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# Primary cardiac neoplasms: do effective treatments exist

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*Boston University*

BOSTON UNIVERSITY  
SCHOOL OF MEDICINE

Thesis

**PRIMARY CARDIAC NEOPLASMS:  
DO EFFECTIVE TREATMENTS EXIST?**

by

**VANESA BARBARA NOEL**

B.S., Boston University, 2013

Submitted in partial fulfillment of the  
requirements for the degree of  
Master of Science

2015

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## **DEDICATIONS**

I would like to dedicate this work to the most amazing, driven, and loving woman I know; my mother Marie; because without her I would not have made it this far.

## **ACKNOWLEDGEMENTS**

I would first like to thank and acknowledge Dr. Carl Franzblau and Dr. Naomi Ko for their time and contributions. I would also like to thank the faculty and staff of Boston University School of Medicine's Graduate Medical Sciences program for all of the knowledge and confidence they have imparted to me. Last but not least, I would like to thank the Church at Haverhill for all of their prayers and many words of encouragement.

# **CARDIAC NEOPLASMS: DO EFFECTIVE TREATMENTS EXIST**

**VANESA BARBARA NOEL**

## **ABSTRACT**

Primary cardiac neoplasms (PCNs) represent the rarest form of neoplastic growths worldwide with an incidence ranging from 0.001 – 0.3% in autopsy series (Yu et al., 2014) (“Primary Cardiac Neoplasms,” 2014). The rarity of these tumors has contributed to the challenges associated with their diagnosis and treatment (“Primary Cardiac Neoplasms,” 2014). Primary heart tumors are generally classified as benign or malignant based on whether or not the tumors cells invade their surrounding tissue. Primary benign heart tumors can be further sub-classified as non-complicated or complicated. Non-complicated tumors are those that are stable, occur alone, and do not invade the cardiac conduction system. Conversely, complicated primary benign cardiac neoplasms are those that tend to break off into systemic circulation increasing the risk for embolization, have multicentered origins within the heart and/ or invade the cardiac conduction system which may lead to heart block and sudden death (“Cardiac Tumors: Merck Manual Professional,” n.d.). These distinctions have been shown to significantly impact the efficacy of treatment. Primary tumors in general tend to involve either the myocardium, i.e. the heart muscle itself, or the endocardium; i.e. the membrane that lines the heart cavities. In either case, the tumors most often appear in the left atrium (Roberts, 2001). Among primary cardiac neoplasms, myxomas (a type of non-cancerous heart tumor) are the most common accounting for approximately 40-50% of these growths (“Primary

Cardiac Neoplasms,” 2014). Clinicians tend to rely heavily on imaging procedures for the diagnosis of primary heart tumors because there are no characteristic clinical signs exclusive to primary cardiac neoplasms (Bartoloni & Pucci, 2013). Further, these growths have a tendency to mimic the symptomology of other better known conditions such as heart failure, stroke, and coronary artery disease (“Cardiac Tumors: Merck Manual Professional,” n.d.).

The mean age of diagnosis for these tumors is approximately 50 years of age but many PCNs have been identified in children (Bartoloni & Pucci, 2013; “Primary Cardiac Neoplasms,” 2014). Further, sources disagree on the relative incidence of these neoplasms among men and women. Some report a higher prevalence in women while others hold that the frequencies are equal for both sexes and across all races (Bartoloni & Pucci, 2013; “Primary Cardiac Neoplasms,” 2014).

The standard of care for the treatment of primary cardiac neoplasms are; as with other neoplastic conditions; radiation therapy, chemotherapy, surgical resection, and; in some instances; cardiac transplantation. However, due to the differences in tumor histology, i.e. the structure and molecular characteristics of tumor cells, many of the current treatment options available to and considered curative in patients with non-complicated benign PCNs do not confer the same survival benefits in patients with complicated benign PCNs nor in patients with malignant PCNs. With treatment, the prognosis associated with primary cardiac neoplasms is heavily dependent upon the type of tumor. Primary benign non-complicated neoplasms tend to have very positive



prognoses. Even with incomplete resection, reports have shown no evidence of recurrence in patients with this tumor type (Jr et al., 1987). On the other hand, primary malignant neoplasms of the heart are associated with the poorest prognoses. The longest reported median survival time is only 16.5 – 17 months after diagnosis and surgical excision of the primary tumor (Chahinian, Gutstein, & Fuster, 2000; Ostrowski, Marcinkiewicz, Kośmider, & Jaszewski, 2014; Simpson et al., 2008).

In this thesis we examine the reported outcomes of the above four forms of treatment that are regarded as the standard of care for primary cardiac neoplasms. We do this by reviewing the currently available literature characterizing the results of these respective courses of therapy. We then evaluate the efficacy of these treatments relative the definition of effective treatments developed herein. Finally, based on the evidence, we conclude that effective treatments do exist for approximately 38% of people with PCNs. This minority represents the people with primary benign non-complicated cardiac neoplasms. We also regrettably conclude that for the other 62% (37% with benign complicated cardiac neoplasms and 25% with malignant cardiac neoplasms) of people with primary cardiac tumors effective treatments do not exist. For this reason, we propose the further investigation of two promising therapies. These are cardiac autotransplantation and targeted gene therapy. We believe that elucidating the possible advantages of these therapies in the heart will lead to treatments that can be deemed effective in treating complicated primary benign cardiac neoplasms as well as primary malignant cardiac neoplasms.

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## LIST OF ABBREVIATIONS

<u>Abbreviation</u>	<u>Origin*</u>	<u>Page First Used</u>
<b>BRCA-1</b>	<b>BReast CAncer gene 1</b>	<b>6</b>
<b>DNA</b>	<b>DeoxyriboNucleic Acid</b>	<b>6</b>
<b>HER2</b>	<b>Human Epidermal growth factor Receptor 2</b>	<b>6</b>
<b>HPV</b>	<b>Human PapillomaVirus</b>	<b>5</b>
<b>OHT</b>	<b>Orthotopic Heart Transplant(ation)</b>	<b>31</b>
<b>p53</b>	<b>tumor Protein 53 (also known as TP53)</b>	<b>6</b>
<b>PCN</b>	<b>Primary Cardiac Neoplasm</b>	<b>6</b>
<b>PCORI</b>	<b>Patient Centered Outcomes Research Institute</b>	<b>18</b>
<b>RT</b>	<b>Radiation Therapy or RadioTherapy</b>	<b>19</b>

\*for clarity, only the letters used in the abbreviations are capitalized

## I. INTRODUCTION

### Neoplasms

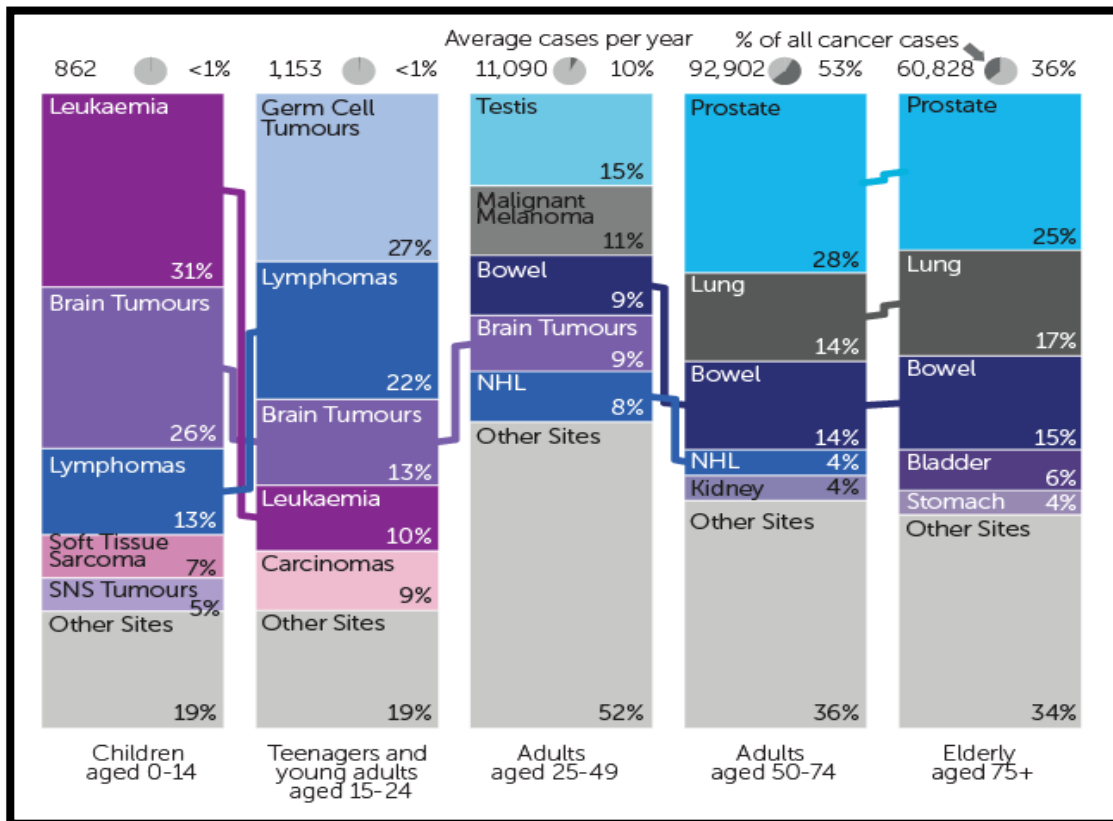
Neoplasms, or tumors, are abnormal masses of tissue resulting from the dysregulation of cell growth and/ or death. These masses may be benign (non-cancerous) or malignant (cancerous). The varied origins of tumors has led to the development of an extensive nomenclature aimed at classifying the growths by the tissues in which they occur and by their malignancy. The suffix –oma following the cell type is generally used to refer to benign growths. There are, however, some malignant tumors and non-tumors conditions that have been mistakenly named in this way (“Decoding the ‘-Omas’ - Intelihealth,” n.d.). For example, melanomas are very well known malignant disease of the skin and glaucoma is simply a condition caused by increased pressure in the eye. (“Decoding the ‘-Omas’ - Intelihealth,” n.d.). As seen in Table 1 below, neoplasms may derive from primitive embryonic tissue, epithelial ducts and surfaces, and/or from soft tissues. Examples of epithelial surfaces and ducts are the skin, the respiratory track, and breasts. Bone, lymph vessels, and the heart are all examples of soft tissue. (“Pathology of neoplasia for medical education,” n.d.). Growths resembling primitive embryonic tissues are named with the ending “-blastoma”. Tumors arising from epithelial surfaces and ducts are categorized as carcinomas and those arising from soft tissues are known as sarcomas (“Pathology of neoplasia for medical education,” n.d.).

**Table 1: Tissue Origins of Common Neoplasms<sup>30</sup> \***

<b>Primitive Embryonic Tissue</b>	<b>Epithelial Surfaces and Ducts</b>	<b>Soft Tissues</b>
Retinoblastoma Neuroblastoma Hepatoblastoma Medulloblastoma	Squamous cell carcinoma of the cervix <sup>+</sup> Adenocarcinoma of the stomach <sup>+</sup> Hepatocellular carcinoma <sup>+</sup> Renal cell carcinoma <sup>+</sup>	Leiomyosarcoma* Chondrosarcoma* Osteosarcoma* Liposarcoma*

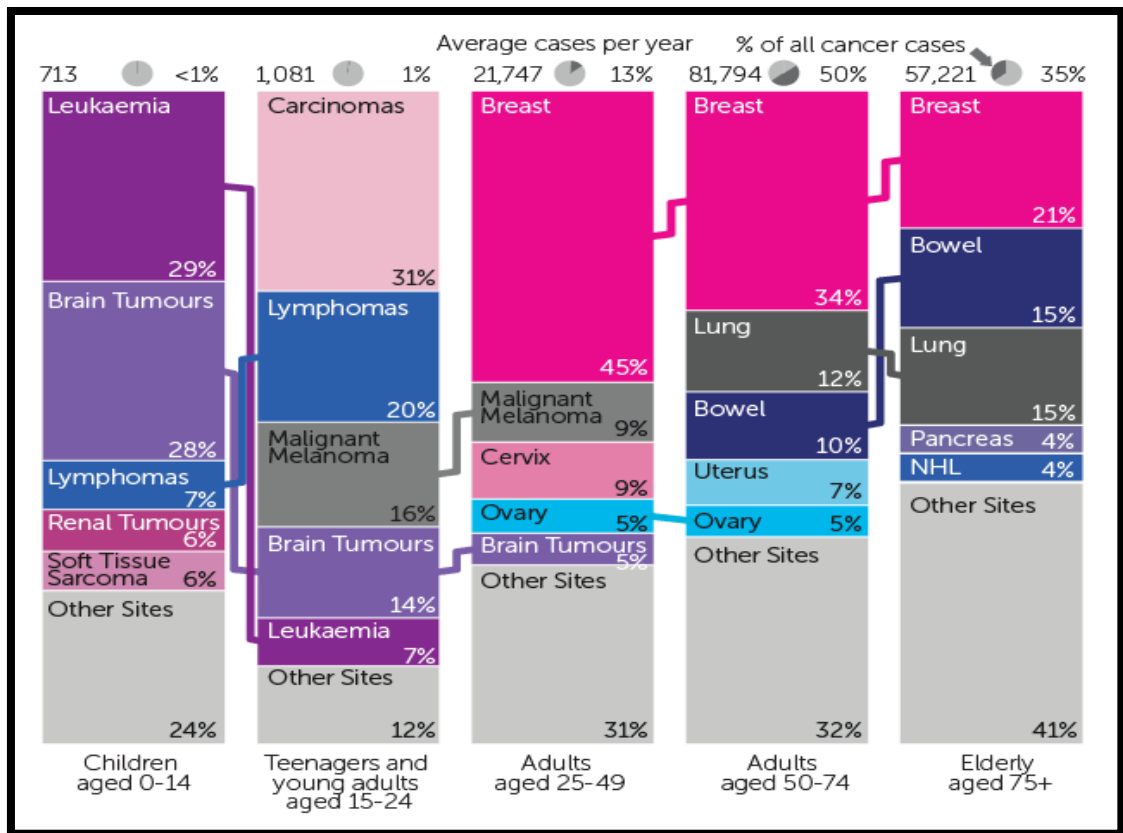
+ derived from ectoderm or endoderm, \* derived from mesoderm adapted from \*adapted from (“Pathology images and text for medical education - WebPath,” n.d.)

Neoplastic conditions tend to have gender specific predilections and they also have a tendency to occur only in certain age and ethnic groups (Figure 1 & 2) (UK, 2014b). This partiality is often the result of obvious anatomical deviations and/or certain hereditary factors. For example, while some men do get breast cancer, it is over 100 times more likely to occur in women. On the other hand, lung cancers are more prevalent in men and prostate tumors occur exclusively in men. In regards to age, leukemias and brain tumors prevail in early childhood while bowel tumors and tumors of the reproductive organs tend to occur more in later adulthood (UK, 2014b). As to race, genetics undoubtedly plays a role in the distribution of tumor incidence. By tumor type alone, renal neoplasms are more prevalent in the American Indian/Alaskan Native populations, pancreatic tumors are more common in African American populations, and ovarian cancers occur more often in Caucasian populations (Eheman et al., 2012). Of note, while reports indicate a higher overall prevalence of some neoplasias in Caucasian populations, disparities in care have led to higher mortality in minorities (Berz et al., 2009).



**Figure 1: 5 Most Commonly Diagnosed Cancers in Males by Age<sup>47</sup>**  
 Among males certain neoplastic conditions are more prevalent in certain age groups





**Figure 2: 5 Most Commonly Diagnosed Cancers in Females by Age<sup>47</sup>**  
 Among females certain neoplastic conditions are more prevalent in certain age groups

The symptomology of neoplasms depend upon the type, size, and location of the tumor. Benign growths tend to be more clinically silent than malignant diseases. This is of course until they begin to invade vital pathways. Small tumors are less likely to be clinically relevant but they do carry an increased risk of thromboembolization. Finally, the location of the tumor is important; not only symptomatically but also in consideration of the efficacy of certain therapies. For example, renal cell carcinomas are slow growing tumors that can reach a considerable size before detection due to the amount of space

available in the retroperitoneum (Kumar, Abbas, & Aster, 2012). Conversely, growths within the central nervous system often become immediately symptomatic due to the confines of the axial skeleton. Any additional mass within the skull or the spinal canal will displace and compress vital structures, thus affecting normal function.

While the exact cause of neoplasms is unknown, many theories, with a reasonable amount of supporting evidence, have been set forth. To date, there are two broad and widely recognized factors influencing tumor development. These are environmental factors, in which the growths are categorized as sporadic, and hereditary predispositions, in which they are known as familial neoplastic conditions. (“Neoplasia,” n.d.).

Environmental factors include carcinogenic chemicals such as acetaldehyde; found in alcoholic beverages; cigarette smoke, and outdoor air pollution (“Known and Probable Human Carcinogens,” n.d.). Oncogenic viruses are also considered to be environmental causes. These include the human papillomavirus (HPV), to which some squamous cell carcinomas are attributable, and the hepatitis B virus which has been directly linked to the development of hepatocellular carcinomas (“Pathology of neoplasia for medical education,” n.d.). Further, radiation; whether it be ultraviolet radiation, X-rays, or gamma rays; has also been known to promote neoplastic changes within cells. Still, other environmental factors such as diet have been linked to the incidence of at least one out of every ten cases of neoplasia (UK, 2014a).

Familial neoplasms occur when a chromosome is inherited with missing or defective anti-oncogenes. In many cases, these effected oncogenes seem to carry racial predilections (“Pathology of neoplasia for medical education,” n.d.). The causes of

hereditary tumors are just as numerous, if not more so, as the environmental causes. However, the variation comes not in the mode of damage but rather in the gene that is altered. For instance, a mutation in either the HER2 oncogene or the BRCA-1 oncogene can potentially lead to the development of breast cancer (Table 2). Furthermore, mutations in p53 typically manifest as a host of tumors which distribute themselves without prejudice throughout the body in a condition known as Li Fraumeni syndrome. Familial neoplastic conditions tend to be more aggressive physiologically and thus more difficult to treat clinically. Fortunately, these inherited forms only account for approximately 10-15 % of all cases. Due to the variations in the mode of damage and in the segments of DNA that can be affected, each of these causes, whether environmental or hereditary, has its implications in the progression of the disease states.

**Table 2: Oncogenes and their Associated Neoplasms<sup>27\*</sup>** Neoplasias can be the result of hereditary mutations in a variety of genes

<b>Oncogene</b>	<b>Associated Tumors (benign &amp; malignant)</b>
HER2	Breast and Ovarian Carcinomas
RAS	Various Carcinomas and Leukemias
C-MYC	Lymphomas
BRCA-1	Breast & Ovarian Carcinomas
APC	Colonic adenocarcinomas
p53	Various, many carcinomas
BCL-2	Chronic lymphocytic leukemia, lymphomas

\*Adapted from (“Neoplasia,” n.d.)

Regardless of etiology, neoplasms are characterized by an inaugurator incident of damage to a cell's genetic material. If this damage is left unchecked, it will cause the cell to progress through a series of steps in which the cell will acquire or lose the machinery necessary to evade the normal cell cycle. These steps may involve insertions, deletions, or translocations of entire sections of DNA in a process known as transformation. Once transformation has taken place cells are said to have "escaped" from the bounds of normal physiological regulation and control. This loss of control manifests as either an increase in the proliferation of affected cells or a decrease in their natural cell death (Kumar et al., 2012).

### **In the Heart**

As tumors go, cardiac neoplasms represent the rarest form worldwide with an incidence of ranging from 0.001 – 0.3% in autopsy series (Yu et al., 2014). This represents, as reported by Reynen in 1995, approximately 17 – 2,800 primary heart tumors in every million autopsies (Reynen, 1995). While the percentages may sound dismissively small, in a world of roughly six billion people it may represent approximately 60 million lives affected by this potentially devastating disease. Heart tumors may be either primary, originating in heart, or secondary, a result of metastasis from distant tissue sites (Kumar et al., 2012). Primary tumors can also be further classified as benign or malignant with benign primary cardiac tumors accounting for more than three quarters of all primary cases (Meng et al., 2002).

Although we tend to think of benign tumors as innocuous, in the heart they can

lead to significant morbidity and mortality by obstructing circulation, invading the cardiac conduction system, and by the formation of thromboemboli (“Cardiac Tumors: Merck Manual Professional,” n.d.; Meng et al., 2002). On the other hand, while primary malignant tumors occur a great deal less frequently than benign growths, their death toll is no less pervasive. The difficulty associated with treating these more aggressive tumor types result in a greater overall rate of mortality (Leja, Shah, & Reardon, 2011). Also, relative to extracardiac malignancies, the prognosis associated with malignant heart tumors remains very poor (Simpson et al., 2008). As measured by Hamidi and her colleagues, the median survival in patients with primary cardiac sarcomas; the most common form of primary malignant cardiac neoplasms; was 6 months. This was significantly less than the 93 months reported as the median survival in patients with non-cardiac sarcomas (Hamidi, Moody, Weigel, & Kozak, 2010).

Chahinian et al report that the first primary cardiac tumor was described in 1845 (Chahinian et al., 2000). Before the 1930s primary tumors of the heart were still considered a rarity and a post mortem diagnostic event (Meng et al., 2002). Antemortem identification of these tumors did not occur until 1934, 30 years after the invention of the echocardiogram (Meng et al., 2002). Since that time, many other primary cardiac tumors have been identified and characterized. Today, as seen in Table 3, we have over 20 types of primary cardiac neoplasms with approximately half of these being characterized as malignant (Silverman, 1980).

**Table 3: Classification of Primary Cardiac Tumors<sup>43\*</sup>**

---

<b>Classification</b>
Benign (75%)
myxoma (50%,)
rhabdomyoma (20%)
Lambl's excrescence
fibroma
lipoma
hemangioma
lymphangioma
mesothelioma
teratoma
thyroid adenoma
chemodectoma
neurilemmoma
ganglioneuroma
valve cyst
granular cell myoblastoma
Malignant (25%)
sarcoma (20%)
angiosarcoma
hemangioendotheliosarcoma
Kaposi's sarcoma
rhabdomyosarcoma
leiomyosarcoma
osteosarcoma
chondrosarcoma
neurogenic sarcoma
lymphoma
plasmacytoma
mesenchymoma

---

\*Adopted from (Silverman, 1980)

While myxomas represent the most common primary, benign cardiac neoplasm, there are over 10 other nonmyxomatous benign primary tumor types. Nonmyxomatous lesions have a tendency to be harder to treat than myxomas. These lesions may be considered complicated by virtue of their histology, their location within the heart, or their tendency to become unstable. These include rhabdomyomas, lipomas, and mesotheliomas; among others (Table 3) (Silverman, 1980). Unlike patients with myxomas, patients with these other tumor types do not as readily benefit from conventional treatment. For example, rhabdomyomas are notoriously associated with poor prognoses. Despite the benign histology of these tumors, their tendency to occur in clusters, their poor encapsulation, and deep myocardial location make surgical resection difficult; if not impossible (Silverman, 1980). Neither are lipomas, half of which arise from the subendocardium, easily excised. Further those originating from the heart valves are only treated by complete valve excision and prosthetic replacement. Additionally, surgical resection of primary cardiac mesotheliomas has not even been attempted. These benign lesions arise selectively from the atrioventricular node and are known to cause sudden death as a result of complete heart block (Silverman, 1980). Still other benign tumors have been deemed surgically unresectable and in others radiation and chemotherapy has not been efficacious.

The invention of modern diagnostic techniques like the echocardiogram, along with advances in cardiac surgical procedures, have turned primary cardiac tumors from a disease rarely diagnosed before autopsy into a condition potentially curable given the right conditions (Centofanti et al., 1999). With the advent of echocardiography clinicians

were able to visualize the chambers and tumors of the heart in vivo. Since then, echocardiography has proven the most useful tool in terms of the diagnosis of cardiac tumors (Tj, 2000). In practice, clinicians have been able to locate and define the extent of cardiac tumors using echocardiography (Tj, 2000). Further, other types of diagnostic imaging such as Magnetic Resonance Imaging (MRI) has been useful in identifying cardiac tumor cell types (Tj, 2000). Today, myxomas are recognized as the most common primary benign tumor of the heart while sarcomas represent the most common primary malignant cardiac disease (Sarjeant, Butany, & Cusimano, 2003). Despite these advances, the rarity of primary cardiac tumors has been the primary contributor to the challenges associated with their diagnosis and treatment (“Primary Cardiac Neoplasms,” 2014).

Demographically, sources disagree on the relative incidence of primary cardiac neoplasms (PCNs) among men and women. While some report a higher prevalence in women, others hold that the frequencies are equal for both sexes and across all races (Bartoloni & Pucci, 2013; “Primary Cardiac Neoplasms,” 2014). Despite the lack of definitive demographic characterizations with regards to gender, investigators have noted that specific types of primary cardiac tumors tend to affect certain areas of the heart and occur predominately in certain age groups (Table 4) (“Cardiac Tumors: Merck Manual Professional,” n.d.). For example, 90% of Rhabdomyomas, a primary benign tumor, occur in children and are found intramurally within the septum or free wall of the left ventricle. Conversely, sarcomas, a primary malignant tumor, affect mostly middle aged adults and originate in the atrium generally involving the pericardium (“Cardiac Tumors:



Merck Manual Professional,” n.d.).

**Table 4: Types and Sites of Cardiac Tumors**<sup>5</sup> Examples of tumors and where they occur in the heart.

Type	Examples	Site
Benign Primary Tumors	Myxomas	Left Atrium
	Papillary fibroelastoma	Aortic and Mitral Valves
	Rhabdomyomas	Septum or Free Wall of Left Ventricle
Malignant Primary Tumors	Sarcomas	Right atrium and pericardium
	Pericardial Mesothelioma	Pericardium
	Primary Lymphomas	Right atrium & right ventricle

\*Soft tissues: cartilage, bone, fascia, smooth & skeletal muscle, blood & lymph vessels etc.

The morphologies of cardiac neoplasms also vary. Tumor shapes range from pedunculated to sessile, or flat, and from solid and stable to friable with increased risk of systemic embolization (“Cardiac Tumors: Merck Manual Professional,” n.d.). Due to the varied morphology and originating locations of these tumors, their symptomology is also characterized by a considerable amount of variation. Patients may experience anything from arrhythmias and sudden death to being completely asymptomatic with a lesion that is not detected until examinations are performed for other reasons (“Cardiac Tumors: Merck Manual Professional,” n.d.).

### **What's missing?**

In short, while primary cardiac neoplasms (PCNs) are clinically significant lesions with potentially life threatening consequences that affect patients of all ages, many sources report no statistically significant difference between the survival of patients with complicated benign lesions or malignant lesions who received treatment and those who did not (Meng et al., 2002; Yu et al., 2014). More than this, cardiac neoplasms often remain clinically silent or present with symptoms similar to those of other cardiac diseases. For this reason, the majority of these tumors are diagnosed in late or advanced stages where the efficacy and availability of therapies are known to be limited (Perchinsky et al., 1997; Simpson et al., 2008). Further while, many primary heart tumors appear to be impartial, having no apparent predilection for race, age, nor gender, over 150 years after the discovery of the first cardiac there is still very little, if any, complete demographic descriptions of the incidence and prevalence of the diseases in live populations. Undoubtedly a function of the rarity and complexity of cardiac tumors, many sources offer conflicting information presented in dissimilar ways which make comparison challenging. Moreover, for many primary complicated benign tumors and primary malignant tumors, standard treatments are aimed largely at prolonging life rather than eradicating the disease. Despite this, to our knowledge, there has been no comprehensive evaluation of the quality of longer life these patients live as a result of the palliative treatment. Thus, with no complete national or worldwide demographic characterization on the prevalence and incidence of primary cardiac neoplasms in vivo; no universally accepted notion of best practice in their treatment; and no documentation

of patient quality of life pre- and post- treatment; this begs the question; do effective treatments exist for primary tumors of the heart?

## II. SPECIFIC AIMS

While the rarity of primary cardiac neoplasms is undoubtedly the primary contributor, it is clear that there is a lack of consensus among researchers regarding certain aspects of the disease. Current literature often provides contradictory information about the prevalence, incidence, and mortality of these tumors. In addition, studies that have included subject demographic information and have drawn conclusions on the most effective forms of treatment were done in very specific populations which makes generalizations very difficult. Most importantly, while various treatment options for primary cardiac neoplasms exist, their efficacy in the treatment of certain tumor types remains questionable.

Thus, the goal of this study is to determine whether the treatment options available for both benign and malignant primary cardiac neoplasms can be considered effective. Specifically we will;

- Provide a working definition of Effective Treatment
- Review literature published on the outcomes associated with four “standard of care” treatments for primary cardiac neoplasms
- Evaluate the efficacy of each treatment relative to the given definition

It is our hope to establish whether or not the standard of care treatments for primary cardiac neoplasms can be considered effective taking into account the risks and benefits of the respective therapies. In the end, we propose the further investigation and

implementation of promising and innovative therapies that could, if proven effective, lead to a significant decrease in the overall number of cardiac cancer related deaths.

### **III. REVIEW**

#### **Define: Effective Treatment**

For the purposes of this paper we adapt the National Library of Medicine's definition of effective treatment. First, an effective treatment is one that alleviates the associated symptoms of the disease. In everyday life, as well as in published literature, we see symptom relief at the top of patient reported concerns (Df, 1995). Therefore, to be considered effective, targeted therapies must address patient reported symptoms. Further, effective treatments should be shown to increase patient survival rates in a way that is significantly greater than patients who do not receive treatment. If administered treatments do not significantly improve survival beyond what is attainable with no treatment, then we risk venturing into the dimensions of undue trauma. Accordingly, effective therapies must not cause any undue trauma. Understandably, there are cases in which the actual survival benefit is relatively small or otherwise unknown. In these cases, as is common practice, patients should decide whether the possibility of a longer life is worth the certainty of pain and discomfort. Last, effective treatments for primary cardiac neoplasms should result in a post-treatment quality of life that is greater than what would be the patient's quality of life without treatment. This, we say, includes rapid recovery. Quick recovery is essential to a greater quality of life because patients should be allowed to painlessly enjoy most of the time they have been given. In the end, we choose these to constitute our definition of effective treatment because these outcomes are, above all, patient centered. Patient centered outcomes are the outcomes that have been shown to

matter most to patients and to influence patient satisfaction with providers and with health care delivery as measured using Health Quality of Life surveys (Fleurence, 2012). As the inauguration of the Patient Centered Outcomes Research Institute (PCORI) in 2010 would show, patient centered outcomes in clinical effectiveness research has become a priority. Finally, we note here, that for different therapies these definitions of effective treatment may be mutually exclusive. We understand and consider that while some treatments can improve a patient's quality of life, they will not necessarily confer longevity.

### **Treatment Options**

Currently there exists four standard treatments for primary cardiac neoplasias. These are radiation therapy, chemotherapy, surgical excision, and heart transplantation. These therapies, individually and together, are used to treat neoplasias in many different organ systems; not just in the heart. Heart transplantation, while not routinely considered as a primary form of treatment for primary cardiac neoplasms, it is used extensively to treat many of the other heart disease whose symptoms PCNs tend to mimic. Thus, we consider it here to gauge the possible advantages in the treatment of primary heart tumors. While these treatments overall represent the standard of care for most cancers, when it comes to the heart, some of these therapies may prove more toxic than curative. For some of these, their toxicity can be felt throughout the body almost immediately and any collateral damage appears before the inciting pathogen can be deemed eradicated.

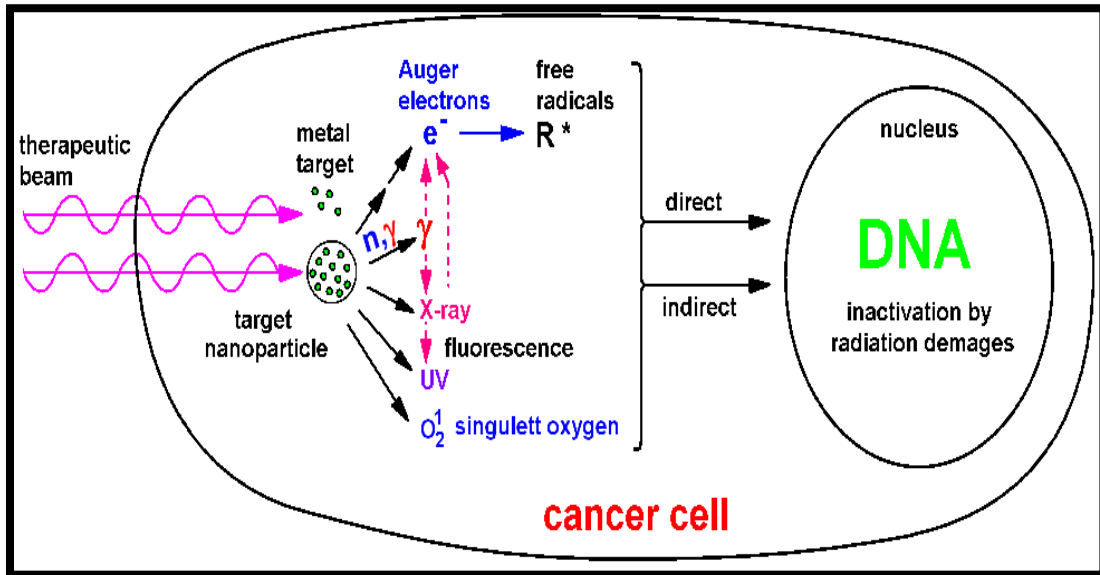
For others, the wounds remain relatively superficial and damage is localized to the cardiovascular system. The heart, though lauded for its adaptability, is quite sensitive to the noxious agents and the considerable amount of trauma associated with standard treatment (Roberts, 2001). Moreover, for certain tissue types, these therapies have not been shown to confer any increased survival (Butany et al., 2005). These noxious effects may tip the scale in regards to the overall effectiveness of the respective treatments. In these cases, with no clear answers regarding best practice, traditionally, the value in such measures are determined by individuals and their providers. We present these therapies here from the least to the most invasive, irrespective of the possible adverse effects associated with each.

### **Option One: Radiation Therapy**

Radiation therapy, or radiotherapy (RT), uses high-energy radiation in the form of X-rays, gamma rays or other charged particles to kill cancer cells by targeting their DNA (Figure 3)(“IRT,” n.d.). Unfortunately, the effects of these rays are also felt by all of the surrounding normal tissue cells. This ultimately leads to the side effects associated with radiotherapy (“Radiation Therapy for Cancer,” n.d.). Radiation therapy can be delivered externally in which a machine is position to irradiate the desired location on the patient’s body. This type of radiation is known as ‘external beam radiation therapy’ (“Radiation Therapy for Cancer,” n.d.). On the other hand radiation may be delivered internally, in which radioactive substances are placed in the body and travel in the blood to attack and



kill cancerous cells (“Radiation Therapy for Cancer,” n.d.). This type of radiation is often referred to as ‘internal radiation therapy’ or ‘implant radiation therapy’ (“Radiation Therapy for Cancer,” n.d.).



**Figure 3: Radiation’s Effect on Cancer Cells**<sup>18</sup> Radiation fights cancer by targeting the cell’s DNA (adopted from Nawroth, 2008).

Today, the benefits or efficacy of radiation therapy in patients with cardiac tumors is still largely unknown. The literature is eerily silent in this regard. This is no doubt in some ways a consequence of the low number of people affected by this form of heart disease. Still, none have been able to elucidate and/nor demonstrate the benefits of radiotherapy in this rare form of heart disease. All who have tried have come away with more reasons why radiation to the heart may do more harm than good. While admitting that the numbers were too small to be conclusive, Simpson et al report that the role of radiotherapy alone or in adjuvant is, at best, limited (Simpson et al., 2008). They note that

the effective dose used to treat extracardiac tumors is poorly tolerated by the heart and is thus not useful (Simpson et al., 2008). Further, as reported by Butany and his colleagues, what would be considered an effective dose in the heart is more likely to cause a serious radiation cardiomyopathy or chronic inflammation of the membrane lining the outside of the heart (Butany et al., 2005). Among these adverse effects, investigators have also noted cardiac hemorrhage and cardiac infection as consequences of radiotherapy used to treat cardiac neoplasms (Roberts, 2001). In sum, Butany and his team reported that the value of radiation therapy in the heart is limited due to the heart's sensitivity to the specific types of radiation injury noted above (Butany et al., 2005). Further, they state that there is only anecdotal evidence to suggest that radiation therapy may be useful in preventing local tumor recurrence after complete excision (Butany et al., 2005). Despite this, these possible beneficial effects have not been studied or reproduced in any significant way.

Despite the unpromising findings of Butany and his team, Hamidi and her colleagues set out to discover what, if any benefit, lay in radiation therapy for primary malignant cardiac tumors. In 2010 they released a report featuring 210 patients diagnosed with primary cardiac sarcomas, the most common PCN, focusing on the outcomes of radiotherapy. Their study, retrospective in nature, also compared intra-cardiac sarcomas, to extracardiac sarcomas. The comparison was done with regards to all aspects related to patient, tumor, and treatment factors affecting outcome. What they found was that radiation therapy, was not an effective primary treatment for primary malignant cardiac

tumors and that adjuvant RT conferred no statistically significant survival advantage (Hamidi et al., 2010).

### **Option Two: Chemotherapy**

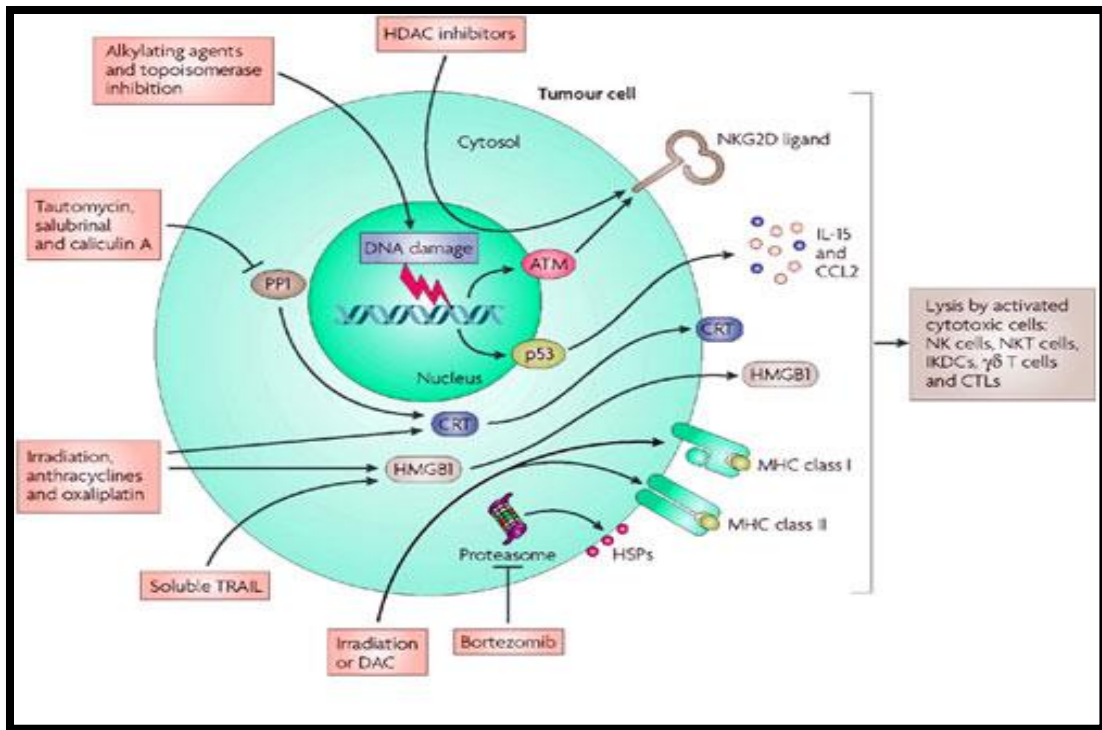
Chemotherapy is the use of medications to fight cancer or prevent pre-cancerous growths. It is a generalized treatment that targets and kills rapidly dividing cells.

Chemotherapy was first used to treat cancer in the 1950s and today there are over 100 cancer chemotherapy drugs available. The object of these drugs is to fight cancer by blocking different functions associated with cell growth and replication (Figure 4)

(Zitvogel, Apetoh, Ghiringhelli, & Kroemer, 2008). For example, alkylating agents work by blocking DNA replication which interferes with cell growth. On the other hand,

Nitrosoureas interfere with the enzymes that repair DNA. The specific medication used to treat a cancer is decided by the prescribing physician and depends on several factors.

These include the type, stage, grade, and histology of the tumor as well as the patient's age and the presence of comorbidities ("Deciding which chemotherapy drugs to use," n.d.).



**Figure 4: Chemotherapy's Effect on Cancer Cells<sup>49</sup>** Chemotherapy targets various functions related to cell growth and replication.

Fortunately, for patients and providers alike, much more has been published in regards to the efficacy of chemotherapy in the treatment of primary cardiac neoplasms. Due to the general success of surgical excision in the treatment of non-complicated benign PCNs and the potential for cardiac toxicity, chemotherapy, as with radiation, is usually not warranted nor considered for patients with these tumor types (Roberts, 2001). In some cases though, chemotherapy has been shown to be of use in reducing the overall size of benign neoplasms in preparation for surgical resection (Butany et al., 2005). Generally, however, surgical removal of the primary tumor is usually successful and patients with these types of tumors are simply monitored with echocardiography for

approximately 5-6 years to rule out recurrence (“Cardiac Tumors: Merck Manual Professional,” n.d.). However, in the cases of patients with complicated benign PCNs, where complete surgical resection is usually not achievable, the potential benefits of chemotherapy has not previously been completely characterized. On the other hand while chemotherapy’s effects on malignant PCNs have been characterized the results are not favorable.

In 1991 Putnam et al released a report featuring 21 patients with primary malignant heart tumors. Noting that there was no unequivocal evidence regarding the benefits of adjuvant chemotherapy, the authors set out to resolve this issue. Their findings were not unlike what other studies had shown. What they found is that postoperative chemotherapy did not enhance survival in patients with incomplete surgical resections; which is usually the case with malignant tumors (Putnam Jr et al., 1991). Moreover, in 1998, after analyzing the cases of 15 patients, ages 16-66, undergoing adjuvant chemotherapy for non-metastatic primary malignant cardiac tumors, Llombart-Cussac and his team concluded that chemotherapy had failed to modify the progression of the diseases (Llombart-Cussac et al., 1998). This conclusion came after 13 of the 15 (87%) had a recurrence of the tumor with five (33%) of those occurring during active treatment (Llombart-Cussac et al., 1998). The authors reported that median time to disease progression was approximately 10 months with some occurring in as little as 3 months.

Going further than both Putnam and Llombart-Cussac et al, Butany and his team, in their 2005 article, noted no survival benefit of adjuvant chemotherapy for any adult

soft tissue sarcoma; less in the heart (Butany et al., 2005). This is most probably due to the fact that many chemotherapy agents are not only cytotoxic but are also radiation sensitizers i.e. they make the heart more susceptible than usual to the adverse effects of the high intensity beams of radiotherapy (Butany et al., 2005). Further, the toxic effect of chemotherapy agents on the heart have been shown to manifest themselves in many ways. One such way is via impaired left ventricular systolic function (Roberts, 2001).

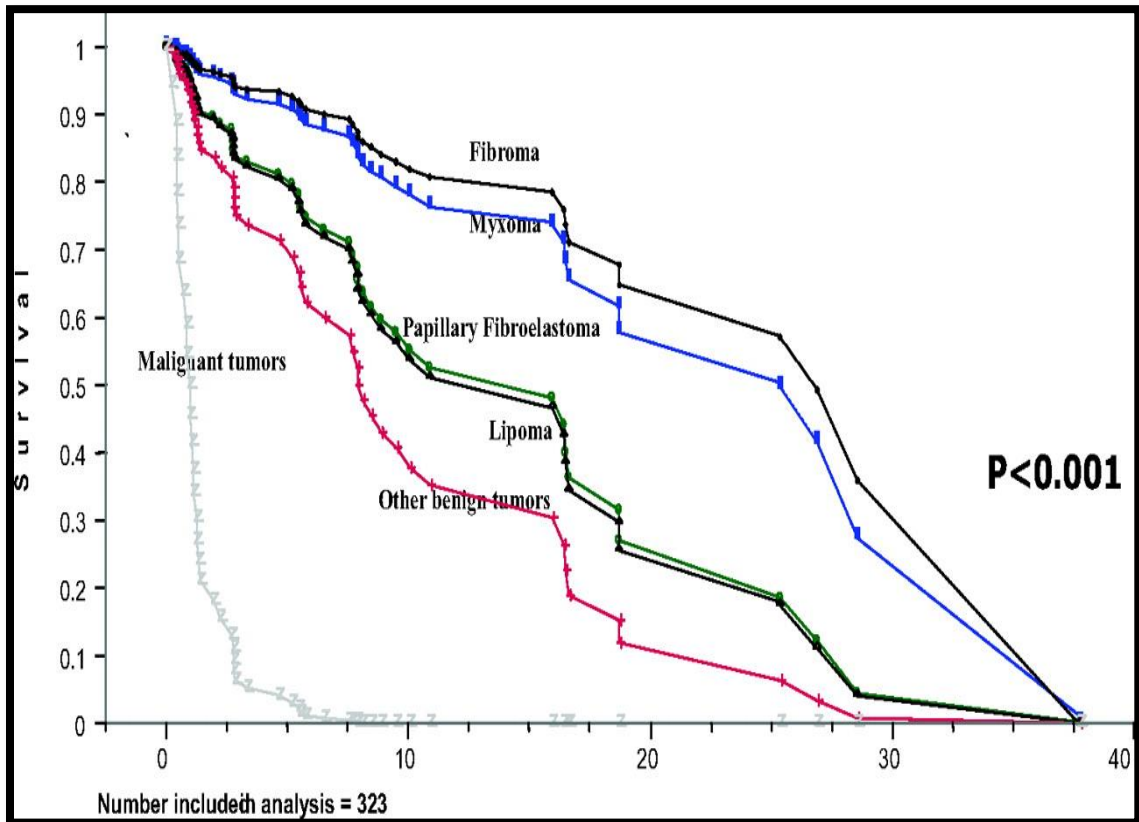
In sum, when needed, chemotherapy may be used both pre- and post- operatively to successfully treat benign primary cardiac neoplasias. However, with respect to primary malignant cardiac neoplasias the role of chemotherapy as a primary form of treatment or as an adjuvant therapy remains poorly defined (Hamidi et al., 2010). Thus, the prognosis for patients afflicted with these subtypes remain dismal.

### **Option Three: Surgical Excision/Resection**

While neoplastic conditions of the heart had been recognized as a human infirmity for over 450 years, the first successful resection of a primary cardiac tumor did not take place until 1951 (Silverman, 1980). From then it would be another 57 years before ElBardissi and his colleagues would publish the first comprehensive study examining the long term survival characteristics of patients whose primary cardiac tumors were treated with surgical resection (ElBardissi et al., 2008). Before this, between 1951 and 2008, most studies focused on the pathologic and epidemiologic characteristic of the disease while only a few focused on the outcomes of treatment (Majano-Lainez, 1997; Meng et

al., 2002; Reynen, 1995). The efforts of these studies would later be spurred by Shattenberg's introduction of echocardiography in 1986 as a reliable imaging technique for cardiac tumors as well as by other technological advancements in diagnosis and surgery (Silverman, 1980).

Elbardissi's study synthesizes 48 years of experience with the surgical treatment of primary cardiac neoplasms. They analyzed the cases of 323 patients and reaffirmed, in their report, the notion of surgical excision as a viable and highly successful option for patients with benign non-complicated diseases. However, the authors did note a group of non-myxoma benign tumors, those with complicated histologies, which still had uncharacteristically low prognoses following surgical excision. The mortality rate in these patients with non-myxoma primary benign cardiac tumors was 3.7 times the mortality rate of similar patients with myxomas (ElBardissi et al., 2008). Further, Elbardissi's report also delivered the morose affirmation of the incurable nature of primary malignant cardiac diseases. With this data in hand the authors quantified the relative survival risk to patients with differing cardiac growths with respect to cardiac myxomas; a benign tumor which represents the most common and surgically curable PCN (Figure 5) (ElBardissi et al., 2008). In this figure, the x-axis represents study follow up in years extending out to 38 years with a mean follow up of  $6.16 \pm 6.88$  years. The y-axis represents the likelihood of patient's survival based on their specific type of primary cardiac tumors as compared to patients with myxomas. As can be seen, the survival risks to patients whose tumor subtype was something other than a myxoma is both clinically and statistically significant.



**Figure 5. Proportional Hazards Estimate of Tumor Subtypes<sup>13</sup>** Patients with other types of PCNs had poor long term survival than patients with myxomas.

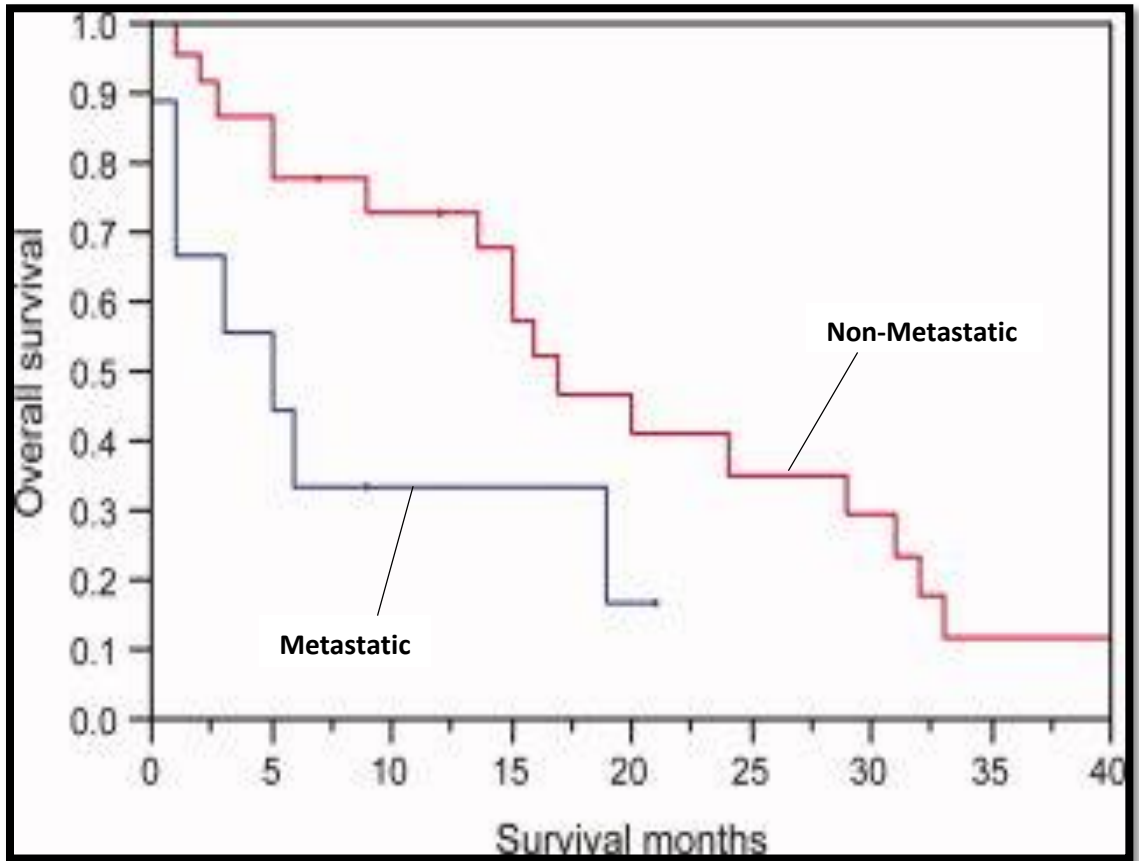
Prior to 2008, studies focusing specifically on the surgical outcomes of patients with malignant PCNs are almost non-existent. The reports that do feature this tumor subtype are mostly case reports and reviews in which benign cardiac tumors dominate (Simpson et al., 2008). Fortunately, sensing the need, Simpson et al published a study focusing specifically on malignant primary cardiac tumors. As stated previously, while these traditionally cureless growths represent the minority of primary cardiac neoplasms,



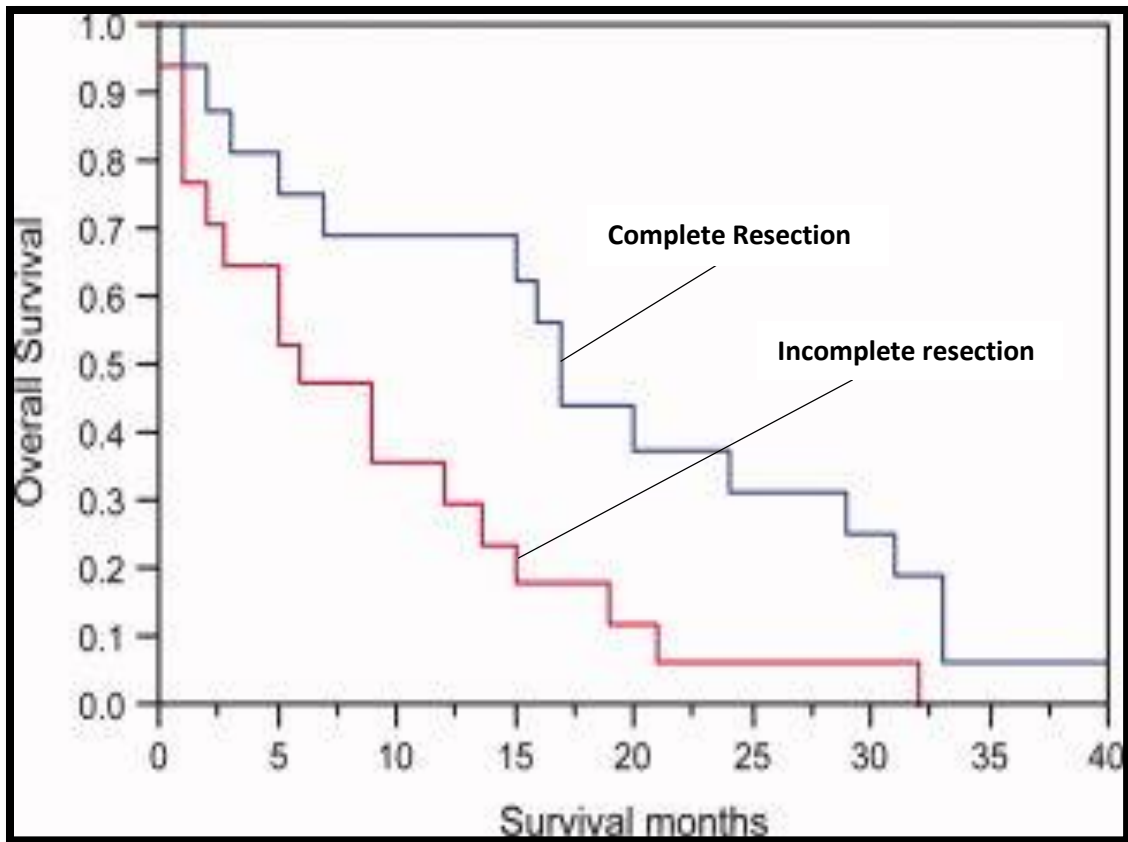
they are also the most lethal with death occurring in up to 6 months without treatment (Simpson et al., 2008). However essential this study was to the advancement of the field, it offered no more hope to patients with malignant PCNs. Simpson featured the cases of 34 patients seen for primary malignant cardiac neoplasms in the Mayo clinic over a 32 year period. Of these, 23 underwent attempted resection with only 15 (65%) being complete. Among these 15 patients, the median survival was only 17 months after complete surgical excision which was significantly ( $P=0.01$ ) more than the median survival of just 6 months seen in patients in whom complete resection was not achieved (Simpson et al., 2008). In the end, all patients eventually died from the progression of their disease. This outcome highlights the stark and grim fate of patients afflicted with malignant PCNs. It is representative of the larger population treated with surgical intervention for malignant primary cardiac neoplasms. With these grim findings, Simpson issued a call to action stating that the field required innovative treatment strategies if these more aggressive and advanced staged tumors were ever to be adequately addressed.

As reported by Butany et al in their 2005 article, it seems that only patients with complete surgical excision of the primary tumors have a real chance at survival. However, in practice, for complicated benign and malignant primary tumors, widely clear margins are rarely achieved and local recurrence is more common than not (Butany et al., 2005). Moreover, like Elbardissi and his colleagues, Simpson's team produced survival curves that not only elucidates the poorer survival of patients with malignant disease but also depicts the poorer survival of patients in whom complete surgical resection was not

possible as is the case with complicated benign primary tumors (Figure 6 & 7) (Simpson et al., 2008).



**Figure 6: Survival with Metastatic & Non-Metastatic Disease<sup>44\*</sup>** Patient who have non-metastatic PCN at the time of presentation tend to have better overall survival  
\*adapted from(Simpson et al., 2008)



**Figure 7: Survival With and Without Complete Tumor Resection<sup>44\*</sup>** Patients in whom complete surgical excision was achieved had better overall survival \*adapted from (Simpson et al., 2008)

Today surgical excision remains treatment of choice for cardiologist in regards to heart tumors. In addition, survival prognosis is based heavily upon whether the presenting growth is deemed resectable or unresectable. This is primarily because for specific PCNs surgical excision has been shown to be extremely effective. For example, the survival of patients after the resection of a primary cardiac myxoma is not significantly different from the general populace when these numbers are adjusted for age and gender (ElBardissi et al., 2008). Thus, when it works, surgical excision is considered the gold

standard of neoplastic therapies. However for the subset of patients with malignant disease, due to the trauma associated with surgery and the fact that surgery has not been shown to confer any additional survival advantage, the risks in this case may just outweigh the benefits.

#### **Option Four: Orthotopic Heart Transplantation**

Orthotopic heart transplantation (OHT) is the process of replacing a recipient's heart with a donor heart. This is in contrast to the other less common procedure known as heterotopic heart transplantation where the recipient's heart is simply connected or 'piggybacked' onto a donor heart that can act as a backup or assist device should the patient need it. For our purposes the latter procedure would be fallacious since the recipient's own heart is the source of the disease we are trying to remove from the body. Accordingly, in this thesis OHT is often simply referred to heart transplantation.

Before and after cardiac transplantation, recipients receive immunosuppressive or anti-rejection drugs, some in the form of corticosteroids, to ensure the proper assimilation of the donor heart as a functioning part of its new body. However, because of the need for this immunosuppression following transplant, OHT has not routinely been considered for patients with neoplastic conditions of the heart because of the increased possibility of tumor recurrence and the possibility of immunosuppression stimulating further tumor growth (Gowdamarajan & Michler, 2000). Further, some clinicians are weary of using heart transplantation as a primary course of treatment for PCN because prolonged

exposure to corticosteroids, given to some patients as the first form of immunosuppression following transplantation, has been shown to produce cardiac adiposity or “the corticosteroid treated heart” (Lindenfeld et al., 2004; Roberts, 2001). This condition, in which excessive amounts of fat are deposited in the heart, can stimulate pericardial effusion (Roberts, 2001). Still others, assert that OHT may not be a viable option for patients with neoplastic heart conditions for reasons outside of the pathology of the disease. They hold that the paucity of available heart donors would limit providers’ acceptance of OHT as a viable form of management (Hamidi et al., 2010). If true, heart transplantation would be deemed an unreliable, if inadequate, form of treatment.

Orthotopic heart transplants are generally not performed in patients with benign, non-complicated cardiac neoplasms. As previously stated, In these cases the primary surgery is considered curative (Sarjeant et al., 2003). However, when these ‘benign’ growths begin to impede upon systemic blood flow, cardiac conduction or become dangerously unstable, as is the case with complex benign PCNs, heart transplantation has been shown to confer a significant survival benefit to these patients (Gowdamarajan & Michler, 2000). The median survival of the patients in this report with benign PCNs which were considered inoperable, was 46 months.

As early as 1987 researchers and clinicians, were calling for the further investigation of orthotopic heart transplantation as an alternative therapy for patients with primary cardiac neoplasms. It was not until 1990, however, that Siebenmann et al featured the case of a patient with a primary synovial sarcoma of the heart. Five years

later, in 1995, Goldstein et al released a study featuring eight patients undergoing OHT for their unresectable heart tumors. Four of these patients had malignant primary cardiac tumors and the other four had locally invasive neoplasms at the time of diagnosis. Their findings were promising. The authors reported that in patients whose heart transplant was completed with tumor free or negative surgical margins, i.e. 6 of the 8, OHT conferred long term survival (range 14-78 month) without tumor recurrence despite immunosuppression. On the other hand, the two patients in whom tumor free surgical margins were not attainable (i.e. positive margins) did not reap the survival benefits of the procedure despite receiving adjuvant chemotherapy (Dj, Mc, Ea, P, & Re, 1994). The authors saw this as evidence of the great potential of orthotopic heart transplantation and noted the further need for investigation.

With the paucity of cases to examine it would be another 5 years before Gowdamarajan et al could publish a study featuring enough patients with various tumors histologies to make their findings generalizable. Their findings were less auspicious however. Of the 28 patients included in this study 7 had tumors with benign histology and 21 had malignant diseases. All patients underwent orthotopic heart transplant as their primary form of treatment (Gowdamarajan & Michler, 2000). What they found is that patients with benign tumors greatly benefited from the procedure in that their overall postoperative survival was longer than the patients with malignant diseases. The median survival for their patients with benign primary cardiac tumors was 46 months compare to only 12 months in their patients with malignant primary cardiac tumors (Gowdamarajan & Michler, 2000). Of note, the authors did not report on the condition of the surgical

margins. With no apparent benefit to report for patients with malignant tumors the authors concluded that the role of transplantation in these patients remained unclear and that further experience and follow up was needed (Gowdamarajan & Michler, 2000).

In 2003, Jiménez-Mazuecos and his colleagues released an article to specifically answer the question of whether or not orthotopic heart transplant was a viable therapeutic option for primary cardiac neoplasias. Their study focused more specifically on cardiac sarcomas which are the most common malignant PCN and the tumor type most treated by OHT (Mazuecos et al., 2003). The study featured the case of eight patients of which, after screening, only six were deemed suitable for the procedure. These six were the ones who had no detectable extracardiac extension of the primary tumor as seen on pre-surgical echocardiography and/or computed tomography. Aside from the very low patient population, one of the greatest limitations the authors noted with this study is the inadequacy of current imaging techniques to detect extracardiac extension before surgery. Once in the operating room, following thoracotomy, three of the six patients deemed eligible in the beginning, were found to have obvious extracardiac extension of the primary tumor (Mazuecos et al., 2003). In these cases the surgical team could not continue with the transplants. In the end, the authors found that not only was survival in patients who received orthotopic heart transplants similar to other patients with primary cardiac sarcomas who received conventional treatment; i.e. surgical excision, radiotherapy, and chemotherapy; but also that survival rates did not significantly differ from those patients in whom no orthotopic heart transplant was performed (Mazuecos et al., 2003). Further, the authors note that their data seem to indicate that the specific

histology of the primary malignant tumor is more important than the mere presence of a malignant disease in deciding whether or not to perform a heart transplant. This conclusion came after noting that subjects with less aggressive tumor types had higher survival rates than those with more aggressive tumor histologies. Thus, they report, the presence of an angiosarcoma, aggressive in nature due to its high vascularity, would be a contraindication to OHT whereas the presence of a less aggressive tumor such as a rhabdomyosarcoma might make OHT a more viable option (Mazuecos et al., 2003). Despite these unfavorable findings, in response to Hamidi's misgivings about the availability of heart donors, Jiménez-Mazuecos and his team reported that the average time from inclusion on the transplant waiting list to the actual procedure was only 34 days; with a range of 8 to 48 days (Mazuecos et al., 2003). This suggests that if OHT had been shown to be effective in treating certain types of PCNs then the supply of hearts would be enough to meet the demands for transplant.



#### IV. CONCLUSION

Primary cardiac neoplasms (PCNs) are rare. We see this reflected in the paucity of reports published about these neoplastic heart conditions. Additionally, even in the studies that have been published, one of the greatest limitations is the small sample size. The lack of subject data available for analysis has greatly limited the generalizability and replicability of the studies. The rarity of PCNs is further reflected in the general lack of success in their early diagnosis. Both, Silverman, in his 1980 report, and Majano-Lainez, 17 years later, agreed that a that a high level of clinical suspicion and expertise is necessary to effectively and efficiently diagnose these protean disorders (Silverman, 1980) (Majano-Lainez, 1997). The invention of many diagnostic imaging techniques has in many ways aided physicians in this regard (Silverman, 1980). However, once clinicians arrive at a definitive diagnosis, the question still remains; do effective treatments exist for these patients? In 1999, Centofanti and his colleagues suggested that the answer may be subject to a tumor type effect that is still very much apparent today.

Patients whose cardiac neoplasms are benign, non-complicated lesions such as myxomas, are given the greatest positive prognosis. In almost all instances these patients appear to reap the greatest benefits from conventional therapy. First, radiation and chemotherapy are usually not warranted with these types of tumors. This is because these tumor types are more often than not successfully managed with surgery (Sarjeant et al., 2003). Further, because of the potential for adverse effects, these treatments are often times contraindicated (Butany et al., 2005; Hamidi et al., 2010; Roberts, 2001). In some

cases, however, when it is need chemotherapy has been shown to be useful as a neoadjuvant treatment to shrink the indicated tumor in preparation for surgery. Radiation therapy, on the other hand, has not been shown to effectively reduce tumor size prior to surgical excision; thus it is usually not of use as a neoadjuvant treatment. Furthermore, radiation therapy has not been shown to confer any survival benefit following surgical resection as the minimum effective dose is usually too cardio-toxic (Simpson et al., 2008). In patients with these non-complicated primary benign tumor types, surgical excisions seems to be the most effective primary treatment. Following surgical resection, the survival rate for these patients is not statistically different from the general population (ElBardissi et al., 2008). Rarely, these benign tumors types can grow in such a way that they affect cardiac conduction; a function intrinsic to the heart; or other vital functions of the heart. Fortunately, in these cases, when complete resection may not be possible, patients with complicated benign PCNs have been shown to benefit from OHT (Gowdamarajan & Michler, 2000).

Lastly, as shown in Table 3, 25% of patients with primary cardiac neoplasms have a malignant tumor type. These tumor types are more aggressive in that they are very volatile lesions (i.e. they tend to grow, spread, and invade the cardiac parenchyma more quickly than benign tumors). These tumors are known to break off and travel in the blood stream to invade distant sites, involve greater portions of the heart tissue than benign tumors, and they tend to have multi-centered origination (Meng et al., 2002; Yu et al., 2014). For these patients chemotherapy and radiation has not been shown to have a beneficial effect outside of palliation (Hamidi et al., 2010). In addition, while surgical

resection remains the mainstay of conventional treatment, in patients with malignant neoplasms, it seems to represent only an effective form of palliation (Hamidi et al., 2010). Still some report that surgery is the only treatment capable of improving outcome even after palliative resection (Llombart-Cussac et al., 1998). Despite this, due to the natural unresectability of primary malignant cardiac tumors, prognosis remains poor with survival measured in only weeks and months (Silverman, 1980). Finally, while at one point orthotopic heart transplant seemed a promising option for these patients, some investigators are not sure (Mazuecos et al., 2003). In 2002, Jiménez-Mazuecos and his colleagues reported that OHT had emerged as an alternative treatment for these patients. However, after failing to demonstrate any survival benefit, the authors concluded that this may, in part, be due to other factors. For example, they state that diagnostic techniques sensitive enough to discriminate with certainty those patients who would be good candidates for OHT did not exist. Further, they note that the role of immunosuppressive drugs in tumor recurrence is yet unknown. By 2010, Hamidi et al were still not convinced of the efficacy of OHT citing case studies demonstrating that heart transplantation lead only to limited improvements in survival (Hamidi et al., 2010).

As stated above, in 1999, Centofanti and colleagues noted a tumor type effect related to the efficacy of conventional treatment. They reported that, “In general, survival chances are excellent for patients with myxomas, fair for those with nonmyxomatous benign tumors, and dismal for patients with malignant tumors” (Centofanti et al., 1999). Over 15 years later, as this review has shown, this trend holds. Thus, for approximately 38% of the people afflicted with cardiac neoplasms, it can be said that, yes, effective

treatments do exist. Conventional therapy has been shown to confer symptom relief and significantly increase survival though nothing has been reported on the patients' post treatment quality of life (ElBardissi et al., 2008). On the other hand, these beneficial effects have only been reported for certain types of nonmyxomatous benign cardiac tumors (Butany et al., 2005). Thus, for the other 37% of patients with primary benign heart tumors that have had the misfortune of developing a nonmyxomatous lesions, the answer may be a little less definitive. For example, while chemotherapy is effective in treating primary cardiac lymphomas it can do little for rhabdomyomas though both are benign PCNs (Sarjeant et al., 2003; Silverman, 1980). Furthermore, while surgical resection is generally curative in fibromas it is contraindicated in primary cardiac mesotheliomas (ElBardissi et al., 2008; Silverman, 1980). In regards to orthotopic heart transplants for these patients, as stated, the efficacy is dependent upon whether or not tumor cells are present at the surgical margins. As Goldstein et al reported in 1995, OHT provided long term survival to those patients in whom cardiectomy resulted in tumor free surgical margins (Dj et al., 1994).

For the final quarter of all patients stricken with this rare disease, the answer to whether or not effective treatments exist seems to be no. In regards to symptom relief radiation and chemotherapy may be used in these patients but, as Vander noted, without great expectation of success (Tj, 2000). Further, Hamidi et al reported that adjuvant radiation therapy did not confer any statistically significant survival benefit and Llombart-Cussac et al noted the failure of adjuvant chemotherapy to have any significant effect (Hamidi et al., 2010; Llombart-Cussac et al., 1998). While Llombart-Cussac and

his colleagues also believed that surgery was the only treatment capable of improving outcomes in these patients, Sarjeant and her team noted that these procedures are typically not successful as complete resection of malignant cardiac tumors is usually not possible (Llombart-Cussac et al., 1998; Sarjeant et al., 2003). Finally, orthotopic heart transplantation has not been shown to be an effective treatment for primary malignant heart tumors. After undergoing this high risk operation, these patients' survival rates were very similar to their counterparts who had not undergone the procedure (Mazuecos et al., 2003). Thus, in regards to symptom relief, increased survival, and increased quality of life, neither radiation, chemotherapy, surgical resection, nor orthotopic heart transplantation can be shown to be effective.

### **Next Steps**

Despite this disparaging conclusion, the future may hold greater hope for patients with primary cardiac neoplasms. Many investigators have been working to correct the tumor type prognostic disparities plaguing a subset of patients with primary cardiac neoplasms. Today, cardiac autotransplantation is gaining momentum as the treatment of choice for complicated heart tumors. Further more individualized treatments, such as targeted gene therapies, have been investigated as possible new treatments for cardiac tumors. Finally, many researcher are now looking to directly target the process of metastasis which could presage a new age for all metastatic cancers. With the development of new technologies and further investigation, these new approaches, as

explained below, hold the promise of effective treatment for all patients with primary cardiac tumors.

Cardiac autotransplantation is the process of explanting the heart from the body, excising the indicated tumor(s), performing reconstructions to the heart where necessary, and re-implanting the heart into the patient's thoracic cavity (Reardon, Walkes, DeFelice, & Wojciechowski, 2006). During the entire procedure patients are sustained on cardiopulmonary bypass while surgeons work to excise the tumor from the cardiac muscle tissue (Reardon, DeFelice, Sheinbaum, & Baldwin, 1999). The procedure was first introduced to treat complicated benign tumors in 1985 by Cooley et al and, in 1999, Reardon and his colleagues used autotransplantation to treat primary malignant cardiac tumors (Blackmon et al., 2008). Despite the fact that the first procedure was successfully performed approximately 30 years ago, the rarity of primary cardiac neoplasms has precluded the thorough investigation of the benefits of this procedure. Further, as Blackmon et al report, this rarity leaves institutions and surgeons alike with few cases from which to draw conclusions (Blackmon et al., 2008). Since then, however, approximately 40 patients have been treated in this way (Ramlawi et al., 2014; Reardon et al., 2006; Selman A, Ubilla S, Espinoza H, & Muñoz P, 2012).

In 2006, Reardon et al released the first case report describing the surgical resection of a primary malignant left ventricular tumor via cardiac autotransplantation. They did this, they report, in order to overcome the anatomic challenges of left heart tumors (Reardon et al., 2006). Due to location, the resection of left heart tumors generally

require cutting into healthy cardiac muscle. Therefore, Reardon and his colleagues reported, explanting the heart prior to tumor excision allowed excellent exposure of the left ventricular cavity and prevented the possible impairment of left ventricular function (Reardon et al., 2006). Three years after the surgery, the patient was reported to be well with no evidence of recurrent disease (Reardon et al., 2006). Thus, the authors concluded that cardiac autotransplantation was a useful approach in the treatment of primary malignant heart tumors.

In 2008, Blackmon et al published an article featuring 20 patients who underwent cardiac autotransplantation. In 2014, Ramlawi et al released an updated report describing the results of 35 autotransplantation procedures performed in 34 patients; including the 20 who were featured in the first report. What they found is that the median survival rate in patients with primary malignant cardiac tumors undergoing autotransplantation was 22 months. (Blackmon et al., 2008). This is double the rate reported with conventional treatment (Putnam Jr et al., 1991). They also reported that autotransplantation addressed many of the shortcomings of orthotopic heart transplantation. First, as Hamidi et al feared, the shortage of heart donors can be seen as one of the disadvantages of using OHT to treat cardiac tumors (Hamidi et al., 2010). With autotransplantation the donor is also the recipient. Thus, in essence, there is a one to one supply and demand ratio. This is especially important because, even though Jiménez-Mazuecos et al reported that his subjects only spent 8-48 days waiting for donor hearts, in the case of heart tumors every second counts. Treating patients as soon as possible prevents the most lethal aspects of cardiac tumors such as extracardiac tumor extension, congestive heart failure, heart

block, and possible tumor embolization (Blackmon et al., 2008). Due to the success in their patient population, Ramlawi et al concluded that cardiac autotransplantation was a viable option for obtaining complete tumor resection which is a positive prognostic factor (Blackmon et al., 2008; Dj et al., 1994). Further, the authors concluded that autotransplantation was ‘feasible and safe technique for resection of complex left-side tumors’ (Ramlawi et al., 2014). In addition to solving the problem of donor shortages, cardiac autotransplantation also does away with the need for pre- and post- operative immunosuppressive therapy. This is especially advantageous in these patients with a history of cancer because, as Gowdamarajan et al reported, the role of immunosuppressive therapies in tumor recurrence is still not known (Gowdamarajan & Michler, 2000). Thus, not only do we eliminate the risk of promoting tumor recurrence we also prevent the development of cardiac adiposity which is a precursor to pericardial effusion in patients whose immunosuppressive agent is a corticosteroid (Roberts, 2001). Further, eliminating the need for immunosuppressive therapy gives researchers a control group off which to base the further investigation of immunosuppression as a tumor promoting agent. In a randomized control trial it would be feasible to measure the time to recurrence in patients treated with orthotopic heart transplantation and subsequent immunosuppression versus the time to tumor recurrence in those patients treated with cardiac autotransplantation without subsequent immunosuppression. In this way, the link between tumor recurrence and immunosuppressive agents could either be established or confidently invalidated. Either way, clinicians would be better able to treat their patients with the full knowledge of all of the possible consequences of each respective therapy.



Another promising new approach to cardiac tumor treatment is targeted gene therapy. While this form of treatment is not new to the field of medicine, it has not been thoroughly investigated as a primary form of treatment for cardiac tumors. According to some authors, such treatments could be administered as part of a multifaceted approach to the treatment of the most clinically aggressive lesions (Neragi-Miandoab, Kim, & Vlahakes, 2007). As stated in Neragi-Miandoab et al's 2007 article, advancements in molecular biology has revealed some reproducible genetic translocations in cancer cells that could serve as targets for new drugs (Neragi-Miandoab et al., 2007). In vivo these translocations can give rise to the intermediate steps that cause malignant changes within normal cells. With the knowledge of such translocations in mind, investigators and clinicians alike would have a more specified target in the treatment of certain cancers. With the development of such drugs it may then be possible to avoid some of the widespread effects of certain conventional chemotherapeutic agents. For example, one translocation that has been noted in some cancers is the translocation of chromosome 12 and 15. This rearranging of the chromosomes causes a transcription factor to fuse with a tyrosine kinase yielding a product that has oncogenic potential (Neragi-Miandoab et al., 2007). In such cases tyrosine kinase inhibitors may prove effective in slowing the progression of the disease. Further, the over expression of the mdm-2 gene, an oncogene that binds and inhibits the tumor suppressor gene p53, has been seen in many sarcomas (Neragi-Miandoab et al., 2007). These high levels of mdm-2 are associated with, among other things, angiogenesis which is crucial to the persistence and possible metastasis of cancer cells (Neragi-Miandoab et al., 2007). Thus, medications that target these this gene

could prove effective in the treatment of sarcomas which, in the heart, account for approximately 20% of primary malignant cardiac neoplasms. Despite all of the information we now have on these and other possible targets for anti-cancer drugs, a lot more work is required to prove their efficacy and safety for use in humans and in the heart. As Neragi-Miandoab et al stated, more clinical studies are needed before these approaches can be effectively included in the neoadjuvant or adjuvant treatment of cardiac tumors (Neragi-Miandoab et al., 2007).

In closing, as stated above, there is much work to be done before we can ever hope to arrive at therapies that can effectively treat complicated benign and malignant forms of primary cardiac neoplasms. We need studies that will further the investigation of some of the newer treatment modalities and characterize their potential benefits in the treatment of heart tumors. This will help us to know where our efforts are best spent. Further, we need researchers and engineers working towards discovering more and more specific genetic targets for anti-cancer drugs which will prevent the adverse systemic side effects currently associated with conventional therapy. We need the comprehensive implementation of currently available therapies, such as cardiac autotransplantation, for the purpose of proving or disproving their clinical efficacy. Moreover, we need studies that will collect, characterize, and compare data on the quality of life of patients with primary cardiac neoplasms treated with the various treatment modalities. Finally, there must be investigators who will consider the more occult causes and treatments for cancer. For example, with the knowledge that inflammatory responses play decisive roles in the various stages of tumor development, it may be worthwhile to begin to develop anti-

inflammatory and immune stimulatory cancer therapies (Grivennikov, Greten, & Karin, 2010). In so doing, the continued efforts put forth by these groups will lead to a greater hope for patients who's PCNs are not easily treated with conventional therapies.

Eventually with continued investigation, these promising therapeutic techniques will be used to afford symptom relief, increased survival, and a better quality of life to patients whose primary heart tumors are either complicated or malignant. In the end, with the further development of these therapies, it is our hope that effective treatment will be available for all patients with primary cardiac neoplasms regardless of the etiology and/or the histology of the respective diseases.

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