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Barriers and Facilitators to Attendance at an Initial Long-Term Follow-Up Clinic Visit by Survivors of Childhood Cancer

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An abstract of

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Abstract

Barriers and Facilitators to Attendance at an Initial Long-Term Follow-Up Clinic Visit by Survivors of Childhood Cancer

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Purpose: Childhood cancer survivors are at risk for a variety of adverse health outcomes. Regular follow-up at a specialized long-term follow-up program is important to ensure the prevention and early detection of these morbidities. The purpose of this study was to describe the survivor population and characterize factors related to engagement in survivor care at Children's Healthcare of Atlanta: a large, regional pediatric clinical care hospital system in the southeastern region of the United States.

Methods: We sought to distinguish barriers and facilitators to attendance in an initial survivor healthcare appointment by conducting a retrospective review of a cohort of children and young adults who have been off-therapy for cancer for at least 2 years. Our study was restricted to survivors greater than 2 years of age; who were diagnosed with and treated for cancer (other than a brain/central nervous system cancer) at a Children's Healthcare of Atlanta location between January 1, 2007 and December 31, 2013; and who were alive and at least 2 years off therapy following their most recent cancer event as of December 31, 2015. We examined demographic, medical, and survivor visit logistic factors related to attendance in Leukemia/Lymphoma and Solid Tumor survivors; and characterized select factors in cancer survivors treated exclusively with surgical intervention and those diagnosed with Retinoblastoma or Other Hematopoietic Disease.

Results: Of the 835 subjects that comprised the primary analysis and modeling cohort of Leukemia/Lymphoma and Solid Tumor survivors 576 (69%) had completed an initial survivor healthcare appointment, while 259 (31%) had not. Variations were seen in diagnosis by age, and therapy history by diagnosis. Race/ethnicity, diagnosis, therapy history, primary treatment location, and time eligible for clinic were found to be significantly associated with clinic attendance after adjusting for other important factors.

Conclusions: Despite the importance of regular follow-up at a specialized long-term follow-up program, our study results suggest that a significant portion of the Children's Healthcare of Atlanta cancer survivor population has not completed an initial survivor healthcare appointment. Our results can be used to help inform future recruitment and retention interventions at this and similar clinics.

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This thesis is lovingly dedicated to my favorite cancer survivor:

My mother, **Janice Dianne Clark**

Whose selflessness, generosity, and love has allowed me to reach where I am today.

And to **my Grandmother (Margaret)** and **Grandfather (William)** who were taken from us too soon by cancer.

"I give thanks to you, O Lord my God, with my whole heart,
and I will glorify your name forever."
–Psalm 86:12

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Section 1: Background/Literature Review

Introduction to Cancer Survivorship

Over 300,000 adults in the Unites States (US) between the ages of 20 and 39 years old, or 1 in every 640, is a survivor of childhood cancer (1). This number continues to grow each year as the incidence rates of pediatric cancer increase and the death rates decrease (2). Currently, as a result of dramatic improvements in treatment over the past several decades, approximately 80% of the children and adolescents diagnosed with cancer become 5-year survivors (3). Unfortunately, these same life-saving treatments predispose patients to a variety of serious adverse health conditions.

Survivors have been shown by the Childhood Cancer Survivor Study (CCSS), a multi-institutional ongoing research initiative, to have a 73% cumulative incidence of chronic disease 30 years after their cancer diagnosis, with 42% experiencing severe or life threatening conditions including death (4)(5). The CCSS has also shown that childhood cancer survivors are at a 3.3 times greater adjusted relative risk of any chronic condition compared with siblings, and have an adjusted relative risk of 8.2 compared with siblings for a severe or life threatening condition (5). Specific adverse health outcomes survivors are at risk for include: having subsequent neoplasms; being over or under-weight; having abnormal growth; and having issues related to sexual development, fertility, pregnancy, and reproductive function. They are also at a higher risk of developing organ dysfunction, including pulmonary and cardiac complications. Survivors have additionally been shown to be at an increased relative risk of having a stroke; as well as neurological and neurosensory morbidities including hearing and vision impairments, coordination and motor problems, cognitive dysfunction, and seizure

disorders (6). Regular medical follow-up, particularly at a specialized long-term follow-up program, is important to ensure the prevention and early detection of these morbidities (7).

The Importance of Survivor Care

The Institute of Medicine recommends childhood cancer survivors have a plan for life-long survivorship care (8). However, it is estimated that while close to 90% of adult survivors of childhood cancer report receiving some form of regular general medical care, only around 30% receive survivor-focused care, and less than 20% report discussing long-term risk reduction and ordering screening tests based on their prior cancer (9). Further, as adult survivors become older they become less likely to report a general physical examination, a cancer-related medical visit, or a visit to a cancer center. Thus, during the period when the incidence of late effects is increasing, and screening and intervention are of particular importance, survivors are failing to receive adequate follow-up care (10). Noted barriers to adult survivor health care include: lack of patient knowledge regarding their health risks, low socio-economic status, lack of health insurance or inadequate insurance, female gender, lower treatment intensity, and living a greater distance from survivor care (11) (12).

Given the importance of long-term survivorship care it is essential for survivorship clinics to determine factors influencing attendance by survivors of childhood cancer, so that recruitment strategies can be developed to target groups failing to receive care. However, while several past studies have examined long term follow-up clinic attendance in adult childhood cancer survivor populations, there is limited research addressing factors influencing long-term follow-up among the pediatric population of

survivors of childhood cancer, especially in the United States. Studies conducted in the United Kingdom have found that childhood cancer survivors under the age of 18 appear to be more likely than their adult counterparts to attend a long-term follow-up program, and sociodemographic factors have been shown to be the most important barrier to long-term follow-up attendance (7). In the US, a study conducted over a 1-year period at a major non-profit research hospital found nearly 15% of childhood cancer survivors did not attend their clinic visit within 6 months of their first scheduled appointment date; despite hospital-provided free medical care, meals, lodging, and transportation to patients attending their survivorship clinic. Survivors who failed to attend their visit were more likely to have not experienced secondary cancer events, be non-white, be without insurance, and travel by car to their visit (13).

Purpose and Improvements upon Previous Work

The purpose of this study was to describe the survivor population and characterize factors related to engagement in survivor care at Children's Healthcare of Atlanta: a large, regional pediatric clinical care hospital system in the southeastern region of the United States. We sought to distinguish barriers and facilitators to attendance in an initial survivor healthcare appointment by conducting a retrospective review of a cohort of children and young adults who have been off-therapy for cancer for at least 2 years. We evaluated patient demographic, medical, and survivor clinic attendance logistic factors to determine differences between those who attend and do not attend an initial long-term survivor follow-up clinic appointment.

The current study improves upon previous work by focusing on attendance at a diverse, regional US center that does not generally provide free medical care or

coordinate travel for patients, informing future recruitment and retention interventions for this and similar clinics. Our study also looks specifically at initial survivor clinic appointment attendance, and as such we uniquely describe the differences between childhood cancer survivors who have had any or no survivor follow-up care.

Completion of an initial survivor visit is of particular importance for survivors because it begins the education process that constitutes survivor care and at this appointment survivors receive a Survivor Healthcare Plan (or SHP). SHPs include a medical summary of the survivor's cancer diagnosis and treatment, an individualized risk profile detailing out what late effects can take place after cancer treatment, and a personalized surveillance plan that outlines tests a survivor needs to screen for late effect and how often to have these tests. This plan serves as a roadmap for patient's future survivor care and a useful tool to assist providers the survivor may see in the future (14).

Section 2: Methods

Subjects

For this institutional review board approved retrospective study, candidates were identified by study personnel using an active clinical database which contained patient demographic, cancer diagnosis and treatment, off-therapy, and survivor follow-up information collected from the patient's electronic medical records and data reported to the Georgia Comprehensive Cancer Registry [GCCR] by the Children's Healthcare of Atlanta Cancer Registrar team. Our study was restricted to survivors greater than 2 years of age; who had a cancer diagnosis date between January 1, 2007 and December 31, 2013; who received treatment at a Children's Healthcare of Atlanta location; and who were alive and at least 2 years off therapy following their most recent cancer event as of December 31, 2015. Subjects with a primary diagnosis of a malignant or benign brain/central nervous system (CNS) cancer were excluded from this analysis as these survivors are seen in a separate multi-disciplinary clinic for brain tumor survivors.

Outcome

To determine if survivors were classified as having been seen for a long-term survivor follow-up appointment by the Cancer Survivor Program Clinic at the Children's Healthcare of Atlanta Aflac Cancer Center, we identified subject's initial completed survivor healthcare appointment date. Those with an initial visit date after the off therapy date for their most recent cancer event and before January 1, 2016 were defined as "Seen". All others (including those scheduled but not seen as of January 1, 2016; and those who canceled, and did not complete, an appointment) were defined as "Not Seen".

Predictors

Demographic, medical, and survivor visit logistic factors were collected for each patient. Demographic information obtained included gender (male/female), and race (Non-Hispanic White, Non-Hispanic Black, Asian, Hispanic, and Other/Mixed Race). Medical information included year of diagnosis (2007-2013), additional cancer events (any relapse, disease progression, or second malignancy as of January 1, 2016), and primary treatment campus (Egleston Hospital, Scottish Rite Hospital, and Other; as reported to the GCCR). Missing data for the primary treatment campus variable were imputed using the patient's primary oncologist (as reported to the GCCR). Age at diagnosis (in years) was subsequently grouped into the following categories: 0-3, 4-7, 8-11, 12-15, and 16+.

Additional medical factors collected included disease type and histology data (for the patient's primary diagnosis, as reported to the GCCR) which were used to designate subject's primary diagnosis as: Leukemia, Lymphoma, Bone/Soft Tissue Sarcoma, Kidney Cancer, Neuroblastoma, Other Solids Tumor, Retinoblastoma, or Other Hematopoietic Disease. For primary analysis and modeling, survivors were further categorized as belonging to either the Leukemia/Lymphoma or Solid Tumor (consisting of Bone/Soft Tissue Sarcomas, Kidney Cancers, Neuroblastomas, and Other Solids Tumors; excluding Retinoblastomas) disease categories.

Data regarding the survivors' first line of therapy (yes/no: surgery, chemotherapy, radiation, bone marrow transplant [BMT], and other therapeutic modality), as reported to the Georgia Comprehensive Cancer Registry 1-2 years following diagnosis, were used to categorize the subjects as: Surgery Only, Chemotherapy (No radiation or BMT, with or

without surgery), Radiation (No chemotherapy or BMT, with or without surgery), Chemotherapy and Radiation (No BMT, with or without surgery), Bone Marrow Transplant (with or without chemotherapy, radiation, and/or surgery), Other Therapeutic Modality (treatment other than chemotherapy, radiation, or BMT; with or without surgery) and Unknown.

Survivor visit logistic factors included age (in years, at clinic eligibility) which was categorized as Young (less than 12), Teen (12 to 17), and Adult (18 and older). Time eligible for clinic was defined as the time since the patient reached 2 years from their cancer off-therapy date as of January 1, 2016; and was used to categorize survivors as either greater or less than 1.5 years eligible. The subjects' zip code (as reported to the GCCR at diagnosis) was used to identify survivors from an area designated as low income by Centers for Medicare and Medicaid Services (CMS) and to calculate the distance from the patient's home to the clinic (in miles) (15). Distance was subsequently categorized into the following groups: < 10, 10-25, 26-50, >50, and Unreported.

Statistical Analysis

Chi-square tests were used to examine the univariate associations of demographic, medical, and survivor clinic logistic factors with completion of an initial survivor healthcare appointment, and logistic regression was used to determine which associations remained significant after controlling for other predictors. All variables were initially considered as candidates for inclusion in the final multivariate model. In the stepwise method used to select a final model, variables with the most significant P value (<0.10) were added to the model consecutively, and variables that did not retain significance (P value <0.10) after each variable entered were removed.

Histograms were produced to illustrate the association between age at diagnosis and disease category, and diagnosis and therapeutic modality received. Box plots were formed to elucidate associations between year of diagnosis and time eligible for clinic in days. To further explore the relationship between year of diagnosis and time eligible for clinic, the Kaplan-Meier (KM) Method was used to plot a curve of the probability of failure over time, where failure was defined as a completed initial survivor clinic visit. Data were analyzed using SAS software, version 9.4 (SAS Institute).

Section 3: Results

Study Sample

Of the 1,106 candidates identified as eligible, 55 subjects who were known to have moved and transferred care to another treatment facility, or who had transitioned to an adult oncologist/adult survivor care were excluded from the primary statistical analysis and model development; as were an additional 53 subjects who transferred care to Children's Healthcare of Atlanta after being diagnosed and initially treated at another facility (Figure 1).

For primary statistical analysis and model development, subjects were further restricted to those with a diagnosis of Leukemia/Lymphoma or a Solid Tumor who had received a therapeutic modality besides surgical intervention (excluding 125 survivors of various disease types who had received only surgical intervention and 38 survivors with a diagnosis of Retinoblastoma or Other Hematopoietic Disease) (Figure 1). This decision was made because of the structure of the Children's Healthcare of Atlanta Childhood Cancer Program and the recruiting process of the Survivor Program Clinic.

The Childhood Cancer Program is divided into teams of Leukemia/Lymphoma and Solid Tumor physicians at two separate locations (Egleston Hospital and Scottish Rite Hospital). Though survivors with Retinoblastoma and Other Hematopoietic Diseases who are at risk for late effects are eligible to attend Survivor Clinic, they are generally followed by the Ophthalmology and Hematology Programs (respectively) as opposed to the Childhood Cancer Program. Survivors who received only surgical intervention (regardless of their diagnosis) are eligible for, but not currently actively recruited to, the Survivor Clinic as current research suggests these patients have a low potential for late

effects. As such, it was determined that these patient populations were best represented in a separate analysis (Table 3).

Overall Attendance and Descriptive Statistics of Leukemia/Lymphoma and Solid Tumor Survivors

Of the 835 subjects that comprised the primary analysis and modeling cohort of Leukemia/Lymphoma and Solid Tumor survivors 576 (69%) had completed an initial survivor healthcare appointment, while 259 (31%) had not. 52% of the subjects were Male, and nearly 80% of the survivor population was either Non-Hispanic White (50%) or Black race (28%). The youngest age groups were most common at diagnosis (32% 1-3 years) and eligibility (53% Young [less than 12 years]). Survivors were more likely to have a diagnosis of Leukemia/Lymphoma than a Solid Tumor (57% vs. 43%). Finally, a majority of survivors received chemotherapy (without radiation or BMT) as their first line of therapy (62%).

Univariate Findings for Leukemia/Lymphoma and Solid Tumor Survivors

The results of univariate analysis (Table 1) demonstrated that survivors diagnosed with a solid tumor ($p<0.001$) and those eligible to attend clinic for a shorter period of time ($p<0.001$) were less likely to have a completed visit. Other significant differences existed by race/ethnicity, year of diagnosis, age at diagnosis, therapeutic modalities received, and primary treating campus (Table 1).

Age at diagnosis was found to be strongly correlated with diagnosis (Figure 2). While Leukemia was the most common cancer for eligible subjects age 0-11 at diagnosis, Lymphoma was most common for older survivors (12+). Neuroblastoma and Kidney Cancers were the second and third most common types of cancer for survivors age 0-3 at diagnosis, but are entirely absent from subjects older than 12. Bone/Soft Tissue Sarcomas

and other solid tumors, meanwhile, made up a large portion of cancers for older survivors, while they are less common in subjects younger than 8.

Year of initial cancer diagnosis was found to be primarily correlated with time eligible for clinic (Figure 3). The Kaplan-Meier (KM) Method was used to plot a curve of the probability of failure over time, where failure was defined as a completed initial survivor clinic visit. The probability of having completed an initial survivor clinic visit appeared to increase as the number of days eligible for clinic increased. The steepest increase is seen within the first two years of becoming eligible (Figure 3, A). Meanwhile, there is evidence to suggest that the mean number of days eligible for clinic is different by year of diagnosis (overall F test p-value <0.001), with the average time eligible decreasing by year of diagnosis (Figure 3, B).

Correlation was also found to exist between diagnosis category and therapeutic modality history (Figure 4). Chemotherapy alone was the most common first-line therapy for all eligible subjects, regardless of diagnosis. However, receiving radiation, whether alone or as part of a combination with chemotherapy, appeared to be more common for solid tumor survivors. Subjects who received bone marrow transplants almost exclusively had a diagnosis of Leukemia.

Logistic Regression Modeling and Adjusted Associations for Leukemia/Lymphoma and Solid Tumor Survivors

A stepwise selection procedure was utilized to develop a logistic regression model to determine which associations remained significant after controlling for other predictors. All variables were initially considered. However, age at diagnosis (in years)

and year of initial cancer diagnosis were ultimately dropped from consideration to reduce problems related to multicollinearity.

Ultimately, five variables met the criteria to be retained in the model (Table 2) which showed that Non-Hispanic Black, Asian, and Other/Mixed/Unknown Race survivors were less than half as likely to have completed an initial survivor healthcare appointment than their Non-Hispanic White counterparts ($P<0.001$, $P=0.058$, and $P=0.040$). Survivors with a primary diagnosis of a solid tumor were 2.8 times more likely to have not attended the Survivor Clinic than those with a Leukemia/Lymphoma diagnosis ($P<0.001$). Those who received radiation (but no chemotherapy or BMT) were 4.8 times as likely as those who received chemotherapy (but no radiation or a BMT) to have not completed survivor follow-up visit ($P<0.001$), and those who received a therapeutic modality other than chemotherapy, radiation, or a BMT were 10 times less likely compared to the same group ($P=0.01$). Subjects treated at the Egleston Hospital were less than half as likely to have attended Clinic compared to those treated at Scottish Rite Hospital ($P<0.001$). Finally, those at least 2 years off cancer therapy and eligible to attend an initial survivor healthcare appointment for more than 1.5 years were nearly 6 times more likely to have a completed visit compared with those eligible for a shorter period of time.

Descriptive Statistics of Other Survivor Populations

The Retinoblastoma, Other Hematopoietic Disease, and Surgery Only survivor populations had low rates of survivor visit attendance (20%, 50%, and 5% respectively) (Table 3). The most common disease categories for subjects who received only surgical intervention was Other Solid Tumor (34%), Bone/Soft Tissue Sarcoma (18%), and Retinoblastoma (16%). Retinoblastoma and Surgery Only survivors were both more

likely to have been treated at Scottish Rite Hospital than Egleston Hospital (95% and 45%, respectively).

Like the Leukemia/Lymphoma and Solid Tumor survivor groups, survivors in this population were primarily Non-Hispanic White or Black race, and young at diagnosis. In particular, 100% of the Retinoblastoma population who received a therapeutic modality besides surgery were diagnosed at 0-3 years old. Also similar to the Leukemia/Lymphoma and Solid Tumor population, Retinoblastoma survivors who received a therapeutic modality besides surgery were most likely to have received chemotherapy without radiation or BMT (95%), as were Other Hematopoietic Disease survivors who received a therapeutic modality besides surgery (44%).

Section 4: Discussion

Childhood cancer survivors are at risk for a variety of adverse health outcomes. These late effects range from having subsequent neoplasms; to the development of organ dysfunction; to issues related to sexual development, fertility, pregnancy, and reproductive function (6). Regular follow-up at a specialized long-term follow-up program is important to ensure the prevention and early detection of these morbidities (7). However, this study found that 31% of a cohort of childhood cancer survivors diagnosed with Leukemia/Lymphoma or a Solid Tumor and treated with a therapeutic modality other than surgery at Children's Healthcare of Atlanta (a large, regional pediatric clinical care hospital) between 1/1/2007 and 12/31/2013 had not completed an initial survivor healthcare appointment at the Survivor Program Clinic. Results of this study suggest visit completion may be associated with factors that could help inform future recruitment and retention strategies within this and similar survivor follow-up programs.

Non-White subjects (with the exception of those of Hispanic ethnicity) were found to be significantly less likely to have completed an initial survivor healthcare appointment than their Non-Hispanic White counterparts, consistent with previous results and suggesting the need for interventions targeted specifically to racial minority groups (13). Also as expected, those eligible to attend clinic for a shorter period of time were less likely to have a completed visit than those eligible longer. However, our findings suggest that the probability of being seen in clinic does not approach its maximum and begin to plateau until nearly 3 years after a survivor becomes eligible to attend clinic. As such, efforts should be made to recruit survivors to clinic promptly after reaching 2 years off therapy to begin the education process of survivor care. In contrast to previous studies,

we did not find additional cancer events to be a significant predictor of clinic attendance (13).

Our study also found a solid tumor diagnosis to be associated with decreased survivor visit attendance, as was treatment with radiation (but no chemotherapy or BMT) which appeared in our analysis to be somewhat correlated with a solid tumor diagnosis (Figure 4). This finding is of particular concern considering patients who received any radiation during their cancer therapy have been shown in previous studies to be at a significantly increased risk of chronic health conditions, and that risk increases even further if the patient received chest or pelvic irradiation (5). As survivors have been shown prior to attending clinic to have low and incorrect perceptions of their personal risk for late effects, it is possible that these patients may be failing to engage in survivor care due to incorrect late effects risk perception (16). Additional education regarding late effects risks prior to survivor visit attendance and encouragement from providers to attend the survivor clinic may help to facilitate initial visit completion by this population (16).

Subjects primarily treated at Egleston Hospital were also found less likely to have completed a survivor visit. As Children's Healthcare of Atlanta's Childhood Cancer Program functions in teams of Leukemia/Lymphoma and Solid Tumor providers at each of the two main campuses, coupled with the low attendance associated with a Solid Tumor diagnosis our findings suggest that the Egleston Solid Tumor team may be a particularly good target for potential interventions at both the patient and provider level. Efforts should be made to engage patients and providers in this group in survivor care, to assess perceived risk for late effects, and to determine both patient and provider health

beliefs relating to survivor care. Evaluation of survivor clinic referral patterns by oncologists on both teams at Egleston Hospital, and those on the Solid Tumor Team at Scottish Rite Hospital, should also be considered to determine areas for potential improvement.

Regarding the reduced odds of attendance seen in the Egleston survivor population, consideration should also be given to the fact that the Survivor Program Clinic is currently located at the Scottish Rite Hospital campus. In addition to our findings that the distance to clinic for survivors was not a significant predictor of clinic attendance, Scottish Rite Hospital is located only 10 miles north of Egleston Hospital, at the intersection of two of the greater Atlanta area's largest freeway systems, and is located in close proximity to a Metropolitan Atlanta Rapid Transit Authority (MARTA) rail station. As such, it seems unlikely that transportation-related factors are the main driving force between the Egleston and Scottish Rite population attendance differences observed in this study. Further studies should examine psychosocial factors that may be impacting the willingness of Egleston patients to visit Scottish Rite for survivor follow-up care. Consideration should also be given to expanding the Survivor Program Clinic to provide follow-up services at Egleston to help facilitate attendance by that survivor population.

Though comparatively lower than those who receive chemotherapy and/or radiation, cancer survivors who do not receive chemotherapy or radiation have still been shown to be at a statistically significant increased relative risk of chronic health conditions in adulthood compared to cancer-free siblings (5). As such, consideration should be given to ensuring these survivors complete at least an initial survivor

healthcare appointment to establish a foundational understanding of their late effects risk. Greater attention should also be provided to ensuring Retinoblastoma and Other Hematopoietic Disease survivors receive appropriate survivor follow-up care as a significant subset of these patients have been exposed to chemotherapy during the course of their treatment.

In conclusion, despite the importance of regular follow-up at a specialized long-term follow-up program to detect and prevent late effects, our study suggests that a significant portion of the Children's Healthcare of Atlanta cancer survivor population has not completed an initial survivor healthcare appointment. Race/ethnicity, diagnosis, therapeutic modality history, primary treatment location, and time eligible for clinic were found to be significantly associated with clinic attendance after adjusting for other important factors in Leukemia/Lymphoma and Solid Tumor patients. Our findings suggest future recruitment and retention interventions should target racial minority populations, the Egleston Hospital survivor population, and Solid Tumor survivors at both of Children's Healthcare of Atlanta's oncology locations. Further attention should also be provided to survivor care for patients who receive only surgical intervention, Retinoblastoma survivors, and Other Hematopoietic Disease survivors.

Section 5: Strengths, Weaknesses, and Future Directions

Strengths

The survivor cohort from this study was obtained from a large, regional US center that does not provide free medical care or coordinate travel for patients. Over 70% of survivors resided less than 50 miles from the Survivor Program Clinic. These factors, in addition to the racial/ethnic diversity of our population (which mirrors the overall US population) improve the generalizability of our results. Our study also looked specifically at initial survivor clinic appointment attendance, and uniquely describes the differences between childhood cancer survivors who have had any or no survivor follow-up care.

In addition, we were able to obtain a large sample size of subjects (835 subjects in our modeling cohort, 998 overall) that represented a 6 year diagnosis period, which served to reduce random error and increased study power. Finally, as the data were ascertained from an active clinical database that captures information reported by providers and cancer registry staff, it is less likely to be heavily influenced by recall or misclassification bias.

Weaknesses

Several limitations must be considered when interpreting the results of this study. First, data for many variables of interest (including: primary treatment campus, primary oncologist, therapeutic modalities received, and zip code) were available as they were reported to the Georgia Comprehensive Cancer Registry 1-2 years following diagnosis by the Children's Healthcare of Atlanta Cancer Registrar. Consequently, it is possible that the values of these variables could have changed since that time and may no longer be accurate for a subset of patients. Second, measurement of socioeconomic status was

limited to whether the subject's zip code was classified as a low income area by the Centers for Medicare and Medicaid Services. As socioeconomic status can vary widely within zip codes, particularly in metropolitan areas, this may not have been an exact predictor of true household socioeconomic status.

Additional limitations included the fact that though age at diagnosis and year of diagnosis were excluded from the model to reduce problems with collinearity, correlation between predictors of interest remained (ex. disease category and therapeutic modalities). As a result, had another variable selection procedure been used, further valid multivariable models may have been produced. Furthermore, Brain/CNS cancer survivors were excluded from this study as they are seen in a separate multi-disciplinary clinic for brain tumor survivors, as were subjects who transferred to or from the Children's Healthcare of Atlanta system for treatment. As such, this study does not characterize these survivor populations.

Additionally, this study focused entirely on data available from survivor's medical records. We could therefore not assess psychosocial factors (such as health beliefs, understanding of the importance of survivor care, and accurate perception of risk for late effects by the survivor and caregivers) or personal factors that may have made it more difficult for subjects to attend a clinic visit (e.g. physical/cognitive factors that make travel more difficult for the subject, lack of reliable transportation, and scheduling difficulties resulting from caregiver work schedule). Finally, this study concentrated on whether survivors completed an initial survivor healthcare appointment. It did not address repeat clinic attendance, SHP compliance, or late effects outcomes in the context of clinic attendance.

Future Directions

In addition to the demographic, medical, and survivor clinic logistic factors addressed in this study, future studies should address psychosocial and health belief factors related to completion of an initial survivor healthcare appointment to further identify barriers and facilitators to attendance. Future work should also assess the retainment of survivors beyond an initial visit, adherence to SHP guidelines, and late effects outcomes as a result of clinic attendance (or non-attendance). Finally, a similar analysis should be completed to address predictors of attendance at the multi-disciplinary clinic for brain tumor survivors in the Brain/CNS cancer survivor population.

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Section 7: Tables

Table 1. Characteristics of a cohort of childhood cancer survivors eligible for survivor care (N=835)[a]

	Eligible Survivors (n=835)		Seen in Clinic (n=576)		Not Seen in Clinic (n=259)		P Value
	No.	%	No.	%	No.	%	
Demographic Factors							
Gender							0.703
Male	437	52.34	304	69.57	133	30.43	
Female	398	47.66	272	68.34	126	31.66	
Race/Ethnicity							0.001
White, Non Hispanic	420	50.30	313	74.52	107	25.48	
Black, Non Hispanic	236	28.26	138	58.47	98	41.53	
Asian	31	3.71	18	58.06	13	41.94	
Hispanic	120	14.37	90	75.00	30	25.00	
Other/Mixed Race/Unknown	28	3.35	17	60.71	11	39.29	
Medical Factors							
Year of Initial Cancer Diagnosis							<0.001
2007	142	17.01	116	81.69	26	18.31	
2008	129	15.45	109	84.50	20	15.50	
2009	163	19.52	120	73.62	43	26.38	
2010	133	15.93	93	69.92	40	30.08	
2011	106	12.69	70	66.04	36	33.96	
2012	104	12.46	56	53.85	48	46.15	
2013	58	6.95	12	20.69	46	79.31	
Age at Diagnosis (Years)							0.003
0-3	268	32.10	194	72.39	74	27.61	
4-7	157	18.80	115	73.25	42	26.75	
8-11	122	14.61	92	75.41	30	24.59	
12-15	173	20.72	100	57.80	73	42.20	
16+	115	13.77	75	65.22	40	34.78	
Disease Group[b]							<0.001
Leukemia/Lymphoma	472	56.53	370	78.39	102	21.61	
Solid Tumor[c]	363	43.47	206	56.75	157	43.25	
Additional Cancer Event?[d]							0.663
Yes	38	4.55	25	65.79	13	34.21	
No	797	95.45	551	69.13	246	30.87	
Therapeutic Modalities[e]							<0.001
Chemotherapy (No Radiation/BMT)[f]	521	62.40	384	73.70	137	26.30	
Radiation (No Chemotherapy/BMT)[f]	44	5.27	20	45.45	24	54.55	
Chemotherapy & Radiation (No BMT)[f]	159	19.04	110	69.18	49	30.82	
Bone Marrow Transplant[g]	12	1.44	6	50.00	6	50.00	
Other Therapeutic Modality[h]	6	0.72	2	33.33	4	66.67	
Not Reported/Unavailable	93	11.14	54	58.06	39	41.94	
Primary Treating Campus							<0.001
Scottish Rite Hospital	404	48.38	311	76.98	93	23.02	
Egleston Hospital	381	45.63	241	63.25	140	36.75	
Other Facility	50	5.99	24	48.00	26	52.00	

Continued on the Following Page

Table 1. Characteristics of a cohort of childhood cancer survivors eligible for survivor care (continued)[a]

	Eligible Survivors (n=835)		Seen in Clinic (n=576)		Not Seen in Clinic (n=259)		P Value
	No.	%	No.	%	No.	%	
Logistic Factors							
Age at Eligibility (Years)							0.109
<12	446	53.41	318	71.30	128	28.70	
12-17	224	26.83	155	69.20	69	30.80	
18+	165	19.76	103	62.42	62	37.58	
Time Eligible (Years)							<0.001
<1.5 Years	237	28.38	110	46.41	127	53.59	
1.5 Years+	598	71.62	466	77.93	132	22.07	
From a Low Income Area?[i]							0.754
Yes	177	21.20	118	66.67	59	33.33	
No	638	76.41	444	69.59	194	30.41	
Unknown/Unreported	20	2.40	14	70.00	6	30.00	
Distance from Clinic (Miles)[j]							0.139
<10	87	10.42	64	73.56	23	26.44	
10-25	297	35.57	209	70.37	88	29.63	
26-50	224	26.83	161	71.88	63	28.13	
>50	207	24.79	128	61.84	79	38.16	
Unreported	20	2.40	14	70.00	6	30.00	

[a]Subjects must have been diagnosed with Leukemia/Lymphoma or a Solid Tumor at Children's Healthcare of Atlanta between 1/1/2007 and 12/31/2013; be alive and at least 2 years off of cancer therapy and eligible for Survivor Clinic as of 12/31/2015; and have receieved a therapeutic modality besides surgery

[b]Based on initial cancer diagnosis

[c]Bones/soft tissue sarcomas, neuroblastomas, kidney cancers, or other solid tumors (excluding retinoblastomas)

[d]Any recorded relapse, progression, or subsequent malignancy following initial cancer diagnosis

[e]First-line therapy as reported to the cancer registry; BMT=Bone Marrow Transplant

[f]May have also received surgical intervention

[g]May have also received chemotherapy and/or radiation therapy and/or surgical intervention

[h]No chemotherapy, radiation therapy, or bone marrow transplant; may have also received surgical intervention

[i]As defined by Centers for Medicare and Medicaid Services

[j]Distance from clinic based on zip code provided at the time of initial cancer diagnosis

Table 2. Multivariable regression model and adjusted associations between having a completed cancer survivor visit versus no completed visit and predictors for a cohort of childhood cancer survivors eligible for survivor care (N=835)[a]

	Seen (N)	Not Seen (N)	β	X^2	P value	OR	95% Confidence Interval (CI)	
Race/Ethnicity								
White, Non-Hispanic[b]	313	107	-----	-----	-----	-----	-----	-----
Black, Non-Hispanic	138	98	-0.69	11.95	<0.001	0.50	0.34	0.74
Asian	18	13	-0.82	3.59	0.058	0.44	0.19	1.03
Hispanic	90	30	0.02	0.01	0.937	1.02	0.60	1.73
Other/Mixed Race/Unknown	17	11	-0.92	4.22	0.040	0.40	0.17	0.96
Disease Group[c]								
Leukemia/Lymphoma[b]	370	102	-----	-----	-----	-----	-----	-----
Solid Tumor[d]	206	157	-1.02	31.34	<0.001	0.36	0.25	0.51
Therapeutic Modalities[e]								
Chemotherapy (No Radiation/BMT)[b,f]	384	137	-----	-----	-----	-----	-----	-----
Radiation (No Chemotherapy/BMT)[f]	20	24	-1.56	18.37	<0.001	0.21	0.10	0.43
Chemotherapy & Radiation (No BMT)[f]	110	49	-0.07	0.09	0.77	0.93	0.59	1.47
Bone Marrow Transplant[g]	6	6	-0.48	0.51	0.48	0.62	0.16	2.33
Other Therapeutic Modality[h]	2	4	-2.33	6.06	0.01	0.10	0.02	0.62
Not Reported/Unavailable	54	39	-0.29	0.96	0.33	0.75	0.42	1.34
Primary Treating Campus								
Scottish Rite Hospital[b]	311	93	-----	-----	-----	-----	-----	-----
Egleston Hospital	241	140	-0.87	21.95	<0.001	0.42	0.29	0.60
Other Facility	24	26	-1.07	7.61	<0.001	0.34	0.16	0.73
Time Eligible (Years)								
<1.5 Years[b]	110	127	-----	-----	-----	-----	-----	-----
1.5 Years+	466	132	1.78	88.10	<0.001	5.95	4.10	8.64

[a]Subjects must have been diagnosed with Leukemia/Lymphoma or a Solid Tumor at Children's Healthcare of Atlanta between 1/1/2007 and 12/31/2013; be alive and at least 2 years off of cancer therapy and eligible for Survivor Clinic as of 12/31/2015; and have receieved a therapeutic modality besides surgery

[b]Reference group

[c]Based on initial cancer diagnosis

[d]Bones/soft tissue sarcomas, neuroblastomas, kidney cancers, or other solid tumors (excluding retinoblastomas)

[e]First-line therapy as reported to the cancer registry; BMT=Bone Marrow Transplant

[f]May have also received surgical intervention

[g]May have also received chemotherapy and/or radiation therapy and/or surgical intervention

[h]No chemotherapy, radiation therapy, or bone marrow transplant; may have also received surgical intervention

Table 3. Select characteristics of a cohort of childhood cancer survivors not diagnosed with leukemia/lymphoma or a solid tumor, or who received only surgical intervention as part of their first-line of therapy (N=163)[a]

	Retinoblastoma (n=20)[b]		Other Hematopoietic Disease[bc] (n=18)		Surgery Only (n=125)	
	No.	%	No.	%	No.	%
Seen In Clinic						
Yes	4	20.00	9	50.00	6	4.80
No	16	80.00	9	50.00	119	95.20
Gender						
Male	10	50.00	9	50.00	68	54.40
Female	10	50.00	9	50.00	57	45.60
Race/Ethnicity						
White, Non Hispanic	12	60.00	8	44.44	69	55.20
Black, Non Hispanic	6	30.00	4	22.22	30	24.00
Asian	1	5.00	0	0.00	5	4.00
Hispanic	1	5.00	3	16.67	14	11.20
Other/Unknown	0	0.00	3	16.67	7	5.60
Age at Diagnosis (Years)						
0-3	20	100.00	7	38.89	50	40.00
4-7	0	0.00	6	33.33	13	10.40
8-11	0	0.00	0	0.00	22	17.60
12-15	0	0.00	3	16.67	26	20.80
16+	0	0.00	2	11.11	14	11.20
Disease Category[d]						
Bone/Soft Tissue Sarcoma	---	---	---	---	23	18.40
Kidney	---	---	---	---	5	4.00
Leukemia	---	---	---	---	0	0.00
Lymphoma	---	---	---	---	6	4.80
Neuroblastoma	---	---	---	---	16	12.80
Other Hematopoietic Disease	---	---	---	---	12	9.60
Other Solid Tumor	---	---	---	---	43	34.40
Retinoblastoma	---	---	---	---	20	16.00
Therapeutic Modalities[e]						
Chemotherapy (No Radiation/BMT)[f]	19	95.00	8	44.44	---	---
Chemotherapy & Radiation (No BMT)[f]	0	0.00	2	11.11	---	---
Not Reported/Unavailable	1	5.00	8	44.44	---	---
Primary Treating Campus						
Scottish Rite Hospital	19	95.00	5	27.78	56	44.80
Egleston Hospital	1	5.00	3	16.67	48	38.40
Other Facility	0	0.00	10	55.56	21	16.80
Time Eligible (Years)						
<1.5 Years	3	15.00	9	50.00	31	24.80
1.5 Years+	17	85.00	9	50.00	94	75.20

[a]Patients must have been diagnosed with a non-brain/central nervous system cancer (other than leukemia/kymphoma or a solid tumor) between 1/1/2007 and 12/31/2013; be alive and at least 2 years off of cancer therapy and eligible for survivor clinic as of 12/31/2015

[b]Excluding those who receieved only surgical interention as part of their first-line treatment

[c]Including: Langerhans cell histocytosis, Mast cell sarcoma, Mycosis fungoides, Polythemia vera, Refractory anemia

[d]Disease category based on initial cancer diagnosis

[e]First-line therapy as reported to the cancer registry; BMT=Bone Marrow Transplant

[f]May have also received surgical intervention

Section 8: Figures and Figure Legends

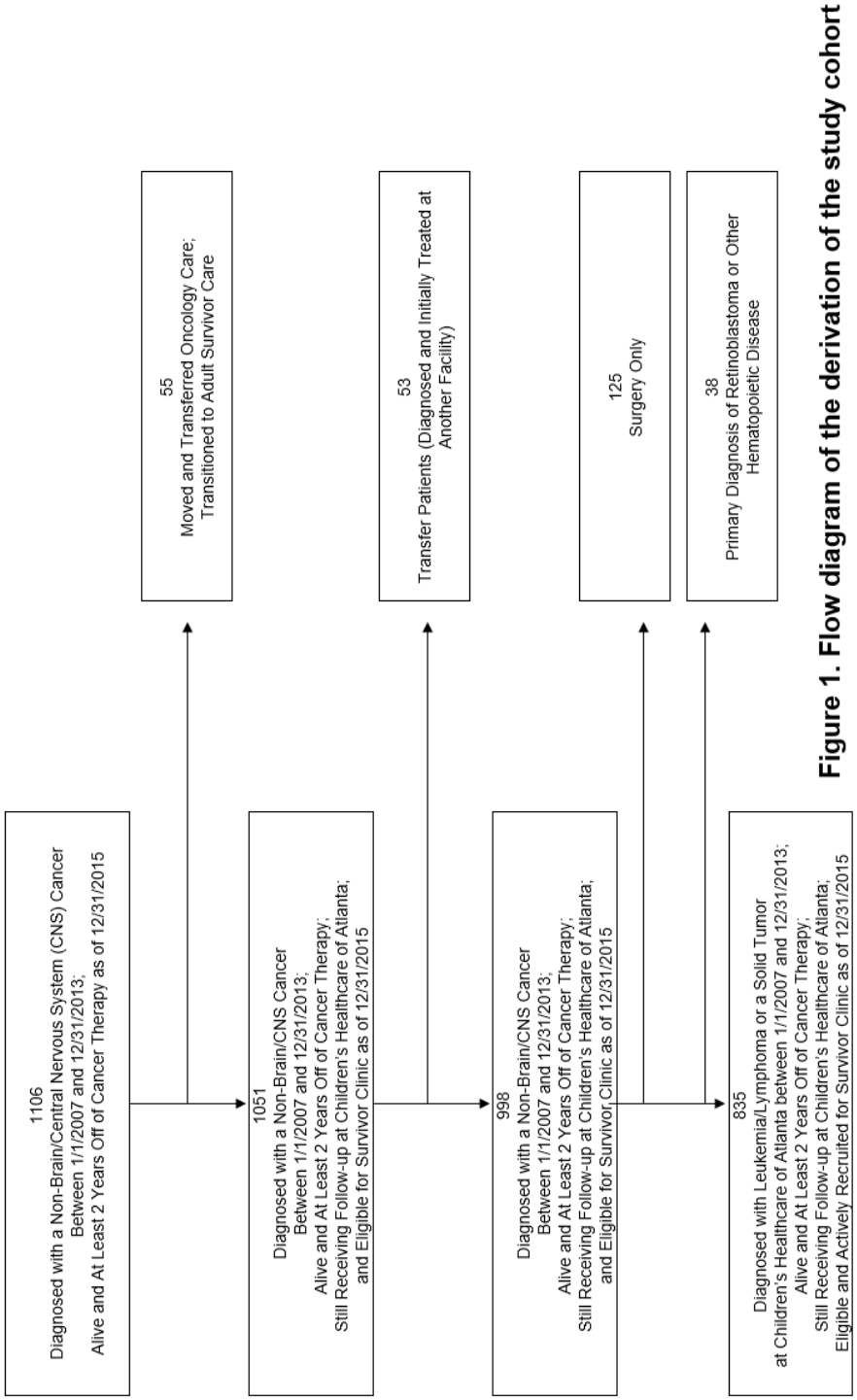

Figure 1. Flow diagram of the derivation of the study cohort

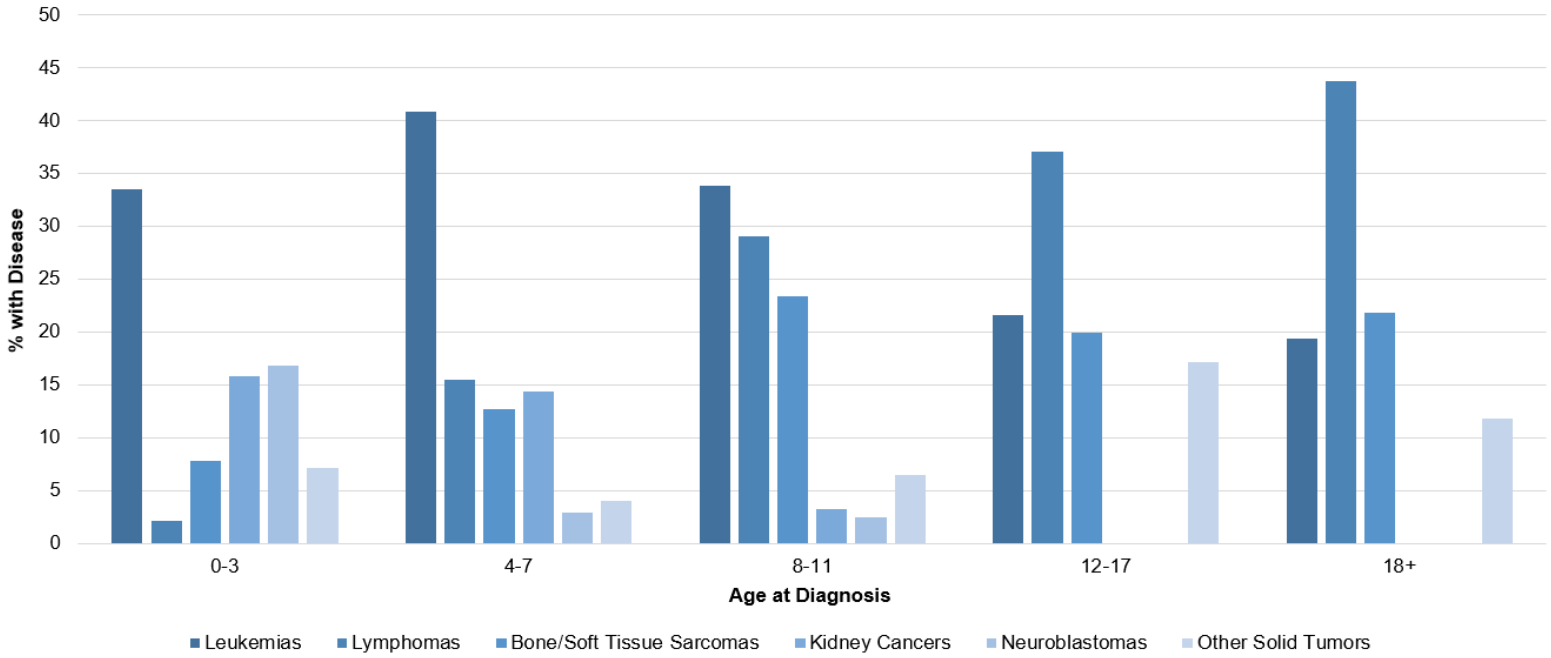

Figure 2. Variations in primary diagnosis by age at diagnosis for a cohort of childhood cancer survivors eligible for survivor care (N=835). Leukemia is the most common diagnosis for eligible survivors age 0-11 at diagnosis, while for older subjects (12+) it is lymphoma. Neuroblastoma and kidney cancers are the second and third most common types of cancer for survivors age 0-3 at diagnosis, but are entirely absent from subjects older than 12. Bone/soft tissue sarcomas and other solid tumors, meanwhile, make up a large percentage of cancers for older survivors, while they are less common in subjects younger than 8.

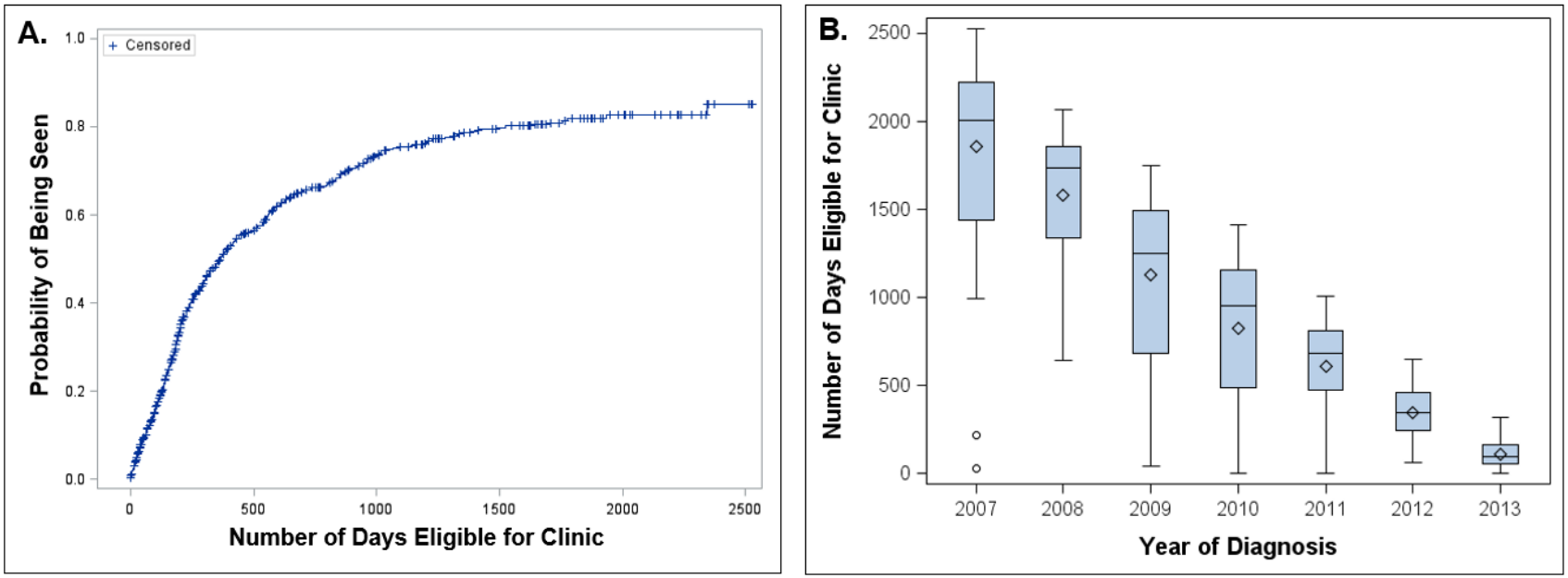

Figure 3. (A.) Kaplan-Meier failure curve representing the probability of having a completed initial survivor clinic visit by time eligible for clinic (days); and (B.) the time eligible for clinic in days by year of diagnosis for a cohort of childhood cancer survivors eligible for survivor care (N=835). The probability of having completed an initial survivor clinic visit appears to increase as the number of days eligible for clinic increases. The steepest increase is seen within the first two years of becoming eligible. Meanwhile, there is evidence to suggest that the mean number of days eligible for clinic is different by year of diagnosis (overall F test p-value <0.001), with the time eligible decreasing by year of diagnosis. These trends suggest that the decrease in percentage of survivors seen by year of diagnosis may primarily be due to reductions in time eligible for clinic.

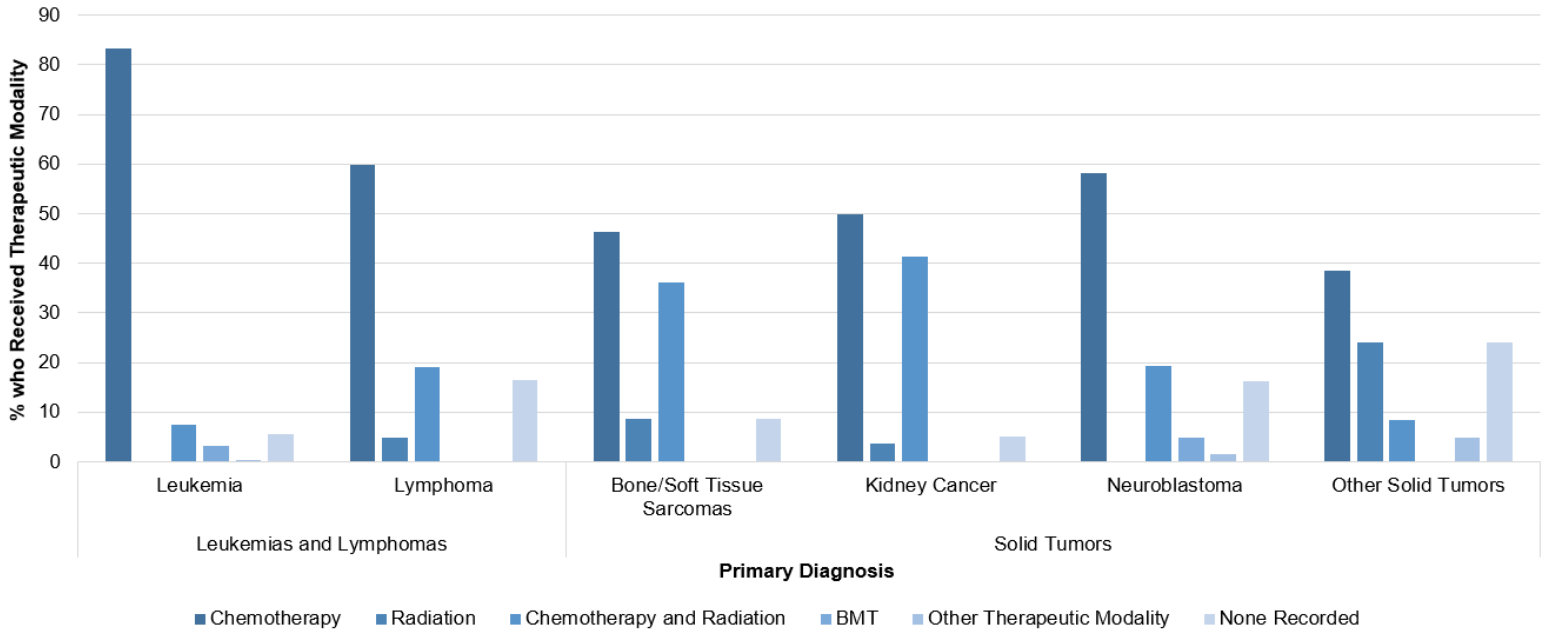

Figure 4. Variations in therapeutic modality history (as reported to the cancer registry) by primary diagnosis for a cohort of childhood cancer survivors eligible for survivor care (N=835). Patients may have also received surgical intervention. BMT=bone marrow transplant. BMT patients may have also received chemotherapy and/or radiation therapy. Other therapeutic modality patients had no recorded chemotherapy, radiation therapy, or bone marrow transplant. Chemotherapy alone is the most common first-line therapy for all eligible patients, regardless of diagnosis. Receiving radiation, whether alone or as part of a combination with chemotherapy, appears to be more common for solid tumor patients. Patients who received BMTs almost exclusively had a diagnosis of Leukemia.