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Outcomes of Cancer Treatment for Rare Pediatric Tumors in an Adolescent and Young Adult (AYA) Population in the State of Georgia

By

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# Outcomes of Cancer Treatment for Rare Pediatric Tumors in an Adolescent and Young Adult (AYA) Population in the State of Georgia

By

Thomas Cash

B.S., Auburn University, 2002

M.D., University of Alabama School of Medicine, 2007

Advisor: Ann Mertens, Ph.D.

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A thesis submitted to the Faculty of the James T. Laney School of Graduate Studies of Emory University

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Abstract

Outcomes of Cancer Treatment for Rare Pediatric Tumors in an Adolescent and Young Adult (AYA) Population in the State of Georgia

By Thomas Cash

Adolescent and young adult (AYA) patients with cancer have not experienced the same improvement in survival as that seen in younger or older patients. Part of the challenge in managing these patients is deciding where and how they should be treated for their malignancy. This is especially difficult for patients in late adolescence or very early adulthood (15-21 years) who have an adult-type malignancy, such as a carcinoma or a melanoma, which is rarely seen in pediatrics. We performed a retrospective analysis using the Georgia Cancer Registry (GCR) of 15-21-year-old patients with a malignant, rare pediatric tumor diagnosed during the 10 year period from 2000-2009. Patients were identified as being treated at one of five Georgia pediatric cancer centers or at an adult center. Data were analyzed for 10-year overall survival, patient characteristics associated with death, and characteristics present at diagnosis that influenced the choice of treatment center. There was a total of 479 patients in our final study population, of which 379(79.1%) were treated at an adult center and 100(20.9%) were treated at a pediatric center. Patients treated at an adult center had a 10-year overall survival of 86% compared to 85% for patients treated at a pediatric center (log-rank p-value= 0.31). Patients with thyroid carcinoma had a decreased hazard ratio (HR) for death compared to those with melanoma (HR=0.052; 95% CI=0.007-0.409). Patients with regional (HR=4.660; 95% CI=2.065-10.516) and distant (HR=20.967; 95% CI=7.728-56.891) stage disease were more likely to die than those with local stage disease. Race and poverty status were not significantly associated with death. Older (19-21 years) patients were less likely to be treated at a pediatric center (OR=0.219; 95% CI=0.129-0.371). Those with nasopharyngeal (OR=7.384; 95% CI=2.295-23.754) and other (OR=2.643; 95% CI=1.248-5.598) carcinomas were more likely to be treated at a pediatric center. Patients with distant stage (OR=4.242; 95% CI=1.710-10.520) and higher poverty (OR=2.316; 95% CI=1.229-4.365) were also more likely to be treated at a pediatric center. Our data suggests that there is no difference in survival for 15-21 year old patients with rare pediatric tumors when treated at an adult or a pediatric center.

# Outcomes of Cancer Treatment for Rare Pediatric Tumors in an Adolescent and Young Adult (AYA) Population in the State of Georgia

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# INTRODUCTION

The adolescent and young adult (AYA) population has been given many age-range definitions, but the one used most commonly for oncology patients is 15-29 years of age. Because this age range does not fall completely within an adult or pediatric age group, they have in many ways been a neglected population prior to the last decade. Because of the lack of focus given to this group the survival rates for AYA oncology patients have not kept pace with the improvements seen in either the younger or older-aged populations. Part of the challenge in managing these patients is deciding where and how they should be treated for their malignancy. There is strong evidence to show that patients in this 15-21 year old age range who have pediatric-type malignancies, such as ALL, Ewing sarcoma, and medulloblastoma, have better survival rates when treated at pediatric centers on pediatric treatment protocols. Conversely, it has been hypothesized that the same aged patients with adult-type malignancies, carcinomas and melanomas, may have better survival rates at adult centers, although this has never been proven. These adult-type malignancies are considered to be rare tumors in the pediatric population.

A second challenge in the AYA population is a lack of participation in prospective clinical trials, and multiple authors have cited this as the single most important factor that has prohibited the improvement in survival for AYA patients. It has been shown that clinical trial participation decreases with increasing age (1). For example, around 70-80% of those < 15 years of age are treated on clinical trials, compared to only 10% of those who are 15-19 years of age, and this number falls even lower for those 20-29 years of age (1). Studies also show that clinical trial participation decreases the rarer the tumor

histology (2,3), and AYA patients with rare pediatric tumors would certainly fall into this category. When one considers that AYA patients with these rare pediatric tumors are a population that does not participate in clinical trials because of both their age and their diagnosis, it becomes easy to understand why survival rates have not improved for this patient population. These challenges in studying AYA patients with rare pediatric tumors emphasize the need for good observational data in this patient population. This data would allow for the identification of the center where these patients can achieve their best clinical outcomes. Then, once identified, research efforts could be focused on this center with the ultimate goal of improving the survival disparity seen in this patient population.

The Georgia Cancer Registry (GCR) is a statewide population-based cancer registry. It offers the unique opportunity to study uncommon malignancies such as rare pediatric tumors. The purpose of our study was to test the hypothesis that the center (adult vs. pediatric) where 15-21 year old patients with rare pediatric tumors are treated affects their survival, and this effect is mediated in part through differences in their treatment. In order to test this hypothesis we utilized the GCR to identify the factors present at diagnosis that influence whether 15-21 year old patients with rare pediatric tumors receive treatment at an adult or pediatric center, to determine the effect of treatment center on therapy received, and to determine the effect of treatment center on survival.

# BACKGROUND

Adolescent and young adult (AYA) patients with cancer have not experienced the same improvement in survival as that seen in younger or older patients. This failure to improve survival has occurred during a time when the incidence of cancer has increased faster in this age group than in any other time of life (1).The discrepancy in survival, often referred to as the "AYA Gap," has occurred in part due to the lack of recognition of this population as a distinct specialty that requires focused attention to the unique biology of its malignancies and to its psychosocial and supportive care needs. AYA patients have not received the focus of either researchers or clinicians, whether that is pediatric or adult. Part of the challenge in treating AYA patients is deciding where and how they should be treated for their malignancy. This is difficult for the entire 15-29 year old AYA population, but becomes even more challenging for the subset of AYA patients that are 15-21 years of age, because they truly could be treated at either a pediatric or adult center. Currently the majority (64%) of patients with cancer in the 15-19 year old age range are treated at adult centers (4). The evidence suggests that patients with pediatric-type malignancies such as ALL (5,6), Hodgkin and non-Hodgkin Lymphoma (7), Ewing sarcoma (8), and rhabdomyosarcoma (9) have better outcomes if they are treated at pediatric centers on pediatric treatment protocols. Conversely, it has been theorized that AYA patients with adult-type malignancies, such as carcinomas and melanomas, may have better outcomes at adult centers, since these types of malignancies are more commonly seen in adults, although this has never been proven. Data from Howell et al (10) did show a trend for better survival for 15-19 year old carcinoma patients when they were treated at adult centers, although their numbers were too small to show statistical

significance. Due to the lack of survival improvement for this population of patients, it is critical to know where they can achieve their best clinical outcomes in order to maximize treatment strategies.

It has been stated that the single factor that correlates most highly with the AYA Gap is lack of participation in clinical trials (1). In pediatric oncology nearly all the advancements in survival that have been made have come through patients being treated at comprehensive cancer centers on cooperative group clinical trials. Participation in these trials is excellent for patients less than 15 years of age, with more than 90% being managed at institutions that participate in NCI-sponsored clinical trials with 70-80% being treated on clinical trials (11). In contrast, only around 20% of patients who are 15-19 years of age are treated at such institutions, and only 10% of patients in this age group participate in clinical trials (1). The numbers are even worse among 20-29 year olds, where only 10% are treated at institutions that are members of either adult or pediatric cooperative groups, and only 1% participates in either adult or pediatric cooperative group trials (1). Poor enrollment on clinical trials is even more noticeable among AYA patients with rare pediatric tumors. A recent study from the Infrequent Tumor Committee of the Children's Oncology Group (COG) demonstrated a marked reduction in registration for their clinical trials in patients 15-19 years of age compared to those less than 15 years, and for those who had a rare pediatric tumor histology, such as those seen more commonly in adults (2). This observation has also been supported by other investigators (3). The reason for low clinical trial enrollment for rare pediatric tumors may be in part due to the lack of available clinical trials for these malignancies, but there is data that shows low registration rates on COG tumor registries, suggesting that these

patients aren't being seen at pediatric centers where these trials would potentially be available (2).

Much speculation has been made as to what patient characteristics might influence whether a patient in the 15-21 year old age range is treated at an adult or pediatric center. Proposed factors include socioeconomic status, treatment, distance needed to travel to a particular center (adult or pediatric), insurance status, access to healthcare, and provider referral practices and knowledge of available clinical trials. While many of these reasons are intuitive, few have been adequately described in an objective manner for AYA patients with these rare tumors. Once the treatment center that has the better survival rate is identified, a better understanding of the characteristics of patients treated at the preferred center will allow for more targeted recruitment efforts for available clinical trials. Increased participation in clinical trials is critical if any progress is to be made in closing the AYA gap.

# METHODS

## Hypothesis

The center (adult vs. pediatric) where 15-21 year old patients with rare pediatric tumors are treated affects their survival, and this effect is mediated in part through differences in their treatment.

## Specific Aims

The specific aims of this study were 1) to identify the factors present at diagnosis that influence whether 15-21 year old patients with rare pediatric tumors receive treatment at an adult or pediatric center, 2) to determine the effect of treatment center on therapy received for 15-21 year old patients with rare pediatric tumors, and 3) to determine the effect of treatment center on survival for 15-21 year old patients with rare pediatric tumors.

## Study Design and Data Source

This is a retrospective cohort study performed with data collected from the Georgia Cancer Registry. The Georgia Cancer Registry (GCR) is a statewide population-based cancer registry collecting all cancer cases diagnosed among Georgia residents since January 1, 1995. It is a participant in the National Program of Cancer Registries (NPCR), the North American Association of Central Cancer Registries (NAACCR), and became a statewide SEER Registry in 2010 contributing diagnoses dating back to 2000. The incident capture rate for the GCR has been reported to be 98% or greater for patients 0 to 19 years of age (10).

Characteristics of the Study Population

Patients included in the study were those aged 15-21 years with a malignant, rare pediatric tumor diagnosed during the 10 year period from 2000-2009. All patients who did not fit this description were excluded. Defining rare tumors in pediatrics is difficult considering that pediatric cancer as a whole is a rare disease with only 12,400 new cases diagnosed yearly in the United States in patients under age 20 years (15). In our study, we defined rare pediatric tumors as those malignancies that are classified as 'Other Malignant Epithelial Neoplasms and Melanomas' in the International Classification of Childhood Cancer (ICCC) subgroup XI of the SEER database (2, 16).

Data Collected and Explanation of Variables

The data collected from the GCR included tumor histology, behavior, grade, stage, primary site, laterality, and sequence; sex, race, ethnicity, age at diagnosis, diagnosis year, type of treatment (radiation, surgery, chemotherapy, combined, or none), treatment center (adult vs. pediatric), distance to the closest pediatric center, poverty status, date of last contact, and survival status.

Patients were divided into two age groups comprised of a young (15-18 years) and an old (19-21 years) group. Race and ethnicity data were combined into a single race variable with four groups: non-Hispanic white, black, Hispanic white, and other. Patients were divided into the four diagnosis groups of melanoma, thyroid carcinoma, nasopharyngeal carcinoma, and other carcinomas. The tumor stage variable used was a summary staging variable available in the GCR that divides patients into those with local,

regional, and distant stage disease. The primary site data collected from the GCR was consolidated into the organ system-based primary site locations of head and neck, gastrointestinal (GI), lung, skin, genitourinary (GU), thyroid, and other.

Patients in our study were identified as being treated at either an adult or pediatric center. The five hospitals designated as pediatric treatment centers were Children's Healthcare of Atlanta, The Children's Hospital at Memorial University Medical Center in Savannah, Medical College of Georgia (MCG) Health Children's Medical Center in Augusta, The Children's Hospital at The Medical Center of Central Georgia in Macon, and Columbus Regional Healthcare System in Columbus. If patients were diagnosed or ever treated at one of the five pediatric centers, then they were designated as being treated at a pediatric center, otherwise they were designated as being treated at an adult center. Data on the specific center the patients were treated at was not released from the registry.

Socioeconomic status was assessed by obtaining information about economic poverty. Studies have shown that poverty status is the most robust area-based measure to detect socioeconomic inequalities in cancer incidence and mortality (15). Patients in the GCR are geocoded to the block group level based on their address at the time of diagnosis. Each patient in our study was linked by their geocode to 2000 U.S. Census data to determine the percentage of people in their geocode that lived below the poverty line. All patients in our study were then grouped into one of four categories, those living in a geocode where 1) $< 5\%$, 2) $\geq 5\%$ but $< 10\%$, 3) $\geq 10$ but $< 20\%$, or 4) $\geq 20\%$ were living below the federal poverty line. An area where $\geq 20\%$ live below the poverty line is considered a federal poverty area. We then categorized the patients in our study into a low poverty group (groups 1-3 above) and a high poverty group (group 4 above).

The effect of distance in our analysis was tested by calculating the distance that each patient lived from the closest pediatric center. We obtained the latitude and longitude coordinates for each patient's home address at the time of their diagnosis as well as the latitude and longitude coordinates for each pediatric center, and then calculated the distance to all five centers for every patient. Then we selected the distance to the closest pediatric center for each patient and used this distance in our analysis. For patients who were actually treated at a pediatric center, this was not necessarily the actual pediatric center where they received treatment. Since knowledge of the exact treatment center constitutes a patient identifier we were not able to obtain this information from the GCR. In our analysis we categorized the distance needed to travel to the closest pediatric center into three groups: 1) $\leq$ 25 miles, 2) > 25 but $\leq$ 50 miles, and 3) > 50 miles.

Statistical Analysis

To analyze specific aim 1, we first compared the distribution of factors present at diagnosis for patients treated at an adult or pediatric center by using a chi-square or Fisher's exact test for categorical variables and a 2-sample t-test for continuous variables. Factors compared in this analysis included treatment center, age group, race, gender, diagnosis, stage, primary site, poverty group, and distance group. Multivariate logistic regression was performed to identify patient characteristics present at diagnosis that were associated with treatment center, while controlling for other covariates. The outcome for this analysis was treatment at a pediatric center.

To analyze specific aim 2, we first divided all the patients up by diagnosis and then compared how their treatments differed by treatment center (adult vs. pediatric) by using a chi-square or Fisher's exact test.

To analyze specific aim 3, we performed a Kaplan-Meier analysis to determine the effect of treatment center on survival. Also, a multivariate analysis was performed using a cox proportional hazards model to determine the association between 10-year overall survival and treatment center, while controlling for other covariates. Since we wanted to assess the effect of treatment, we did not control for this in our model. The outcome of interest was death from any cause.

## Human Subjects Protection

In accordance and compliance with federal and institutional guidelines for conducting research, approval for this study was obtained from the institutional review board (IRB) at the Georgia Department of Public Health and Emory University. A Health Insurance Portability and Accountability Act (HIPAA) waiver was obtained from the IRB.

# RESULTS

## Study Participants

Our initial cohort contained 10, 781 patients who were diagnosed with cancer between the ages of 0-29 years from 2000-2009 in the state of Georgia. Applying our age criteria, we excluded 8,563 patients, leaving us with 2,218 between the ages of 15-21 years (Figure I). Next we limited our cohort to only rare pediatric tumors, excluding 1,594, and leaving us with 624 patients. Lastly, we included only those whose tumors had malignant behavior, which left us with a final study population of 479 patients. Of these 479, there were 171 (35.7%) melanomas, 157 (32.8%) thyroid carcinomas, 126 (26.3%) other carcinomas, and 25 (5.2%) nasopharyngeal carcinomas (Figure II).

## Factors present at diagnosis that influence treatment center

Patient characteristics present at diagnosis were compared by treatment center (adult vs. pediatric) (Table 1). In all there were 379 (79.1%) patients treated at an adult center and 100 patients (20.9%) treated at a pediatric center. There were significant differences between treatment center groups for the baseline demographic factors of age, race, and gender. The median age for patients treated at adult centers was 18.9 years compared to 17.5 years for pediatric centers ($p = < 0.0001$), and accordingly, a higher percentage of patients treated at adult centers were in the older age group (63.6%), whereas a higher percentage of patients treated at pediatric centers were in the younger age group (68.0%) ($p = < 0.0001$). For race, there was a higher percentage of non-Hispanic white patients treated at adult centers (75.5% vs. 65.0%), but a higher percentage of black patients

treated at pediatric centers (14.8% vs. 30.0%) (p= 0.0107). Lastly for gender, 71.2% of the patients treated at adult centers were female compared to only 59.0% at pediatric centers (p= 0.0189).

There were significant differences in treatment center groups in regards to the tumor-related factors of diagnosis, stage, and primary site. The percentage of patients with thyroid carcinoma was roughly equivalent between adult (32.5%) and pediatric (34.0%) centers, however there were higher percentages of patients with nasopharyngeal (2.9% vs. 14.0%) and other (24.5% vs. 33.5%) carcinomas treated at pediatric centers, and a higher percentage of melanoma patients treated at adult centers (40.1% vs. 19.0%) (p= < 0.0001). There was a higher percentage of regional (25.3% vs. 34.0%) and distant (4.0% vs. 17.0%) stage patients treated at pediatric centers (p= < 0.0001). Comparison of treatment center groups according to primary site revealed that there was a higher percentage of all primary sites at pediatric centers with the exception of skin primaries for which there was a higher proportion treated at adult centers, and thyroid primaries for which there was no discernible difference.

There were no significant differences between treatment center groups for poverty status or distance to the closet pediatric center. The proportion of patients in the high poverty group was 31% at pediatric centers and 20.1% at adult centers, but this did not quite meet statistical significance (p= 0.0626). The average distance to the closest pediatric center was 38.1 miles for patients treated at adult centers and 33.8 miles for patients treated at pediatric centers (p= 0.2420).

Those factors that were significantly associated with treatment at a pediatric center included age, diagnosis, stage, and poverty (Table II). Patients in the older age group

were less likely to be treated at a pediatric center compared to patients in the younger age group [odds ratio=0.219 (95% confidence interval= 0.129-0.371)]. Patients with both nasopharyngeal carcinoma and one of the other carcinomas were more likely to be treated at a pediatric center than those with melanoma, but patients with thyroid carcinoma were not. Patients with distant stage disease had an increase odds ratio of 4.242 (95% confidence interval = 1.710 – 10.520) of being treated at a pediatric center compared to patients with local stage disease.

Neither race nor distance to the closest pediatric center showed a significant association to be being treated at a pediatric center, but poverty status did. Specifically those in the high poverty group had an odds ratio of 2.316 (95% confidence interval = 1.229 – 4.365) compared to those in the low poverty group. The following interaction terms were tested, but all were non-significant and did not contribute to the model: poverty-race, poverty-distance, age-stage, age-diagnosis, sex-diagnosis, diagnosis-stage, and race-stage.

The effect of center on treatment received

Diagnoses where the treatments differed by center were thyroid and nasopharyngeal carcinoma, but there was no significant differences seen for patients with melanomas and other carcinomas (Table III). An equal proportion of patients with thyroid carcinoma received surgery at both adult (96.8%) and pediatric (97.1%) centers (p= 1.00), but a significantly higher proportion of patients received radiation (61.0 vs. 82.4, p=0.0202) and combined therapy (61.0 vs. 82.4, p=0.0202) at pediatric centers. For patients with nasopharyngeal carcinoma (NPC), all 14 (100.0%) of the patients treated at pediatric

centers received chemotherapy compared to only (63.6%) at adult centers (p= 0.0261). For patients with NPC treated at pediatric centers, a higher proportion received radiation (81.8% vs. 100%) whereas a lower proportion received surgery (54.6% vs. 14.3%), but neither quite met significance. The treatment for the vast majority of patients with melanoma was surgery alone, and this was true for both treatment centers (98.7% vs. 94.7%; p= 0.2992). For patients with other carcinomas, in general there were higher proportions of patients who received chemotherapy, radiation, and combined therapy at pediatric centers compared to a higher proportion of patients receiving surgery at adult centers, but none of these differences were significant.

The effect of treatment center on survival

There was no difference in 10-year overall survival for patients treated at adult (86%) versus pediatric (85%) centers (log rank p-value= 0.3056) (Figure III). Factors significantly associated with death included diagnosis and stage, but not treatment center, age, race, distance, or poverty (Table IV). For diagnosis, patients with thyroid carcinoma had a hazard ratio for death of 0.052 (95% confidence interval= 0.007-0.409) compared to those with melanoma, while those with nasopharyngeal and other carcinomas showed no significant association with death. Patients with both regional [hazard ratio=4.660 (95% confidence interval= 2.065-10.516)] and distant [hazard ratio=20.967 (95% confidence interval= 7.728-56.891)] stage had an increased hazard ratio compared to those with local stage disease (p= < 0.0001). The hazard ratio for pediatric treatment center compared to those treated at an adult center was 0.834 (95% confidence interval=

0.362-1.923). Testing for interaction was performed between treatment center and all other covariates, however none were significant.

# DISCUSSION

These results suggest that treatment center (adult or pediatric) does not affect survival for 15-21 year old patients with rare pediatric tumors. The 10-year overall survival was almost identical for both centers with 86% survival at adult centers and 85% survival at pediatric centers. This is particularly interesting considering there were a significantly higher proportion of patients with regional and distant stage disease treated at pediatric centers. However, after controlling for stage in our multivariate survival analysis, treatment center was not associated with survival at 10 years. This is different than what is seen for pediatric-type malignancies in this age group, where there is evidence to support that patients have better treatment outcomes when treated at pediatric centers on pediatric treatment protocols (5-9).

Patient characteristics that were associated with survival include diagnosis and stage of disease. Specifically, higher stage was associated with death, while having thyroid carcinoma was associated with survival when compared to patients with melanoma. Notably race and poverty were not associated with worse outcomes in our study. This is in contrast to previous reports that show worse outcomes for most pediatric cancers in those who are black or Hispanic, as well as for those with lower socioeconomic status (SES) (17-20).

Almost 80% of the patients in our study were treated at adult centers. This is higher than previous reports showing that about 2/3 of all AYA oncology patients are treated at adult centers. This number could be higher in our study due to the fact that these malignancies are adult-type tumors, but also because there are many more adult oncology centers in the state of Georgia than the five pediatric oncology centers we included. Also,

there was a large disparity in melanoma diagnoses between treatment centers, with the larger proportion being seen at adult centers. As supported by our data, the treatment for the majority of melanoma patients is surgery alone. This is due to the fact that most have local stage disease, 138/171 (81%) in our study, that many times can be excised in clinic or through a minor procedure. In clinical practice, experience shows that when melanoma patients are seen by pediatric oncologists, they usually have higher stage disease that requires chemotherapy in addition to surgery. This is supported by the data in our study that shows that 83% of the melanoma patients treated at adult centers had local stage disease compared to only 63% of those treated at pediatric centers ($p= 0.0429$). Because local excision is the definitive treatment for most of these patients and due to the easy accessibility of adult surgeons compared to pediatric, many of these patients are seen at adult centers for their procedure and then never require any further therapy.

As might have been expected, patients treated at adult centers were significantly older than those treated at pediatric centers. An older adolescent or young adult patient may not want to be treated at a pediatric center because socially they would prefer to be treated as an adult. Interestingly for race, there was a higher proportion of black patients treated at pediatric centers (30%) compared to adult (14.8%). We propose that this is due to pediatric oncology centers being more likely to accept a given patient regardless of their insurance status. This is supported by evidence showing an association between minorities and lower SES, as well as our clinical practice. There were a higher proportion of females at both treatment centers, but significantly more at the adult centers. The incidence for this entire group of rare tumors is higher in females than males, but most notably is the 4-fold higher incidence rate for thyroid carcinoma in females than males

(21). Patients treated at pediatric centers had a higher proportion of patients with both regional and distant stage disease. This is consistent with what is seen in practice as well as what has been reported in the literature for this population of patients (10).

In our multivariate analysis, age, stage, diagnosis, and poverty status were the factors present at diagnosis that influenced treatment center. Patients in the older age group were less likely to be treated at a pediatric center. Controlling for age and the other covariates, patients with higher-stage disease were still more likely to be treated at a pediatric center. Contrary to what we hypothesized, distance did not significantly influence treatment center, but poverty did. Patients in the high poverty group were significantly more likely to be treated at a pediatric center. No interaction was found between distance and poverty, suggesting that patients with high poverty were more likely to be treated at pediatric centers regardless of distance needed to travel.

We stratified the patients by diagnosis and then analyzed the treatment they received at their respective treatment center. For patients with thyroid carcinoma, a roughly equal proportion of patients received surgery between treatment centers, but a higher proportion of patients treated at pediatric centers received radiation and therefor combination therapy. We believe this is due to patients presenting with higher stage disease requiring more aggressive therapy. A significantly higher proportion of patients with nasopharyngeal carcinoma (NPC) treated at pediatric centers received chemotherapy, and a higher proportion received radiation, but this was not statistically significant. Conversely, a higher proportion of NPC patients treated at adult centers received surgery, but this also did not quite reach significance. We hypothesized that these results for NPC patients are indicative of pediatric surgeons being less likely to perform aggressive

surgeries compared to adult surgeons, and also due to the fact that patients treated at pediatric centers are likely to be present with more advance stage disease that requires combination therapy to obtain disease control. The mainstay of treatment for patients with melanomas is surgery alone regardless of treatment center, and this is the most likely explanation for why no treatment differences were seen for this diagnosis. Lastly, no treatment differences were seen for other carcinoma patients. This is likely attributable to the heterogeneous nature of the diagnoses included in this diagnosis group.

Our study comprises a large sample size of rare pediatric tumors. An additional feature of our study is the comprehensive list of rare pediatric tumor diagnoses, which is notable considering that most other reports on rare tumors focus only on one cancer diagnosis. The Georgia Cancer Registry has been recognized for its quality and completeness, and so it provided a reliable database to perform our study. One unique feature of our study was our ability to identify the type of treatment center (adult vs. pediatric) for each individual patient, and to perform meaningful analysis based on this information. Another strength of this study is the information obtained about poverty status. Geocoding has been shown to provide more homogenous and accurate groupings than other area-based measures (15). Our ability to link each patient's geocode to the 2000 census data provided a close representation of each individual's overall socioeconomic status. Distance has been proposed in many studies as a barrier to receiving treatment at specialized centers, including pediatric oncology centers. Our study is the first to measure this in an objective way for AYA patients.

Our study was limited by not knowing the exact pediatric treatment center for those patients who were treated at a pediatric facility. Since this information might allow for

patient identification it could not be released by the GCR, so we made the assumption that the pediatric center closest to the patient was the likely treating center. We also had to assume that those patients who were designated as treated at a pediatric center were actually treated by a pediatric oncologist, which should have been the case for most if not all patients. It is also possible that patients diagnosed in Georgia actually received treatment in another state, or that patients living near state lines went to a bordering state for their diagnosis and treatment; however, given the regularly scheduled data-share agreements between state cancer registries, the effect of this bias is thought to be very small. Another limiting factor is that this is an observational study, which makes it susceptible to unmeasured confounders. There is data to show that there is underreporting both for patient diagnoses and treatment in SEER registries, and so this could have affected the accuracy of our data (22, 23). Also, we were limited by the lack of specific treatment details available in the GCR, such as the chemotherapeutic agent, dose, and schedule used.

In conclusion, our findings suggest that there is no difference in survival for 15-21 year-old patients with rare pediatric tumors when treated at adult or pediatric centers. To our knowledge this is the largest study comparing survival by treatment center in this study population. While larger numbers may eventually show a survival difference, this would be very challenging given the overall excellent survival for patients with these diagnoses. The implication of our study since no treatment center seems to produce superior survival is that oncologists at pediatric and adult centers need to collaborate to perform clinic trials and to standardize treatment protocols for these patients. The Adolescent and Young Adult Initiative of the Children's Oncology Group has been

established as a means to increase the enrollment of AYA patients on clinical trials, and hopefully will facilitate joint cooperative group trials for rare pediatric tumors like it already has for more common pediatric malignancies. Age, stage, diagnosis, and poverty affect where a patient with a rare pediatric tumor will be treated, but interestingly not distance. Patients with thyroid and nasopharyngeal carcinoma have higher stage disease when they are treated at pediatric centers, and as a consequence require more intensive combination therapy. Contrary to most other studies, poverty and race did not impact survival in our study. Future studies should investigate this finding to see if it can be confirmed.

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TABLES

**Table I. Comparison of Patient Characteristics Present at Diagnosis by Treatment Center (Adult vs. Pediatric) for 15-21-year-old Patients with Rare Pediatric Tumors Diagnosed Between 2000-2009 in the State of Georgia**

| **Characteristic** | **Adult N (%)** | **Pediatric N (%)** | **P-value*** |
|---|---|---|---|
| Facility (N=479) | 379 (79.1) | N=100 (20.9) | <0.0001 |
| Age [mean (SD)] (years) | 18.9 (±1.8) | 17.5 (±2.1) | <0.0001 |
| Age Group | | | |
| Young (15-18 years) | 138 (36.4) | 68 (68.0) | < 0.0001 |
| Old (19-21 years) | 241 (63.6) | 32 (32.0) | |
| Race | | | 0.0107 |
| Non-Hispanic White | 286 (75.5) | 65 (65.0) | |
| Black | 56 (14.8) | 30 (30.0) | |
| Hispanic White | 20 (5.3) | 4 (4.0) | |
| Other | 12 (3.2) | 1 (1.0) | |
| Unknown | 5 (1.3) | 0 (0.0) | |
| Ethnicity | | | 0.6697 |
| Non-Hispanic | 358 (94.5) | 96 (96.0) | |
| Hispanic | 21 (5.5) | 4 (4.0) | |
| Gender | | | 0.0189 |
| Male | 109 (28.8) | 41 (41.0) | |
| Female | 270 (71.2) | 59 (59.0) | |
| Follow-up Time [mean (SD)] (years) | 5.4 (±3) | 4.9 (± 2.8) | 0.1487 |
| Follow-up Time For Censored [mean (SD)] (years) | 5.7 (±2.9) | 5.3 (± 2.7) | 0.2841 |
| Tumor Histology | | | <0.0001 |
| Thyroid Carcinoma | 123 (32.5) | 34 (34.0) | |
| Nasopharyngeal Carcinoma | 11 (2.9) | 14 (14.0) | |
| Other Carcinomas (46 subtypes) | 93 (24.5) | 33 (33.0) | |
| Melanoma | 152 (40.1) | 19 (19.0) | |
| Stage | | | <0.0001 |
| Local | 255 (67.3) | 48 (47.0) | |
| Regional | 96 (25.3) | 34 (34.0) | |
| Distant | 15 (4.0) | 17 (17.0) | |
| Unknown Stage | 13 (3.4) | 1 (1.0) | |
| Primary Site | | | 0.0001 |
| Head & Neck | 37 (9.8) | 20 (20.0) | |
| GI | 22 (5.8) | 10 (10.0) | |
| Lung | 7 (1.9) | 7 (7.0) | |
| Skin | 152 (40.1) | 18 (18.0) | |
| GU | 24 (6.3) | 9 (9.0) | |
| Thyroid | 123 (32.5) | 33 (33.0) | |

| | | | |
|---|---|---|---|
| Other | 11 (2.9) | 2 (2.0) | |
| Unknown | 3 (0.8) | 0 (0.0) | |
| Treatment | | | |
| Chemotherapy | 43 (11.4) | 30 (30.0) | <0.0001 |
| Surgery | 353 (93.1) | 79 (79.0) | <0.0001 |
| Radiation | 102 (26.9) | 52 (52.0) | <0.0001 |
| Combined | 118 (31.1) | 58 (58.0) | <0.0001 |
| None | 15 (4.0) | 3( 3.0) | 1.00 |
| Survival Status | | | 0.3605 |
| Alive | 345 (91.0) | 88 (88.0) | |
| Dead | 34 (9.0) | 12 (12.0) | |
| Poverty Status (% below poverty line) | | | 0.0765 |
| < 5% | 101 (26.7) | 16 (16.0) | |
| ≥ 5% but < 10% | 99 (26.1) | 23 (23.0) | |
| ≥ 10% but < 20% | 96 (25.3) | 28 (28.0) | |
| ≥ 20% | 76 (20.1) | 31 (31.0) | |
| Unknown) | 7 (1.9) | 2 (2.0) | |
| Poverty Group | | | 0.0626 |
| Low Poverty | 296 (78.1) | 67 (67.0) | |
| High Poverty | 76 (20.1) | 31 (31.0) | |
| Unknown | 7 (1.9) | 2 (2.0) | |
| Average Distance to Closest Pediatric Center [mean (SD)] (miles) | 38.1 (± 33.1) | 33.8 (± 31.7) | 0.2420 |
| Distance to Closest Pediatric Center | | | 0.7060 |
| ≤ 25 miles | | | |
| > 25 but ≤ 50 miles | 189 (49.9) | 50 (50.0) | |
| >50 miles | 90 (23.8) | 27 (27.0) | |
| | 100 (26.4) | 23 (23.0) | |

Abbreviations: SD=standard deviation, GI=gastrointestinal, GU=genitourinary

*P-value calculated by chi-square and Fisher's exact test for categorical variables and 2-sample t-test for continuous variables

*2-sided p-value calculated at alpha=0.05

**Table II. Multivariate Analysis of the Association Between Patient Characteristics Present at Diagnosis and Treatment at a Pediatric Center for 15-21-year-old Patients with Rare Pediatric Tumors Diagnosed Between 2000-2009 in the State of Georgia**

| Characteristic | Odds Ratio For Treatment at a Pediatric Center | 95% Confidence Interval | P-value* |
|---|---|---|---|
| Distance to Closest Pediatric Center | | | 0.2014 |
| ≤ 25 miles | Ref | | |
| > 25 but ≤ 50 miles | 1.282 | 0.700-2.347 | |
| >50 miles | 0.654 | 0.336-1.275 | |
| Diagnosis | | | 0.0055 |
| Melanoma | Ref | | |
| Thyroid Carcinoma | 1.921 | 0.992-3.720 | |
| Nasopharyngeal Carcinoma | 7.384 | 2.295-23.754 | |
| Other Carcinomas | 2.643 | 1.248-5.598 | |
| Stage | | | 0.0029 |
| Local | Ref | | |
| Regional | 1.628 | 0.920-2.879 | |
| Distant | 4.242 | 1.710-10.520 | |
| Age Group | | | < 0.0001 |
| Young (15-18 years) | Ref | | |
| Old (19-21 years) | 0.219 | 0.129-0.371 | |
| Race | | | 0.4636 |
| Non-Hispanic White | Ref | | |
| Black | 0.948 | 0.475-1.891 | |
| Hispanic White | 0.620 | 0.188-2.051 | |
| Other | 0.147 | 0.017-1.262 | |
| Poverty Group | | | 0.0297 |
| Low Poverty | Ref | | |
| High Poverty | 2.316 | 1.229-4.365 | |

Abbreviations: Ref=reference group

*P-value calculated using multivariate logistic regression model

*2-sided p-value calculated at alpha=0.05

**Table III. The Effect of Center on Treatment by Diagnosis for all 15-21 year old patients with Rare Pediatric Tumors Diagnosed between 2000-2009 in the State of Georgia**

| Diagnosis | Adult N (%) | Pediatric N (%) | P-value* |
|---|---|---|---|
| Thyroid Carcinoma (N=157) | | | |
| Chemotherapy | 0 (0.0) | 0 (0.0) | —— |
| Surgery | 119 (96.8) | 33 (97.1) | 1.0000 |
| Radiation | 75 (61.0) | 28 (82.4) | 0.0202 |
| Combined | 75 (61.0) | 28 (82.4) | 0.0202 |
| None | 4 (3.3) | 1 (2.9) | 1.0000 |
| Other Carcinomas (N=126) | | | |
| Chemotherapy | 32 (34.4) | 15 (45.5) | 0.2596 |
| Surgery | 78 (83.4) | 26 (78.8) | 0.3813 |
| Radiation | 18 (19.4) | 10 (30.3) | 0.1937 |
| Combined | 31 (33.3) | 15 (45.5) | 0.2140 |
| None | 9 (9.7) | 1 (3.0) | 0.4526 |
| Nasopharyngeal Carcinoma (N=25) | | | |
| Chemotherapy | 7 (63.6) | 14 (100.0) | 0.0261 |
| Surgery | 6 (54.6) | 2 (14.3) | 0.0810 |
| Radiation | 9 (81.8) | 14 (100.0) | 0.1833 |
| Combined | 8 (72.7) | 14 (100.0) | 0.0717 |
| None | 0 (0.0) | 0 (0.0) | —— |
| Melanoma (N=171) | | | |
| Chemotherapy | 4 (2.6) | 1 (5.3) | 0.4492 |
| Surgery | 150 (98.7) | 18 (94.7) | 0.2992 |
| Radiation | 0 (0.0) | 0 (0.0) | —— |
| Combined | 4 (3.6) | 1 (5.3) | 0.4492 |
| None | 2 (1.3) | 1 (5.3) | 0.2992 |

*P-value calculated by chi-square and Fisher's exact test

*2-sided p-value calculated at alpha=0.05

**Table IV. Multivariate Analysis of the Association Between 10-year Overall Survival and Treatment Center for 15-21-year-old Patients with Rare Pediatric Tumors Diagnosed Between 2000-2009 in the State of Georgia**

| Characteristic | Hazard Ratio For Death | 95% Confidence Interval | P-value |
|---|---|---|---|
| Distance to Closest Pediatric Center | | | 0.9856 |
| ≤ 25 miles | Ref | | |
| > 25 but ≤ 50 miles | 0.951 | 0.439-2.059 | |
| >50 miles | 0.946 | 0.446-2.003 | |
| Facility | | | 0.6708 |
| Adult | Ref | | |
| Peds | 0.834 | 0.362-1.923 | |
| Diagnosis | | | 0.0003 |
| Melanoma | Ref | | |
| Thyroid Carcinoma | 0.052 | 0.007-0.409 | |
| Nasopharyngeal Carcinoma | 0.168 | 0.020-1.428 | |
| Other Carcinomas | 2.027 | 0.907-4.530 | |
| Stage | | | < 0.0001 |
| Local | Ref | | |
| Regional | 4.660 | 2.065-10.516 | |
| Distant | 20.967 | 7.728-56.891 | |
| Age Group | | | 0.1570 |
| Young | Ref | | |
| Old | 1.709 | 0.814-3.589 | |
| Race | | | 0.9353 |
| Non-Hispanic White | Ref | | |
| Black | 0.879 | 0.394-1.962 | |
| Hispanic White | 1.573 | 0.421-5.883 | |
| Other | 0.711 | 0.137-3.693 | |
| Poverty Group | | | 0.4569 |
| Low | Ref | | |
| High | 1.556 | 0.779-3.111 | |

Abbreviations: Ref=reference group

*P-value calculated using cox proportional hazards model

*2-sided p-value calculated at alpha=0.05

FIGURES

**Figure I. Application of Study Inclusion/Exclusion Criteria**

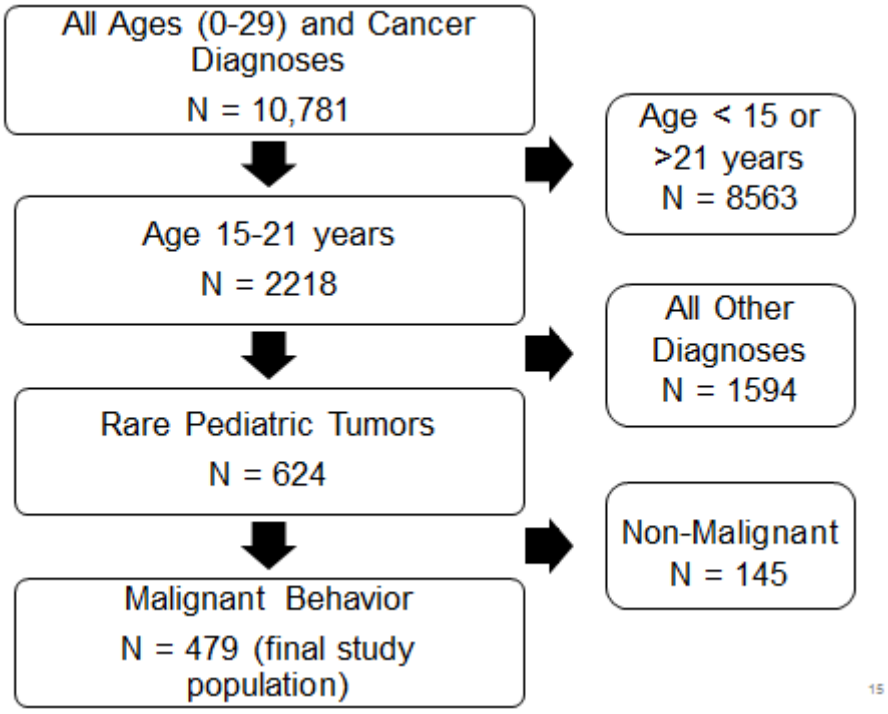


**Figure II. Distribution of Diagnoses for 15-21-year-old Patients with Rare Pediatric Tumors Diagnosed Between 2000-2009 in the State of Georgia**

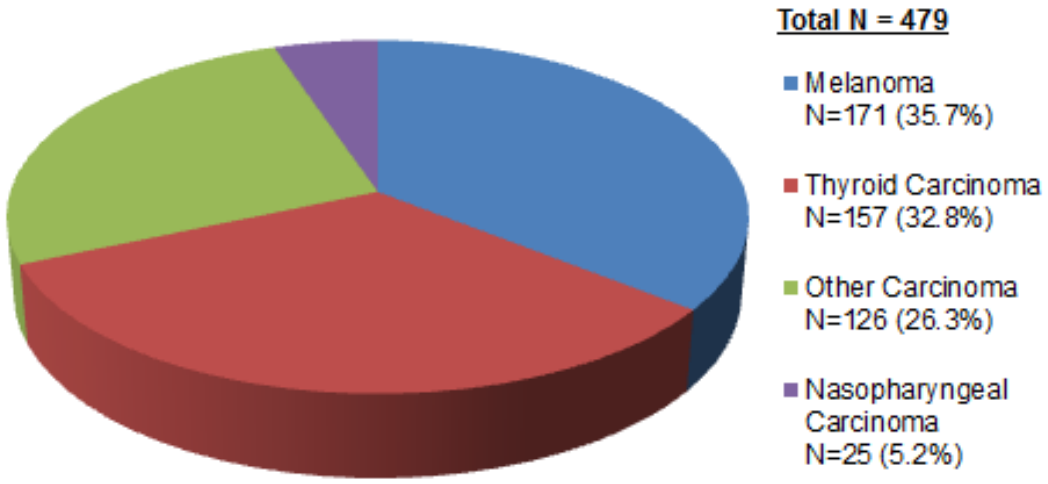
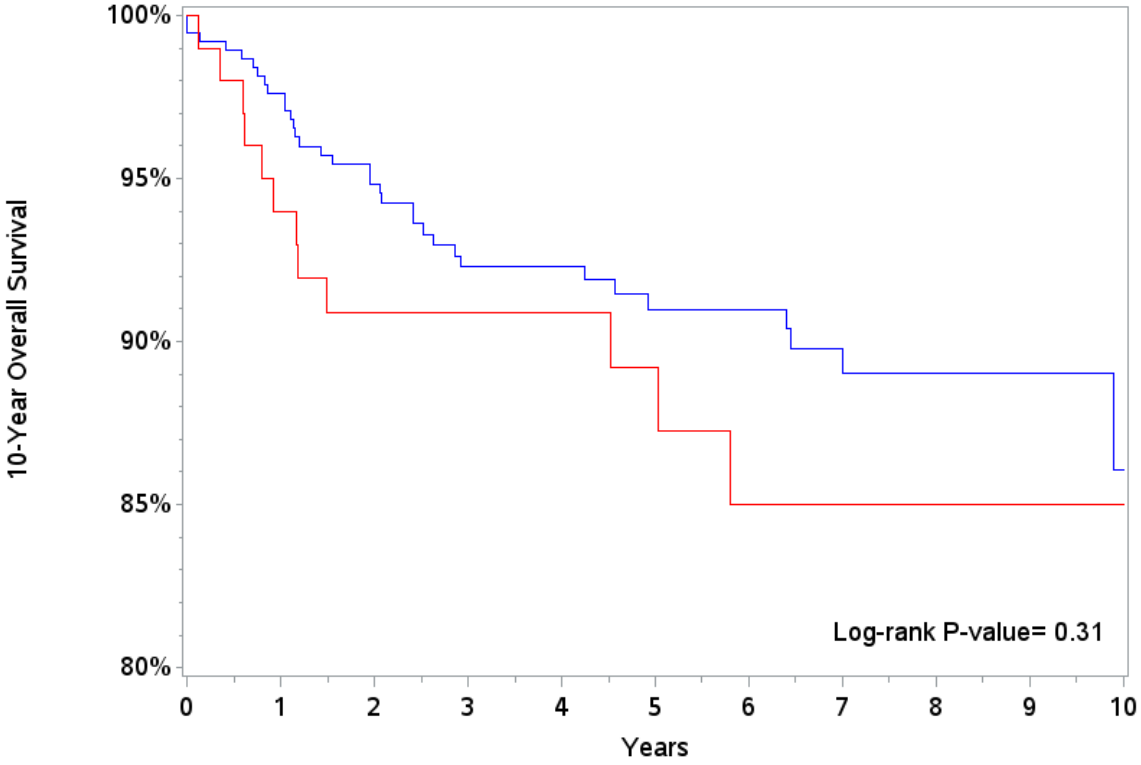


**Figure III. Kaplan-Meier Estimates Comparing 10-Year Overall Survival by Type of Center**




| Number at Risk | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Years** | **0** | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10** |
| **Adult** | 379 | 365 | 321 | 270 | 235 | 194 | 160 | 127 | 93 | 59 | 25 |
| **Peds** | 100 | 94 | 82 | 70 | 56 | 46 | 34 | 23 | 18 | 9 | 5 |

Center — Adult — Peds