Title: Chemoradiation for Pediatric Primary Cardiac Leiomyosarcoma: Case Report and Review of Literature

Short Running Title: Post-op radiation for teen atrial leiomyosarcoma

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Abbreviations

ECHO	Echocardiogram
MRI	Magnetic Resonance Imaging

MRA	Magnetic Resonance Angiography
MR	Magnetic Resonance
SVC	Superior Vena Cava
IVC	Inferior Vena Cava
RBE	Relative Biological Effectiveness
CTV	Clinical Target Volume
CTCAE	Common Terminology Criteria for Adverse Events
4DCT	Computed Tomography scan accounting for motion over time

Abstract

A 13-year-old healthy girl presented with dizziness and palpitations, found to have a left atrial mass. An 8 cm tumor was removed. Pathology confirmed leiomyosarcoma, Grade 3 with positive margins. She was treated with ifosfamide and doxorubicin prior to radiation with concurrent ifosfamide alone. She was treated to 66 Gy in 33 fractions to the operative bed. Prospectively graded toxicities included Gr 2 esophagitis and Gr 1 anorexia, dermatitis and fatigue. She completed a total of 6 cycles of ifosfamide. One year after treatment she had no evidence of disease with normal ECHO and no cardiac, pulmonary or esophageal symptoms.

Introduction

Primary cardiac tumors are uncommon with autopsy estimates of 0.001-0.3% and epidemiological studies estimating an incidence of roughly 1.4 per 100,000 people per year.[1,2] Of primary cardiac tumors, 75-90% are benign (usually myxomas) with the majority of malignant tumors being sarcomas.[3] Angiosarcomas are the most predominant malignant subtype and tend to arise in the right heart with other subtypes generally arising in the left heart.[3] Leiomyosarcomas are usually located in the left atrium and frequently involve the pulmonary veins or mitral valve. They are generally more well-differentiated than other subtypes, with a better prognosis. Research on this disease has been sparse and limited to case reports and series. Pediatric cases of primary cardiac sarcoma are even rarer, though there are multiple case reports of patients diagnosed as young adults[4–6] and a couple case reports of pediatric patients.[7,8]

In general, the primary treatment of sarcomas is surgery. Adjuvant therapies are indicated for positive margins, recurrence, or in high-risk subtypes like angiosarcoma. While adjuvant radiation to sarcomas involving the extremities is well-tolerated by most patients, similar doses to the heart can cause significant acute and late toxicity. In addition to risk of radiation pneumonitis and esophagitis, radiation to a cardiac tumor carries a risk of acute pericarditis and late cardiomyopathy, conduction system defects, accelerated atherosclerosis, constrictive pericarditis, and valvular regurgitation or stenosis. These risks must be weighed against risk factors for recurrence and should be assessed individually in accordance with patient and family values. We report a case of a

13-year-old girl found to have an 8 cm primary cardiac leiomyosarcoma of the left atrium treated with resection, ifosfamide and doxorubicin, and proton radiotherapy.

Case Description

A 13-year-old girl with no significant past medical history presented with dizziness and palpitations to an emergency room and had an echocardiogram (ECHO) showing a large left atrial mass. A subsequent cardiac MRI demonstrated what was thought to be three intra-cardiac tumors in the left atrium extending through the mitral valve. The largest measured 6.9 x 2.9 x 2.4 cm and protruded into the mitral valve funnel during ventricular systole while a smaller one appeared to attach to or originate from the right upper and middle pulmonary veins (Figs. 1A and 1B). An MRI Brain, Abdomen, and Pelvis showed no other lesions to suggest secondary spread to the heart. She was taken for surgery with the presumption of a myxoma.

She had midline sternotomy with resection of thymus, cannulation of SVC and IVC prior to aortic cross-clamping for total ischemic time of 69 minutes. The atrial septum was opened through a vertical incision, which exposed the huge, lobulated, left atrial mass. The connection seemed to run from the inferior portion of the atrial septum all the way between the right and left pulmonary veins up superiorly. The entire mass was excised in one piece, taking all the affected septum and posterior left atrial wall with it. The pulmonary veins were inspected and found to be unobstructed, and the mitral valve appeared normal. Autologous pericardium used to epithelialize back wall of atrium. Upon return of circulation, she entered normal sinus rhythm with 1:1 conduction.

Pathology showed 8 cm high grade leiomyosarcoma with multifocal positive margins. No gross disease visualized on post-operative cardiac MRI. She recovered well from the surgery with some moderate fatigue but no further dizziness or palpitations.

Based upon a multi-disciplinary discussion, she was offered adjuvant radiation and chemotherapy. She was treated with chemotherapy similar to the ARST0332 protocol.[9] Chemotherapy consisted of 6 cycles of ifosfamide (3 g/m2 on days 1-3) and one cycle of doxorubicin (37.5 mg/m2 on days 1-2) every 3 weeks. She started her first cycle four weeks before initiation of radiation with both ifosfamide and doxorubicin. Doxorubicin was not administered for subsequent cycles, because proton radiation to her heart began on day one of cycle two.

She was recommended to receive proton therapy in an effort to spare the uninvolved heart. She underwent 4DCT simulation with IV contrast, which showed minimal cranio-caudal motion allowing for treatment to be delivered free breathing. She was treated to 52.8 Gy (RBE) to the preoperative tumor extent with 10-15 mm anatomically margin in 1.6 Gy per fraction (CTV size 186.9 cm^3) with a simultaneous integrated boost to 66 Gy (RBE) in 2 Gy per fraction to the operative bed (CTV size 108.1 cm^3) with representative axial slice shown in Figure 1C. The coverage was 98% of the high dose target received at least 66 Gy and 99.98% of the low dose target received at least 52.8 Gy. Dose to Organs at Risk summarized in Table 1. She had one unplanned admission for neutropenic fever on day 13 of her second cycle of chemotherapy with mucositis and scalloping of buccal mucosa noted on that admission. Prospectively

graded toxicities according to CTCAEv5.0 included Grade 2 esophagitis and Grade 1 anorexia, dermatitis and fatigue.

After radiation, she ultimately completed her sixth and final cycle of chemotherapy without complications or delays. Four months after completing radiotherapy an MRI Heart and MRA chest were done. MR imaging showed no residual or recurrent mass, no pericardial or pleural effusions, and no suspicious adenopathy. CT Chest, one year after completing radiotherapy, showed no evidence of recurrent or residual disease. Serial ECHOs were done every 3 to 4 months. One year after completing all treatment, her transthoracic ECHO showed mildly prolapsed mitral valve with mild mitral valve regurgitation, but otherwise normal left and right ventricular size, strain, and systolic function, without change compared to prior ECHOs. Her left ventricular ejection fraction was 76% with peak ejection mitral valve Doppler 128 cm/s. At one year follow-up, she denied any chest pain, shortness of breath, pain with swallowing, or difficulty swallowing; however, she did have intermittent, self-resolving episodes of palpitations and tachycardia to 180 beats per second.

Discussion

Primary malignant cardiac tumors are exceedingly rare in pediatric patients, warranting multi-disciplinary discussion of care. A review of Indiana's institutional experience showed a 38% mortality for malignant cardiac tumors but did have multiple long-term survivors.[8] Per a systematic review of primary cardiac leiomyosarcomas

specifically, there were 79 patients in 72 reports as of 2015 (3 pediatric). Worse median overall survival was noted with incomplete resection (13 months vs 84 months) and without adjuvant chemotherapy and/or radiotherapy (9 months vs 41 months), though there were no details on radiotherapy.[10] There are three reports of adults with primary cardiac leiomyosarcomas treated with radiotherapy. A 53 year old woman, who received adjuvant radiation to 66 Gy following margin-positive resection without recurrence after 9 years.[11] A 40 year old woman, treated with adjuvant chemoradiation after surgery for first recurrence (unknown dose), had disease free survival of 42 months.[12] A 19 year old man treated with surgery alone initially, and surgery with adjuvant radiotherapy to 60 Gy after recurrence, subsequently developed widespread metastases within 4 months of the radiation.[13] We report on a case where proton therapy allowed for safe treatment delivery with sparing of the uninvolved heart and adjacent organs at risk though further follow-up and research is warranted to better assess safety and efficacy of this approach for pediatric patients.

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Legend:

Figure 1. Pre-op MRI revealing lobulated mass in left atrium extending through mitral valve and attached to pulmonary veins and proton radiation plan. A) Axial Haste sequence showing lobulated tumor invading left ventricle (star). B) Sagittal STIR sequence showing heterogenous mass in left atrium and left ventricle (arrow). C) Representative CT axial slice of proton radiotherapy plan with anterior heart receiving no radiation dose (star) and scale in Gy. Red line indicating high risk CTV planned to receive 66 Gy (RBE).

Table 1. Dosimetric data from proton radiotherapy plan