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PULMONARY ARTERY SARCOMA

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Introduction

Primary heart tumors are rare, and malignant primary heart tumors are only a small subset of these. Most primary malignant heart tumors are sarcomas arising from the cells of the structural elements of the heart such as blood vessels, muscle, connective tissue, fat and even bone. Unlike most malignancies, where cell type often dictates treatment choices and prognosis and is used for classification, the histology in primary cardiac sarcoma plays little role in determining therapeutic options or prognosis. We have found that anatomic location within the heart is the major determining factor in clinical presentation, treatment options and prognosis in cardiac sarcoma. Therefore, we accordingly classify primary cardiac sarcomas into right heart sarcomas, left heart sarcomas and pulmonary artery (PA) sarcomas.

Since the first autopsy report of a primary PA sarcoma in 1923, there have been fewer than 250 cases reported in the English literature. Most of these reports have been single autopsy or case reports, and patient prognosis has generally been dismal. Since few institutions and even fewer individual physicians acquire much exposure to this disease, the diagnostic and treatment approaches have remained unresolved. Our cardiac sarcoma group working at the Methodist DeBakey Heart & Vascular Center and the MD Anderson Cancer Center has undertaken a systematic study of this disease, and operated on 9 patients using a radical resection with curative intent and multimodality approach. Based on this work, we have suggested a diagnostic strategy, treatment approach and staging system for primary PA sarcoma. A substantial improvement in patient survival over historical controls has also been demonstrated and will be discussed in this review.

Discussion

Cardiac sarcomas are rare tumors, and primary PA sarcoma is an unusual subset of these already unusual entities. The first case of primary PA sarcoma was reported in an autopsy study in 1923,[1] and fewer than 250 cases have been reported in English literature since then. We recently published our series and treatment approach to primary PA sarcoma, and reviewed the current literature to establish a treatment plan and examine our outcomes in this difficult group of patients.[2] In this report, we did a literature search to identify cases of surgical resection of primary PA sarcoma for historical controls, and reviewed the databases of the MDHVC and the MD Anderson Cancer Center to identify all cases of primary PA sarcoma having surgical resection at our institutions. In our search, we selected all cases that adequately described the surgical technique and survival to allow analysis. This yielded 60 patients, with 25 having complete resections, 24 having debulking resections or endarterectomy, and 11 having a poorly reported resection technique but good survival data. We identified 8 patients who underwent surgery for PA sarcoma at our institutions, and we included an additional patient who recently was operated on by our group for primary PA sarcoma. These 9 cases serve as the basis for this review.

The clinical presentation of patients with PA sarcoma can be easily confused with other entities that affect pulmonary circulation. Symptoms almost always

included cough and dyspnea, with hemoptysis and chest pain occurring less frequently, in a picture that may mimic pulmonary embolus (PE). Constitutional symptoms were often present, including fever, anemia, and weight loss, and are more consistent with malignancy than PE. These mass lesions will not decrease in size with anticoagulation but will continue to grow. In our recently reported series, all 8 patients had cough and dyspnea, 7 of 8 had constitutional symptoms of fever and anemia, and only 1 of 8 had chest pain. A lack of history or findings of deep venous thrombosis should also help guide the clinician towards consideration of malignancy.

The difficulty in establishing the diagnosis of PA sarcoma is highlighted by the fact that the typical duration between symptom onset and diagnosis ranges from 3 to 12 months. The most common initial misdiagnosis is PE, but pulmonary hypertension, congenital pulmonary stenosis, fibrosing mediastinitis and lung tumor have all been confused with PA sarcoma. By the time the correct definitive diagnosis is achieved, about 50% of these patients will have metastatic lung involvement.[3] These patients usually present to the clinician with right heart failure and pulmonary hypertension of often substantial levels that requires urgent treatment. Since this presentation is not infrequently confused with chronic pulmonary emboli, pulmonary artery thromboendarterectomy is often recommended. While tumor endarterectomy can be achieved once sarcoma is found rather than thrombosis, and will relieve pulmonary artery obstruction, it is associated with rapid tumor regrowth and poor survival outcomes. Therefore, establishing the correct diagnosis to allow appropriate planning for radical surgical resection is important if we are to increase patient survival in this disease.

Establishing the correct diagnosis relies on appropriate imaging. Imaging has proven crucial in our approach to these tumors, and we have used a variety of imaging techniques in these cases to ascertain the correct diagnosis, since tissue diagnosis prior to open surgery has been difficult to obtain. We have used computed tomography angiography (CTA), transthoracic echocardiography (TTE), transesophageal echocardiography (TEE), magnetic resonance imaging (MRI) and positron emission tomography (PET) scans to characterize these mass lesions. Since this entity mimics the much more common PE, a CT scan with PE protocol is often the initial diagnostic test chosen. All of our patients who had CT scans showed hyperdense lesions and actual distention of the artery lumen in areas where the tumor completely filled the artery (Figure 1). The extent of these tumors and dilatation of

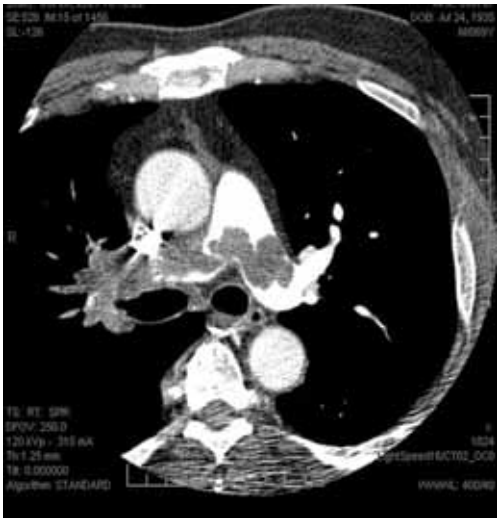

Figure 1. CT scan showing pulmonary artery sarcoma.

the artery itself should steer the clinician away from a diagnosis of chronic PE and towards 1 of PA sarcoma. MRI scan has been particularly useful in identifying PA sarcoma as the tumor enhances with gadolinium contrast more than thrombus.[4-10] MRI scan is also helpful in the follow-up of these patients if new pulmonary artery masses appear after surgery, to differentiate from post-operative hematoma or clot. The degree of tumor differentiation, myxoid matrix content and thrombus content has been shown to correlate with the degree of gadolinium enhancement.[11] The hyperactivity of these tumors make them PET avid and will help the clinician differentiate tumor from thrombus as well as look for extra cardiac disease (Figure 2).[12, 13]

Accurate preoperative imaging is crucial to allow appropriate surgical planning, since tumor debulking or endarterectomy is associated with poor survival and complete radical resection improves the patient's prog-

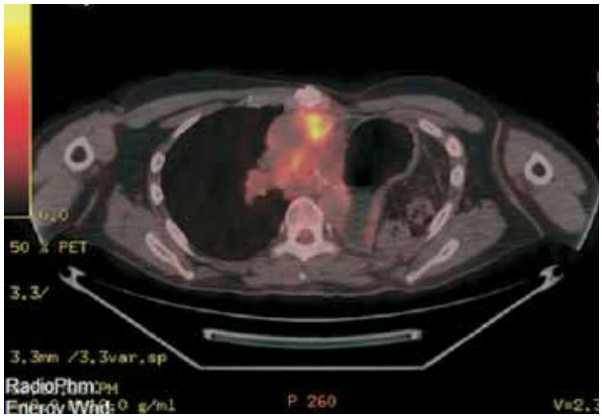

Figure 2. PET avid pulmonary artery tumor.

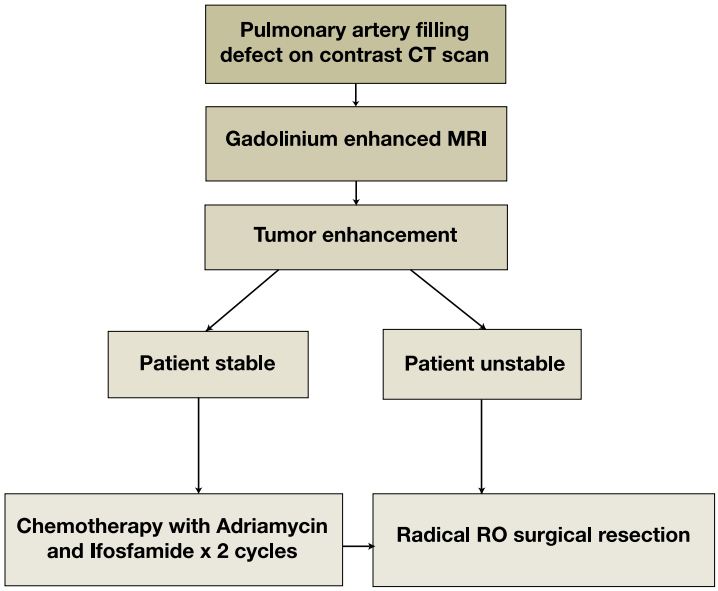

Figure 3. Diagnosis and treatment protocol for patients with pulmonary artery mass that has clinical features of pulmonary artery sarcoma or does not resolve on anticoagulation. CT: computed tomography; MRI: magnetic resonance imaging.

nosis. Unfortunately, obtaining a tissue diagnosis is difficult prior to surgery and most often is not obtained until the time of surgery. We have attempted transvenous catheter biopsy of these tumors but have had limited success in obtaining the tissue needed. We currently employ a treatment algorithm shown in Figure 3 for these patients. Patients considered for operation are those with adequate cardiopulmonary reserve, adequate lung function if pneumonectomy is contemplated, disease limited to the main pulmonary artery system — or, if outside this, manageable with chemotherapy — and surgical judgment of resectability. Although preoperative imaging is helpful, we have found that the ability to completely resect the tumor cannot be fully assessed prior to surgery. We have also proposed our own staging system for PA sarcoma shown in Table 1.

Table 1. Staging system for primary pulmonary artery sarcoma.

Stage 1	Tumor limited to main pulmonary artery
Stage II	Tumor involving 1 lung and main pulmonary artery
Stage III	Bilateral lung involvement
Stage IV	Extrathoracic spread

Anatomically, these tumors tend to arise from the dorsal surface of the main pulmonary artery just beyond the pulmonary valve.[14] They form from multipotential mesenchymal cells from the muscle remnant of the bulbus cordis[15] in the intimal and subintimal surfaces.[16, 17] The tumor then tends to grow distally along the artery, rarely penetrating the actual wall of the artery but rather distending it, which is an important point in the surgical resection. Distal extension can go to the lung parenchyma itself as emboli, infarction or metastasis.[14] Although some have shown survival differences based on cell histology in limited cases,[3] that has not been our experience in cardiac sarcoma in general.[17] This is further complicated by the wide variety of histology we have seen in these patients, with 1 unclassified sarcoma, 2 leiomyosarcomas, 2 angiosarcomas, 1 high-grade sarcoma and 1 spindle cell sarcoma being seen in our published series[2] as well as angiosarcoma in our recently added patient.

Pulmonary artery sarcoma is a very aggressive disease, and survival after diagnosis is often discussed as weeks or months rather than years. The results of chemotherapy alone have been disappointing, with numerous studies reporting a lack of tumor response.[18-23] The response to chemotherapy alone has been so poor that a recent paper published from Japan claimed to be the first case of PA sarcoma responding to chemotherapy.[24] The role of radiation therapy also is unsettled, although more applicable, due to tumor location above the myocardium. Surgical resection remains

the primary method of treatment in patients with PA sarcoma, and the only method shown to increase survival.[25]

Although surgical resection is the mainstay of therapy for these patients, the techniques used have varied from local debulking to tumor endarterectomy to complete radical resection. We believe only complete radical resection allows a reasonable increase in survival and plan our surgery accordingly. Unfortunately, the ability to completely resect the tumor cannot always be determined from preoperative imaging studies, and can only be definitively assessed at surgery. Since exposure of the right main pulmonary artery may require division of the aorta and possibly the superior vena cava (SVC), we plan surgical cannulation for cardiopulmonary bypass accordingly. We use dual venous cannulation with direct SVC cannulation and normal inferior vena cava (IVC) cannulation via the right atrium. Arterial cannulation via the ascending aorta is normal. Both SVC and IVC are looped with tourniquets to isolate the right heart. Cardiopulmonary arrest is achieved with cold potassium blood cardioplegia. Fortunately, these tumors rarely penetrate the pulmonary artery wall, allowing reasonably easy mobilization. The main pulmonary artery has always been involved in our experience, and the pulmonary valve is involved about 30% of the time.[14] An assessment is made of the distal extent of the tumor into each main pulmonary artery. These arteries can be relatively easy to resect out to their first branch points on each side, and we resect as far as is necessary to go beyond the tumor, up to this branch point.

In cases where 1 pulmonary artery is relatively free and the other involved is all the way out into the lung and completely obstructing blood flow, we have chosen to do a pneumonectomy to completely remove the disease. When a pneumonectomy is performed, the pulmonary veins and main bronchus are dissected and divided before cardiopulmonary bypass (CPB) is instituted to avoid bleeding while heparinized. The branch PAs and main PA are mobilized, and then CPB is instituted and the involved main PA divided. In these cases, the involved lung had no blood flow, and hemodynamics were actually improved by pneumonectomy and removing the obstruction of the contralateral artery. Once each PA has been divided — or the lung, in the case of pneumonectomy — and its main PA removed, the main PA trunk can be assessed for pulmonary valve involvement. If the pulmonary valve is involved, the entire PA trunk must be removed and replaced by a pulmonary allograft. Removal of the entire PA trunk and replacement by an allograft is similar to its mobi-

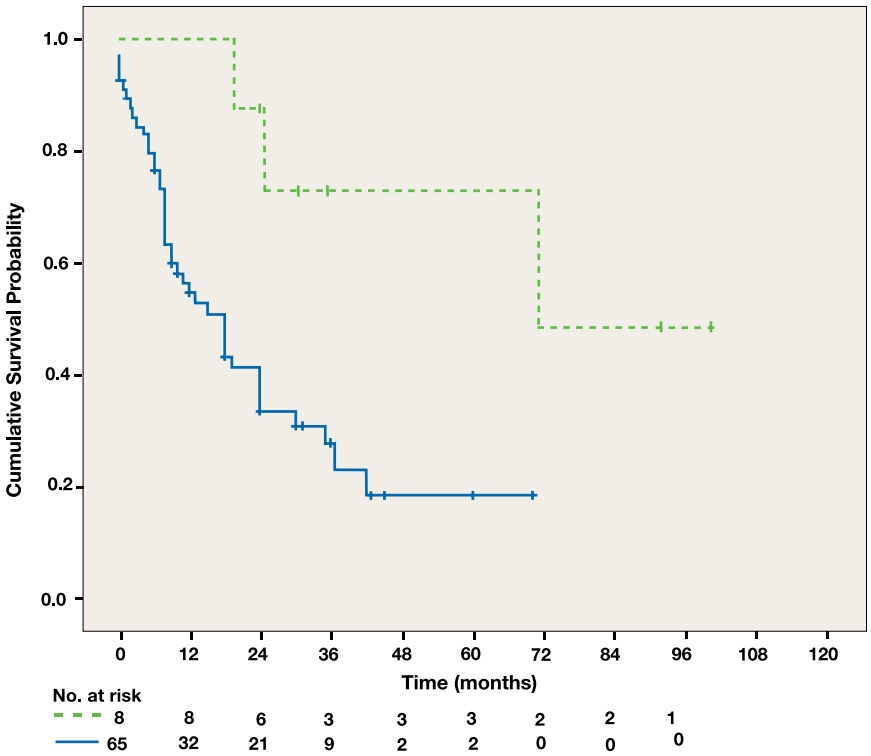

Figure 4. Five-year cumulative survival probability in the current case series (dotted line) vs. a combined series (solid line) of all historical controls since 1990.

lization and replacement for a Ross procedure, which we have previously described.[26] If the resection of the right and/or left main PA is limited, then the allograft branches may surmise to span the defect. When the extension had been too extensive for this, we used an appropriately sized Gore-Tex graft to go from distal right PA resection point to distal left PA resection point, and then implanted the pulmonary allograft into the side of this graft. Despite the extensive nature of the resection, separation from CPB had not been difficult since the surgery relieves the patient of the severe PA obstruction that is present preoperatively.

We had no hospital deaths in our reported series or in our additional case. Survival rates of primary cardiac sarcoma has been historically dismal and generally reported for all cardiac sarcomas as a group, rather than with the anatomic classification our group has put forth. Survival without surgical resection has been reported to be about 10% at 9 to 12 months.[27] The Mayo Clinic has reported its experience over 34 years with 32 patients undergoing surgical resection for cardiac sarcoma with a median survival of 12 months.[28] The combined series of the Texas Heart Institute and MD Anderson Cancer Center looked at 21 patients over 26 years who had surgical resection of cardiac sarcoma to yield a survival of 14% at 2 years.[29] To confine our analysis to PA sarcoma only, we chose to use historical controls from the literature representing only PA sarcoma resections. Historical controls in this study had a mean survival of 18 months, and our series yielded a median survival of 71 months. The survival curve for both is shown in Figure 4. This improved survival clearly suggests that the surgeon should strive for complete resection, and that limited procedures such as tumor endarterectomy are less effective. All patients are offered adjuvant chemotherapy, but not all patients in this series had postoperative chemotherapy. To continue our study of this disease, we have standardized our diagnostic and treatment approach included in our institutional database and established an international registry of PA sarcoma.

Conclusion

We believe that we have substantially improved the survival rate of patients with pulmonary artery sarcoma due to our use of aggressive radical resection with curative intent and multimodality therapy. Of the 9 patients we have currently treated, 5 are still alive and 3 have no evidence of disease. We have proposed a standard treatment protocol and a staging system for pulmonary artery sarcoma. The continued and expanded use of multimodality biologic therapy, in addition to surgical resection, represents the greatest area for potential advances in this difficult disease.

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