
A. Vaporciyan, M.D.

RIGHT HEART SARCOMAS

Ara Vaporciyan, M.D., Michael J. Reardon, M.D.
The University of Texas MD Anderson Cancer Center, Houston, Texas
Methodist DeBakey Heart & Vascular Center, Houston, Texas

Introduction

Primary cardiac tumors are unusual, and primary cardiac sarcomas constitute a rare subset of these. In cardiac sarcoma, unlike many malignancies, the histologic cell type does appear to affect the treatment options or prognosis in a significant way. The presenting symptoms, treatment options and, indeed, prognosis are largely controlled by the tumor's anatomic location.

We have proposed a classification system based on anatomic location that divides cardiac sarcoma into left heart, right heart and pulmonary artery sarcomas. In our experience, right heart sarcoma tends to be bulky, grow in a more exophitic manner, be more infiltrative, and metastasize earlier than left heart or pulmonary artery sarcoma. Right heart sarcoma also presents less often in congestive heart failure or with compromised hemodynamic status than left heart and pulmonary artery sarcoma, which are usually highly symptomatic at presentation. The prognosis for right heart sarcoma without surgery is dismal. Complete surgical resection remains the goal of therapy and the only treatment modality shown to increase survival. Complete surgical resection is complicated both by the bulky infiltrative nature of right heart sarcoma and the high incidence of metastatic disease at presentation.

The current approach of our cardiac sarcoma group to right heart sarcoma has been to begin neoadjuvant chemotherapy once a definitive tissue diagnosis of sarcoma is achieved. After 4 to 6 rounds of chemotherapy, the patient is considered for surgical resection. This standardized treatment has been approved in our IRB protocol: A Clinical Trial to Assess the Safety and **E**fficacy of a Novel Radical Tumor Re**S**ection **P**rocedure used in conjunction with N**E**oadjuvant Chemothe**R**apy to treat Malignant Primary Right Heart Cardiac Tum**O**rs — the **ESPERO** trial. This protocol is designed to compare our existing 24 index cases of surgical resection of right heart sarcoma using a nonstandardized treatment plan, with routine neoadjuvant chemotherapy, and a standardized treatment plan to see if the rate of microscopically complete resection can be improved from its current level of 33% and if this will improve patient survival. In this review, we will discuss the experience with right heart sarcoma.

Discussion

Primary cardiac tumors are unusual, with about 75% being benign and the other 25% malignant. Of the malignant tumors, about 75% are sarcomas.[1] With primary cardiac sarcoma, we previously found that histology did not significantly influence surgical approach, clinical outcomes or survival.[2] Our findings therefore led us to classify primary cardiac sarcoma according to anatomic location, which is the main determinant of clinical presentation and surgical approach.[3-5] In our experience, right heart sarcomas tend to be bulky and exophitic, and do not usually cause heart failure from obstruction of intracardiac blood flow, as is common in left heart and pulmonary artery sarcomas. They also tend to present with metastatic disease at a higher early rate than left heart sarcomas. These characteristics allow us to approach right heart sarcomas with

neoadjuvant chemotherapy and treatment planning that can differ from left heart and pulmonary artery sarcomas.

Right heart sarcoma occurs in a young patient population. Our series had a mean age of 40.7 years and a range of 17 to 61 years. The signs and symptoms in right heart sarcoma are often nonspecific and constitutional, and early diagnosis often eludes the clinician.[6] Pericardial effusion associated with nonspecific chest pain has been a common initial presentation in our experience. Despite the often large size of these tumors, heart failure is usually not a prominent feature until very late for right heart sarcomas. Multiple lung lesions later found to be metastatic angiosarcoma have been common at presentation.

The nonspecific nature of presenting the symptoms and young ages of these patients has led to a number of diagnostic tests for initial assessment. The 3 most common modalities employed initially in patients referred to our group were transthoracic echocardiography (TTE), computer tomography (CT) scan of the chest and standard chest X-ray. When we suspect cardiac sarcoma in a patient referred to our group without diagnosis, our initial diagnostic test has been TTE. This diagnostic modality rarely misses these large tumors. CT scan of the chest and abdomen is obtained in all patients, allowing better characterization of the extent of local tumor involvement than TTE. This local tumor involvement often can extend to the superior vena cava (SVC), aorta, pulmonary artery and other upper mediastinal structures. CT scan also allows a screen for metastatic disease that is common at presentation for right heart sarcoma, especially pulmonary metastatic disease. PET/CT scan is obtained in all patients at presentation. The level of 18-fluorodeoxyglucose (FDG) uptake or the standardized uptake valve (SUV) in the primary tumor will allow us to follow the response to neoadjuvant chemotherapy and screen for distant metastatic disease.

We have found the right coronary artery to be involved in about one-third of our cases, and we routinely perform cardiac catheterization with coronary arteriography to define the right coronary anatomy in case resection and replacement is needed. These diagnostic tests usually allow good definition of a large right heart mass and a strong suspicion of malignancies, but do not allow a definitive diagnosis. Unlike left atrial masses that are usually benign myxomas even when large, the majority of large right atrial masses are malignant. Definitive tissue diagnosis is crucial in order to rule out other disease processes, such as lymphoma, and to establish histologic proof of sarcoma prior to initiating neoadjuvant chemotherapy. If metastatic disease is present and amenable to biopsy, this allows tissue diagnosis without approaching the heart. Percutaneous approaches to biopsy the primary cardiac mass have not been routinely successful in our experience, and pose risks that our radiology department prefers to avoid. A subxiphoid pericardial window and tumor biopsy can often establish the diagnosis. When a pericardial window is unsuccessful, right anterior thoracotomy and sometimes even median sternotomy may be required to allow safe biopsy for definitive diagnosis.

We currently treat all biopsy-proven right heart sarcomas on our IRB based protocol, the ESPERO trial. All patients without overt heart failure that might force an early surgery are started on neoadjuvant chemotherapy, doxorubicin hydrochloride (75 mg/m^2) and ifosfamide (106 mg/m^2), in an attempt to cytoreduce the tumor bulk and sterilize the infiltrative, microscopic fingers

Figure 1. CT scan of large angiosarcoma filling right atrium and right ventricle, causing severe heart failure.

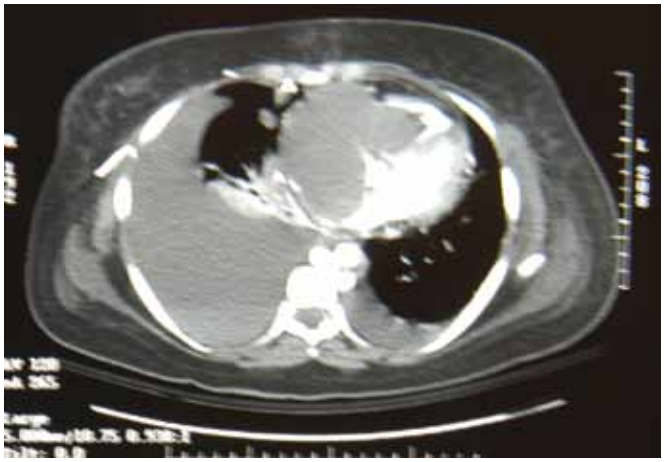
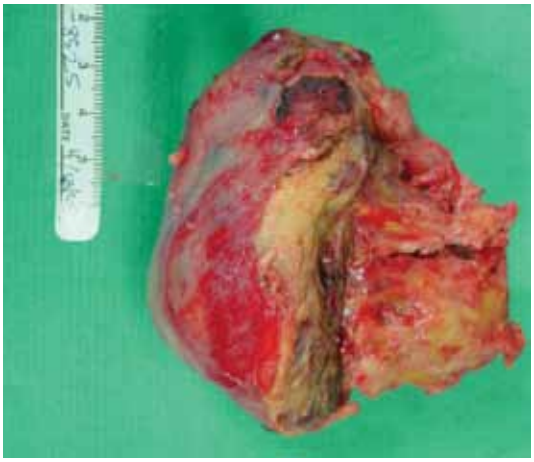


Figure 2. Surgical specimen of tumor seen in Figure 1.



of disease that tend to invade the margins of even wide resections. This was introduced because only about 33% of our right heart sarcoma resections had microscopically negative margins (R0 resection) in our initial data analysis. After every second round of chemotherapy, the imaging is repeated to assess tumor response. Our goal is to consider surgical resection when appropriate after either the fourth or sixth round of chemotherapy, based on tumor response. Tumors considered for surgical resection at this point are tumors without extra cardiac extension that appear to be anatomical candidates for complete resection. Patients whose tumors presented with limited metastatic disease that responds well to chemotherapy and are considered anatomically resectable are offered surgery. Patients with tumors that presented with limited metastatic disease that did not respond well to chemotherapy, or that developed new metastatic disease while on treatment, are not considered candidates for surgery. Patients with widely metastatic disease are not considered candidates unless severe symptoms warrant palliative surgery (Figures 1 and 2). All patients are offered continuation of their chemotherapy after recovery from surgery.

In patients treated without surgical resection, the survival is only about 10% at 12 months.[7] Complete surgical resection with negative margins has been shown to extend survival,[8] and an R0 resection is always the goal. The margins for surgical resection should be wide to encompass all diseases, but they are limited by anatomic constraints of what cannot be replaced or reconstructed after resection. Resection can include the SVC, a short segment of inferior vena cava (IVC), the entire right atrium, the tricuspid valve, the right coronary artery, and up to about 30% of the right ventricular muscle mass if right ventricular function is normal to begin with. These tumors can be quite large, and based on the anatomic extent of tumor and the margins needed for resection, venous cannulation for cardiopulmonary bypass must be carefully planned and individualized to each patient (Figure 3).

We have routinely cannulated directly into the high SVC for upper-body drainage. Usually we can cannulate directly into the IVC at the diaphragm, but occasionally we need to use percutaneous femoral venous cannulation to allow exposure for complete inferior resection. Aortic cannulation is a standard fashion as it is distant from the tumor. The right atrium can be completely resected and replaced with bovine pericardium. If the resection involves the SVC or IVC, we use a vascular stapler to recreate the vein segment and leave the rest of the pericardium open to replace the atrium (Figure 4). The 1 area of real danger to the surgeon is where the right atrium meets the root of the aorta; overzealous resection here will take the surgeon into the fibrous skeleton of the heart, and this can be very difficult to repair.

The most common reason we have seen for a failed complete resection in patients referred to us has been the surgeon's reluctance to resect the right coronary artery that can be involved by the tumor. Incomplete resection that leaves gross disease will only lead to rapid regrowth of the tumor, and should be avoided whenever possible. When we suspect right coronary artery involvement, we mobilize the right internal mammary artery at the beginning of the operation. If needed, it is simple to either clip distally and use as a pedicle graft, or divide proximally and use as a free graft as needed. The right ventricular wall can be replaced with Bovine pericardium or, if it is the area

Figure 3. Surgical view of large right heart sarcoma.

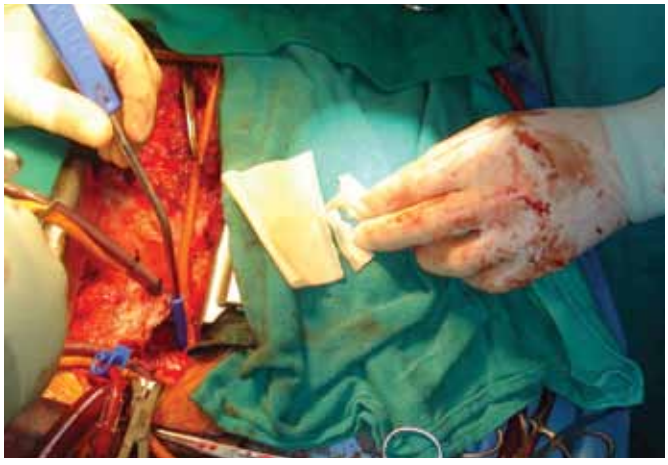
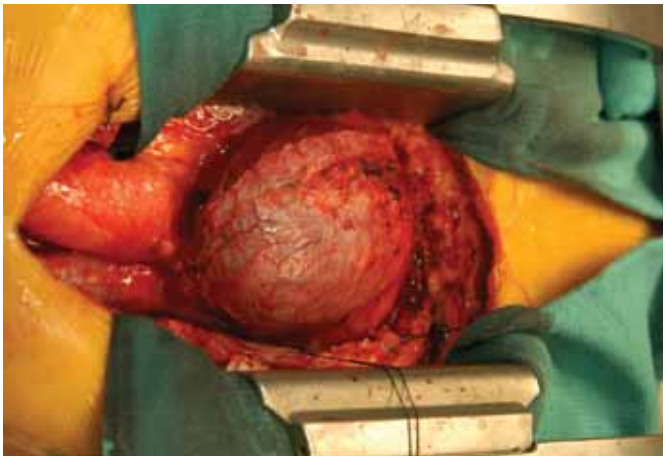


Figure 4. Recreating superior vena cava and right atrium with bovine pericardium.



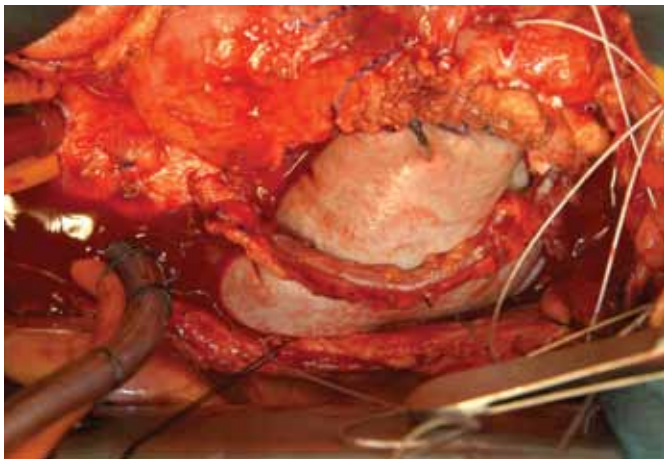


Figure 5. Completed repair.

along the anterior tricuspid valve where the right coronary was resected, it is simply advanced forward to the prosthetic tricuspid valve used for valve replacement (Figures 5 and 6).

We have preliminary data on 24 patients that we have operated on with right heart sarcoma. Of these, 22 of 24 (92%) were right atrial, and 2 of 24 (8%) were right ventricular. We had an equal distribution of 12 males and 12 females. The age range was 17 to 61 years of age with an average age of 40.7 years. Angiosarcoma was found in 18 of 24 (75%), synovial cell sarcoma in 3 of 24 (13%),

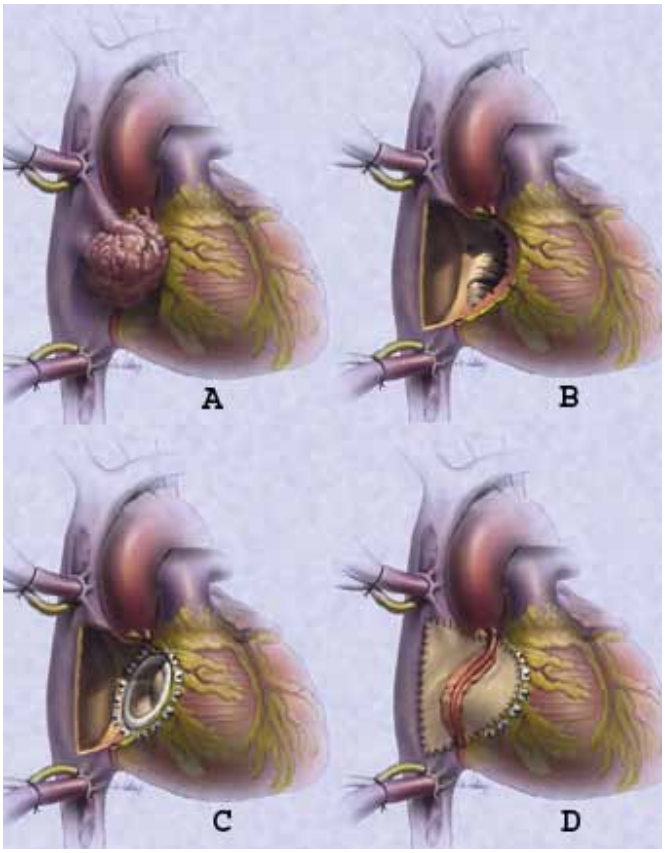
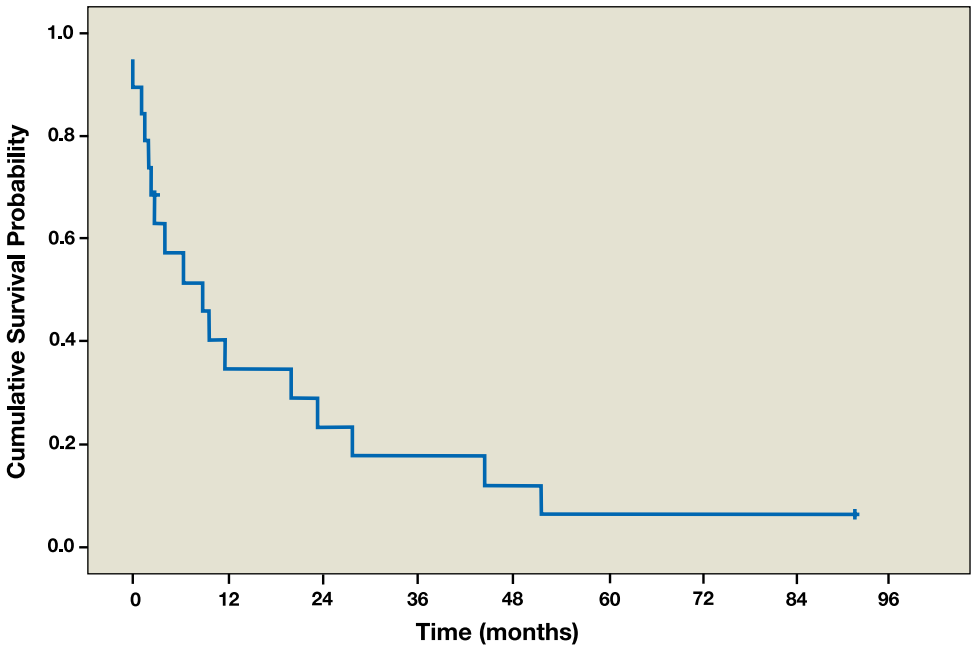


Figure 6. (A) Right atrial sarcoma; (B) extent of resection; (C) tricuspid valve replacement; (D) reconstruction with bovine pericardium and right internal mammary artery graft.

Figure 7. Cumulative survival probability for all right heart sarcomas with surgical resection.



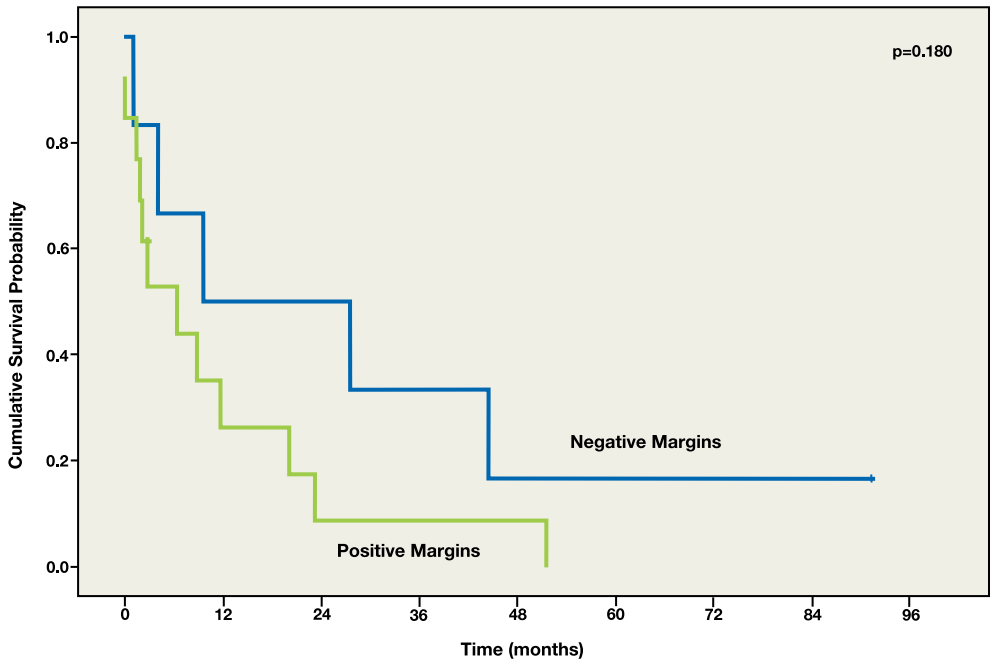


Figure 8. Cumulative survival for R0 and R1 resections of right heart sarcoma.

rhabdomyosarcoma in 1 of 24 (4%), undifferentiated sarcoma in 1 of 24 (4%), and leiomyosarcoma in 1 of 24 (4%). This is the initial data used to write our current IRB protocol for treating these tumors. In 16 of 24 (66.6%) patients, we had microscopic disease at the margin (R1 resection), and achieved an R0 resection with negative margins in only 8 of 24 (33.3%) patients. Hospital mortality was 8%, with 1 being from right heart failure and 1 from bleeding in a patient with extensive radiotherapy to the heart and mediastinum. Overall survival for our preliminary data is seen in Figure 7 and survival for R0 and R1 resections is seen in Figure 8. Although this remains a difficult disease, the survival with surgical resection far exceeds that of medical therapy alone, and we now have survivors of almost 10 years and still living. The hypothesis of our current protocol is that standard use of neoadjuvant chemotherapy will lead to a higher rate of R0 resection and hence a higher long-term survival, compared with this historical cohort.

Conclusion

Right heart sarcomas are unusual tumors that continue to pose difficult therapeutic problems to the clinician. Our initial data suggests reasonable surgical risk for resection and survival of up to 10 years, but the ability to obtain microscopically negative margins occurs only about 33% of the time. We have initiated a protocol-driven diagnosis and treatment of right heart sarcomas that incorporate routine neoadjuvant chemotherapy, and we hope to include 25 patients over 5 years. We hypothesize that this approach will let us increase our rate of complete resection with negative margins and further improve survival in this patient group.

References

1. Reardon MJ, Malaisrie SC, Walkes JC, Vaporciyan AA, Rice DC, Smythe WR, DeFelice CA and Wojciechowski ZJ. Cardiac autotransplantation for primary cardiac tumors. Ann Thorac Surg. 2006 Aug;82(2):645-50.
2. Kim CH, Dancer JY, Coffey D, Zhai QJ, Reardon M, Ayala AG, Ro JY. Clinicopathologic study of 24 patients with primary cardiac sarcomas: a 10-year single institution experience. Hum Pathol. 2008 Jun;39(6):933-8.
3. Reardon MJ, Walkes JC, Benjamin R. Therapy insight: malignant primary cardiac tumors. Nat Clin Pract Cardiovasc Med. 2006 Oct;3(10):548-53.
4. Blackmon SH, Patel A, Reardon MJ. Management of primary cardiac sarcomas. Expert Rev Cardiovasc Ther. 2008 Oct;6(9):1217-22.
5. Blackmon SH, Reardon MJ. Surgical treatment of primary cardiac sarcomas. Tex Heart Inst J. 2009;36(5):451-2.
6. Lam KY, Dickens P, Chan AC. Tumors of the heart. A 20-year experience with a review of 12,485 consecutive autopsies. Arch Pathol Lab Med. 1993 Oct;117(10):1027-31.
7. Neragi-Miandoab S, Kim J, Vlahakes GJ. Malignant tumours of the heart: a review of tumour type, diagnosis and therapy. Clin Oncol (R Coll Radiol). 2007 Dec;19(10):748-56.
8. Putman JB Jr, Sweeney MS, Colon R, Lanza LA, Frazier OH, Cooley DA. Primary cardiac sarcomas. Ann Thorac Surg. 1991 Jun;51(6):906-10.