

35128 Padova, Italy

Tel: l 0039-049-8212427

Fax: 0039-049-8212409;

E-mail: massimo.padalino@unipd.it

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Abstract:

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-18 years). Sixty-three patients (68.5%) presented with symptoms. Surgery consisted in complete resection in 62 (69.7%), partial in 21 (23.6%), and cardiac transplant in 4 (4.5%). Most frequent histotypes (93.2%) were benign (rhabdomyoma, myxoma, teratoma, fibroma and hemangioma). Post-operative 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 NYHA class I. There were no statistically significant differences in survival, post-operative 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 affect negatively 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.

Key words: cardiac surgery; cardiac tumors; congenital cardiac defects; outcomes; pediatrics

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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]

The current literature is reporting mostly on surgical resection of primary cardiac tumours, particularly myxomas, in 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 (ECHSA), in order to evaluate indications and results after surgery for cardiac tumors in a large cohort of pediatric patients.

Material and methods

Patients who underwent surgery for primary cardiac tumor in the pediatric age (≤ 18 years), between January 1st, 1990, and December 31st, 2005 were included. Sixteen centers were enrolled in this study. Review of medical records was approved by each hospital 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 **Supplemental Table 1**.

Preoperative echocardiographic findings were defined as "hemodynamic impairment" in the presence of one of the following: right or left ventricular outflow tract obstruction (R/LVOTO), defined as significant when peak systolic pressure gradient was > 50 mm Hg; mitral valve (MV) regurgitation (greater than mild) or stenosis (significant if trans-mitral 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/non cardiac 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 clinical variables' effect on survival. Since 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 analyse 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 non-cardiac tumor recurrence, cardiac reoperation) were 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 three major clinical variables (i.e., presence of arrhythmia, congestive heart failure, and echocardiographic pathological findings) before and after surgical repair. Survival functions were constructed with Kaplan-Meyer estimates[13]. P-values less than 0.05 were considered statistically significant. Analyses were performed using SAS System, version 9.2.

Results

Early outcomes

Eighty-nine patients were collected for this surgical series (M/F: 41/48, mean age at operation: 4,2 yrs, median age 4.3 months, range 1 day-18 years). Forty-six patients underwent operation under the age of 4 months.

Surgery was advocated because of the presence of symptoms, electrocardiogram (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 (**Supplemental Table 2**), consisting in 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 to pleural or pericardial effusions) were present in the remaining 17 symptomatic patients (**Supplemental Table 2**).

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

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

At echocardiographic evaluation, 63 patients (70.8%) presented with hemodynamic impairment which was caused by AV valve distortion in 20 patients (22.5%), LVOTO in 18 (20.2%), RVOTO in 11 (12.4%), and other findings in 14 (15.7%). Echocardiographic findings are listed in detail in **Supplemental Table 2**.

In order to achieve a complete diagnosis, in addition to echocardiography, magnetic resonance imaging (MRI) and computed tomography (CT) 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 multiple (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%), while it was extracardiac in 13 patients (14.6%); finally it was

found in both atrial and ventricular cavities in 3 patients (3.4%, **Supplemental Table 2**).

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 to be 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 greater than 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%, **Supplemental Table 3**). Non cardiac 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 both showed 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 %) and cardiac transplant in 4 (4.5%) (**Table 2**). In one 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 manoeuvres were performed in 34 patients (**Supplemental Table 4**).

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

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

patients and complete in 2.

Overall median Intensive Care Unit (ICU) stay was 3 days (range 1-32 days), with a median mechanical Intermittent Positive Pressure Ventilation (IPPV) of 18 hours (1-430 days). A longer hospitalization was observed after heart transplant (mean ICU stay: 23.7±14.5 days, mean IPPV time 120.0±86.5 hours).

Postoperative complications occurred in 26 patients (29.2%, **Table 4**).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 AV valve regurgitation in 19.0%, and trivial or mild aortic or pulmonary valve stenosis or regurgitation in the remaining patients.

Eighty-five out of 89 patients, (95.5%) were discharged home in good clinical conditions. Four patients died within 30 days after surgery, accounting for an early mortality rate of 4.5%: three patients (2 with malignant neoplasms, 1 with a benign teratoma) died for postoperative low cardiac output syndrome; another patient with rhabdomyoma, who was previously submitted to brain surgery, died late for massive intraparenchimal brain haemorrhage. 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 NYHA 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 one 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 for severe pneumonia two-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 (CI 95%: 0.577-1.0), 76.3% at 10 years (CI 95%: 0.654-0872).

Freedom from cardiac tumor recurrence was 94.9% at 10 years (CI 95%: 0.892-1): a myxoma recurred in 2 patients with a late diagnosis of Carney complex; a benign teratoma was re-operated 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 (CI 95%: 0.832-0.982): 8 patients needed a cardiac re-operation, which consisted in MV plasty in 2, tricuspid valve plasty in 2, a redo heart transplant in 2, and a recurrent myxoma resection in 2.

Freedom from non-cardiac tumor recurrence was 93.2% at 10 years (CI 95%: 0.867-0.997): a brain tumor occurred in 2 patients (after heart transplant in one 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).

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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 when compared to patients with a benign tumor (overall mortality is 60.0% vs. 6.5%, respectively; p=0.0008, **Table 4**). In contrast, there is no statistical association between tumor malignancy and post-operative 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 post-operative 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 post-operative complications, while a significant incidence of adverse events at follow-up is detected (18.5% in complete vs. 43.7% in partial; Fisher's Exact Test p=0.009). Cardiac transplant is significantly associated to a higher overall mortality (25.0% vs. 2.7%; p=0.006). Simultaneous surgical repair of associated cardiac anomalies does not increase either the surgical mortality risk or the incidence of post-operative complications or adverse events at follow-up. In addition, postoperative overall mortality is not influenced by the association with a non cardiac anomaly. Complicated postoperative course do have a negative effect on survival in patients with benign cardiac tumors (75% vs. 27.8%; p=0.026), while occurrence of adverse events at follow up influence negatively survival in all patients (100% vs. 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 (CHF) before operation, while only 1 patient among these 17 was showing persisting CHF postoperatively and during follow-up (p=0.033). Finally, 48 patients had echocardiographic hemodynamic impairment before operation, while only 16 had its persistence 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 approximately 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 about 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 unconclusive. For this reason, we have started a multicenter study within the ECHSA in order 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.

Since 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. Nontheless, surgery was advocated even in bsence of symptoms, whenever instrumental data (echocardiography or ECG) were indicating a life- threatening condition (**Table 1**). Despite a potential regression might have occurred in some of these cases, surgery was considered as a prophylactic strategy, in order to prevent from mass related

potentially fatal complications (tumor embolization, severe valve regurgitation or stenosis, impinging AV 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 2/83 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 post-operative complications between complete and partial resection of the tumor other than myxoma, especially for those tumors which 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 whom development of tuberous sclerosis may be a common adverse event. Moreover, there was no re-growth 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 is involving 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 CPBP and aortic cross clamp in most cases, especially when the mass is intracardiac. Gentle manipulation of the heart is suggested, so as to avoid cardiac mass fragmentation and embolization (i.e myxomas). Since surgical approach (i.e. 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 which 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 RV patch reconstruction after fibroma resection.

Overall, 8 patients died in this series (9.0%); mortality was associated to the malignant nature of the mass (3 cases), or to onset of non-cardiac events (4 cases), whereas only one 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 definetly 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 ones (**Figure 1**). These patients with a malignant mass may actually benefit clinically from palliative surgery, such as a partial resection, associated to 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) which 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), when compared to conservative surgery, and a mild tendency to higher rate of postoperative complications occurrence (p=0.069). Thus, according to current data on results after cardiac transplant in children[19-21], we believe thata 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 is described as high as 60% of cases [1,2,10,21,22]. These data are confirmed in our surgical series, where 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 (**Supplemental Table 2**).

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) when compared to other histotypes, and they were often operated in the absence of symptoms (about 50% of cases), because of their intracavitary growth, in order to prevent from life-threatening complications.

Our analysis shows a relationship between tumor histotype and cardiac localization, i.e. rhabdomyoma in the ventricles, myxoma in the atria, teratoma mostly intrapericardial and extracardiac (**Figure 2**), despite this association resulted 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], in our series we were not able to demonstrate a statistically significant association.

Our study has stressed once more the crucial role of two-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, CT and MRI remain a second level exam, which was required in about one third of our patients, especially when a malignant mass was suspected, in order 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, mostly consisting of rhabdomyomas, as reported elsewhere[10, 21,22,29]. Noteworthy, in our study, the incidence of multiple myxomas is slightly higher (12.5%) than what reported in literature (10%)[5,30], and were found only in patients with associated Carney complex, i.e. 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 younger than 18 years. In addition, the rare finding of tumor recurrence in our series was associated with Carney complex.

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, it is not representing 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 counselling[45].

As previously underlined, our series is a surgical one and does not reflect the characteristcs 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 types are very rare. These data differ substantially from what reported in previous surgical series[10-14,21], where fibroma was considered the most common cardiac tumor requiring surgery. On the other side, they confirm the prevalence and the age-distribution of tumors' histotypes in the general

pediatric population[1,2,11,46]. In addition, the distribution of the various tumors' 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, while myxomas are more frequent in older children, as reported also elsewhere[2,10,21]. This confirms on a large scale what has been often reported in previous case reports [7,9,15,46,47], and it may support the "acquired" origin of myxomas [48], when compared to other histotypes which 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 to plan and optimize the 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 to significant differences in operative mortality or postoperative complications when compared to patients without fetal diagnosis. This may be due to the fact that this surgical series is including patient with different ages, the majority of whom was 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. Since 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, while 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 post-operative complications and adverse events at follow-up. Cardiac transplant should be considered only for un-resectable cardiac masses which are impairing the cardiac function, because of the increased mortality risk, post-operative complications, adverse events at follow- up, and the significant worsening of the quality of life. At a mean follow-up of more than 6 years, overall mortality rate is 8.9%. Mortality is mainly related to malignancy, associated diseases, post-operative complications and adverse events during follow-up. Recurrence of a benign cardiac tumor is rare and usually related to Carney complex.

Conflict of Interest Disclosures: None.

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Table 1. Indications to surgery according to tumor histotype.

Tumor histotype (number of pts)	Presence of symptoms (pts, % of histotype)	Abnormal ECG (pts, % of histotype)	Echocardiographic hemodynamical impairment (pts, % of histotype)
Rhabdomyoma (32 pts)	23 (71.8)	9 (28.1)	26 (81.2)
Myxoma (18 pts)	10 (55.5)	0 (0.0)	14 (77.7)
Teratoma (12 pts)	7 (58.3)	3 (25.0)	4 (33.3)
Fibroma (9 pts)	5 (55.5)	1 (11.1)	9 (100.0)
Hemangioma (8 pts)	8 (100.0)	2 (25.0)	3 (37.5)
Sarcoma (5 pts)	5 (100.0)	3 (60.0)	3 (60.0)
Other* (5 pts)	3 (60.0)	0 (0.0)	4 (80.0)
Total (89 pts)	61 (68.5)	18 (20.2)	63 (70.8)

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

Table 2. Primary surgical procedures and early and late death rates according to tumor histotype.

Histotype	N pts	Complete resection	Partial resection	OHT	Other surgery	Early death (within 30 days from operation)	Late death (after 30 days 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 and % of tumor histotype. OHT: orthotopic heart transplant.
Other tumor histotypes: includes: pseudotumor (3), papilloma (1), malignant teratoma (1). Other surgery: Cavo-pulmonary anastomosis in one, midline sternotomy and incisional biopsy in another.
[*]2 pts lost at follow up; [†]post operative brain hemorrhage; [‡] malignant teratoma; [§]S/P heart transplant.

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Table 3. Postoperative complications according to tumor histotype

Histotype	n. pts	LCO	Postoperative Arrhythmia	PNX	Pleural and/or pericardial effusion	Phrenic nerve injury	Other complication	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 and % of tumor histotype. Other tumor histotypes include: pseudotumor (3), papilloma (1), malignant teratoma (1). Other complications include: undetermined minor secondary complications (3); acute cardiac transplant rejection (1); multi-organ failure (1); superior vena cava thrombosis post heart transplant (1); respiratory insufficiency requiring long term mechanical ventilation; (1) cerebral haemorrhage on previous brain surgery site (1). Legend: LCO: low cardiac output syndrome; PNX: pneumothorax.

Table 4. Significance of clinical variables as significant risk factors for outcomes.

Clinical Variables	Overall mortality		Post-Op complication	Adverse events at follow-up
	Log-Rank test	Fisher's Exact Test	Fisher's 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 non-cardiac 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 op < 6 months	0.211	///	0.717	0.694
Age at op < 12 months	0.140	///	0.795	0.822
Post-op complications for benign tumor	///	**0.026**	///	///
Adverse events during follow-up	///	**0.005**	///	///

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Table 5. Effects of surgery on patients' clinical conditions evaluated by McNemar Test.

		Post-Op		Total	**McNemar p value**
ECG Rhythm		SR	no SR		
Pre-Op	SR	65	2	67	**0.0075**
	no SR	12	6	18	
Total		77	8	85	
CHF		No	Yes		
Pre-Op	No	52	6	58	**0.033**
	Yes	16	1	17	
Total		68	7	75	
Echo alteration		No	Yes		
Pre-Op	No	18	4	22	**<0.0001**
	Yes	32	16	48	
Total		50	20	70	

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

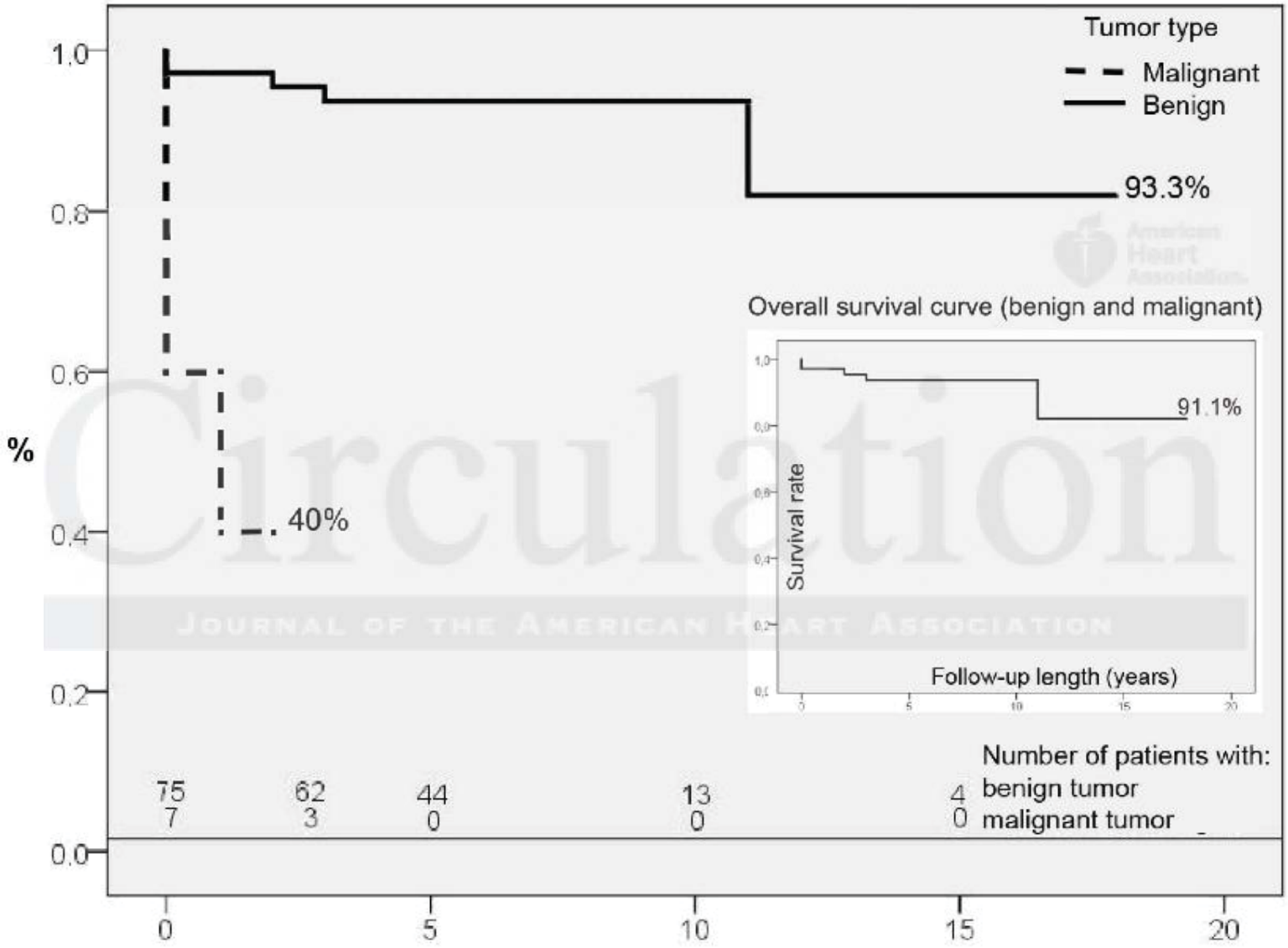
Figure Legends:

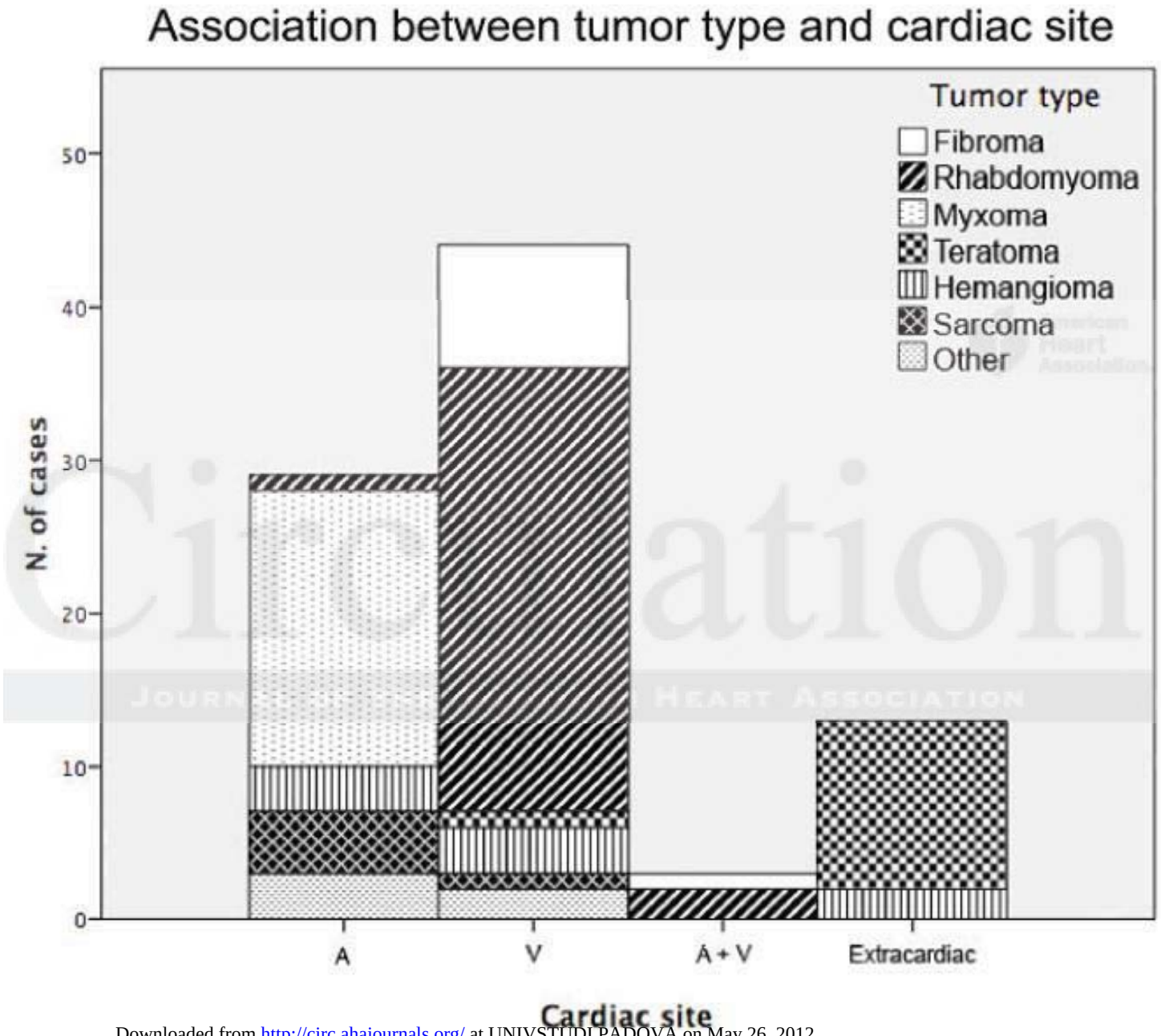
Figure 1. Survival curves according to Kaplan Meier analysis: the survival estimate for surgical patients affected by a malignant tumor is significantly lower when compared to patients with a benign tumor (p=0.0008). In the bottom line of the diagram, along the X axis (years if follow up), we have listed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

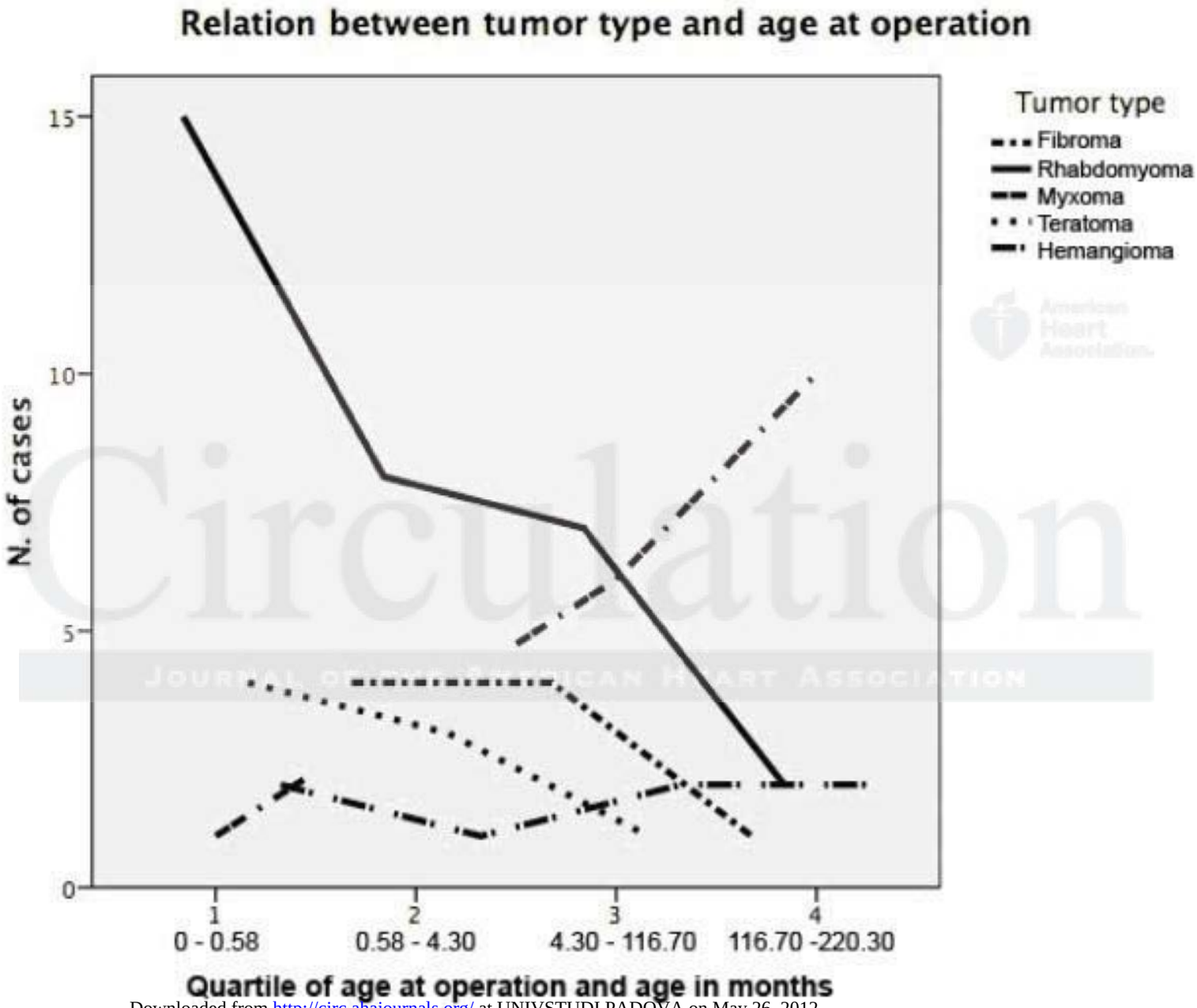
Figure 2. Bar chart showing association between cardiac tumor histotype and cardiac site (p value at Fisher Exact Test < 0.0001).

Figure 3. Relationship between tumor histotype and age at operation. It is evident that the need of surgery for rhabdomyomas decreases as age grows, while myxomas increase in frequency at older ages (p-value at ANOVA test applied to age in its original scale <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, so as to give a clearer visual display

Overall survival curve (Kaplan - Meier) according to mass malignancy







Supplemental Material

Supplemental Table 1. Data were collected according to a common database which was constructed by one of the authors (MAP). Collected variables were grouped in pre-operative, intra-operative, post-operative, pathological and follow up data.

Pre-operative	***Intra-operative***	***Post-operative***	***Pathological***	***Follow up***
Gender	Surgical technique	IPPV time (hrs)	Histotype	Occurrence of adverse events
Age	Cardiopulmonary bypass times	ICU stay (d)	Dimensions (mm)	ECG findings
Weight	Minimal body temperature	Postoperative complications	Weight (gr)	Echocardiographic findings
Symptoms		ECG findings		Medications
Mass characteristics		Echocardiographic findings		NYHA class
ECG findings				Psychosomatic growth
Echocardiographic findings				Self perception of quality of life
Cardiac Computed Tomography				
Cardiac Magnetic Resonance Imaging				
Other Cardiac Anomalies				
Other non Cardiac Anomalies				

Supplemental Table 2. Clinical, ECG and echocardiographic findings according to tumor histotype.

Tumor		Gender		Prenatal diagnosis	Symptoms and findings						ECG rhythm				Number of masses		Echo findings					Cardiac site			
Histotype	N pts (% of all pts)	Male (% of histotype)	Female (% of histotype)		CHF (% of histotype)	M (% of histotype)	Arrhythmia (% of histotype)	CNS (% of histotype)	Other[a] (% of histotype)	none (% of histotype)	SR (% of histotype)	Atrial flutter (% of histotype)	Paroxysmal SVT (% of histotype)	Other[b] (% of histotype)	Single (% of histotype)	Multiple (% of histotype)	LVOTO (% of histotype)	RVOTO (% of histotype)	AVVI (% of histotype)	Other[c] (% of histotype)	None (% of histotype)	A (% of histotype)	V (% of histotype)	A+V (% of histotype)	Extra (% of histotype)
Rhabdomyoma	**32 (36.0)**	14 (43.8)	18 (56.3)	8 (25.0)	6 (18.8)	3 (9.4)	7 (21.9)	1 (3.1)	6 (18.8)	9 (28.1)	23 (71.9)	1 (3.1)	1 (3.1)	7 (21.9)	11 (34.4)	21 (65.6)	15 (46.9)	6 (18.8)	3 (9.4)	2 (6.3)	6 (18.8)	1 (3.1)	29 (90.6)	2 (6.3)	0 (0.0)
Myxoma	**18 (20.2)**	5 (27.8)	13 (72.2)	0 (0.0)	6 (33.7)	0 (0.0)	0 (0.0)	1 (5.6)	3 (16.7)	8 (44.4)	18 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	16 (88.9)	2 (11.1)	0 (0.0)	0 (0.0)	11 (61.1)	3 (16.7)	4 (22.2)	18 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)
Teratoma	**12 (13.5)**	5 (41.7)	7 (58.3)	8 (66.7)	2 (16.7)	1 (8.3)	0 (0.0)	0 (0.0)	4 (33.3)	5 (41.7)	9 (75.0)	0 (0.0)	0 (0.0)	3 (25.0)	12 (100.0)	0 (0.0)	1 (8.3)	0 (0.0)	1 (8.3)	2 (16.7)	8 (66.7)	0 (0.0)	1 (8.3)	0 (0.0)	11 (91.7)
Fibroma	**9 (10.1)**	6 (66.7)	3 (33.3)	2 (22.7)	4 (44.4)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	4 (44.4)	8 (88.9)	0 (0.0)	0 (0.0)	1 (11.1)	9 (100.0)	0 (0.0)	2 (22.2)	3 (33.3)	1 (11.1)	3 (33.3)	0 (0.0)	0 (0.0)	8 (88.9)	1 (11.1)	0 (0.0)
Hemangioma	**8 (9.0)**	3 (37.5)	5 (62.5)	2 (25.0)	1 (12.5)	2 (25.0)	2 (25.0)	1 (12.5)	2 (25.0)	0 (0.0)	6 (75.0)	1 (12.5)	1 (12.5)	0 (0.0)	8 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (12.5)	2 (25.0)	5 (62.5)	3 (37.5)	3 (37.5)	0 (0.0)	2 (25.0)
Sarcoma	**5 (5.6)**	5 (100.0)	0 (0.0)	0 (0.0)	3 (60.0)	0 (0.0)	2 (40.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (40.0)	1 (20.0)	0 (0.0)	2 (40.0)	4 (80.0)	1 (20.0)	0 (0.0)	1 (20.0)	2 (40.0)	0 (0.0)	2 (40.0)	4 (80.0)	1 (20.0)	0 (0.0)	0 (0.0)
Other	**5 (5.6)**	3 (60.0)	2 (40.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (20.0)	2 (40.0)	2 (40.0)	5 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (100.0)	0 (0.0)	0 (0.0)	1 (20.0)	1 (20.0)	2 (40.0)	1 (20.0)	3 (60.0)	2 (40.0)	0 (0.0)	0 (0.0)
Total	**89 (100.0)**	41 (46.1)	48 (53.9)	20 (22.5)	22 (24.7)	6 (6.7)	12 (13.5)	4 (4.5)	17 (19.1)	28 (31.5)	71 (79.8)	3 (3.4)	2 (2.2)	13 (14.6)	65 (73.0)	24 (27.0)	18 (20.2)	11 (12.4)	20 (22.5)	14 (15.7)	26 (29.2)	29 (33.0)	44 (49.0)	3 (3.0)	13 (15.0)

All data are shown as number of patients and % of tumor histotype.
Other tumor histotypes includes: pseudotumor (3); papilloma (1); malignant teratoma (1).
Other[a] symptoms and findings: pleural or pericardial effusion; respiratory distress; palpitations; chest pain.
Other[b] ECG: atrial or ventricular ectopic beats; ventricular tachycardia.
Other[c] Echo findings: pericardial effusion; bicuspid aortic valve; associated congenital heart disease.
AVVI: atrioventricular valve impairment; CHF: congestive heart failure; CNS: central nervous system; ECG: electrocardiogram; LVOTO: left ventricular outflow tract obstruction; M: murmur; RVOTO: right ventricular outflow tract obstruction; SR: sinus rhythm; SVT; supraventricular tachycardia.

Supplemental Table 3. Associated cardiac anomalies

Cardiac Anomaly	n. of patients (n=89)	%
None	70	78.7
ASD	6	6.7
PFO	4	4.5
VSD	3	3.4
PDA	3	3.4
AV septal defect	1	1.1
ASD + VSD	1	1.1
TGA	1	1.1

ASD: atrial septal defect; AV: atrio-ventricular; PFO: patent foramen ovale; PDA: patent ductus arteriosus; TGA: transposition of the great arteries; VSD: ventricular septal defect

Supplemental Table 4. Associated surgical procedures

Surgical procedure	n. of patients(n=34)	%
ASD closure	8	24.2
Atrial patch plasty	6	18.2
AV valve plasty	5	15.2
Ventricular patch plasty	2	6.1
PDA closure	2	6.1
PV plasty	2	6.1
Aorto-pulmonary shunts	2	6.1
AVSD closure	1	3.0
Damus Kaye Stensel	1	3.0
Pneumonectomy	1	3.0
Ross Procedure	1	3.0
SAS resection	1	3.0
VSD closure	1	3.0

ASD: atrial septal defect; AV: atrio-ventricular; AVSD: atrioventricular septal defect; .PDA: patent ductus arteriosus; SAS: subaortic stenosis; VSD: ventricular septal defect