ABSTRACT

Preliminary Analysis of Body Mass Index and Long-Term Health Effects in Adolescent and Young Adult Hodgkin's Lymphoma Survivors

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Hodgkin's Lymphoma (HL) is among the most common malignancy diagnosed in the adolescents and young adults (AYA). Fortunately, prognosis for HL patients is positive, and many return to normal life after treatment. Nonetheless, both radiation therapy and anthracyclines are known to cause heart damage and other health effects. The longer post-cancer survival of AYAs led us to hypothesize about the long-term treatment effects these patients experience. Through retrospective chart abstraction, the records of 147 AYA HL survivors treated at MD Anderson were examined for long-term health outcomes. Our preliminary analysis revealed that survivors are at risk of dramatic weight gain assessed over an average of 7.58 years post-treatment, which may stress the cardiovascular system, exacerbating the heart damage associated with certain chemotherapy regimens. Greater knowledge of these risk factors will allow high-risk patients to be closely monitored by cardiologists and nutritionists to curb these negative effects of cancer treatment through early intervention and continued follow-up.

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PRELIMINARY ANALYSIS OF BODY MASS INDEX AND LONG-TERM HEALTH EFFECTS IN ADOLESCENT AND YOUNG ADULT HODGKIN'S LYMPHOMA SURVIVORS

A Thesis Submitted to the Faculty of

Baylor University

In Partial Fulfillment of the Requirements for the

Honors Program

By

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Waco, Texas

May 2020

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ACKNOWLEDGMENTS

This thesis would not have been possible without the guidance and support of many significant individuals. First, I would like to thank Dr. Erika Abel, my thesis advisor at Baylor University, and Dr. Michelle Hildebrandt, my research mentor at MD Anderson Cancer Center. These two inspiring women and scientists pushed me to become a better researcher and made the process of writing a thesis educational and enjoyable. I would also like to express my gratitude to the other two members of my committee, Dr. Marcie Moehnke and Dr. Gabrielle Miller from Baylor University. I have been so fortunate to learn from both of these professors during my time as a student at Baylor. I am also extremely grateful to Xiaohui Tang for her assistance and expertise in data analysis throughout my work on this thesis. I would also like to thank my family and friends who encouraged me throughout this entire process and had faith in me when my own began to falter.

CHAPTER ONE

Background and Introduction

Hodgkin's Lymphoma

As cancer treatment options grow and effectiveness of treatment improves, the population of cancer survivors continues to grow. One of the largest groups of cancer survivors are those with Hodgkin's Lymphoma, specifically those diagnosed at a young age. As these survivors continue beyond their years of treatment, they begin to face the long-term effects of their treatment, previously undocumented due to the unlikelihood of a long survivorship of a cancer patient. An examination of this cohort may offer insight into the challenges that will be faced by these survivors as their number of years of survival post-treatment continues to increase. Hodgkin's Lymphoma (HL) is a cancer of the lymphatic system that is most common in younger adults. Regardless of its stage at diagnosis, the cure rate is relatively high.

Cancer is not one specific disease, yet it is a general term used to describe more than 200 more complex and individual diseases. Identifying the specific type of cancer allows healthcare providers to understand the "geographical and temporal" characteristics of each disease (Schultz, 2005). The cause of cancer is often multifactorial and may include "chemical, physical, or biological carcinogens" (Schultz, 2005). Despite these complex characteristics that differentiate each type of cancer, there are commonalities between them. Some common properties include increased cellular proliferation, changes in metabolism, and instability of genetic material (Schultz, 2005). Ultimately, the differentiation of cancer is important in the selection of treatment. Certain criteria must

be considered when determining an effective treatment strategy. Localized and metastatic cancers are prescribed different treatments, as are early and advanced stage illnesses. Treatments also vary based on histological subtype, mutation variation, and other biological factors (Schultz, 2005).

As described by the American Cancer Society, lymphomas are a group of cancers that appear in the lymphatic system and originate white blood cells called lymphocytes (Ansell, 2015; Bartlett & Foyil, 2014). Lymphocytes are players in the body's immune system, responsible for controlling or killing invading antigen-bearing microbes or substances (Pearce et al., 2013). Lymphocytes can be categorized as T cells, B cells, or natural killer (NK) cells. Any of these three types of lymphocytes described may become cancerous and thus, cause the development of lymphoma.

In normal function, these cells play critical roles in the two types of immunity in the human body: innate (NK cells) and adaptive (B and T cells) immunity. Further, there are two main branches of adaptive response: humoral (B cells) and cell-mediated immunity (T cells). HL specifically develops from the lymphocytes of the humoral adaptive immune system.

Lymphomas are subdivided into Hodgkin's Lymphoma (HL) and Non-Hodgkin's Lymphoma (NHL). From a histological standpoint, the distinguishing characteristic is the presence or absence of Reed Sternberg cells, respectively (Ansell, 2015; Bartlett & Foyil, 2014; Küppers & Hansmann, 2005). Reed Sternberg cells are abnormally large cells with multiple nuclei and are derived irregularly from B cells. These cells have developed a variety of mechanisms to avoid apoptosis and support inappropriate cell proliferation (Küppers & Hansmann, 2005). Additionally, Reed Sternberg cells have increased

proliferation due to the over-activation of CD30 and CD15, which are two proteins important to cell maintenance (Barry et al., 2003; Felberbaum, 2005). An experienced pathologist can easily detect Reed Sternberg cells with the use of haematoxylin and eosin staining (Tumwine et al., 2003). Identification of these cells is pertinent in diagnosing the patient and therefore determining specific treatment and prognosis. As seen in the image below, Reed-Sternberg cells are drastically larger than surrounding normal cells and often contain multiple nuclei.

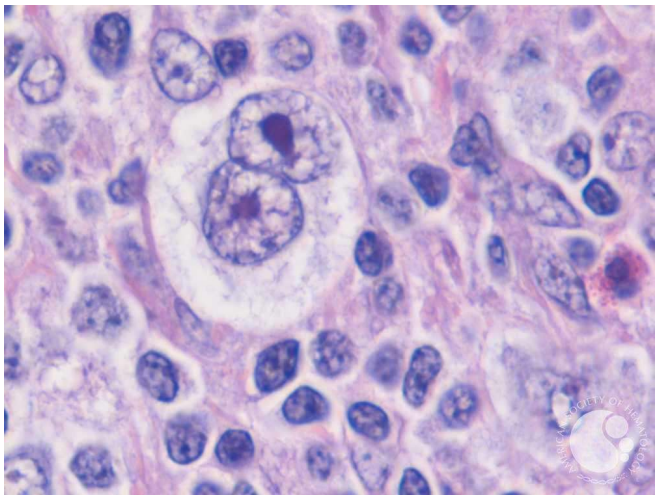

Figure 1: Image of Reed Sternberg Cell seen in Hodgkin's Lymphoma, developed through immunohistochemistry (*Reed Sternberg Cell*, n.d.)

By comparison to NHL, HL differs in prevalence, prognosis, and presentation. NHL is much more common than HL and two-thirds of NHL patients are diagnosed at the age of 60 or older (Shankland et al., 2012). Conversely, HL is significantly less common and is known to affect a younger cohort of patients. HL is most prevalent in adolescents and young adults, specifically between the ages of 25 and 34 (Brenner et al., 2008). While it is estimated that there would be 74,200 newly diagnosed cases of NHL in

the United States in 2019 (Freedman et al., 2015), only about 9,000 new cases of HL are diagnosed in the United States each year (American Cancer Society, 2020). Additionally, while both are types of lymphomas and are initially detected in the lymph nodes, HL specifically originates in the lymph nodes of thorax, while NHL may originate in any area with lymph nodes present (Brenner et al., 2008; Shankland et al., 2012).

NHL and HL patients also differ significantly in their prognosis. The HL patient's prognosis is more optimistic due in part to its early detection. HL is normally diagnosed after patients notice swelling in their lymph nodes. These swellings are often palpable just under the surface of the skin and are easy to detect on physical examination. The most common locations to detect swollen lymph nodes in HL patients are in the axillary area, neck, upper chest, groin, or abdomen (Ansell, 2015). Other symptoms of HL include night sweats, unexplained and unintentional weight loss, and fatigue (Ansell, 2015). After a physician confirms the presence of a worrisome mass, a blood test may be ordered to send to a pathologist to confirm the presence of disease. Typically, samples of affected lymph nodes are surgically removed for histological analysis, and the presence of Reed-Sternberg cells is diagnostic of HL (Ansell, 2015). As with most other cancers, each HL diagnosis is accompanied by a numerical stage describing the extent of disease. Stage I indicates that the malignancy is located only within one lymph node region or organ. Stage II is still limited to only one section of the body but may include an additional region of lymph nodes or a nearby organ. Stage III indicates that the cancer has invaded tissues both above and below the diaphragm. Stage IV is the most severe form of HL. This stage signifies that the disease has spread significantly throughout lymph nodes and lymphatic organs and has metastasized to other body systems (Bartlett & Foyil,

2014). HL can be classified further depending on the symptoms experienced by the patient. The designation of "A" indicates that the patient did not experienced additional symptoms, while "B" infers that the patient experienced some of the most common symptoms, as mentioned previously (Morgan, 2009). Typically, those with B symptoms have poorer prognosis (Bartlett & Foyil, 2014).

Even in its more advanced stages, HL has a positive prognosis. The American Cancer Society reports that the overall five-year survival rate from day of diagnosis of patients with HL is 87% (American Cancer Society, 2020). This number varies depending on the location and metastasis of the lymphoma. For localized cancers, patients see a 92% five-year survival rate, while patients with cancer found in sites distant from the original cancer, the five-year survival rate drops to 78% (American Cancer Society, 2020). Another source presents that for those diagnosed at stage 1 or 2, the five-year survival rate is greater than 90%, and those diagnosed at stage 3 or 4, between 75% and 90% (Townsend & Linch, 2012). These rates have improved over time with the development of new technologies and treatments. One study reported that the overall five-year survival rate for patients of all stages with HL was 73% in 1983 and 82% in 2006 (Fairchild et al., 2015). Survival rates are also dependent on the treatment received. Studies have noted that patients who received ABVD (a common chemotherapy regimen for HL patients) has a significantly higher survival rate than those of the same stage receiving other treatment (Ahmadzadeh et al., 2014; Townsend & Linch, 2012). Furthermore, the prognosis for HL for AYA patients is even more promising. Cancer Research UK reports the 5-year survival rates by age category and found that AYA men

and women have a 5-year survival rate for all stages of 95.3% and 94.1%, respectively (Nash, 2015).

Treatments of HL

Many factors impact the overall survival rate associated with HL, and knowledge of these factors influences treatment selection. Determining factors include age at diagnosis, stage of cancer, and presenting symptoms (Morgan, 2009). Treatment options include various chemotherapy regimens and/or radiation. Chemotherapy is commonly used because it is able to reach cells in most parts of the body through systemic circulation (Morgan, 2009). Radiation may also be used as a treatment, often coupled with chemotherapy, as it is able to shrink the size of a tumor and can lessen the pain associated with the cancer (Morgan, 2009). Contrary to chemotherapy, radiation therapy is a localized treatment (Morgan, 2009). While there are various treatment options available for HL, research has yielded insight into the most successful and effective options.

The first treatment option developed for HL consisted of high-dose radiation therapy, which proved to be only successful for patients with early stage disease (Candela, 2016). In the 1960s, the development of a chemotherapy regimen, MOPP (mechlorethamine, Oncovin, prednisone, and procarbazine), became the new standard of care (Candela, 2016). However, it was noted that this treatment often led to secondary cancers, typically leukemia, and commonly resulted in gonadotoxicity (Candela, 2016). Therefore, when the ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) chemotherapy regimen was introduced in the 1970s, it was praised for eliminating those harmful effects. Various studies showed that the use of ABVD was more beneficial than

that of MOPP (Bonadonna et al., 1975; Sutcliffe et al., 1979). Although ABVD became the more beneficial standard treatment, it introduced new side effects. One of the most harmful side effects of ABVD was its cardiotoxic effects (Ali et al., 1994; Candela, 2016; Ferrans, 1978; Frishman et al., 1997; Lenaz & Page, 1976; Praga et al., 1979; Steinherz & Steinherz, 1991). This regimen was used for patients of all ages and is still a widely used chemotherapy regimen today. Radiation therapy may also be used in conjunction with this treatment (Candela, 2016). As mentioned previously, it is well documented that patients who receive ABVD as their treatment have a better prognosis than those who do not (Ahmadzadeh et al., 2014; Townsend & Linch, 2012).

Most HL patients receive a combination of chemotherapy, radiation therapy, and/or stem cell transplantation in order to eradicate the cancer (Morgan, 2009). Combining chemotherapy with radiation therapy lowers the rate of relapse and allows for radiation to be limited to a more specific area (Bonadonna et al., 1975; Engert et al., 2007; Townsend & Linch, 2012). MD Anderson Cancer Center has developed an algorithm to determine the appropriate treatment for each patient based on the stage and presentation of the patient's disease (*Adolescent and Young Adult Program*). A common treatment plan includes a chemotherapy regimen of ABVD followed by guided radiation therapy. Each component in ABVD targets a different aspect of tumorigenesis and collectively, ABVD is considered the most effective form of treatment for HL (Bonadonna et al., 1975; Engert et al., 2007; Sutcliffe et al., 1979).

As with many chemotherapy regimens, some of the most common side effects of ABVD agents include nausea, hair loss, mouth sores, risk of infection, and fatigue (Bartlett & Foyil, 2014). However, these specific drugs cause additional side effects,

many of which arise after the completion of treatment. It is known that bleomycin can cause pulmonary toxicity in patients, and the dosage may be decreased or eliminated altogether for patients that experience this side effect (Hay et al., 1991; Martin et al., 2005; Sleijfer, 2001; Sun et al., 2011). Less specifically, these treatments may also cause secondary cancers or infertility in younger patients (Wasilewski-Masker et al., 2014). As previously mentioned, it has been well documented that doxorubicin causes cardiac damage in some patients, and the dosage given to the patient is highly dependent on the risk of cardiotoxicity (Ferrans, 1978; Frishman et al., 1997; Lenaz & Page, 1976; Praga et al., 1979; Tacar et al., 2013).

Doxorubicin is an anthracycline chemotherapeutic agent. Anthracyclines are of specific interest because they cause damage to the DNA of tumor cells, which leads to cell death (Hortobágyi, 1997). Cells need to successfully replicate their DNA in order to divide and create new cells. Cancer cells are characterized by their uncontrolled proliferation, thus damaging their DNA can halt this rapid division, and halt tumor growth. More specifically, doxorubicin blocks topoisomerase II by intercalating within DNA (Pommier et al., 2010; Tacar et al., 2013). This enzyme is crucial during DNA replication. DNA exists as a double stranded helix, meaning the two strands are twisted together in a right-handed direction. In order to make a copy of this double-stranded DNA, the two strands must be separated from one another by helicase. However, this creates supercoiling of the helix, increasing tension between the strands, which may cause irreversible DNA damage. In order to prevent breakage, topoisomerase II creates nicks in both strands, introduces negative coils, and reseals the DNA, thus, relieving dangerous tension between the two strands (Lodish et al., 2000; Pommier et al., 2010).

Without the actions of topoisomerase II, the DNA would experience extensive breakage during attempted replication (Capranico et al., 1997; Moro et al., 2004). This DNA damage would mark the cell for destruction. In this way, by inhibiting the functions of topoisomerase II, doxorubicin causes DNA damage, which leads to the destruction of the tumor cells (Capranico et al., 1997; Moro et al., 2004).

With this mechanism, anthracyclines, specifically doxorubicin, have been an extremely successful form of cancer therapy and have consistently been used against a variety of cancers. Almost every chemotherapy regimen to treat HL contains some variation of anthracyclines (Engert et al., 2007; Sutcliffe et al., 1979). However, the use of anthracyclines in treating cancer is accompanied by significant cardiotoxicity (Candela, 2016; Krischer et al., 1997; Townsend & Linch, 2012).

The first anthracycline discovered was daunomycin. After its initial usage, it was quickly noted that it was accompanied with negative cardiotoxic effects. One of the first articles to make note of this side effect was by Raskin. In this study, he documented cardiac damage of eight children who received daunomycin for their acute lymphocytic leukemia (Raskin et al., 1973). After this study, investigations continued to emerge noting these effects from other anthracycline treatments.

The first study that documented the cardiotoxicity associated with adrimycin specifically came out of the work by Lefrak (Lefrak et al., 1973). Since then, cardiotoxicity caused by the use of anthracyclines has been studied extensively (Ali et al., 1994; Ferrans, 1978; Frishman et al., 1997; Lenaz & Page, 1976; Praga et al., 1979; Steinherz & Steinherz, 1991). Ferrans noted specifically the cardiac pathology that resulted from use of an anthracycline. This study documented atrophy of cardiac muscle

cells and changes in cardiac dilatation, among other effects (Ferrans, 1978). Frishman et al. wrote of the delayed cardiotoxicity seen in patients who had received an anthracycline as part of their treatment. The study details the variety of ways that cardiotoxicity can present itself in patients over the many years of survivorship (Frishman et al., 1997). Cardiotoxicity is overwhelmingly present in research concerning use of an anthracycline to treat cancer patients. However, there is limited information specifically examining cardiotoxicity found in AYA HL patients. Again, the AYA population appears to be underrepresented in research, which may affect their ability to prevent or be treated adequately for side effects such as cardiotoxicity.

Despite the well-documented cardiotoxicity associated with this treatment, medical professionals have not been deterred from utilizing these drugs. Often, the beneficial effects of anthracyclines outweigh the possible cardiac damage that these patients may develop (Lenaz & Page, 1976; Volkova & Russell, 2011) . Physicians have used dose-limiting tactics to harness the powerful effects of the drug while diminishing the negative effects of it. A study by Lenaz and Page noted that toxicity caused by Adriamycin is a significant dose-limiting factor in treatment and does not permit long-term usage for treatment (Lenaz & Page, 1976). Volkova and Russel detail other methods to decrease the effects of cardiotoxicity. Their study recommends the use of cardiac medication for maintenance of negative cardiac effects, as well as a tight line of communication between a patient's oncologist and cardiologist throughout treatment (Volkova & Russell, 2011). Ultimately, the benefits of anthracycline treatments are often seen to outweigh the possible, negative cardiac damage that is coupled with it.

While there is currently no singular definition of cardiotoxicity, simply put, it is any damage to the heart caused by toxic drugs (Yeh & Bickford, 2009). Various quantitative methods for detecting and documenting cardiotoxicity are described in an article published by the American College of Cardiology (Yeh & Bickford, 2009). These methods use data collected from an echocardiogram, a test producing sound waves to develop an image of the heart and its movement to determine the functionality of the heart muscle. It measures the ejection fraction of the left ventricle, which is the percentage of blood pushed from the ventricle with each contraction of the heart (Wang et al., 2015).

A satisfactory ejection fraction is typically above 50%. The American College of Cardiology states that a significant drop in ejection fraction (an ejection fraction below 50%) is an indicator of cardiotoxicity (Lambert & Thavendiranathan, 2016). Often, patients who are experiencing cardiotoxicity are prescribed a cardiac medication, such as a beta-blocker or an ACE inhibitor (Cardinale Daniela et al., 2015).

Significant cardiac events are typically the result of many compounding factors, including genetic predisposition, stress, diet and exercise, and tobacco use (Anderson et al., 1991; Stamler et al., 1993). These factors may accentuate the cardiotoxic effects caused by anthracyclines in HL patients treated with ABVD or other anthracycline-inclusive regimens (Lambert & Thavendiranathan, 2016; Wang et al., 2015; Yeh & Bickford, 2009). In summary, while anthracyclines are successful in the treatment of HL for many patients, these patients face significant risk of cardiovascular disease after treatment, leading to increased morbidity and mortality.

Radiation therapy is also used frequently in the treatment of HL. Involved-site radiation therapy is often used to direct the radiation beams at the affected lymph nodes (Leukemia and Lymphoma Society, 2015). The goal of this involved-site radiation is to minimize radiation exposure to healthy tissues. This strategy is important because radiation therapy has also been shown to cause irreversible damage to other organs, including the heart (Yeh & Bickford, 2009; Monsour, 2012).

Radiation is known to cause cardiomyopathy, coronary artery disease, pericarditis, along with many other cardiovascular diseases (Adams et al., 2003; Boivin et al., 1992; Glanzmann et al., 1998; Singal & Iliskovic, 1998). Many HL patients require radiation therapy directed to the mediastinum, the compartment which houses the heart. Given that treatment with anthracyclines and radiation therapy may cause cardiac damage, HL patients are at a significantly increased risk for cardiovascular disease and issues (Candela, 2016; McGowan et al., 2017; Townsend & Linch, 2012).

While the overall survival rate is high in comparison to other cancers, some patients experience relapse or refractory disease. For patients with refractory or recurrent disease, high dose chemotherapy followed by stem cell transplant is an option (Townsend & Linch, 2012). Patients with refractory or recurrent disease may benefit from higher doses of chemotherapy but damage to the bone marrow is dose-limiting. Healthy bone marrow is important for cancer patients because it helps to regenerate the cells that make up the blood, most importantly, the white blood cells. Without these white blood cells, patients are unable to fight infection, leaving them susceptible to illnesses that could be extremely detrimental (Dritschilo & Sherman, 1981). When faced with disease that is less responsive to standard treatment, physicians may harvest the patient's own bone marrow

for stem cells to freeze before administering further chemotherapy. The high dose chemotherapy treatment is followed by reintroduction of the preserved stem cells to regenerate bone marrow (Bartlett & Foyil, 2014). This process involves patients receiving their own stem cells and is therefore called an autologous stem cell transplant. However, if this method does not prove successful, the patient may receive an allogenic stem cell transplant, in which they receive stem cells from a well-matched donor, often a sibling (Bartlett & Foyil, 2014).

Survivorship

The term "cancer survivor" is relatively new in the realm of oncology. In 1986, a conference comprised of various medical professionals led to the creation of the National Coalition for Cancer Survivorship. This group decided that the term "cancer victim" would be replaced by "cancer survivor" (Morgan, 2009). Since this conference, various organizations have advocated for the needs of cancer survivors (Morgan, 2009). The importance of survivorship was initially noted in the treatment of childhood leukemia (Ganz, 2003). This cancer was known to have a high relapse rate, especially in the central nervous system. Consequently, new aggressive protocols were developed using cranial radiation and intrathecal chemotherapy. While these treatments were widely effective in treating the cancer, the children later experienced extreme intellectual delays, neurological damage, and cognitive deficits (Ganz, 2003). This prompted clinicians to find new treatment strategies that not only treated the cancer, but also were devoid of harmful side effects. Minimizing harmful long-term effects became a new goal for physicians with patients with a projected long-term survival (Ganz, 2003).

While in 1975, there were only 3.6 million cancer survivors in the United States, it is projected that there will be 26.1 million by the year 2040 (Avis & Deimling, 2008). Expansion of the cancer survivor population is due to improvements in early-screening and treatment of cancers as well as effective supportive care, and this number is predicted to continue to grow as novel and more effective treatments are developed (Avis & Deimling, 2008). With this rise in cancer survivors, many more physicians will come into contact with this patient group. This will require all physicians to have the ability to recognize cancer survivors as having unique health risks. They must also understand the long-term health implications associated with cancer treatment. Many cancer survivors do not routinely visit with their oncologist, but rather, consult a primary care physician. Therefore, it is pertinent for all healthcare providers to be well-educated on the possible late effects so they are better equipped to notice and react to these common outcomes (Ganz, 2003).

Survivorship begins at the time of diagnosis and continues for the remainder of a survivor's life (Avis & Deimling, 2008). While survivorship care is most prevalent post-treatment, consideration of survivorship can begin as early as the treatment plan. Important long-term effects of treatments to consider include the aforementioned cardiotoxicity, secondary cancers, infertility, and neurological damage (Ali et al., 1994; Candela, 2016; Ferrans, 1978; Frishman et al., 1997; Ganz, 2003; Lenaz & Page, 1976; Praga et al., 1979; Steinherz & Steinherz, 1991; Wasilewski-Masker et al., 2014). However, lack of knowledge regarding long-term effects of cancer treatment hinders medical professional's ability to take long-term factors into consideration when planning

treatment (Ganz, 2003). Therefore, studying cancer survivorship can yield critical insight concerning the treatment of cancer patients and the quality of long-term health.

While research concerning survivorship in general has increased in the past few decades, survivorship research for patients diagnosed as AYAs is still severely limited in scope (Zebrack et al., 2010). This gap in knowledge is important to investigate because AYA cancer survivors face post-treatment issues that are different than the other age categories, including education attainment, employment difficulties, and psychosocial impacts (Fillon, 2013). Additionally, AYA patients simply have a longer remaining life expectancy than older patients diagnosed with HL.

As cancer research has continued to advance, scientists have become better able to distinguish between many specific cancer subtypes. However, this specificity makes studying survivorship of individual cancer types challenging due to the lack of available subjects in each specific categories (Ganz, 2003). Therefore, in researching survivorship, it is ideal to study cancers that are both common and have a high cure rate. These cancers, including HL, have the potential to provide significant information concerning long-term outcomes for these cancer survivors. After conclusions have been drawn for cancers, the data may be extrapolated to include other less common cancers, as well.

Due to the increasing population of survivors, physicians are called to consider personalized care for cancer survivors after the completion of their treatment, as well as modify treatment to provide better long-term outcomes for their patients, rather than simply ridding the patient of cancer. A greater understanding of the survivorship of cancer patients is needed to provide them with the highest quality care.

Adolescents and Young Adults

The adolescent and young adult (AYA) patient population is defined as patients between the ages of 15 and 39 (Bleyer et al., 2006). In terms of cancer diagnosis and treatment, this population has been understudied. Previously, these patients were divided between pediatric and adult treatment plans, even though the AYA population presents many unique and distinguishable characteristics (Johnson, 2013; Meeneghan & Wood, 2014). Recently, researchers have noticed disparities with this population in respect to their cancer treatment. First, researchers noticed that the increase in survivorship in childhood and adult cancers was not realized at the same magnitude in the AYA population (Bleyer et al., 2006; Fillon, 2013; Johnson, 2013; Meeneghan & Wood, 2014; Tai et al., 2012).

Studies have closely documented the imbalance of mortality between AYA and adult populations (Fernandez et al., 2011; Freyer et al., 2013; Janeway et al., 2012; Khamly et al., 2009). This may be attributed to the fact that the treatment protocols for AYAs are derived from that of pediatric or adult patients. However, AYA patients vary significantly in physiological and social factors, and therefore, these treatments are not appropriate for this age range AYA patients not only present with difference cancer biology, but also with different social factors, such as access to medical care and medical insurance (Bleyer, 2007; Meeneghan & Wood, 2014).

AYA patients are also extremely underrepresented in clinical trials, another reason they have not experienced the same progress in cancer survival as other age categories. This can be attributed to the fact that there are few trials available for this population (Bleyer, 2007; Meeneghan & Wood, 2014). Even when studies are available,

these patients are typically not made aware of them. One study stated that 90% of pediatric cancer patients are treated at institutions with NCI-sponsored clinical trials, while the same is true for only 20-35% of patients from 15 to 19 years old, and fewer than 10% of patients from 20 to 29 years of age (Bleyer, 2007). AYA patients are not frequently seen at institutions with active clinical trials and therefore are rarely participants in these important studies. Other studies have noted that although the cancer biology of 15-year-old patients mirrors that of 18-year-old patients, they lack the age requirements to be included in many age-restricted clinical trials (Bleyer et al., 2006). There is a fundamental disadvantage awarded to AYAs, as national clinical trials were built to focus on childhood cancers and cancers that affect the adult population with an average age of 40 (Bleyer et al., 2006). Further, while advancements in cancer survival in adult patients have come from earlier screening and detection, the advancements for pediatric patients have come from clinical trials (Bleyer et al., 2006; Van Leeuwen et al., 2016). Therefore, AYA cancer patients miss the opportunity to improve their survival statistics by their exclusion from and lack of availability of clinical trials. In reality, there are a plethora of reasons to explain the lower engagement in clinical trials for AYAs, but it is clear that this is a well-documented fact.

Additionally, many of the cancers that are most common in AYAs are far less common in the other age populations. HL is one of these cancers. HL also peaks in incidence in the AYA years. This is suggestive of the idea that the biology of these cancers is actually different in the AYA patients than in the other age categories (Johnson, 2013). Possible explanations for this difference in biology include a physiological or pharmacological difference in AYA patients. For example, body

composition is different in this unique population in terms of adiposity versus lean body mass (Bleyer et al., 2006). Additionally, pharmacological differences between the AYA population and other age categories include drug tolerance and absorption. AYA patients have higher functioning kidneys than older patients, and therefore may experience under-treatment, as their bodies are better equipped to handle and process the chemotherapy they are receiving (Bleyer et al., 2006).

In 2006, the Adolescent and Young Adult Oncology Progress Review Group worked to establish goals and guidelines for the effective treatment of AYA cancer patients (Johnson, 2013). One of the main goals of this organization was to identify the unique characteristics of AYA cancer patients. Lymphomas specifically were noted to be of high priority for research, due to their proportionally high prevalence in the AYA population (Johnson, 2013). The group's summary also noted the need for further data concerning the genetic susceptibility that AYA patients have for certain cancer (Johnson, 2013). Given that certain cancers are most prevalent in the AYA population, further research is needed to understand the genetic component behind the timing of these cancers.

Beyond differences in biology and prevalence of cancer in the AYA population, other environmental factors affect this population (Bleyer, 2007; Fillon, 2013; Zebrack et al., 2010). The AYAO PRG lists six important characteristics to consider for each AYA cancer patient: intellectual, interpersonal, emotional, practical, existential/spiritual, and cultural factors (Johnson, 2013). For example, this population has the highest uninsured rate of any age group (Bleyer, 2007; Johnson, 2013). Lack of adequate insurance impacts care because this population is less likely to seek out medical attention when encountered

with symptoms due to their lack of insurance, which may impact stage at diagnosis, access to care, and treatment compliance.

Body Mass Index and Obesity

As noted above, young adults differ in body composition by comparison to children and older adults. Thus, BMI and obesity should be investigated specifically within the AYA population, as research in these areas for other age categories may not be applicable for AYAs. Obesity is commonly defined as a calculated BMI of 30 or greater, and severe obesity as a BMI of 40 or greater (Garrow & Webster, n.d.; Jensen et al., 2013). The World Health Organization defines being obese or overweight as "abnormal or excessive fat accumulation that presents a risk to health," (World Health Organization, n.d.). Obesity is coupled with numerous adverse effects including diabetes, cardiovascular disease, and some cancers (Reilly et al., 2003). These conditions increase a patient's morbidity and mortality, adding to the risks already acquired by cancer survivors.

While obesity causes complications during treatment, research shows that there is a higher incidence of obesity in survivors of a variety of cancers, including endometrial, breast, and colon cancers (Connor et al., n.d.; Jernigan et al., 2013; Sinicrope et al., 2010). One study recognized the harm of obesity on survivors of gynecologic cancers and discussed physicians' willingness to address these important topics with their patients (Jernigan et al., 2013). Another study found that survivors of endometrial cancers were unable to accurately classify their own weight, especially those who fell into the obese category (Connor et al.). This study highlights the importance of a proper physician

intervention regarding weight, as many patients are unable to recognize it and the danger it presents. However, these types of studies are not available for all cancer types and age categories.

On top of the effects of pre-existing obesity on treatment efficacy, weight gain is another factor found in the cases of a variety of cancer survivors. There are numerous studies examining the weight gain in women diagnosed with breast cancer or breast cancer survivors (Bradshaw et al., 2011; Heinrich et al., 2012; Van Leeuwen et al., 2016). One study conducted concerning breast cancer survivors noted that a weight gain post-diagnosis led to a poorer prognosis for the patients and found that patients with a greater original BMI measurement were more likely to experience weight gain (Bradshaw et al., 2011). Additionally, a study was conducted to determine if television viewing time contributed to weight gain in colorectal cancer survivors. By decreasing this weight gain, the study hoped to also decrease the survivors' risk of other conditions associated with weight gain and obesity (Wijndaele et al., 2009).

Survivors of HL are known to be at risk for a variety of health issues post-treatment, including secondary cancers, hypothyroidism, stroke, transient ischemic attack, and others (Boivin et al., 1992; Tai et al., 2012; Townsend & Linch, 2012). However, few studies have examined HL survivorship and incidence of obesity or weight gain. One study investigated the weight gain and presence of obesity in adult leukemia and lymphoma survivors, broadly. The study indicated that specific characteristics predispose patients to weight gain, including the presence of B symptoms, patients of a younger age, and those with a lower original BMI (Lynce et al., 2012). While this study provides an interesting groundwork for further studies, the AYA population specifically

has not yet been examined; it is unknown whether similar patterns are found in the AYA population of HL survivors.

Gap in Knowledge

As previously mentioned, the AYA population of HL patients and survivors has not been adequately studied in terms of treatment efficacy or unique survivorship concerns. Not only does this population have different psychosocial needs than younger and older populations, but they also may present with a significantly different cancer biology or different physiologic response to treatment, as well. Further, this unique population may have long-term health risks that differ from pediatric or adult patients. Studying survivorship can help influence treatment of patients in real time. By determining what long-term effects survivors are experiencing, healthcare providers can learn to tailor the initial cancer treatment plan to avoid or diminish negative health consequences in the future.

At this time, it is unknown how AYA patients differ from other patient groups in long-term risks of cardiotoxicity. Further, how BMI is impacted in AYA HL survivors before and after treatment by comparison to other groups is also unknown. It is further unknown whether risk of elevated BMI or cardiotoxicity is influenced by treatment choice. Understanding how all factors (such as age, treatment choice, BMI, and cardiotoxicity) interact will inform better short-term and long-term treatment plans for AYA HL patients.

Specific Aims

AYA HL survivors may be at an increased risk of both weight gain and cardiotoxicity due to their treatment regimen. Our first aim is to determine what treatment factors would predispose patients to cardiotoxicity. Cardiotoxicity is to be defined as one of two clinical indicators: a prescribed cardiac medication and documentation of an adverse cardiac event or cardiovascular disease. While cardiotoxicity is well documented with the use of an anthracycline, we aim to more specifically understand the patient population that is at the highest risk of developing cardiotoxicity. Our second aim is to determine which patients experience the greatest weight gain between pre- and post-treatment to identify which characteristics predispose a greater risk of weight gain. While other studies have analyzed weight change in patients up to 24 months post-diagnosis, our patient data provides more frequent data points and longer follow-up, with the average time of follow-up being 7.58 years. Additionally, these prior studies include patients from multiple age categories, while our study focuses solely on AYA patients.

CHAPTER TWO

Materials and Methods

Patient Population

This project was a preliminary study conducted as part of an ongoing effort at MD Anderson Cancer Center in Houston, Texas, to better understand the challenges faced by cancer survivors. In particular, this project examines the long-term outcomes from treatment in AYA HL survivors. This research was conducted at MD Anderson Cancer Center under the mentorship of Dr. Michelle Hildebrandt. Our project follows the guidelines of the following IRBs approved for Dr. Hildebrandt's research efforts: PA12-1098, PA16-1063, PA15-0172, and PA18-0697.

The patients included in this study were identified from MD Anderson's Tumor Registry, a database for long-term tracking of each patient seen at MD Anderson. From this list, patients were included if they were diagnosed between 2000 and 2016 and were alive at least two years post diagnosis. These patients also had to have received chemotherapy as part of their treatment and must have received partial or total treatment at MD Anderson Cancer Center. These requirements narrowed the patient population down to approximately 9,700 patients.

The subpopulation of AYA HL patients was then selected based on further criteria. In order to ensure adequate availability of medical records for these patients regarding information such as anthracycline dose and echocardiographic follow-up, patients must have received their initial primary treatment at MD Anderson to be included in the study. They also must have been diagnosed between the ages of 15 and

39. Then, the patients were screened by diagnosis to select only those patients diagnosed with HL. Patients selected were white, non-Hispanic in race/ethnicity. These criteria resulted in 370 patients from the registry. Of those 370 patients, 147 were abstracted for use in this study due to time restraints and the preliminary nature of this investigation. This clinical chart abstraction was conducted for 147 AYA patients who received their primary treatment for HL at MD Anderson Cancer Center with a chemotherapy regimen that included an anthracycline.

Data Collection

This research project was conducted using retrospective data from medical records through chart abstractions from MD Anderson Cancer Center. MD Anderson Cancer Center uses a digital charting system, Epic (Verona, CA) to retain data from their patients. An abstraction form was established and utilized to query data stored in Epic (Verona, CA) for each patient (Appendix). Data collected fell into the following categories: demographics (date of birth, gender, ethnicity, race, marital status), diagnosis information (date of diagnosis, age at diagnosis, cancer type), treatment information (transplant, chemotherapy, use of cardioprotector, primary type of chemotherapy, secondary type of chemotherapy, anthracycline dosage, radiation exposure and dosage), survival information (vital status, date of death), and cardiovascular information (last clinic visit date, weight and height at last visit, calculated BMI, medications at last visit, any documentation of cardiovascular disease or any adverse cardiac events, and date of diagnosis).

Statistical Analysis

For this study, we conducted multiple analyses to compare cardiovascular and BMI endpoints in treatment-related variables. The data were analyzed in Stata using chi-squared tests and Student's T-tests. Data was considered statistically significant with a P-value of $P > .05$ for our analysis. This software was also used to create box-and-whisker plots as well as bar charts to represent the data in graphical form. All mean and standard deviation values were also calculated through Stata. Our analyses included comparisons of post-treatment vs. pre-treatment BMI, high vs. low anthracycline dose, radiation exposure vs. no exposure, and receiving both of these treatment related risk factors (high anthracycline dosage and radiation therapy) vs. not receiving both treatment related risk factors.

CHAPTER THREE

Results

The results collected from this study form a preliminary analysis of long-term effects due to HL treatment that AYA patients experience in survival. Information regarding patients' treatment, demographics, BMI, and cardiovascular health was collected for this investigation. We hypothesized that patients who received more aggressive treatment (such as higher dosage of anthracycline and radiation therapy) would present with more evidence of cardiotoxicity and more negative long-term effects from treatment than those who received a less aggressive treatment regimen as treatment for their HL. This preliminary analysis and these results will set the stage for future studies that will explore the relationships between treatment for AYA HL patients at MD Anderson Cancer Center and their long-term outcomes. Cumulatively, these studies may provide key information about caring for AYA HL survivors and understanding what risks they face disproportionately to the general population.

Patient Characteristics

The abstracted patient characteristics for this population are summarized in Table 1. Out of 147 patients abstracted, 87 were male patients (59.18%) and 60 were female (40.82%). The average age of diagnosis for these AYA patients was 26.26 years (SD = 7.22 years). The patients in this study were diagnosed with HL between 2000 and 2015. The average length of time from date of diagnosis to most recent follow-up was 7.58 years (SD = 4.11 years). Treatment related data was also abstracted from the medical

records of each patient. All 147 patients received chemotherapy including anthracycline for treatment, as per the selection criteria. Of the 147 patients, 123 patients (83.67%) received the ABVD chemotherapy regimen, 13 patients (8.84%) received the CHOP chemotherapy regimen, and 11 patients (7.48%) received another chemotherapy regimen. As previously mentioned, the bleomycin in the ABVD regimen may cause pulmonary toxicity in some patients. Because of this, of the 123 patients who received ABVD, 41 patients (33.33%) had bleomycin removed from their chemotherapy regimen at some point during treatment, and 82 patients (66.67%) received bleomycin for the duration of treatment. The unit used to measure chemotherapy is milligrams per square meter (mg/m^2). This method is known as body surface area-dosing and allows physicians to adjust the amount of chemotherapy a patient receives based on the patient's body surface area (Gurney, 2002). The average total anthracycline dosage received by this patient population over the duration of treatment was 297.03 mg/m^2 (SD = 108.71 mg/m^2). Of 147 patients, 83 patients (56.46%) also received radiation therapy in the treatment of their HL, and 64 patients (43.54%) did not receive radiation therapy. Of the 83 patients who received radiation therapy, the average total radiation dosage was 31.89 Gy (SD = 5.72 Gy).

Considering BMI of these patients, 110 patients (74.83%) had available measurement of height and weight both pre- and post-treatment, and this information was unavailable for 37 patients (25.17%). For this study, post-treatment is defined as the time of most recent follow-up. The average pre-treatment BMI of these 110 patients was 27.04 (SD = 6.19). The average post-treatment BMI of these 110 patients was 29.38 (SD = 6.33). Therefore, the average change in BMI between pre- and post-treatment was 2.34.

Previous studies have noted cardiac damage due to treatment. Elevated BMI could potentially exacerbate these negative effects of cancer treatment, as the heart is put under additional strain with an elevated BMI.

One variable of interest in this study was cardiotoxicity, as it is known that anthracyclines can cause cardiac damage in patients (Ali et al., 1994; Candela, 2016; Ferrans, 1978; Frishman et al., 1997; Krischer et al., 1997; Lenaz & Page, 1976; Praga et al., 1979; Steinherz & Steinherz, 1991; Townsend & Linch, 2012). Given this information, we attempted to identify specific characteristics that may predispose AYA patients to HL therapy-induced cardiotoxicity. Two parameters were chosen as clinical indicators of cardiotoxicity: prescribed cardiac medication or any recorded adverse cardiac event or cardiovascular disease, such as congestive heart failure, hypertension, and cardiomyopathy. For 24 (16.33%) of the 147 abstracted patients, prescribed cardiac medications were listed in the medical records, but not in the medical records of the remaining 123 patients (83.67%). Additionally, the medical records of 13 patients (8.84%) included evidence of an adverse cardiac event or cardiovascular disease at time of most recent follow-up, and the medical records of the remaining 134 patients (91.16%) did not document any adverse cardiac events or cardiovascular disease.

Analysis of Prevalence of Cardiotoxicity

We hypothesized that patients who received a higher dosage of anthracycline ($\geq$300 mg/m^2) would show evidence of cardiotoxicity more frequently than those who had a lower dosage of anthracycline. Of the 147 patients, 21 patients (14.29%) received a high dosage of anthracycline, while 126 patients (85.71%) received a low dosage. Figure

2 shows how many patients were prescribed cardiac medication stratified by anthracycline dosage. Of the 21 patients who received a high dosage, only 1 patient (4.76%) had a recorded cardiac medication in their medical records at time of most recent follow-up. Of the 126 patients who received a low dosage, the medical records of 23 patients (18.25%) showed that they were prescribed a cardiac medication at time of most recent follow-up. Chi-squared test revealed no statistically significant difference between the high dosage group and the low dosage group in terms of prescription of a cardiac medication (P = .121).

The next variable used as evidence of cardiotoxicity was documentation of an adverse cardiac event or cardiovascular disease by time of most recent follow-up. Figure 3 shows how many patients experienced an adverse cardiac event or cardiovascular disease stratified by anthracycline dosage. Of the 21 patients who received a higher dose of anthracycline, the medical records of 9 patients (42.86%) documented evidence of an adverse cardiac event or cardiovascular disease, and the charts of 12 patients (57.14%) did not. Of the 126 patients who received a low dosage, the medical records of 64 patients (50.79%) documented evidence of an adverse cardiac or cardiovascular disease event at their most recent follow-up, while the charts of 62 patients (49.21%) did not. Chi-squared test revealed no statistically significant difference between the high dosage group and the low dosage group in terms of evidence of an adverse cardiac event or cardiovascular disease (P = .501).

The above data do not support the first hypothesis that a higher dosage of anthracycline would predict higher evidence of cardiotoxicity. However, limited sample size, statistical power, selection of clinical indicators of cardiotoxicity, and the presence

of confounding variables may have impacted our ability to detect cardiotoxicity in this population.

Next, we hypothesized that radiation exposure during treatment of HL would increase the prevalence of cardiotoxicity in survivors. Using the same two parameters of cardiotoxicity, patients were stratified based on whether they received radiation during their primary treatment of HL or not. Figure 4 shows how many patients were prescribed cardiac medication stratified by use of radiation therapy in treatment. Of 147 patients abstracted for this study, 83 patients (56.46%) received radiation therapy, and 64 patients (43.54%) did not. First, considering documentation of cardiac medications in the medical records, of the 83 patients who did receive radiation therapy, 17 patients (20.48%) were taking a prescribed cardiac medication at most recent follow-up, and 66 patients (79.52%) were not. Of the 64 patients who did not receive radiation therapy as part of their treatment, 7 patients (10.94%) were using a prescribed cardiac medication at most recent follow-up, and 57 (89.06%) patients were not. Chi-squared test revealed no statistically significant difference in prescription of cardiac medication when patients were divided based on treatment with radiation ($P = .121$).

Continuing to stratify these patients by radiation exposure, Figure 5 shows how many patients experienced an adverse cardiac event or cardiovascular disease stratified by use of radiation therapy in treatment. Of the 83 patients who received radiation therapy, the medical records of 47 patients (56.63%) documented an adverse cardiac event or cardiovascular disease, and the charts of 36 patients (43.37%) did not. Of the 64 patients who did not receive radiation therapy, the medical records of 26 patients (40.63%) documented an adverse cardiac event or cardiovascular disease, and the charts

of 38 patients (59.38%) did not. Chi-squared test revealed no statistically significant difference between the radiation and no radiation groups in terms of evidence of an adverse cardiac event or cardiovascular disease (P = .054).

Although cardiotoxicity is a well-documented and common side effect of cancer treatment, especially after use of an anthracycline, our analysis was unable to show that cardiotoxicity was related to high dosage of anthracycline or radiation therapy. Neither patients who received high anthracycline dose nor patients who received radiation therapy showed a significant difference in cardiotoxicity compared to patients who received low anthracycline dose or no radiation therapy, respectively.

Analysis of Change in BMI

An additional focus of this study was understanding other long-term effects associated with treatment of HL as AYAs. While some studies have noted the higher BMI in cancer survivors than the general aging population (Connor et al., n.d.; Jernigan et al., 2013; Tai et al., 2012), studies have yet to show this for HL individually. Studies have also yet to show how the patients' BMI changes over time beginning at diagnosis. Additionally, in other studies, this information related to BMI is often obtained from a self-reported survey, which often creates some bias in results. Of note in this analysis was patients' BMI at most recent follow-up and change in BMI between pre-treatment and post-treatment measurements.

We first hypothesized that survivors would experience an increase in BMI between pre- and post-treatment measurements. To test this hypothesis, height and weight were retrospectively abstracted for each patient at both the time of diagnosis, prior

to any treatment, as well as at the most recent follow-up appointment. The average length of time between these two dates was 7.58 years (SD = 4.11). Of the 147 patients whose data was abstracted using the standardized form, the medical records of 110 patients (74.83%) contained both a pre- and post-treatment height and weight. The BMI for these 110 patients was then calculated by inputting these values into an online calculator (*Calculate Your BMI - Standard BMI Calculator*, n.d.).

Figure 6 is a box-and-whisker plot which compares pre- and post-treatment BMI of this population of HL survivors. Chi-squared test revealed that there is a significant increase in average BMI seen in HL survivors before treatment versus at most recent follow-up (**P < .001**). The average change in BMI between these two points in time for all patients was 2.27 kg/m^2. Figure 7 shows the distribution of patients' change in BMI. The figure shows a right shift in distribution of these values.

Given that on average, patients experienced an increase in BMI between pre- and post-treatment measurements, we hypothesized that patients who received a high anthracycline dose were more likely to be obese. To test for prevalence of obesity, in Figure 8, patients were stratified by high and low anthracycline dose and divided between obese and non-obese categories. A BMI of 30 or greater is considered obese, while a BMI of less than 30 is considered not obese. There were 129 patients with both a height and weight recorded at their most recent follow-up, and these values were used to calculate BMI. Of the 108 patients who received a low dose of anthracycline, 46 patients (42.59%) were not obese, and 62 patients (57.41%) were obese. Of the 21 patients who received a high dose of anthracycline, 10 patients (47.62%) were not obese, and 11 patients (52.38%) were obese. Chi-squared test revealed no statistically significant

difference in prevalence of obesity between the high anthracycline dose and low anthracycline dose groups (P = .671).

A T-test was conducted next to compare the mean BMI of both the high and low dosage anthracycline groups. The mean BMI at most recent follow-up of the patients who received a low dose of anthracycline was 29.23 (SD = 6.37), and the mean BMI of patients who received a high dose of anthracycline was 29.56 (SD = 7.35). T-test revealed no statistically significant difference between the mean BMI of the high anthracycline dose and the low anthracycline dose group (P = .417). While this difference was not significant, further questions were formulated about this data set as a response to this result.

The focus of the investigation then became the change in BMI that these survivors experienced from the date of diagnosis to the date of their most recent follow-up when stratified by treatment related factors. We hypothesized that patients who received more aggressive forms of treatment would experience a greater elevation in BMI. Figure 9 shows the patient population stratified in three different ways in order to gain insight as to which patients experience the most significant weight gain. In this figure, 110 patients with both a pre- and post-treatment BMI recorded were stratified by the type of treatment they received. Both radiation therapy and treatment with an anthracycline chemotherapy regimen can be risk factors to the long-term health of cancer patients. Thus, this study refers to high anthracycline dose and radiation therapy as “treatment related risk factors.” Patients who received both high anthracycline dose and radiation therapy have received “both treatment related risk factors.”

Every patient abstracted received anthracycline during treatment, as this was a factor in the selection criteria. Therefore, the value 300 mg/m^2 was chosen as the differentiation between high and low anthracycline dose because the average total dosage of anthracycline received by this patient population was 297.035 mg/m^2 (SD = 108.71 mg/m^2).

Figure 9a shows the distribution of changes in BMI in patients who received a low dose of anthracycline (≥300 mg/m^2) and patients who received a high dose of anthracycline (<300 mg/m^2). Chi-squared test revealed no significant difference in change in BMI between the high and low anthracycline dosage groups (P = .12). Figure 9b shows the distribution of changes in BMI in patients who did not receive radiation therapy to those who did receive radiation therapy as part of their treatment of HL. Chi-squared test revealed no significant difference in change in BMI between patients who did or did not receive radiation therapy (P = .45). Figure 9c shows the distribution of changes in BMI in patients who did not receive both treatment related risk factors with patients who received both high dose anthracycline and radiation exposure. Chi-squared test revealed a significant difference in change in BMI between patients who received both treatment risk factors and those who did not (**P = .0011**).

Figure 10 appears similar to Figure 4 but is composed of a smaller patient population. Included are those patients who were not considered obese at their pre-treatment measurements but were classified as obese at their most recent follow-up. The sample size was reduced from 110 patients to 20 patients, yet similar results were found. Figure 10a shows the distribution of changes in BMI in patients who received a low dosage of anthracycline with patients who received a high dosage of anthracycline. Chi-

squared test revealed no significant difference in change in BMI between the high and low anthracycline dose groups (P = .72). Figure 10b shows the distribution of changes in BMI in patients who did not receive radiation therapy as part of their treatment of HL with patients who did receive radiation therapy. Chi-squared test revealed no significant difference in change in BMI between patients that did or did not receive radiation therapy (P = .37). Figure 10c shows the distribution of changes in BMI in patients who did not receive both treatment related risk factors with those who received both high dose anthracycline and exposure to radiation. Chi-squared test revealed a significant difference in change in BMI between patients who received both treatment related risk factors and those who did not (**P = .0072**).

Figure 11 graphically displays how the extremity of BMI change varies depending on treatment type. Of the 110 patients with both a pre- and post-treatment BMI, the average change in BMI was 2.27 kg/m^2. Of these 110 patients, 86 patients (78.18%) experienced an increase in BMI, rather than BMI maintenance or decrease in BMI. Among these 86 patients, the average increase in BMI was 3.33 kg/m^2. Of these 86 patients, 49 patients (56.98%) received both treatment related risk factors, and 37 patients (43.02%) did not receive both treatment related risk factors. Of the 49 patients with both treatment related risk factors, 19 patients (38.78%) had an increase in BMI greater than 3.33 kg/m^2. Comparatively, of the 37 patients that did not have both treatment related risk factors, only 8 patients (21.62%) had an increase in BMI greater than 3.33 kg/m^2.

Patient Characteristics	N (%) or mean (SD)
Total	147
Gender	
Male	88 (59.86%)
Female	59 (40.14%)
Age at Diagnosis	26.26 (7.22)
Years of Follow-Up	7.58 (4.11)
Type of Primary Chemotherapy	
ABVD	123 (83.67%)
CHOP	13 (8.84%)
Other	11 (7.48%)
ABVD: Bleomycin Excluded	
Yes	41 (33.33%)
No	82 (66.67%)
Anthracycline Dose (mg/m2)	297.05 (108.71)
Radiation Therapy	
Yes	83 (56.46%)
No	64 (43.54%)
Radiation Dosage (Gy)	31.89 (5.72)
BMI	
Available	110 (74.83%)
Missing	37 (25.17%)
Pre-Treatment BMI	27.04 (6.19)
Post-Treatment BMI	29.38 (6.33)
One of More Cardiac Meds at Last Follow-up	
Yes	24 (16.33%)
No	123 (83.67%)
Diagnosis of any CVD	
Yes	73 (49.66%)
No	74 (50.34%)

Table 1: Summary of 147 abstracted AYA HL survivors' characteristics, as abstracted using abstraction form found in the Appendix. Characteristics abstracted include information on demographics, diagnosis information, treatment information, and cardiovascular information.

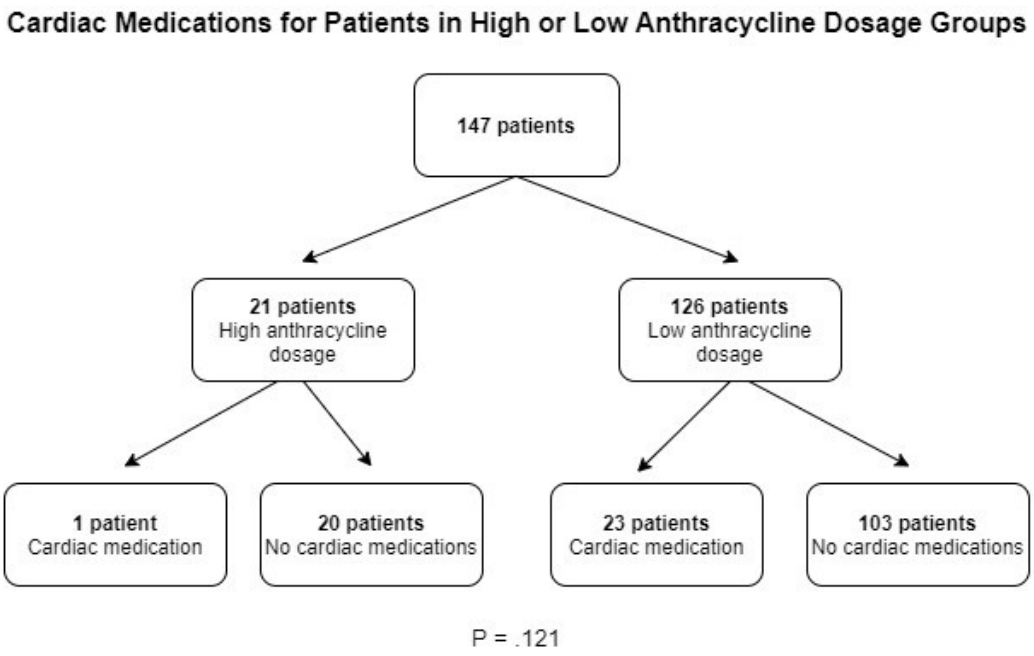

Figure 2: Evidence of cardiotoxicity at most recent follow-up as defined as prescription of a cardiac medication. Patients stratified by low anthracycline dose (<300 mg/m2) and high anthracycline dose (≥300 mg/m2). P-value calculated using chi-squared test.

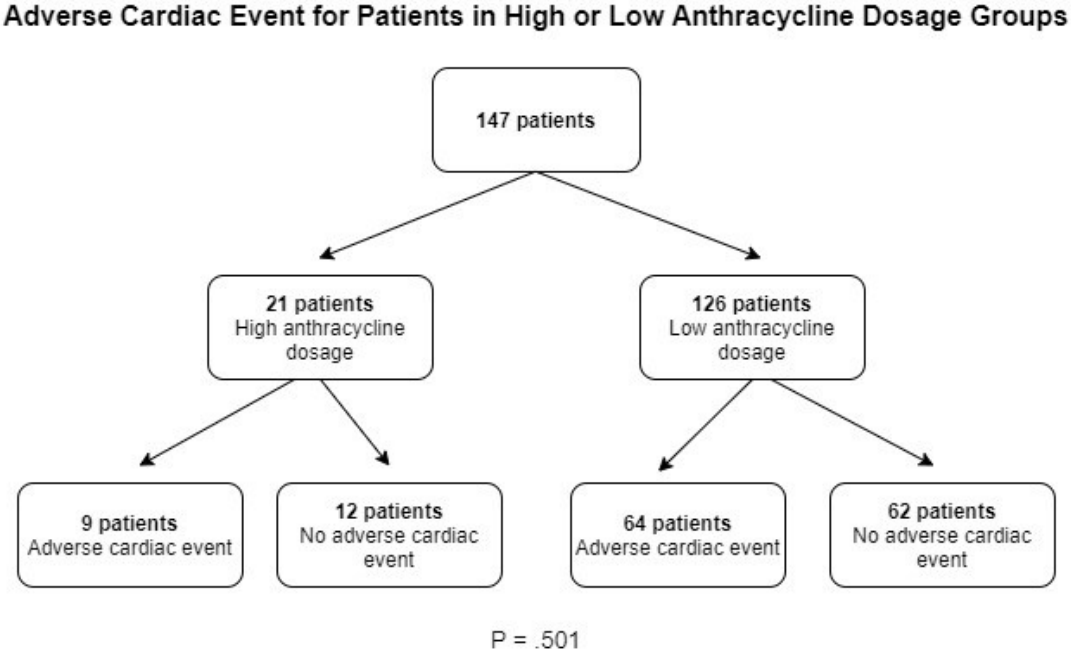

Figure 3: Evidence of cardiotoxicity at most recent follow-up as defined as documentation of an adverse cardiac event or cardiovascular disease. Patients stratified by low anthracycline dose (<300 mg/m2) and high anthracycline dose (≥300 mg/m2). P-value calculated using chi-squared test.

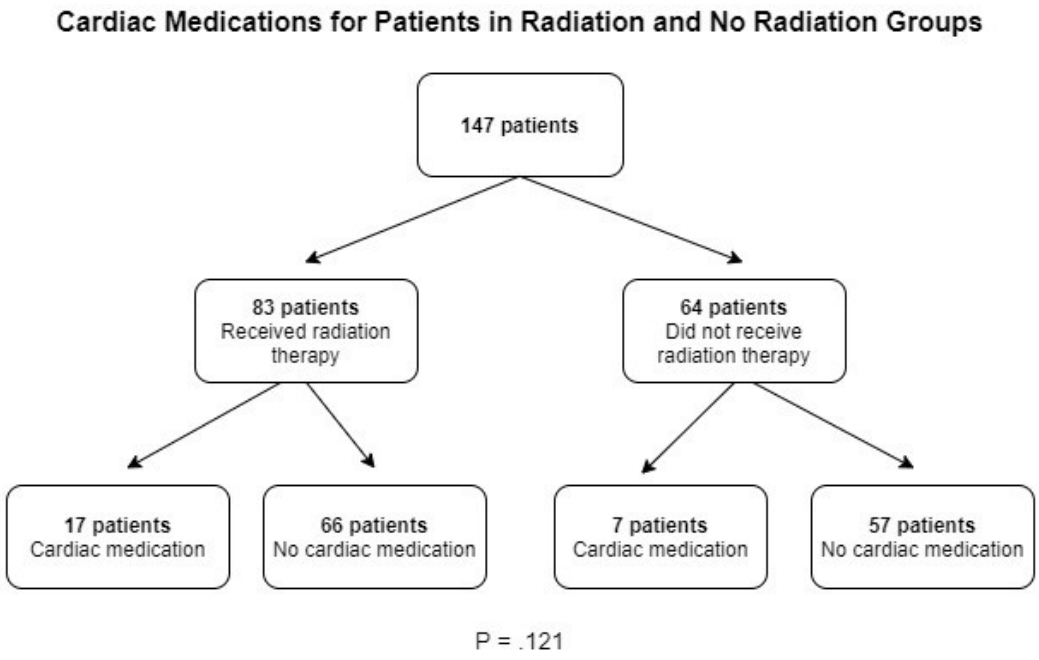

Figure 4: Evidence of cardiotoxicity at most recent follow-up as defined as prescription of a cardiac medication. Patients stratified by use of radiation therapy in treatment in HL or lackthereof. P-value calculated using chi-squared test.

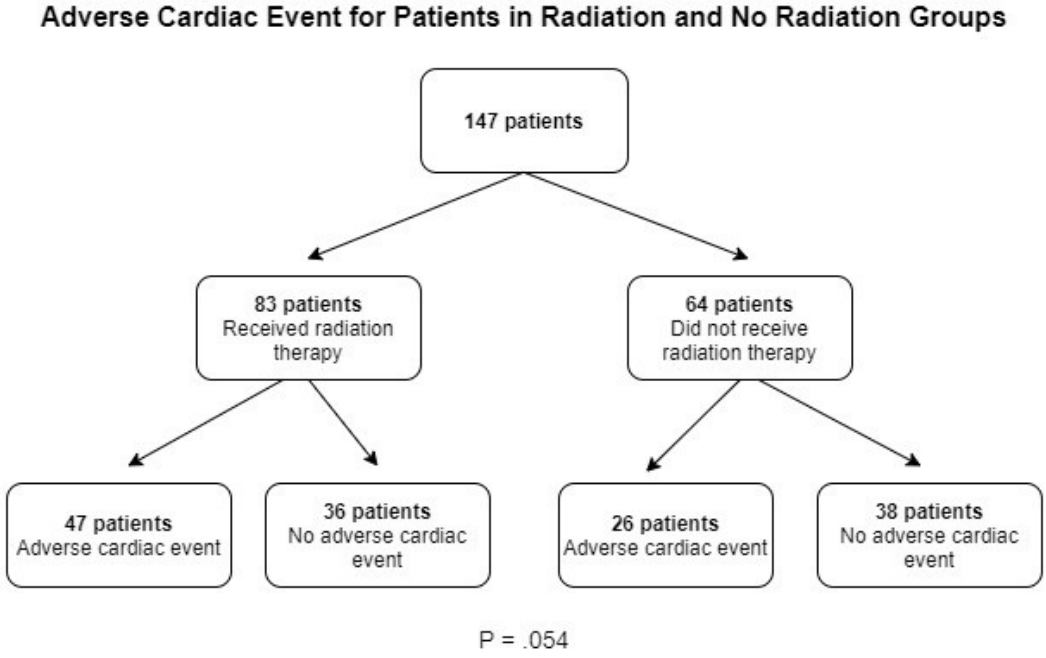

Figure 5: Evidence of cardiotoxicity at most recent follow-up as defined as documentation of an adverse cardiac event or cardiovascular disease. Patients stratified by use of radiation therapy in treatment in HL or lackthereof. P-value calculated using chi-squared test.

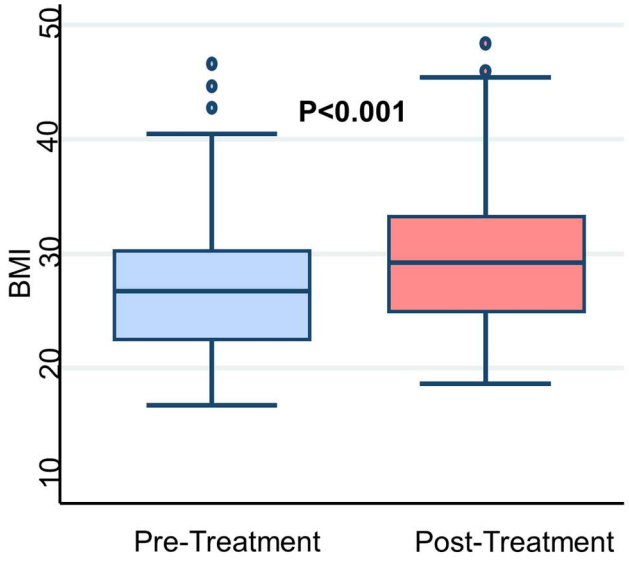

Figure 6: Comparing distribution of BMI of patients at time of diagnosis (pre-treatment) and at most recent follow-up (post-treatment). P-value calculated using chi-squared test.

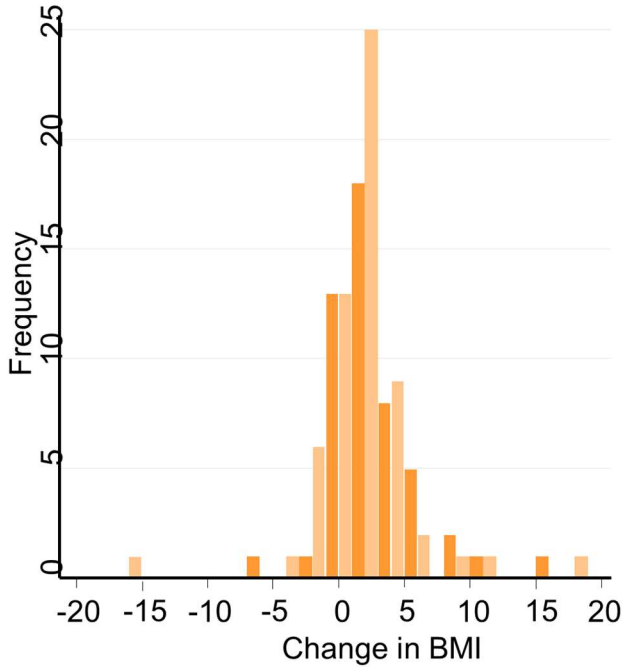

Figure 7: Right shift in distribution of change in BMI for 110 AYA HL patients with height and weight measurements recorded both at date of diagnosis and most recent follow-up.

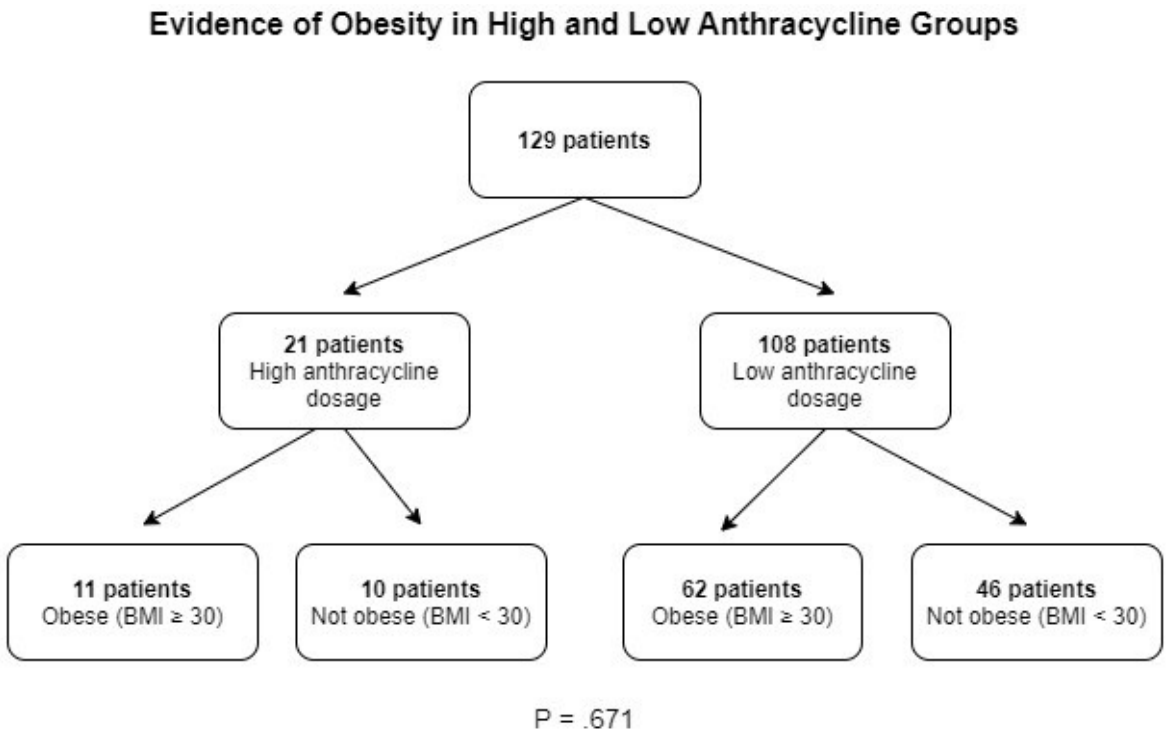

Figure 8: Evidence of obesity at most recent follow-up in patients stratified by low anthracycline dose (<300 mg/m^2) and high anthracycline dose (≥300 mg/m^2). Obese is defined as BMI ≥ 30. Not obese is defined as BMI < 30. P-value calculated using chi-squared test.

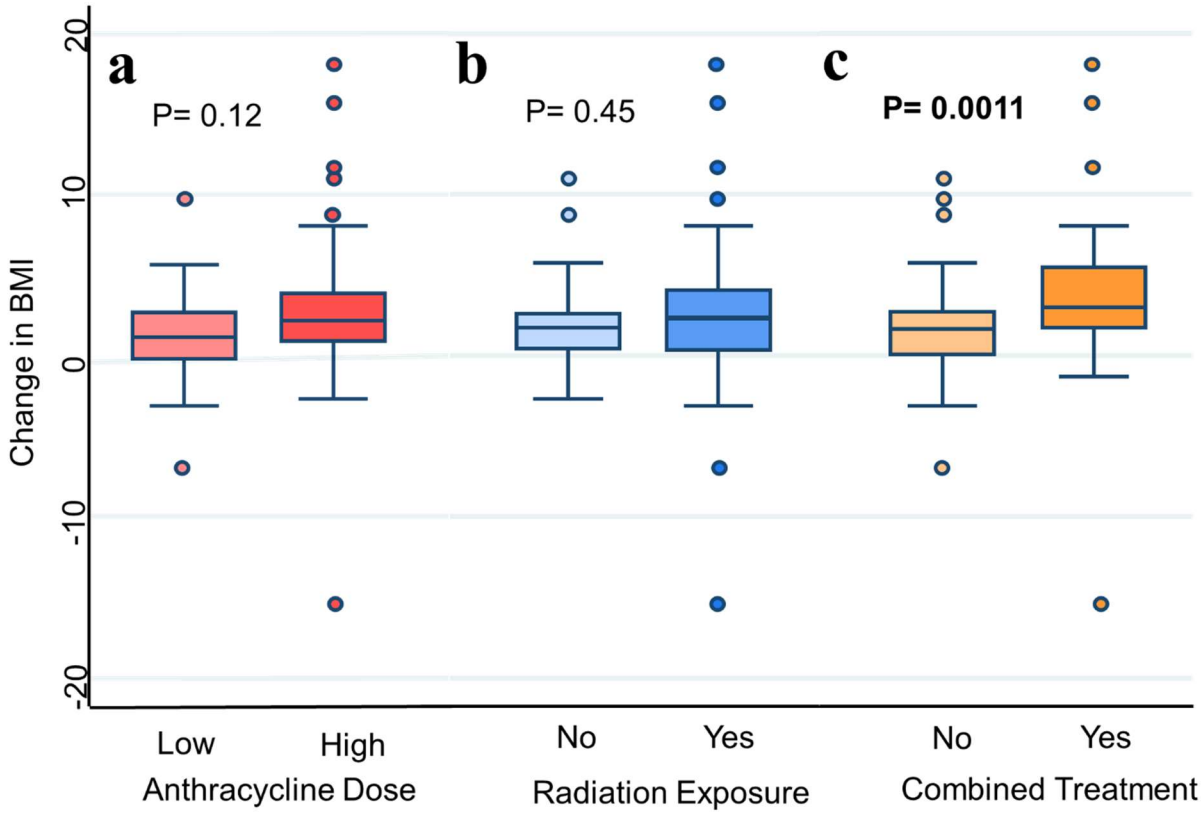

Figure 9: Changes in BMI between pre- and post-treatment measurements with patients stratified by type of treatment received. All P-values calculated using chi-squared test. (a) 147 patients stratified by low anthracycline dose (<300 mg/m^2) and high anthracycline dose (≥300 mg/m^2) and comparing average change in BMI and distribution of change in BMI for both groups (P = .12). (b) 147 patients stratified by their exposure to radiation therapy or lack thereof and comparing average change in BMI and distribution of change in BMI for both groups (P = .45). (c) 147 patients stratified by exposure to both treatment related risk factors (also known as "combined treatment") or lack thereof and comparing average change in BMI and distribution of change in BMI for both groups (**P = .0011**).

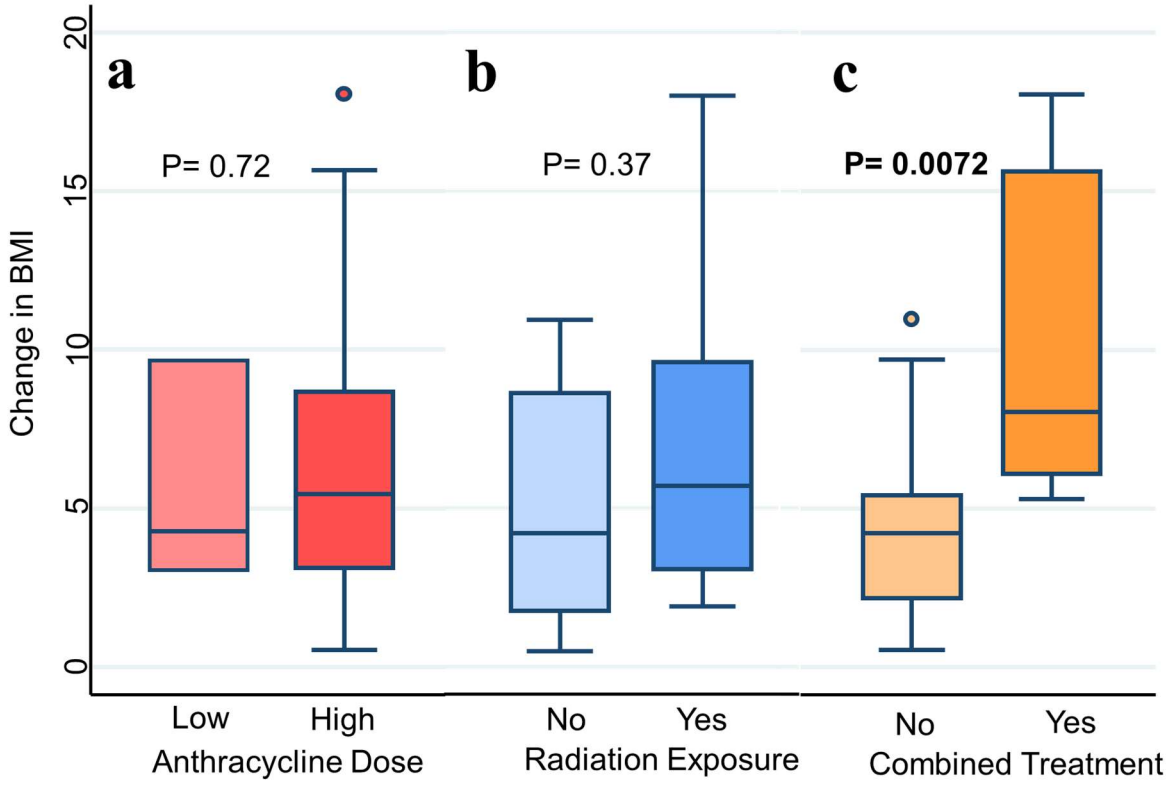

Figure 10: Changes in BMI between pre- and post-treatment measurements of patients who were considered not obese (BMI < 40) before treatment and were considered obese (BMI ≥ 40) after treatment with patients stratified by type of treatment received. All P-values calculated using chi-squared test. (a) 20 patients stratified by low anthracycline dose (<300 mg/m^2) and high anthracycline dose (≥300 mg/m^2) and comparing average change in BMI and distribution of change in BMI for both groups (P = .72). (b) 20 patients stratified by their exposure to radiation therapy or lack thereof and comparing average change in BMI and distribution of change in BMI for both groups (P = .37). (c) 20 patients stratified by exposure to both treatment related risk factors (also known as "combined treatment") or lack thereof and comparing average change in BMI and distribution of change in BMI for both groups (**P = .0072**).

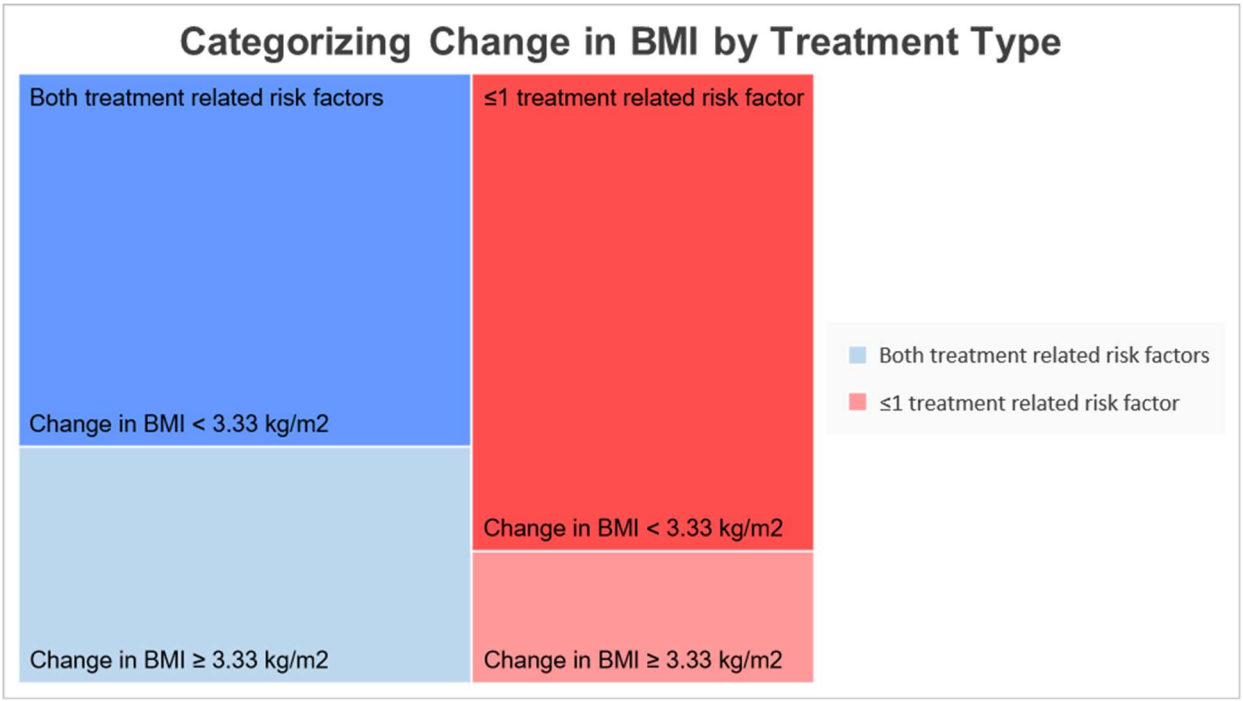

Figure 11: Of 110 patients with available pre- and post-treatment BMI, 86 patients experienced an increase in BMI. The average increase in BMI of these 86 patients was 3.33 kg/m^2. 86 patients were first stratified by treatment type. 49 patients received both treatment related risk factors (high anthracycline dose and radiation therapy) and are coded in blue. 37 patients did not receive both treatment related risk factors and are coded in red. Patients in each category were then separated by those patients with an increase in BMI less than the average (change in BMI < 3.33 kg/m^2), a less dramatic increase in BMI, and those patients with an increase in BMI greater than the average (change in BMI ≥ 3.33 kg/m^2), a more dramatic increase in BMI. 38.78% of patients (19 of 49 patients) who received both treatment related risk factors experienced a dramatic increase in BMI, in comparison to the 21.62% of patients (8 of 37 patients) who did not receive both treatment related risk factors that experienced a dramatic increase in BMI.

CHAPTER FOUR

Discussion

Summary of Results

Although this research is still in its preliminary stages, valuable and interesting data have been obtained. Our study found first that, on average, patients gain weight between time of diagnosis and their most recent follow-up. This finding is similar to what other studies have found with other cancer types. Sinicrope conducted a study which determined that obesity was a prognostic variable related to survival in colon cancer survivors. Obese patients had a reduced average disease-free survival and overall survival (Sinicrope et al., 2010). This study differs from our study as it only examines obesity, while our study also examines weight gain. Additionally, a study conducted by Jernigan noted an association between obesity and risk of death from several women's cancers (Jernigan et al., 2013). Thus, there is a great importance for healthcare providers to discuss weight and changes to lifestyle with their patients in order to improve the long-term health of survivors of women's cancers. This study also suggests that providers should refer at-risk patients to specialists who are best able to provide obesity intervention for them (Jernigan et al., 2013). One study that measures weight gain, similarly to our analysis, was conducted by Bradshaw. The premise of Bradshaw's study was the common weight gain seen after diagnosis for breast cancer patients. This weight gain was associated with a poorer prognosis (Bradshaw et al., 2011). In a study of 1,436 breast cancer survivors, the investigation found that this weight gain takes place specifically within the first year after diagnosis (Heideman et al., 2009). Heideman's

study helps to pinpoint the window of opportunity that providers have for intervention for this weight gain that may lead to poorer prognosis and other adverse events for cancer patients and survivors.

Our study specifically noted that the group that experienced the greatest weight gain was the group that received both a high dosage of anthracycline and radiation therapy. There are many possible reasons explanations for this relationship, and it is likely multifactorial. As presented in the introduction, it has been noted that anthracyclines cause cardiotoxicity (Ali et al., 1994; Ferrans, 1978; Frishman et al., 1997; Lefrak et al., 1973; Lenaz & Page, 1976; Raskin et al., 1973; Steinherz & Steinherz, 1991). In addition, radiation therapy whose field includes the chest or heart, is also often associated with long-term heart damage (Adams et al., 2003; Boivin et al., 1992; Glanzmann et al., 1998; Singal & Iliskovic, 1998). Given that some patients received both of these damaging treatments for their HL, it is not unlikely that they experience some heart damage due to treatment. Heart damage may present itself in a variety of ways, but perhaps alteration in heart function makes it more difficult for patients to maintain an active lifestyle, and therefore results in weight gain. However, many factors may contribute to weight gain, and these additional variables would be important areas of further investigation. The sample size for our preliminary analysis was small and there may have been confounding variables affecting these results, such as outliers for pre-treatment BMI and stage of disease at diagnosis.

Regardless of the rationale behind this finding, it is nonetheless important to pay attention to the weight gain and BMI of AYA HL survivors. Obesity is an extremely common condition in the United States and predisposes individuals to various additional

health conditions, such as diabetes and cardiovascular disease (World Health Organization, n.d.). Given that these patients may already present with heart damage due to their HL treatment, adding additional stress to the heart as a result of obesity would likely increase a survivor's risk of an adverse cardiac event in the future. This is one reason to explain the importance of Figure 4 in this study. Special consideration was given to those patients who were considered not obese prior to treatment yet were classified as obese at their most recent follow-up, as obesity is clearly linked with other negative health factors. The importance of focusing on obese patients is evident in other studies as well. In an investigation by Connor, overweight and obese patients were unable to accurately classify their weight, and therefore were unaware of the risks that accompanied their unhealthy weight (Connor et al., n.d.). This study, as well as the data obtained in our study, support the idea that patients should receive intervention and support to monitor their weight and overall health in order to provide the highest quality survivorship.

Although our data did not show any evidence of cardiotoxicity in our patients, that does not guarantee that these patients have not acquired heart damage due to this treatment. One reason we may not have found evidence of cardiotoxicity was the average length of follow-up. Perhaps 7.58 years is not sufficient time to note cardiac changes due to treatment. While there has not been an average length of follow-up established to predict presentation of cardiotoxicity after use of doxorubicin, multiple studies have noted that cardiotoxicity may not develop for much time after treatment, especially for younger cancer survivors (McGowan et al., 2017; Volkova & Russell, 2011). Or perhaps, cardiotoxicity was not evident using the clinical indicators for cardiotoxicity that we

chose. As we only had clinical patient charts available to us, identifying any cardiac medications and adverse cardiac events seemed to be the most sensible parameters to define cardiotoxicity. However, studies that are able to incorporate a more direct test of cardiac functioning, such as an EKG or an echocardiogram, may have a better opportunity to detect these cardiac changes due to cardiotoxicity. Monitoring ejection fraction and internal diameter may be two variables that could provide a more quantitative analysis of cardiotoxicity in future studies.

Reflection on Research Efforts

This preliminary research study was conducted as a pilot investigation under a newly obtained research grant at MD Anderson Cancer Center. This study is still in early stages, but the data obtained from this investigation will lead to further studies under this same grant. As this is a pilot study, a large amount data was collected from each patient so that this abstracted data could not only be used in this study, but also in further studies. Referring to the abstraction form found in the Appendix, it is clear that there are many categories of data that were abstracted but not used directly in this study. Future analyses will rely upon the accurate data entry to complete high-quality research endeavors.

The effort of abstracting data helped me understand the necessity of detail-oriented abstraction in this type of research. This process is necessary in order to obtain accurate data, as this data will be used in a variety of facets. By reading through the notes taken at each and every appointment that each patient had at this establishment, I was also able to gain additional knowledge on medical jargon, other diseases and conditions, common

treatments for a variety of illnesses, and different styles of charting for medical professionals.

Once I abstracted each patient by recording all the necessary information by hand using the abstraction sheet, I then transferred this information first into a large Excel document, and finally into an online software, RedCap (Nashville, TN). Through this process, I gained knowledge on a variety of data software systems and how to code variables correctly to allow for analysis in computer programs.

While the data that resulted from this study may appear thin in scope, the study taught me much about the research process and data abstraction. Additionally, it gave me a sense of accomplishment knowing that the data I abstracted will be used as a launchpad for further studies to be conducted on similar topics.

Implications of Results

In acknowledgement of the unique risks and needs of the AYA population, MD Anderson Cancer Center created the AYA Program to benefit both cancer patients and survivors (*Adolescent and Young Adult Program*, n.d.). This program offers a variety of services, including psychosocial care, fertility preservation, genetic testing, and support groups (*Adolescent and Young Adult Program*, n.d.). The AYA program includes a team of health care providers who work to address the unique needs of the AYA population to help improve their treatment and long-term health outcomes (*Adolescent and Young Adult Program Team*, n.d.). This clinic has helped address many of the personal needs of the AYA patients. It is one of the first of its kind and will likely serve as a model for other institutions in the future. By providing resources and guidance specifically tailored

to the needs of the AYA population, institutions across the world will be better able to care for their AYA patients long after their cancer treatment has ended. One study from the Netherlands noted the unique needs of HL survivors and established specific guidelines on appropriate treatment of these survivors (Van Leeuwen et al., 2016). The investigators recognized many common conditions and illnesses that seem to be a result of HL or HL treatment, yet obesity has not been identified in this list (Van Leeuwen et al., 2016). There is still a great need for research into the differences in cancer biology and HL treatment needed for the AYA population and our current study is a starting point for MD Anderson in this regard.

Given the concern with long-term cardiotoxicity and general heart health, programs like the AYA Program and the Heart Healthy Program at MD Anderson are uniting forces to continue to serve the AYA population (*Adolescent and Young Adult Program*, n.d.; *Healthy Heart Program*, n.d.). The Heart Healthy Program at MD Anderson provides a variety of programs for its patients, including fitness information, resources on family history of heart health, and information on impact of cancer treatment on heart health (*Healthy Heart Program*, n.d.). Patients who are deemed highest risk (such as those who received both high anthracycline dosage as well as radiation therapy) should be encouraged to visit with professionals focused on heart health in order to diminish preventable risk factors that may accelerate the onset or increase the severity of cardiac issues.

As noted previously, there is a gap in research concerning AYA cancer patients and survivors. As this body of research continues to grow, it will likely be even more

evident that there is a need for specialized programs like the one at MD Anderson to serve the needs of this population.

Study Limitations and Future Areas of Investigation

As mentioned above, humans are extremely complex, and many challenges arise in investigations. For these reasons, the principal investigators chose to limit the current analysis to non-Hispanic whites, in order to avoid genetic variations to add an additional variable to the data. However, there were still many variables that we were unable to control for in this study such as preexisting conditions, variation in stage at diagnosis, and consistency in available medical records data. Additionally, it is not known what portion of the weight gain in these patients was due to natural aging, as opposed to weight gain due to their HL treatment. Further studies should examine the BMI of healthy, non-HL patients to serve as a control to the HL survivors.

Additionally, our sample size for this study was small, and became much smaller on any attempt to stratify patients. For this reason, conducting analyses on the data often produced insignificant results. However, with a much larger sample size, the trends found in this study may be confirmed, and other interesting trends may arise. Fortunately, as this was a pilot project, data is continually being abstracted for use in projects similar to this one. With a larger sample size, survivors could be further stratified into groups by stage at diagnosis, length of follow-up, and other variables that may affect patients' weight gain and cardiotoxicity.

To add to the preliminary data collected from this study, a study evaluating the trajectory of change in BMI of these survivors would be of interest. Given that these

patients appear to experience weight gain, it would be beneficial for medical professionals to understand when this weight gain occurs in survivorship. In this way, medical providers would better be able to target their intervention in order to curb the effects of weight gain and provide these survivors with the resources they need to maintain a healthy lifestyle. This data could potentially be compared to similar studies to look for patterns or differences in the trajectory of weight gain between different types of cancers.

Another factor affecting this study was the chosen clinical indicators used as evidence of cardiotoxicity. While adverse cardiac events and cardiac medications may be indicators of cardiotoxicity, it is not an absolute test to determine cardiotoxicity. Future studies would benefit from using a different variable for analysis, such as comparing data from an EKGs or echocardiograms overtime for these patients. Again, studies like this are already beginning to arise under the broader grant-funded effort. Additionally, it is unknown when cardiotoxic effects are likely to arise for each patient. Therefore, a study monitoring cardiotoxicity for patients farther along in their survivorship may provide us with additional data about the timing of the presentation of cardiotoxicity in AYA HL survivors. This may also help compare the timeline of cardiotoxicity in AYAs to that of pediatric or adult HL survivors. This data would be useful to determine whether the same protocol and follow-up would be appropriate for different age categories.

Further studies could also begin to explore the genetic factors that may predispose patients for obesity and weight gain. With the decrease in cost of genetic testing, researchers have been able to associate genetic variation with a variety of health outcomes. Of interest are single nucleotide polymorphisms (SNPs), which are common

genetic variations at a single locus between different individuals. They may act as biological markers, variation in which may be associated with disease risks (Ahmadian et al., 2000). One health outcome that has been associated with specific SNPs is BMI. Multiple studies have begun to investigate these relationships. One article identified 133 specific loci related to BMI. This study also cites that between 40% and 70% of variability in BMI may be attributed to genetics (Locke et al., 2015), emphasizing the importance of investigating the genetic component of obesity and BMI. This data indicates the importance of seeking genetic testing for patients, especially those who may be at high risk for obesity.

In another study, researchers utilized an algorithm to calculate a "score" to quantify genetic susceptibility to obesity (Khera et al., 2019). The algorithm combined the individual effects of over 2.1 million genetic variants and scored each patient, who were then divided into deciles by score. This study consistently found that the participants with the highest polygenic score had a significantly higher BMI than those with lower polygenic scores. Interestingly, the study noted that the effect of the polygenic score began impacting individuals early in life, and only continued to increase in its effects into adulthood (Khera et al., 2019). This research has helped to further our understanding of genetics as it relates to BMI.

The information gathered from these studies can be used to determine if inheritance of the identified SNPs are predictive of which patients will have the highest risk of weight gain and obesity. This research would be beneficial as it would allow physicians to know in advance whether their patients were predisposed to weight gain and obesity and would indicate which patients were in higher demand for intervention.

Coupling these genetic factors with treatment related factors that may also cause weight gain, early intervention could be potentially live altering for patients. As their hearts may already be prone to experience increased stress due to obesity, physicians could make an added effort to protect the hearts of these patients, by using a lower dosage of anthracycline, prescribing a cardioprotector, focusing radiation therapy further to avoid the heart, and following up after treatment with heart healthy recommendations.

Conclusion

This preliminary research addresses questions concerning the long-term health outcomes of AYA HL survivors, especially concerning their BMI and cardiotoxicity as a result of their treatment regimen. Many further studies are needed in the AYA population, and this study sets the stage for some of these investigations. This investigative process taught me the importance of detailed data abstraction in order to obtain data that is qualified to be utilized in large institutions on various studies. Ultimately, in order to monitor the long-term health of these survivors, medical professionals should closely monitor the BMI of their patients to avoid the negative effects that accompany obesity and drastic weight gain. Simply implementing heart healthy practices into the routine of these survivors could significantly improve the quality of survivorship for this population, but further investigation should be conducted to discover other means of intervention for this at-risk group of survivors.

APPENDIX

Hodgkin's Lymphoma Abstraction

Patient MRN	
Patient Initials	

Abstractor Initials	
Date	

Variable	Coding	Notes
Demographics		
Date of Birth		MM/DD/YYYY
Gender	1: Male 2: Female	
Ethnicity	1: Hispanic 2: Non-Hispanic 99: Not available	
Race	1: White/Caucasian 2: Black/AA 3: Native American 4: Pacific Islander/Native Hawaiian 5: Asian 6: Other 99: Not available	Self-reported
Marital Status	1: Single 2: Married 3: Divorced 4: Legally Separated 99: Not available	
Diagnosis Information		
Date of Diagnosis		MM/DD/YYYY
Age at Diagnosis		
Cancer Type	1: Hodgkin Lymphoma 2: Other	
Treatment Information		
Transplant	1: Yes 2: No	
Transplant Date		MM/DD/YYYY
Chemotherapy	1: Yes 2: No	
Cardioprotector	1: Yes 2: No	

Type of Primary Chemotherapy	1: ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine)	

	2: ASHAP (doxorubicin, methylprednisolone, high dose cytarabine, and cisplatin) 3: BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone) 4: CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) 5: CVPP (cyclophosphamide, vincristine, procarbazine, and prednisone) 6: ICE (ifosfamide, carboplatin, and etoposide) 7: DHAP (high dose cytarabine, cisplatin, and dexamethasone) 8: IGEV (ifosfamide, gemcitabine, vinorelbine, and prednisone) 9: GND (gemcitabine, navelbine, and doxorubicin liposomal) 10: Other	
Primary Anthracycline	1: Yes 2: No	
Primary Anthracycline Dosage		mg/m^2
Type of Secondary Chemotherapy	1: ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) 2: ASHAP (doxorubicin, methylprednisolone, high dose cytarabine, and cisplatin) 3: BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone) 4: CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) 5: CVPP (cyclophosphamide, vincristine, procarbazine, and prednisone) 6: ICE (ifosfamide, carboplatin, and etoposide) 7: DHAP (high dose cytarabine, cisplatin, and dexamethasone) 8: IGEV (ifosfamide, gemcitabine, vinorelbine, and prednisone) 9: GND (gemcitabine, navelbine, and doxorubicin liposomal) 10: Other	

Secondary Anthracycline	1: Yes 2: No	
Secondary Anthracycline Dosage		mg/m^2
Radiation Exposure	1: Yes 2: No	
Chest Exposure	1: Yes 2: No	

Heart Exposure	1: Yes 2: No	
Radiation Dosage		grey (gy)
Survival		
Vital Status	1: Dead 2: Alive	
Date of Death		MM/DD/YYYY
Cardiovascular Information		
Last Clinic Visit Date		MM/DD/YYYY
Weight at Last Visit		kg
Height at Last Visit		m
Calculated BMI		kg/m^2
Medications at Last Visit		
Hypertension	1: Yes 2: No	
Date of Diagnosis		MM/DD/YYYY
Hyperlipidemia	1: Yes 2: No	
Date of Diagnosis		MM/DD/YYYY
Coronary Artery Disease (CAD)	1: Yes 2: No	
Date of Diagnosis		MM/DD/YYYY
Myocardial Infarction (MI)	1: Yes 2: No	
Date of Diagnosis		MM/DD/YYYY
Congestive Heart Failure (CHF)	1: Yes 2: No	
Date of Diagnosis		MM/DD/YYYY
Pericarditis	1: Yes 2: No	
Date of Diagnosis		MM/DD/YYYY
Valvular Heart Disease (VHD)	1: Yes 2: No	

Date of Diagnosis		MM/DD/YYYY
Ischemic Heart Disease (IHD)	1: Yes 2: No	
Date of Diagnosis		MM/DD/YYYY
Arrhythmia	1: Yes 2: No	
Date of Diagnosis		MM/DD/YYYY
Angina Pectoris	1: Yes 2: No	
Date of Diagnosis		MM/DD/YYYY
Transient Ischemic Attack (TIA)	1: Yes 2: No	
Date of Diagnosis		MM/DD/YYYY
Cardiomyopathy	1: Yes 2: No	
Date of Diagnosis		MM/DD/YYYY
Other Cardiovascular Disease	1: Yes 2: No	
Date of Diagnosis		MM/DD/YYYY

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