Radical multidisciplinary approach to primary cardiac sarcomas†

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Abstract

OBJECTIVES: Primary cardiac sarcomas are extremely rare, but aggressive, tumours. The median survival with conventional treatment is 6–12 months. Recent data suggest that a radical multidisciplinary approach may improve patient outcome. We sought to evaluate our institutional experience with these tumours.

METHODS: A multidisciplinary cardiac tumour programme was established 3 years ago based on the experience and support of our collaborating institution. Treatment consisted of pre- and postoperative chemotherapy, complete (R0) resection of the tumour with structural reconstruction and radiation therapy in selected cases. Left atrial tumours were resected using the cardiac autotransplantation technique. Bovine pericardium was used to reconstruct free-chamber walls or the septum. Valves were replaced by bioprostheses. A variety of autologous, allogeneic and synthetic vascular grafts were used to reconstruct the aorta, pulmonary arteries (PAs) and coronary arteries.

RESULTS: Seven patients (3 males), age 51 ± 11 years (35–63), underwent eight operations. Tumour sites were PAs in 2 patients, left atrium in 3, right atrium in 2 and both great vessels in 1. Complete resection was achieved in all cases. There was no operative mortality. Two patients required implantation of a permanent pacemaker. Median survival was 24 months. Three patients died of metastatic disease and 1 sudden death 7, 23, 31 and 33 months after diagnosis. Three patients are alive at 2, 8 and 33 months, in functional Class I or II. One patient developed tumour recurrence and 2 have no evidence of disease.

CONCLUSIONS: A radical multidisciplinary approach to cardiac sarcomas consisting of multimodality treatment and complex, technically demanding surgery, is safe and markedly improves (doubling) patient survival.

Keywords: Cardiac • Sarcoma • Multidisciplinary approach • Surgery

INTRODUCTION

Primary cardiac tumours are rare, with an incidence of 0.0001–0.003% on autopsy [1]. Most primary cardiac tumours are benign, and only 25% are malignant, of which sarcomas are the most common [1–4]. Primary cardiac sarcomas usually affect young patients and are very aggressive. The median survival with conservative treatment is 6–12 months [3–6]. Recent data suggest that a radical multidisciplinary approach may improve the outcome of these patients [6–10]. The aim of the present study was to evaluate our experience with primary cardiac sarcomas using this approach.

MATERIALS AND METHODS

In collaboration with the Methodist DeBakey Heart and Vascular Center, we established a multidisciplinary cardiac tumour programme consisting of the following components—radiology, diagnostic and invasive cardiology, medical and radiation oncology and surgery. Each case was presented and discussed, and a treatment plan was delineated.

The treatment plan was based on the assessment of metastases (intra- or extrathoracic) and the precise definition of the cardiac structures involved. For this purpose, we used multiple imaging studies including transthoracic and transoesophageal echocardiography, 64-slice contrast-enhanced computer tomography (CT) of the heart, chest and abdomen, cardiac magnetic resonance imaging, coronary angiography and total body positron emission tomography (PET) CT.

Treatment consisted of pre- and postoperative chemotherapy, complete (R0) resection of the tumour with structural reconstruction and radiation therapy in selected cases.

The goal of the operation was to achieve complete (R0) resection. Resectability was determined based on careful assessment of the preoperative imaging studies. Integration of the information gathered from two-dimensional (2D) and three-dimensional (3D) cardiac echo, multislice CT, MRI and cardiac catheterization...
was used to determine whether complete (R0) resection was a realistic goal. Patients with tumours that could not be completely resected were deemed inoperable.

Operations were performed via mid-sternotomy incisions using cardiopulmonary bypass. We used closed-system, heparin-bonded cardiopulmonary bypass circuits with low systemic anticoagulation (target activated clotting time 350 s) and mild systemic hypothermia (32–34°C). Arterial and venous cannulae were inserted as distally as possible to allow wide margins of resection and comfortable and safe vascular anastomoses during reconstruction. For this purpose, we routinely used small-bore venous cannulae and kinetic venous assist. Myocardial protection was achieved using antegrade and retrograde cold (4°C) blood cardioplegia supplemented with topical cooling by cold saline solution. Deep hypothermia and circulatory arrest was not required in this series of patients. Left atrial tumours were resected using the cardiac autotransplantation technique [11]. The technique is illustrated in Fig. 1 and shown in Supplementary Video 1. In brief, cardiac autotransplantation is performed via a mid-sternotomy incision. Arterial cannulation is performed via the distal ascending aorta in most cases, or the femoral artery in the repeat autotransplantation procedure. Venous cannulation should enable the complete removal of the right atrium and can be achieved via direct bivacal cannulation, or in combination with the femoral or innominate veins. Myocardial protection is achieved using antegrade cold blood cardioplegia. The heart is explanted by division of the cavae, the left atrium and the great vessels and placed in a bucket immersed in iced saline. Care is taken to leave long-enough cuffs of each vessel to facilitate reanastomosis. The tumour is resected ex vivo with clean margins. Cardiac reconstruction and valve replacement are performed ex vivo as necessary. Doses of cardioplegia are administered directly to the coronary ostia for both myocardial protection and to identify small arterial bleeds within the resection area that are sutured controlled. The heart is then reimplanted in the orthotopic position [11]. Bovine pericardium was used to reconstruct free-chamber walls or the septum. Valves were replaced by bioprostheses. A variety of autologous, allogeneic and vascular grafts were used to reconstruct the aorta, pulmonary arteries (PAs) and coronary arteries.

Chemotherapy consisted of a variety of drug combinations with the mainstay being Adriamycin and Ifosfamide [9, 10, 12]. Postoperative radiotherapy was administered selectively—either as targeted radiotherapy to the tumour area or targeted to distant metastases.

All patients were followed by one surgeon (O.M.S.) who coordinated the entire care. Follow-up imaging studies were performed routinely at 3-month intervals during the first year, or as required clinically.

RESULTS

Seven patients (3 males), age 51 ± 11 years (35–63), underwent eight operations. The details are summarized in Table 1. Tumour sites was PAs in 2 patients, left atrium in 3, right atrium in 2 and both great vessels in 1. Tumour histology was pleomorphic sarcoma in 2, synovial sarcoma in 2, haemangiosarcoma in 1, leiomyosarcoma in 1 and myxofibrosarcoma in 1.

Four of the 7 patients presented with atypical chest pain a few months up to 3 years prior to diagnosis. One patient presented
with severe shortness of breath secondary to hypoxia related to PA obstruction. One patient presented with palpitation due to paroxysmal atrial fibrillation. Initial diagnosis of a cardiac tumour was made by transthoracic echocardiography in 6 patients. The diagnosis was made incidentally in 1 patient (No. 4) by chest CT performed to evaluate blunt chest trauma. A representative preoperative 3D CT and PET CT of a patient with left atrial synovial sarcoma are depicted in Fig. 2. We resected the tumour using the cardiac autotransplantation technique. Figure 3 illustrates a follow-up CT performed 12 months postoperatively.

Preoperative tissue diagnosis was available in 5 patients using a pericardial window (n = 2), transoesophageal ultrasound guide needle biopsy (n = 1), prior surgery (n = 1) and biopsy of pulmonary metastasis (n = 1).

Macroscopic complete resection of the cardiac tumour was achieved in all cases. Two patients had microscopic tumours in the margins found on postoperative histological examination. The extent of resection and type of reconstruction are summarized in Table 1.

Figure 4 illustrates a case of angiosarcoma of the right atrium. Complete resection necessitated excision of the right atrial free wall, right coronary artery and the anterior leaflet of the tricuspid valve. We replaced the tricuspid valve with a bioprosthesis, performed a single-vessel bypass to the right coronary artery and used bovine pericardial patch to reconstruct the right atrium free wall.

Figure 5 illustrates a case of synovial sarcoma of the great vessels. Complete resection necessitated excision of the aortic root, right coronary artery, basal interventricular septum, right ventricular outflow tract and the main and right PAs. We used bovine pericardial patches to reconstruct the right ventricular outflow tract and interventricular septum and to augment the native aorta, porcine bio-root with left main coronary artery reimplantation to replace the aortic root, human pulmonary allograft to replace the main PA, a Gortex™ interposition graft to replace the right PA and a saphenous vein graft to the distal right coronary artery.

Average cardiopulmonary bypass and aortic cross-clamp times were 215 ± 103 (range 76–335 min) and 133 ± 91 (range 28–263 min), respectively. There was no operative mortality. Average length of hospital stay was 13 ± 3 (range 9–16 days). Two patients required implantation of a permanent pacemaker. Average follow-up was 19 ± 14 (range 2–34 months) and was 100% complete.

Actuarial and median survival rates were 26 ± 4 and 24 months, respectively. Three patients died of metastatic disease 7, 23 and 31 months after diagnosis. One patient sustained sudden death 33 months after diagnosis. Two of these patients—one with primary PA sarcoma (Patient no. 1) and the other with right atrial haemangiosarcoma (Patient no. 3) presented with metastatic disease. The first patient was operated on urgently since the tumour sub-totally occluded the main PA. He deteriorated rapidly with severe hypoxia and right heart failure. The second patient was operated on after receiving six courses of chemotherapy resulting in a marked response of the distant metastases, but persistent growth of the primary tumour.

Three patients are alive at 2, 8, and 33 months, in functional Class I or II. One patient developed tumour recurrence and 2 have no evidence of disease.

### Table 1: Patient clinical, operative and follow-up data

<table>
<thead>
<tr>
<th>No</th>
<th>Age/gender</th>
<th>Tumour location</th>
<th>Preoperative chemotherapy</th>
<th>Extent of resection</th>
<th>Reconstruction</th>
<th>Postoperative chemotherapy</th>
<th>XRT</th>
<th>Follow-up months</th>
<th>Status</th>
</tr>
</thead>
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<tr>
<td>1</td>
<td>58 M</td>
<td>PA</td>
<td>No</td>
<td>Main PA, RPA, LPA</td>
<td>RPA-LPA Gortex graft, RV to Gortex pulmonary allograft</td>
<td>Yes</td>
<td>No</td>
<td>7</td>
<td>Dead</td>
</tr>
<tr>
<td>2</td>
<td>46 M</td>
<td>LA</td>
<td>Yes</td>
<td>Posterior LA wall, left PVs</td>
<td>Cardiac autotransplant, Gortex grafts for PVs, bovine pericardium</td>
<td>Yes</td>
<td>Yes</td>
<td>31</td>
<td>Dead, (sudden death) LR</td>
</tr>
<tr>
<td>3</td>
<td>49 F</td>
<td>RA</td>
<td>Yes</td>
<td>Free RA wall, RCA</td>
<td>Bovine pericardium, SVG to RCA</td>
<td>Yes</td>
<td>No</td>
<td>23</td>
<td>Dead</td>
</tr>
<tr>
<td>4</td>
<td>41 F</td>
<td>PA</td>
<td>No</td>
<td>RPA</td>
<td>RPA-LPA Gortex graft, Cardiac autotransplant, bovine pericardium*</td>
<td>No</td>
<td>No</td>
<td>33</td>
<td>Alive, NED</td>
</tr>
<tr>
<td>5</td>
<td>63 F</td>
<td>LA, RA*</td>
<td>Yes</td>
<td>Aortic root, RCA, RVOT, main PA, RPA, basal septum, RA appendage</td>
<td>Porcine aortic bio-root, LPA–RPA Gortex graft, bovine pericardium (septum, RVOT), RV to Gortex pulmonary allograft, SVG to RCA</td>
<td>Yes</td>
<td>No</td>
<td>31</td>
<td>Alive, NED</td>
</tr>
<tr>
<td>6</td>
<td>35 M</td>
<td>Ao, PA</td>
<td>Yes</td>
<td>Dome of LA and RA, interatrial septum, LA appendage, mitral valve</td>
<td>Bovine pericardium, bioprosthetic mitral valve</td>
<td>Yes</td>
<td>No</td>
<td>8</td>
<td>Alive, NED</td>
</tr>
<tr>
<td>7</td>
<td>63 F</td>
<td>LA</td>
<td>No</td>
<td>Dome of LA and RA, interatrial septum, LA appendage, mitral valve</td>
<td>Bovine pericardium, bioprosthetic mitral valve</td>
<td>Yes</td>
<td>No</td>
<td>2</td>
<td>Alive, NED</td>
</tr>
</tbody>
</table>

Patient operated three times—first operation at another institution—incomplete resection of LA sarcoma, second operation cardiac autotransplantation and re-resection of LA tumour and third operation resection of RA metastatic tumour.

XRT: radiation therapy; Ao: aorta; LA: left atrium; RA: right atrium; PA: pulmonary artery; RPA: right pulmonary artery; LPA: left pulmonary artery; PV: pulmonary veins; RCA: right coronary artery; RVOT: right ventricular outflow tract; LR: local recurrence; Met: distant metastases; SVG: saphenous vein graft; NED: no evidence of disease.

*The tumour in the right atrium was a metastasis diagnosed two years after the second operation. It was completely resected in a third operation.
DISCUSSION

The prognosis of primary cardiac sarcoma is poor due to several important factors. Patients typically present late in the course of the disease because of atypical, non-specific symptoms. Patients with right-sided tumours often have distant metastases, while those with left-sided tumours typically have locally advanced disease [2–8]. Non-surgical oncological treatments are only modestly effective [9, 10, 12]. The tumour response to chemotherapy is variable, and most are radio-resistant [10, 12]. Finally, inherent
to this particular organ, surgery of malignant cardiac tumours poses three challenges: exposure, achieving complete (R0) resection with ‘clean’ margins and the need for complex reconstruction to preserve function.

Tumour classification was traditionally based on histological type [1–5]. Following the experience of Reardon and colleagues [9, 13], we have found that presentation, treatment and survival are influenced more by the anatomic location rather than by histological type. We, therefore, classify primary cardiac sarcomas as right heart, left heart or PA. Angiosarcomas mostly involve the right heart, frequently presenting with pulmonary and or distant metastases. Undifferentiated sarcomas mostly involve the left heart, typically presenting with locally advanced tumour. PA tumours commonly present with symptoms and signs related to vascular obstruction associated with intraluminal growth and spread. Tumour histology and metastases are variable [8, 9, 11, 13].

Several series have documented that the prognosis of an individual patient is significantly affected by three determinants—the presence of distant metastases, the side of the tumour (right-sided tumours being worse) and the ability to achieve R0 resection [4–10].

In an effort to overcome these challenges, a multimodality approach has been developed. [6–10]. Treatment consists of preoperative chemotherapy, radical surgery and postoperative consolidation chemo- and radiation therapy. We adopted this approach 3 years ago. Our results support previous reports showing that this multimodality approach effectively prolongs patient survival. Our patients achieved a median survival of 24 months—more than double that achieved using conventional treatment.

There was no chemotherapy- or surgery-related mortality. Furthermore, operative morbidity was low. Thus, all patients were discharged home early postoperatively, enjoying life with their families. In fact, all of them regained excellent functional status. Thus, surgery not only prolonged survival, but was associated with a significant improvement in quality of life—a very important consideration in this specific patient population.

The goals of preoperative chemotherapy are to reduce the extent of the primary tumour mass—increasing the likelihood of R0 resection, as well as to treat distant metastases. A variety of chemotherapeutic agents have been used to treat soft-tissue sarcomas [10, 12]. We have used Adriamycin-based chemotherapy as the mainstay. One has to be particularly careful with...
Adriamycin-related cardiotoxicity. An alternative treatment is the combination of gemcitabine and docetaxel [12]. In line with previous reports, response to therapy in our series was variable. A unique pattern is response of the distant metastases but a growing primary tumour. We observed one such case in a patient with right atrial haemangiosarcoma. The value of surgery in this situation is controversial. While it may not prolong survival, surgery may prevent heart failure secondary to local ill-effects of the growing tumour such as valve dysfunction.

Optimal exposure is mandatory for R0 resection. This is usually not a major issue in right-sided, or great vessel tumours, but may become a major challenge in left-sided, posterior tumours. The technique of cardiac autotransplantation provides an excellent solution to this problem [10]. We have used it successfully in 2 patients with left atrial sarcomas, of which 1 was a second procedure to manage an early local recurrence.

Reconstruction of the resected structures to preserve normal cardiac function is another major surgical challenge. We have used bovine pericardium to reconstruct free-chamber walls or the septum, biological prostheses for valve replacement and a variety of autologous, allogeneic or synthetic vascular grafts to reconstruct the aorta PAs and coronary arteries. The considerations behind the use of biological materials (despite the patients’ young age) were the (i) desire to avoid warfarin in the setting of postoperative adjuvant therapy or need for repeat surgery and (ii) limited survival.

The major limitations of this paper are the small number of patients and the retrospective design. However, cardiac sarcomas are distinctly rare. Most single-institutional reports include only a handful of patients treated over a period of several decades [4–10]. In fact, our series is one of the largest reported with all patients operated on during a relatively short period of time, using current treatment protocols and modern operative techniques and technologies.

In conclusion, our data suggest that a radical multidisciplinary approach to cardiac sarcomas consisting of multimodality treatment and complex, technically demanding surgery is safe and markedly improves (doubling) patient survival and quality of life.

SUPPLEMENTARY MATERIAL

Supplementary material (Video 1) is available at EJCTS online.

Video 1: Resection of recurrent sarcoma of the left atrium using cardiac autotransplantation technique. The first operation was performed elsewhere with a preoperative diagnosis of myxoma.

Conflict of interest: none declared.

REFERENCES


APPENDIX. CONFERENCE DISCUSSION

Dr L. McGrath (Browns Mills, NJ, USA): This paper presents results with a highly challenging cohort of patients. With respect to staging, the international staging system versus SEER staging, what tumour staging did you utilize? And did you use a different system when you were practising in the U.S.?

Dr Shapira: We didn’t use a conventional staging system. The two most important criteria that we looked at are the presence of distant metastatic disease outside the chest or within the chest, and whether the tumour is deemed to be completely resectable.

For clinical staging we used multiple imaging modalities. If the patient has no metastatic disease and the tumour is felt to be resectable, we then go ahead and operate on the patient. I think those are the two most important determinants. There is a classification developed by Dr. Reardon and the group in Houston with stage I, small tumour, no metastatic disease; a resectable stage II with locally advanced tumour; stage III, intrathoracic spread; and stage IV, distal metastatic. This, we believe is the most useful classification, rather than the standard. Because this disease is so rare, I think the standard classifications do not apply.

Dr McGrath: There have been a few reports about the potential role of heart transplantation in this aggressive tumour that affects predominantly young people. Would you comment on what you see as the role for heart transplant in primary cardiac sarcomas?

Dr Shapira: When you look at such gigantic tumours, intuitively you might be tempted to excise those tumours and the heart, and put a new heart in. There are two major limitations to that, one being donor availability. Many of these patients needed urgent rather than elective operation and could not wait for a heart donor. Secondly, previous experience with allogeneic transplantation was poor because of the immunosuppressive effect of the drugs probably causes acceleration of the disease itself. However, there is now a programme in Houston led by Dr. Michael Reardon, that looks at an interim concept of excising the entire heart with the tumour, implanting a total artificial heart for at least one year, and then, if there is no disease recurrence either locally or elsewhere, performing allogeneic cardiac transplantation. They have done only one patient, who actually had a good outcome initially but died of cerebral hemorrhage before receiving the heart transplant. I think this might prove to be a very useful strategy in patients with locally advanced disease.

Dr McGrath: Finally, historically, individuals who have received multimodal therapy have been at increased risk for development of a second neoplasm. Since this is a tumour of younger adults, could you please speak about post-procedural surveillance.

Dr Shapira: Follow-up of these patients is done by a multidisciplinary team. I follow-up the patients personally, in collaboration with our medical
oncologists, cardiologist and radiologists. For the first 2 years follow-up is carried out at 3-monthly intervals, and subsequently at 6-monthly intervals. Most patients so far have died from local disease recurrence or from metastatic disease, rather than from other tumours. As you will have seen, we had 7 patients with 8 operations, because one transplant patient with tumour recurrence had metastatic spread to the right atrium; we resected the right atrial metastasis two years after the initial operation. So frequent monitoring and surveillance are extremely important. We try to do it with the use of as little contrast as possible, so we avoid CT angiography unless absolutely indicated, preferring MRI and echocardiography.

Dr S. Cebotari (Hannover, Germany): I have just a technical question. For your auto-transplantation, how long was your ischaemic time and what kind of preservation did you use in these patients?

Dr Shapira: The technique of auto-transplantation has been well described by Dr. Reardon and Dr. Cooley, who did the first one, and it hasn’t changed much. We systemically cool the patient, to 28°C. We use a closed-system heparin-bonded circuit with low systemic anticoagulation. Myocardial preservation is done using antegrade and retrograde cold blood cardioplegia. After explantation, we place the heart in an ice bucket.

We administer cold blood cardioplegia directly into the coronary ostia both for myocardial preservation and to identify small arterial bleeders that are controlled with 5-0 prolene sutures before putting the heart back, because once you put the heart back in, it is extremely difficult to get control of bleeding. This is particularly important for left-sided tumours, where resection often involves the AV groove, the base of the interventricular septum and the LV.

Usually the total cardiac ischaemic times range between 120 to 180 min, and are very well tolerated using mild systemic hypothermia and the myocardial preservation technique described. Another important point is meticulous cannulation technique. You have to place the cannulae very high in the aorta and very distally on the veins; unlike the usual transplant, there is no excess tissue but just the right amount of tissue. It is important to have long enough sleeves of the great vessels and the major veins to allow comfortable anastomosis.