

# Update on Cardiac Tumors – review (RCD code: VI)

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## Abstract

The prevalence of cardiac tumors is 0.021% (1 person in 5000). These data are based on a meta-analysis of pathological studies from the early decades of the twentieth century. It is likely that nowadays the incidence of cardiac tumors and primary tumors of the heart is greater. The cardiac tumors are very rare and histologically heterogeneous. These leads to, the lack of established diagnostic schemes, that would allow to distinguish cardiac tumors from metastatic tumors, intracardiac thrombus, vegetations on the valves in infective endocarditis or in the process of connective tissue diseases or thrombotic changes of the valves in the process of metastatic disease (called endocarditis marantica). Cardiac tumors may be symptomatic or found incidentally during evaluation for a seemingly unrelated problem or physical finding. In symptomatic patients, a mass can virtually always be detected by echocardiography, magnetic resonance imaging (MRI), and/or computed tomography (CT). Because symptoms may mimic other cardiac conditions, the clinical challenge is to consider the possibility of a cardiac tumor so that the appropriate diagnostic tests can be conducted. There are very few studies, assessing the results of cardiac surgery in the individual centers. There is also lack of set of standards in the chemotherapy of malignant cardiac tumors. Moreover its routine use is sometimes discussed. JRC D 2014; 1 (8): 5–10

**Key words:** rare disease, malignancy, cancer, heart mass

## Introduction

The tumor is an overgrown tissue of unknown (undiagnosed) origin, that may be detected clinically. Cardiac tumor is an additional structure within the heart chambers, myocardium or endocardium.

Malignant rhabdomyoma was the first described cardiac tumor in by von Recklinghausen 1862 [1]. Subsequent reports, mostly on isolated cases diagnosed in the autopsy, were collected and analyzed by Mahaima in 1945 [2], followed by Prichard and Bigelow [3,4]. Initially, cardiac tumors were treated solely as a pathological curiosity. Along with the progress of diagnostic and treatment possibilities of congenital heart diseases, there was also a real chance to save patients suffering from tumors of the heart. The first successful surgical removal of cardiac tumor in adult patient was performed in 1954 [5].

The cardiac tumors are very rare and histologically heterogeneous. These leads to, the lack of established diagnostic schemes, that would allow to distinguish cardiac tumors from metastatic tumors, intracardiac thrombus, vegetations on the valves in infective endocarditis or in the process of connective tissue diseases or

thrombotic changes of the valves in the process of metastatic disease (called endocarditis marantica).

Cardiac tumors may be symptomatic or found incidentally during evaluation for a seemingly unrelated problem or physical finding. In symptomatic patients, a mass can virtually always be detected by echocardiography, magnetic resonance imaging (MRI), and/or computed tomography (CT). Because symptoms may mimic other cardiac conditions, the clinical challenge is to consider the possibility of a cardiac tumor so that the appropriate diagnostic tests can be conducted.

There are very few studies, assessing the results of cardiac surgery in the individual centers. There is also lack of set of standards in the chemotherapy of malignant cardiac tumors. Moreover its routine use is sometimes discussed.

## Epidemiology

The prevalence of cardiac tumors is 0.021% (1 person in 5000). These data are based on a meta-analysis of pathological studies from the early decades of the twentieth century. It is likely that

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nowadays the incidence of cardiac tumors and primary tumors of the heart is greater.

Primary malignant cardiac tumors are rare, regardless of the age group. Based on the results of a large number of dissections, Straus and Merliss reported the incidence rate of 0.0017% [6].

Slightly more frequently tumors of the heart occur in children. Simcha reported the incidence of cardiac tumors in children is 0.08% [7]. He based his conclusion on over 20-year follow-up of the patients hospitalized in his facility. Nadas and Ellison provide the data that evaluated the prevalence among 11 000 children undergoing post-mortem examination at of 0.027% [8].

The pathophysiology of cardiac tumors is heterogeneous and depends on the type of tumor.

Heart tumors are divided into two groups:

- primary heart tumors – deriving from the heart
- secondary heart tumors – most commonly metastatic malignancies of other organs.

The primary heart tumors may be benign (about 75%) or malignant (25%).

## Cardiac tumors – classification

1. Primary cardiac tumors
  - a) Primary benign tumors
    - i. Myxoma
    - ii. Fibroma
    - iii. Lipoma
    - iv. Rabdomyoma
  - b) Primary malignant tumors
    - i. Rabdomyosarcoma
    - ii. Angiosarcoma
    - iii. Lymphoma
2. Metastatic cardiac tumors
  - a) Lung cancer (40–60%)
  - b) Breast cancer (11%)
  - c) Vascular tumor metastasis (10–11%)
  - d) Metastatic tumor cells covering of the serous membranes (9%)
  - e) Metastatic cancer of the esophagus (5%)
  - f) Gastric cancer, pancreas cancer, kidney cancer, skin cancer (each 3%)
  - g) Liver, ovarian, prostate, colon cancers (1%)
3. Thrombus within the heart chambers
4. Vegetations on the heart valves
  - a) Bacterial vegetations
  - b) Fungal vegetations
  - c) Parasitic vegetations
  - d) Protozoan vegetations
5. Inflammatory tumors in the cardiac cavities
  - a) Bacterial granulomas
  - b) Fungal granulomas
  - c) Parasitic granulomas
  - d) Protozoan granulomas
6. Abscesses within the heart chambers and the heart valves
7. Other

## Etiology

In some cases a genetic background has been proven. For example, 10% of cases of atrial myxomas are familial, as a part of the Carney complex (mutation in the PRKAR1A gene on chromosome 17, encoding a regulatory subunit of protein kinase)

Primary cardiac lymphoma raises the suspicion of AIDS.

## The clinical symptoms

At the beginning the heart tumors are usually asymptomatic and therefore are detected incidentally. The clinical manifestations largely depend on the size of the tumor, its localization, mobility and the degree of malignancy (infiltration, mass effect). Specific signs and symptoms generally are determined by the location of the tumor in the heart and not by histopathology.

The most common symptoms are:

- shortness of breath (including paroxysmal nocturnal dyspnea)
- impaired contractility, arrhythmias, heart block, or pericardial effusion with or without tamponade due to direct invasion of the myocardium
- valves regurgitation or stenosis
- embolic events
- systemic features of inflammation.
- obstruction of the coronary arteries, producing symptoms of angina, myocardial infarction, heart failure.

Mechanisms by which cardiac tumors may cause symptoms include:

- Obstruction of the circulation through the heart or heart valves, producing symptoms of heart failure
- Interference with the heart valves, causing regurgitation
- Direct invasion of the myocardium, resulting in impaired contractility, arrhythmias, heart block, or pericardial effusion with or without tamponade
- Invasion of the adjacent lung may cause pulmonary symptoms and may mimic bronchogenic carcinoma
- Embolization, which is usually systemic but can be pulmonary
- Constitutional or systemic symptoms

Risk factors for embolization were evaluated in a report of 323 patients treated surgically from 1957 to 2006 [9]. Eighty patients had presented with an embolic event (cerebrovascular accident 31 [10%], transient ischemic attack 30 [9%], and other systemic or pulmonary event 19 [6%]):

- Aortic valve and left atrial tumors were associated with greatest risk of embolization.
- Patients with smaller excised tumors (<13.3 cm<sup>3</sup>), minimal cardiac symptoms, and no evidence of mitral regurgitation had higher risk of embolization.
- Operative mortality was similar in patients presenting with and without embolism (1 percent versus 3 percent). No recurrent embolic events were observed post-operatively at a mean of six years follow-up.

## Diagnostics

Taking into account the likelihood of cardiac tumors the diagnostic procedures should be performed in all patients with unexplained cardiac murmurs, congestive heart failure, arrhythmias, which are accompanied fever, anemia and weight loss of unknown cause. In such cases the basic laboratory tests should include tumor markers).

Cardiologic diagnostic procedures should be widened with particular emphasis on imaging methods.

ECG may not indicate any change, and some ECG features found in patients with cardiac tumor are usually nonspecific. It has been reported, that tumors of the heart are associated with shortening of P-R interval, the right or left bundle branch block (RBBB or LBBB) or complete heart block [8]. There may also occur recurrent tachycardia [9].

Standard chest radiography may not reveal any changes. Uncharacteristic enlarged heart contour following a tumor appears in connection with heart failure. Asymmetrical enlargement of the heart may occur when the tumor is located within the anterolateral wall of left ventricle. Calcifications are rare, usually in the case of rhabdomyoma and lipoma. Pericardial effusion as the only radiological indicator of cardiac tumor, has been described in the case of the rhabdomyoma associated heart failure [9,10].

Modern echocardiography often provides sufficient data about the presence of cardiac tumor, its location, size, mobility and communication with other anatomical structures of the heart. Echocardiography images both the myocardium and the cardiac chambers and can usually identify the presence of a mass and its mobility. In addition, echocardiography may provide information about any obstruction to the circulation, as well as the likelihood that the tumor could be a source of emboli. Fetal echocardiography allows for early diagnosis of cardiac embryonic tumor [11]. Although transthoracic echocardiography is simpler and usually can identify a tumor, transesophageal echocardiography (TEE) may be more informative. The superior diagnostic utility of TEE is due to the proximity of the esophagus to the heart, the lack of intervening lung and bone, and the ability to use high-frequency imaging transducers that afford superior spatial resolution [12].

Computed tomography and magnetic resonance are performed especially in cases where tumor infiltration other structures of mediastinum requires clarification [13]. Although both cardiac MRI [14,15] and ultrafast CT [13,16] provide noninvasive, high resolution images of the heart, MRI generally is preferred. In addition to furnishing detailed anatomic images, the T1- and T2-weighted sequences reflect the chemical microenvironment within a tumor, thereby offering clues as to the type of tumor that is present [17]. However, CT scanning is still useful when MRI is not immediately available or is contraindicated. An excellent pictorial review of many cardiac tumors and comparison of MRI and CT scanning has been published by Hoey and colleagues [18].

Positron emission tomography (PET) has been useful in identifying cardiac involvement in patients with metastatic tumors, atrial myxoma, or lipomatous septal hypertrophy [19,20].

Coronary angiography is performed to assess the vascularity the tumor and its infiltration of the coronary arteries. This is of

a particular importance in making the decision about surgery and the choice of its techniques.

Cardiac catheterization provides additional information about the hemodynamic consequences of the presence of the tumor of the heart [21].

Transvenous biopsy — Limited data are available on the risks and benefits of transvenous biopsy of suspected cardiac tumors. Because myxomas may embolize, transvenous biopsy is not generally warranted if the appearance is typical on noninvasive imaging. Biopsy is considered reasonable for other cardiac tumors if potential benefits are deemed sufficient to outweigh potential risks.

## Benign tumors

Over 75 percent of primary cardiac tumors are benign [22,23]. In adults, the majority of benign lesions are myxomas; other common benign lesions include papillary fibroelastomas and lipomas. In children, rhabdomyomas and fibromas are the most common.

**Myxomas** are the most common primary cardiac neoplasm in adults, rarely found in children. Histologically, these tumors are composed of scattered cells within a mucopolysaccharide stroma. The cells originate from a multipotent mesenchyme that is capable of neural and endothelial differentiation [24]. Myxomas produce vascular endothelial growth factor (VEGF), which probably contributes to the induction of angiogenesis and the early stages of tumor growth [24,25].

Macroscopically, typical myxomas are pedunculated and gelatinous in consistency; the surface may be smooth, villous, or friable. Tumors vary widely in size, ranging from 1 to 15 cm in diameter, and weigh between 15 and 180 g [26]. About 35 percent of myxomas are friable or villous, and these tend to present with emboli. Larger tumors are more likely to have a smooth surface and to be associated with cardiovascular symptoms.

The cardiovascular manifestations depend upon the anatomic location of the tumor. Approximately 80 percent of myxomas originate in the left atrium, and most of the remainder is found in the right atrium [7,26,27,28].

In addition to their cardiovascular effects, patients with myxomas frequently have constitutional symptoms (eg, weight loss, fever) and laboratory abnormalities that suggest the presence of a connective tissue disease [29]. Although the etiology of these symptoms is not fully understood, the production of various cytokines and growth factors by the tumor may contribute to these clinical and laboratory abnormalities [29,30].

The relative frequencies of different signs and symptoms associated with left atrial myxomas are illustrated by a series of 112 patients, 72 of whom were women [26]:

- Cardiovascular symptoms were present in 67 percent. Most commonly, these resembled symptoms of mitral valve obstruction and were frequently associated with electrocardiographic evidence of left atrial hypertrophy. Although auscultatory abnormalities were found in 64 percent, the classic tumor “plop” was identified in only 15 percent.
- Evidence of systemic embolization was present in 29 percent of patients, and 20 percent had neurologic deficits. Despite the greater frequency of myxomas in women, men were more likely to have evidence of embolization.

- Constitutional symptoms (eg, fever, weight loss) were seen in 34 percent of patients. Laboratory abnormalities (eg, anemia and elevations in the erythrocyte sedimentation rate, C-reactive protein, or globulin level) were present in 37 percent, usually those with systemic symptoms.

Other large series of patients with myxomas have also included a predominance of women (60 to 70 percent), and have reported similar incidences of cardiovascular, embolic, and constitutional symptoms [31,32].

## Treatment and prognosis

Once a presumptive diagnosis of myxoma has been made on imaging studies, prompt resection is required because of the risk of embolization or cardiovascular complications, including sudden death [29,30]. The results of surgical resection are generally very good, with most series reporting an operative mortality rate under 5 percent [31,32,33]. Cardiac autotransplantation (with atrial reconstruction) or transplantation are potential options for treatment of recurrent atrial myxoma [32,33].

Postoperative recovery is generally rapid. However, atrial arrhythmias or atrioventricular conduction abnormalities were present postoperatively in 26 percent of patients in one series [26]. In addition, patients are at risk for recurrence of the myxoma, which may occur in 2 to 5 percent of cases, or the development of additional lesions [26,33]. Development of a second primary myxoma may be more common in patients with a family history of myxoma [34].

## Carney complex

The Carney complex is an inherited, autosomal dominant disorder characterized by multiple tumors, including atrial and extracardiac myxomas, schwannomas, and various endocrine tumors. The cardiac myxomas generally are diagnosed at an earlier age than sporadic myxomas and have a higher tendency to recur [35]. The Carney complex should be distinguished from other syndromes associated with Carney with which it may be confused. Prominent among them are the Carney Stratakis syndrome and the Carney triad, neither of which include cardiac tumors [35,36].

Patients with Carney complex also have a variety of pigmentation abnormalities, including pigmented lentiginos and blue nevi on the face, neck, and trunk. The Carney complex is discussed elsewhere.

**Rhabdomyomas** are very rare in adults, but in children they develop often, mostly before the one year of age. These are predominantly found in the ventricular walls or intraventricular septum. Most rhabdomyomas regress spontaneously, and resection is usually not required unless a child is symptomatic.

**Fibromas** are the second most common pediatric cardiac tumor but can also occur in adults. The most common location is the left ventricular muscle (walls or intraventricular septum). Histologically these are similar to fibromas arising elsewhere in the body (eg fibromas of the uterine). The tumor is usually single, white structure with well defined boundaries.

**Lipomas** are benign tumors, they are found incidentally and usually clinically insignificant. They are built of fatty cells. They usually arise in the subendocardial region.

**Angiomas** may localize in every cavity of the heart, but may also arise on the surface of the heart, leading to a bloody pericardial effusion. Angiomas may also sometimes attack the heart conduction system, causing the arrhythmia.

**Teratoma** – there are only a few cases of this tumor. Generally it is mainly found in the left ventricle or surrounding of the atrioventricular node. The histological studies of excised teratomas showed that the tumor may contain nervous tissue, smooth muscle, bone and cartilage as well as the thyroid and pancreas cells.

**Fibroelastomas** are the second most common primary cardiac tumor in adults. Predominantly these are found on the heart valves, usually on the left side of the heart. They may cause angina, myocardial infarction, sudden death due to valve stenosis or closure of the coronary arteries.

## Primary malignant tumors

Malignant tumors constitute approximately 15 percent of primary cardiac tumors [22]. Sarcomas are the most common, although other tumor types have been reported.

## Sarcomas

Virtually all types of sarcomas have been reported in the heart [38]. Cardiac sarcomas are extremely rare, and for most types, only isolated case reports have been described.

As with benign lesions, the clinical presentation is largely determined by the location of the tumor, rather than its histopathology. The diagnostic approach relies upon echocardiography, MRI, and CT to define the presence of a tumor and its anatomic relationship to normal structures.

The most frequently described sarcomas include:

- **Angiosarcomas** – Angiosarcomas are composed of malignant cells that form vascular channels. The pathology of angiosarcomas may overlap with Kaposi's sarcoma, which can also involve the myocardium. Angiosarcomas arise predominantly in the right atrium. Epithelioid hemangioendothelioma, another sarcoma of vascular origin, has also been reported [38].
- **Rhabdomyosarcomas** – Rhabdomyosarcomas constitute as many as 20 percent of all primary cardiac sarcomas. These tumors are most commonly found in adults, although they have also been described in children. Multiple sites of myocardial involvement are common, and there is no predominant localization within any area of the heart [39].
- **Fibrosarcomas** – Fibrosarcomas and malignant fibrous histiocytomas are white fleshy ("fish flesh") tumors that are composed of spindle cells, and may have extensive areas of necrosis and hemorrhage. These tumors tend to extensively infiltrate the myocardium [40].
- **Leiomyosarcomas** – Leiomyosarcomas are spindle-celled, high-grade tumors that arise more frequently in the left atrium. These sarcomas have both a high rate of local recurrence and systemic spread. Other types include liposarcoma, synovial sarcoma, and undifferentiated sarcoma [40].

## Treatment and prognosis

In general, sarcomas proliferate rapidly, and cause death through widespread infiltration of the myocardium, obstruction of blood

flow through the heart, and/or distant metastases. Although complete resection is the treatment of choice, most patients develop recurrent disease and die of their malignancy even if their tumor can be completely resected. The median survival is typically 6 to 12 months, although long-term survival has been reported with complete resection. Patients with low-grade sarcomas may have a better prognosis [39,40,41].

Adjuvant chemotherapy has been used in an effort to improve on the poor results with resection alone. However, most of the published experience consists of anecdotal case reports, and no randomized trials have been conducted. Radiation has been used infrequently, and primarily as a treatment of metastases [42].

The largest series consists of 34 patients treated at the Mayo Clinic over a 32-year period [43]. The median survival was significantly longer when a complete surgical resection was possible (17 versus 6 months when complete resection was not possible). Similarly, the median survival was longer in those who did not have metastases on presentation (15 versus 5 months in those with detectable metastases at diagnosis).

The poor results with surgical resection have led to occasional attempts to treat patients with cardiac transplantation, if extracardiac disease is not present [44,45]. Most of these patients have undergone chemotherapy and radiation prior to transplantation. In the largest series, results of cardiac transplantation in patients with malignant tumors (most of which were sarcomas) were evaluated in a review of 21 cases [45]. Although mean survival was only 12 months, seven patients were free of recurrent malignancy at a mean follow-up of 27 months.

An alternative treatment, cardiac autotransplantation, has shown promise. In these cases, the heart is excised, the tumor is resected *ex vivo*, and the heart is reconstructed before being reimplanted. The advantage of this procedure is the increased ease with which major resection and reconstruction can be performed, while at the same time avoiding the need for antirejection treatment [46].

Rhabdomyosarcomas may have a better outcome with chemotherapy.

### Other primary cardiac tumors

Primary lymphomas arising in the myocardium have been reported. In a review of 40 cases identified from the literature between 1995 and 2002, the outlook was generally poor [47]. However, 38 percent of cases achieved a complete response with systemic therapy. At least some of these responses may be durable [47].

Other tumors may also arise in the heart, including paragangliomas [48] and extramedullary plasmacytomas [49].

## Secondary cardiac tumors

In contrast to primary malignant cardiac tumors, metastatic involvement of the heart is relatively common. As an example, in one of the largest autopsy series of over 1900 patients dying of cancer, 8 percent had metastatic disease involving the heart [5]. Cardiac involvement may arise from hematogenous metastases, direct invasion from the mediastinum, or tumor growth into the vena cava and extension into the right atrium [50].

Malignant melanomas are particularly likely to metastasize to the heart. Other solid tumors commonly associated with cardiac involvement include lung cancer, breast cancer, soft tissue sarcomas, renal carcinoma, esophageal cancer, hepatocellular carcinoma, and thyroid cancer. There is also a high prevalence of secondary cardiac involvement with leukemia and lymphoma.

Cardiac or pericardial metastasis should be considered whenever a patient with known malignancy develops cardiovascular symptoms, particularly if this occurs in conjunction with cardiomegaly, a new or changing heart murmur, electrocardiographic conduction delay, or arrhythmia. Emboli thought to originate in the heart should also raise the possibility of cardiac involvement with tumor. Cardiac metastases rarely may be the first manifestation of malignant disease [51].

The specific symptoms will reflect the site of cardiac involvement, in a manner analogous to primary cardiac tumors. The diagnostic evaluation is the same as that for primary cardiac tumors and relies upon echocardiography, MRI, and CT to ascertain the extent of cardiac involvement. In very carefully selected patients, resection of cardiac metastases has been used to provide symptom palliation and prolong life [51,52].

Other causes of cardiac symptoms must also be considered. In particular, metastatic disease must be distinguished from the cardiotoxicity that may be associated with chemotherapeutic agents, particularly anthracyclines.

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