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Incidence and Risk Factors Associated with Undernutrition and Weight Loss in Infants and Young Children Undergoing Cancer Treatment

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Abstract

Incidence and Risk Factors Associated with Undernutrition and Significant Weight Loss in Infants and Young Children Undergoing Cancer Treatment

By Daniel V. Runco

Background: Brain tumors are the most common pediatric solid tumor and leading cause of pediatric cancer deaths. Malnutrition increases morbidity and mortality during treatment especially with brain tumors. Unfortunately, definitions and risks for undernutrition in infants and young children during treatment are variable.

Objectives: We created an observational, retrospective cohort to evaluate weight trajectories for pediatric cancer patients less than 3 years old at diagnosis, examining characteristics associated with lower weight-for-age z-scores.

Methods: A chart review included patients diagnosed 2007-2015 at the largest pediatric cancer center in the US. Patients less than 3 years of age at diagnosis, starting treatment at our center, with accurate height and weight measurements prior to treatment initiation, and had sufficient information to classify treatment intensity were included. Treatment intensity was classified using Intensity of Treatment Rating Scale (ITR-3). Exposures included age at diagnosis, tumor type, and treatment intensity and effect on weight-for-age z-score. Clinically significant weight loss was defined as a change in z-score of ≥ 1 with odds of developing significant weight loss examined.

Results: Chart review yielded 434 included patients. Most patients began treatment below the 50th percentile for weight-for-age with mean z-score of -0.14 (44th percentile). No difference in mean weight-for-age z-score was observed between patients with brain tumors versus other malignancies at treatment initiation, 6, 12, or 24 months. Higher treatment intensity caused lower mean weight-for-age z-scores at 12 and 24 months following treatment initiation ($p<0.01$) and higher odds for weight loss (aOR = 2.83, $p<0.001$). Patients less than 1 year old had lower weight-for-age z-scores at 6, 12, and 24 months ($p<0.01$) and higher odds of significant weight loss than 1-2 (aOR=2.73, $p<0.001$) or 2-3 year olds (aOR=2.27, $p<0.001$). The first episode of significant weight loss occurred most frequently within 6 months of treatment initiation.

Conclusion: Younger patients and higher treatment intensity resulted in lower weight and higher odds of significant weight loss following cancer treatment initiation. Future study on effective interventions for high-risk patient is needed focusing on morbidity, mortality, cost, and patient-reported outcomes.

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A. INTRODUCTION

Brain tumors are the most common pediatric solid tumor and the leading cause of pediatric cancer deaths in the United States (1). Worldwide, malnutrition is a contributing factor in 45% of pediatric deaths and is associated with higher rates of infection and premature death (2). Undernutrition is specifically linked to problems with brain myelination and leads to lower intelligence quotient (IQ) in adolescents and adults (3). Prado & Dewey (2014) demonstrate the effect of undernutrition on the development of children. Specifically in pediatric cancer, malnutrition is known to be associated with worse outcomes: more episodes of bacteremia, increased risk of febrile neutropenia, and worse cognitive function and school performance (4-6). Once initiating cancer treatment, there is a rapid increase in nutritional deficiencies which is seen in both developing and developed countries (7).

Estimates for malnutrition in pediatric cancer patients vary widely, ranging from 5% to 80% during the first year following start of therapy (6, 7). Studies on malnutrition are also variable in their methodology: some categorize by tumor location or chemotherapy used, and other studies use non-standardized groups offering little opportunity for generalization to treatment practices. Additionally, use of prophylactic feeding tubes and nutritional supplements vary widely between children's hospitals and pediatric medical providers (6-8). Percutaneous gastrostomy or nasoenteral feeding tubes offer controlled nutritional intake, but increase the risk of fever and neutropenia as well as cellulitis (6, 9, 10). The variability in patient treatment and study methodology make standardized application difficult in patient care or medical practice. Identifying high-risk patients is necessary to make informed decisions on risks and benefits of intervention. While proactive intervention to prevent weight loss can improve morbidity and mortality, there are risks of parenteral and enteral nutrition supplementation including infection, risk of damage to surrounding anatomical structures, electrolyte abnormalities, and liver or kidney injury.

As outcomes in pediatric cancer improve, additional attention must be paid to supportive care interventions that can improve the morbidity experienced by adult survivors of pediatric cancers. Survival of pediatric brain tumors as a whole is greater than 50%, but low-grade malignancies of the central nervous system (CNS) can have over 90% survival (11). In order to improve treatment side effects and morbidity among long-term survivors, multiple professional societies have called for research efforts to focus on nutritional interventions for underweight patients as well as developing standardized assessment and interventions to improve outcomes in this patient population (12, 13). Malnutrition increases direct and indirect costs for the patient and the medical system, but we lack sufficient resources and trained providers necessary to intervene (14, 15). The aim of this project is to identify patient and treatment characteristics that may represent risk factors for significant weight loss during cancer therapy in order to develop prospective feeding intervention studies in undernourished patients.

B. BACKGROUND

Classifying Treatment Intensity

Pediatric cancers can range from lower grade, more benign tumors, to higher grade, more malignant tumors, all of which require different treatment regimens specifically targeted to the pathology, location of the cancer, age of the patient, and the patient's overall health status. During childhood, normal growth and development results in rapidly changing body composition and metabolic needs which in turn affects the metabolism of therapeutic agents, altering both the effectiveness and toxicity of treatments (16). Because different treatments include various combinations of toxic chemotherapy, radiation, surgery, and/or hematopoietic bone marrow or stem cell transplantation, standardizing the intensity of treatment is difficult. Symptoms of fatigue, anxiety, pain, and nausea have begun to be recognized and studied as impacting both the quality of life for patients on therapy as well as the long-term morbidity (17, 18). The Intensity of Treatment Rating Scale (ITR-3) has been published, revised, and validated, to group pediatric patients based on diagnosis and treatment received, which accounts for single or multimodality treatment (19). Utilizing a standardized approach for classifying intensity allows for better identification of patients at risk for more treatment related side effects.

Feeding Risk in Patients with Tumors of the CNS

Retrospective studies have evaluated the probability of malnutrition during cancer therapy, but these studies group different types of patients and ages together (6, 7). For example, Zimmerman et.al (2013) created a group for patients with osteosarcoma, medulloblastoma, and acute myeloid leukemia (AML) from birth to 18 year old (7). However, infants with brain tumors have very different feeding abilities and nutrition requirements than adolescents with leukemia and very little published recommendations exist on specific screening and intervention for feeding dysfunction and weight loss in patients with tumors of the CNS. Brain and spinal cord tumors increase the risk of swallowing and oromotor dysfunction, as well as feeding problems compared to their non-brain tumor peers treated for cancer, largely due to

chemotherapy, radiation, and surgery directed towards the CNS (20-22). Cancer treatment also exacerbates the risk of malnutrition by increasing risk for anorexia, nausea and vomiting, mucositis, infection including at gastrostomy tube sites, critical care admissions, and death (6, 7, 10). At least two studies have shown specific morbidity associated with brain tumors, including weight loss and malnutrition compared to other pediatric malignancies (10, 23). As a result, more patients diagnosed with brain tumors receive prophylactic feeding tubes and aggressive nutrition consultation and management. Pediatric swallowing dysfunction is known in this patient population as well as recognizable and under diagnosed swallowing and feeding dysfunction (8, 21, 24-26).

Importance of Proper Nutrition Early in Life

Infancy and early childhood is a time of rapid growth and changing metabolic and caloric needs. Additionally, patients are not capable of self-feeding which requires a caregiver until the child develops the necessary gross and fine motor skills to feed themselves. Undernutrition in children less than 5 years of age has been associated with increased infections and higher risk for premature death worldwide (2). Even prenatal nutritional deficiencies decrease brain myelination and subsequently, experiencing malnutrition less than 2 years of age leads to lower adolescent and adult IQs (3). Proper nutrition not only impacts cognitive development, but also impacts motor, social, and emotional development. Prado and Dewey (2014) also identified the importance of nutrition in physical activity, growth, and health, and that not all deficiencies are correctable when nutritional status improves.

Feeding Interventions

While several professional organizations have outlined the importance of nutritional monitoring and intervention, screening and treatment for undernutrition are not standardized across pediatric centers or between individual pediatric providers. The use of prophylactic gastrostomy tubes, the availability of nutrition or gastroenterology consultation, and the criteria to initiate enteral or parenteral nutrition supplementation varies widely (6, 8). This leads to

variable time from cancer diagnosis and identification and treatment of subsequent suboptimal nutritional status. One of the few prospective feeding trials in pediatric cancer patients demonstrated that utilizing upfront enteral tube feeding supplement and weekly communication with a registered dietitian leads to less weight loss and improvement in nutritional status among patients (6). Additional studies have shown the importance and improvement of outcomes specifically in adult patients with head and neck cancer as well as those receiving radiation and chemotherapy (27, 28). Unfortunately, these studies have not been replicated in children with brain tumors.

C. METHODS

Research Objectives

1. Develop an observational retrospective cohort to evaluate weight trajectories based on patient and treatment characteristics
2. Understand weight trajectories for patients less than 3 years old undergoing cancer therapy
3. Recognize the effect tumor type, treatment intensity, and age at diagnosis on weight-for-age z-scores following treatment initiation
4. Identify patient characteristics that increase the risk of experiencing clinically significant weight loss during cancer treatment.

Study Design

This retrospective cohort study included data abstracted from the electronic medical record and Aflac Cancer Registry after IRB approval. Of the reviewed subjects, 434 patients were identified for inclusion and followed for two years following initiation of cancer treatment. Patients were included if they were less than or equal to 3 years of age when newly diagnosed with cancer between January 1, 2007 and December 31, 2015. A RedCap® database was designed with demographic information on the patients including specific diagnosis ICD-9 and ICD-10 codes, tumor type (brain tumor or non-brain tumor), and treatment (chemotherapy, radiation, surgery, and/or hematopoietic stem cell or bone marrow transplantation). Using the Intensity of Treatment Rating Scale (ITR-3), treatment intensity was assigned based on diagnosis and treatment modalities (19). Additionally, height and weight measurements were collected at time of diagnosis, monthly for the first year, and quarterly for the second year. Finally, complete demographic information also included date of treatment initiation, off therapy date, death, race, and ethnicity. Patients were excluded if they had no accurate height or

weight recorded prior to treatment initiation, if the patient started treatment at an outside facility, or if they were being treated for a relapsed or second malignancy.

Patients were divided based on their characteristics. Patients were assigned a treatment intensity rating of 1 (lowest intensity) up to 4 (highest intensity). Additionally, patients were further analyzed based on their intensity group: low intensity treatment (combining ITR 1 and 2) and high intensity treatment (combining ITR 3 and 4). A categorical variable was created for age at diagnosis evaluating patients that were diagnosed 0-0.99 years, 1-1.99 years, and 2-2.99 years of age. Individual diagnoses were recorded and patients were also classified as having a brain tumor or non-brain tumor, which included any other type of malignant diagnosis.

Growth Measurements

The date for cancer diagnosis and the first systemic treatment date were recorded. Interval measurements were collected monthly for the first year. The date was chosen one month after initiation and the closest height and weight within two weeks before or after the date were included. If no accurate recording was available within two weeks before or after the date, that time point was excluded. For the second year, heights and weights were evaluated quarterly. If no height or weight was available within one month before or after the date, that time point was excluded. Gross weight measurements were corrected to age and sex adjusted weight-for-age z-scores utilizing data from normative measures of the Centers for Disease Control (CDC). The date on which the weight was recorded was used to convert weight-for-age z-scores for individual patients using SAS® software (version 9.4) coding with normative data provided by the CDC and where appropriate also used for expected weight-for-age percentile.

Statistical Analysis

Descriptive statistics were performed to evaluate characteristics of the patient populations at treatment initiation. Subgroup analyses were also examined with stratification

for exposures of interest. When examining between group differences in means, pooled two sample T-tests were performed. This was utilized to compare mean weight-for-age z-scores between patients with non-brain tumors versus brain tumors and those in the high intensity treatment group versus the low. For analysis of differences between age groups, treatment intensities, race, and ethnicities were evaluated using one-way ANOVA. Subsequent between-group differences in means were evaluated with multiple t-tests and Bonferroni correction with an alpha set at 0.05.

Outcome Measures

Significant weight loss was defined as a decrease of weight-for-age z-score of greater than or equal to 1 (which corresponds to a change in weight-for-age percentile of 32% if the baseline value of z is zero). Each interval measurements for the 2 year study period were compared to the weight-for-age z-score at treatment initiation. Each interval was assessed to determine if there had been a decrease in weight-for-age z-score by greater than or equal to 1 and designated as such with a dichotomous variable (yes/no). Then, the entire study period was reviewed to see if a patient had experienced significant weight loss at any time during the study with a dichotomous variable (yes/no). Finally, the first episode of significant weight loss was noted for time-to-event analysis using Kaplan-Meier estimates.

Univariate logistic regression was performed with the outcome of significant weight loss at any time during the study period. Variables assessed included sex, race, ethnicity, tumor type (brain tumor versus non-brain tumor), treatment intensity rating (1 to 4), treatment intensity group (high or low), and age group at diagnosis (0-0.99 years, 1-1.99 years, or 2-2.99 years). Wald chi-square and odds ratios were calculated with statistically significant and clinically relevant variables being included in the overall model. A multivariate logistic regression was performed using treatment intensity group and age at diagnosis with evaluation of Wald chi-square and adjusted odds ratio results. The proportion of patients who developed significant

weight loss during the study period was also examined for the variables of interest. The presence of significant weight loss by tumor type, intensity group, and age at diagnosis was examined using Chi-squared analysis.

D. RESULTS

Patient demographics

Baseline demographic information on the study participates was collected (Table 1). Of the 434 included participants, 50.9% were male and patients were predominantly Caucasian (59.0%) and Non-Hispanic (84.3%). Most patients were either Treatment Intensity 2 or 3 (39.4% and 42.9%, respectively) with smaller numbers in the least intense rating (ITR 1, 4.8%) and the highest intense rating (ITR 4, 12.9%). The mean age at diagnosis was 1.49 years (SD = 0.88 years) and patients started out with mean weight-for-age and height-for-age z-scores below the 50th percentile. For all patients, the mean weight-for-age z-score was -0.14 (44th percentile, SD = 1.35) and a mean height-for-age z-score of -0.26 (40th percentile, SD = 1.24). The diagnoses reflect the expected malignancy distribution for this age group with 51.2% of patients diagnosed with hematologic malignancies, 35.7% with solid (non-brain) tumors, and 13.1% with brain tumors.

Mean weight-for-age z-scores

Mean weight-for-age z-scores were examined among particular subgroups (Table 2). Patients with brain tumors and non-brain tumors had similar mean weight-for-age z-score at initiation of treatment (Z = -0.22 and -0.27, respectively; p = 0.79) and were at the 41st and 39th percentiles respectively. They remained similar at 6 months (p = 0.94), 12 months (p = 0.71), and 24 months (p = 0.18). Both groups saw a decrease in mean weight-for-age z-score at 6 months, but then increased at both 12 and 24 months. The patients with brain tumors had a lower mean weight-for-age z-score at 24 months (Z = -0.37, 35th percentile) and patients with other malignancies had a higher mean 24 months after treatment initiation (Z = -0.04, 48th percentile), though the groups' means values were not statistically different.

Similarly, at treatment initiation, both patients in the low and high intensity groups had similar mean weight-for-age z-scores (Z = -0.27 and -0.26, respectively; p = 0.94). Although they were statistically similar at 6 months following treatment initiation, at 12 months, patients with high intensity treatment had a lower mean weight-for-age z-score than those with low intensity treatments (Z = -0.53 and -0.13, respectively; p <0.01), corresponding to the 30th and 45th percentiles respectively. High intensity treatment continued to have a lower mean weight-for-age z-score than the low intensity group at 24 months as well (Z = -0.26 and 0.09, respectively; p = 0.03). Compared to treatment initiation, the low intensity treatment group had a higher mean weight-for-age z-score at 24 months (Z = 0.09, 54th percentile) than at treatment initiation, but the high treatment intensity group did not rise above baseline (Z = -0.26, 40th percentile).

The age at which a patient is diagnosed also led to differences in mean weight-for-age z-scores (Table 2). There was no difference between the three groups at treatment initiation (p = 0.13) (Figure 2). There is a difference within the three groups starting at 6 months (p <0.01) (Figure 3). At that time, patients diagnosed less than one year of age had a lower mean weight-for-age z-score (Z = -0.91, 18th percentile) than those diagnosed 2-3 years old (Z = -0.62, 26th percentile; p <0.001). At 12 months, there continued to be a group difference (p <0.001) with those less than 1 year old having a lower mean weight-for-age z-score (Z = -0.87, 19th percentile) than those 1-2 years at diagnosis (Z = -0.34, 37th percentile) and those 2-3 years old (Z = -0.06, 48th percentile) at diagnosis (p = 0.023 and <0.001, respectively) (Figure 4). At 24 months following treatment initiation there remained a group difference (p <0.001) with those less than 1 year at diagnosis continuing to be lower (Z = -0.70, 24th percentile) than those 1-2 years old (Z = 0.03, 51st percentile) or 2-3 years old (Z = 0.25, 60th percentile) at time of diagnosis (p = 0.001 and <0.001, respectively) (Figure 5). When examining the mean weight-for-age z-score at the end of the 24 month study period compared to treatment initiation, patients diagnosed less than

1 year of age ended below the baseline, but patients diagnosed older than 1 year ended the study with a mean weight-for-age z-score above baseline.

Proportion who experienced significant weight loss

When examining the patients who experienced clinically significant weight loss during therapy, there was no difference between patients based on tumor type (Table 3). Of patients with brain tumors, 40.4% experienced significant weight loss at some time during the study period and 38.2% of those with non-brain tumors had weight loss ($X^2 = 0.097$, $p = 0.76$). Comparing the treatment intensities, a higher proportion of patients in the high intensity treatment group experienced clinically significant weight loss at some point during therapy compared to low intensity treatment (48.8% vs. 25.5%, $X^2 = 24.42$, $p < 0.0001$). A higher proportion of patients diagnosed less than 1 year old experienced significant weight loss during the study (52.7%) compared to those diagnosed 1-2 years old (30.5%) or 2-3 years old (31.8%) ($X^2 = 18.95$, $p < 0.0001$).

Univariate and Multivariate Regression

Univariate logistic regression identified two variables of interest that were statistically significant to be included in the multivariate logistic regression model. There were no significant increase odds for experiencing significant weight loss during the study based on race, ethnicity, sex, and tumor type (Table 4). Treatment intensity rating was statistically significant for some of the comparisons, but ITR 2 versus 1 was not different. When patients were grouped into high intensity or low intensity treatment, the high intensity group increased odds of experiencing significant weight loss by 2.78 times (95% CI = 1.84 - 4.19, $p < 0.0001$). Being younger also increased odds of experiencing significant weight loss. Those diagnosed less than 1 year old had 2.39 higher odds of experiencing weight loss compared to those 1-2 years old (95% CI 1.50 - 3.81, $p < 0.0001$) and those diagnosed 2-3 years old 2.53 times higher (95% CI 1.55 - 4.12, $p < 0.0001$).

Based on the univariate regression, treatment intensity group and age at diagnosis were both included in a multivariate logistic regression model (Table 5). When adjusting for age at diagnosis, the high intensity group had 2.83 times higher odds of experiencing significant weight loss compared to low intensity (95% CI 1.85 - 4.31, p <0.0001). Similarly, when controlling for treatment intensity group, patients diagnosed less than 1 year old had 2.73 times more likely to experience significant weight loss than those 1-2 years and 2.27 times more than 2-3 years at diagnosis (95% CI 1.63 - 4.54 and 1.40 - 3.68, respectively; p <0.0001).

Time to first significant weight loss

The time point at which a patient experienced his or her first episode of significant weight loss was also examined in this study. Examining the survival curve for weight loss free survival, 68.9% of patients had not experienced an episode of significant weight loss in the first 6 months (Figure 6). Only 7.4% of patients had their first episode of significant weight loss after 6 months making the 24-month weight loss free survival 61.5% (95% CI 56.8 - 65.9%).

When stratifying by tumor type, there was no difference in the weight loss free survival between the patients with brain tumors and those with non-brain tumors (Log Rank test p = 0.84) (Figure 7). Most initial events of weight loss for patients with brain tumors occurred in the first 6 months with 70.2% not experiencing significant weight loss (95% CI 56.5 - 80.3%) and at the end of the study period, 59.6% of patients had not had an episode of significant weight loss (95% CI 45.8 - 71.0%). Patients with brain tumors followed a similar trend with 68.7% of patients not having an episode of significant weight loss in the first 6 months (95% CI 63.8 - 73.1%) and at 24 months, 61.8% of patients had not experienced any significant weight loss (95% CI 56.7 - 66.5%).

Treatment intensity groups did have statistically different survival curves (Log Rank test p <0.001) (Figure 8). At 6 months, 79.7% of patients in the low intensity treatment group had not had significant weight loss, but only 60.3% of those in the high intensity group remained

weight-loss free (95% CI 73.3-84.7% and 53.9-66.2% respectively). At the completion of the study period, 74.5% of patients remained free of significant weight loss in the low intensity treatment group, but only 51.2% in the high intensity treatment group (95% CI 67.7-80.1% and 44.8-57.3% respectively).

With regards to age at diagnosis (Figure 9, Table 5), there also is a difference in weight loss free survival depending on the group (Log Rank test $p < 0.01$). Of the patients diagnosed less than 1 year old, only 60.3% had not experienced significant weight loss in the first 6 months (95% CI 51.9-67.7%), but at 12 months and 24 months only 52.1% (95% CI 43.7-59.8%) and 47.3% (95% CI 39.0-55.1%) respectively remained without significant weight loss. For patients diagnosed 1-2 years old 74.0% were without significant weight loss at 6 months (95% CI 65.6-80.7%) and this number remained relatively stable through the end of the study. In patients diagnosed 2-3 years old, 72.6% did not have an episode of significant weight loss by 6 months post-treatment initiation (95% CI 64.9-78.9%) and similar to the 1-2 year old group, the number remained relatively stable through the end of the study. The only patients who experienced their first episode of significant weight loss after 12 months post-treatment initiation were patients who had been diagnosed less than 1 year of age.

E. DISCUSSION

While malnutrition is associated with increased morbidity and mortality, little is known about identifying patients at highest risk for weight loss during cancer treatment. From a clinical perspective, patients who have suboptimal nutritional status have increased risks of infection, worse outcomes, and poorer quality of life (16, 29, 30). Undernutrition and nutrition supplementation also cause stress for the patient, caregivers, and medical providers, with higher levels of anxiety and discomfort recorded (24, 31). Although nutrition is not itself a treatment for pediatric cancer, undernutrition does impact the effectiveness and side effects of pediatric cancer treatments and affects the caregivers' ability to care for infants and young children with cancer.

This study aimed to examine prevalence of significant weight loss and risk factors specifically for children diagnosed with cancer less than three years of age. The sample size was larger that many other nutrition studies conducted in pediatric oncology. Very little research has focused specifically on the youngest age group being treated for malignancy and this study is larger than any infant studies on nutrition in pediatric cancer patients. Understanding the trajectories and risk factors for weight loss allows future, prospective research to be conducted with the highest opportunity for impact. Furthermore, being able to predict patients at highest risk for developing malnutrition will have tremendous impact on quality of life and even mortality and health care costs. Dedicated study of infants and young children is important because of the rapid growth in these patients as well as the underdeveloped ability to communicate with immature gross and fine motor skills impacts the patient or parents' abilities to maintain his or her own nutrition.

Despite the limitations, this study provides the structure for future studies that could be focused on different age groups: children, adolescents, and young adults. Additionally this type of research can elucidate differences between different diagnoses. There may be some

distinction between different types of brain tumors, i.e. patients with medulloblastoma may have different weight trajectories than those with ependymoma, and there may be further distinctions for other types of tumors. Regardless, there are meaningful lessons to be drawn from this study and applied to future research.

Mean weight for age z-scores and patterns

The first objective of this study was to determine weight trajectories for patients undergoing cancer therapy. When examining the mean weight-for-age z-scores for patients, it was evident that as a whole, patients began therapy under nourished. The mean weight-for-age z-score was below zero (less than the 50th percentile), regardless of tumor type, treatment intensity, or age at diagnosis with each group experiencing a decline in weight at 6 months. This finding in infants and children less than three years old supports previously published data in older children and adolescents that patients undergoing cancer treatment lose weight in the first three months following treatment initiation (23, 32). While regaining weight is variable in reported literature, most of our patients experienced a regain in weight two years after initiation of treatment, ending above or near their baseline. The patients diagnosed less than one year of age did not follow that pattern. It stands to reason that the youngest children have a more rapid growth velocity than older children. Initiation of chemotherapy or radiation results in an interruption to this growth which is more pronounced due to the infants growing body.

Prior literature regarding patients with brain tumors has demonstrated variable patterns of weight loss, weight gain, and malnutrition (7, 32). However, variability in identifying and reporting malnutrition may be attributable to inconsistent definitions used to diagnose malnutrition as well as the influence of body composition, rather than weight alone, as a measure of nutritional status (33, 34). In fact, patients with brain tumors are known to have different patterns of free fat mass compared to children with other malignancies (32, 34). Early and proactive nutritional support is effective for particular patient populations including those

receiving radiation therapy or those with head and neck cancers (28, 35). Pilot data exists suggesting that early and proactive enteral tube feeding can improve nutritional status and decrease weight loss in pediatric patients undergoing cancer treatment, no consensus exists on how to risk stratify, prevent, or intervene on malnourished patients (6). Tumor type did not show a significant impact on weight loss in this study which is likely due to the within group differences for those with brain tumors and those with other malignancies. Even within the treatment of brain tumors, the effect of surgery only compared to combination surgery, chemotherapy, radiation, and stem cell transplantation will dramatically alter the nutritional status of the patient. Additionally, while there are statistically significant differences in mean weight-for-age z-scores, there are also large standard deviations, suggesting significant individual variation among patients.

While differences in mean weight-for-age z-score exist between the treatment intensity groups at 12 and 24 months, the raw difference is smaller at 24 months. This could potentially signify catch up growth and correction of weight-for-age z-scores as they get farther out from treatment. We only monitored patients for two years following treatment initiation, but future studies could examine the longer term impact of how weight-for-age improves off therapy which would also impact the clinical decision whether or not to place a percutaneous gastrostomy tube. The narrowing between groups is not seen based on the age group at which a patient is diagnosed. Even 24 months after treatment initiation, patients diagnosed less than 1 year of age do not demonstrate catch up growth and are even more dramatically different from the older children. Patients diagnosed in the first year of life do not seem to demonstrate the same improvement in weight for age, even two years after treatment initiation which could argue more strongly for more early and aggressive nutrition intervention for these patients.

Higher treatment intensity causes more weight loss

Conventional thinking and practice suggests that more intense therapies, such as bone marrow transplantation, are associated with worse nutritional status. As previously mentioned, this study utilized a peer-reviewed and validated scale to objectively classify treatment intensity which is unique compared to previously published nutrition studies (19). Determining the impact of the tumor itself versus the treatment causing the weight loss is very difficult. Higher grade malignancies necessitate more aggressive treatment so there is a degree of confounding by indication. However, this study supports that treatment plays a vital role in the development of significant weight loss as evidenced by the decrease in weight-for-age z-score once treatment is initiated when the patients are statistically similar at initiation of therapy. The malignancy itself may contribute some degree of undernutrition given the mean weight-for-age z-score at treatment initiation was already below the 50th percentile. Furthermore, patients who receive higher intensity treatment have lower mean weight-for-age z-scores at 12 and 24 months following treatment initiation and a larger proportion of patients in the high intensity group developed clinically significant weight loss at some point in during the study period. Even when controlling for age at diagnosis, high treatment intensity carries almost twice the odds of developing weight loss during the 2 years following treatment initiation compared to the low intensity group. Higher intensity treatments are associated with more myelosuppression and inpatient hospitalization, but also significant nausea, vomiting, anorexia, and mucositis that interfere with feeding and nutrition (18).

Younger patients are at higher risk for significant weight loss

Infants and young children are known to metabolize medications differently than adolescents and adults, but different patterns of toxicity exist for different diagnoses and treatments (13, 16). For example, in Non-Hodgkin's Lymphoma, older and younger patients seem to have similar toxicity patterns, but patients treated for rhabdomyosarcoma or

osteosarcoma tend to have different toxicities depending on age (36-38). The evidence for age related differences in nutritional status is lacking though and general consensus is that using age and weight-based dosing with appropriate supportive care minimizes any additional toxicities younger patients experience. We found that patients diagnosed with cancer before 1 year of age had more than twice the odds of experiencing significant weight loss during the two years following treatment initiation compared to patients diagnosed over 1 year old. Additionally, patients diagnosed less than 1 year of age have a lower mean weight-for-age z-score at 6, 12, and 24 months compared to older patients with a larger proportion having experienced an episode of significant weight loss at some point during two years following treatment initiation. This patient population is particularly difficult to manage because they do not feed themselves at this point. Also, percutaneous and nasal-enteral feeding tubes are more technically difficult to place on smaller patients and maintain without being pulled out. Finally, the first year of life is a time of rapid growth. Cancer treatment alters both cell growth and metabolism and also causes the decreased side effects mentioned above. If confirmed prospectively, this finding would shift the understanding of toxicity in pediatric cancer treatment and could shift necessary nutrition resources to a more vulnerable population.

Patient and family impact

Availability of dietitians and speech pathologists for patients in need of nutrition support varies by practice and geography. We have outlined and identified risk factors for significant weight loss during the first two years of cancer therapy, specifically for patients diagnosed less than three years of age. Patients diagnosed in the first year of life and those receiving high intensity therapy are at highest risk for experiencing significant weight loss. This retrospective data can help focus on younger patients and those undergoing higher intensity treatment, which is especially important in resource limited settings. Malnutrition is associated with increased hospital lengths of stay, medical costs, and lost earnings for family members (14, 15). Financial

toxicity, especially with regards to the impact on caregivers, factors into the care of pediatric patients with cancer, but the specific impact of nutritional interventions has not been investigated (39, 40). These data can be utilized to develop and implement prospective, interventional trials for nutrition support including personnel, enteral supplements, or parenteral nutrition in specific patient populations. Additionally, associating these nutritional interventions with morbidity and mortality outcomes is vitally important.

Future Directions

As a retrospective cohort study, there are certain limitations to this type of study. Although STROBE guidelines for observational studies were followed, conclusions on the causality for weight loss are less definitive without a randomized approach. We lack the ability to control for additional confounders although descriptive analysis can be helpful. While race and ethnicity did not contribute to likelihood of weight loss, socioeconomic status, parental education, or health literacy, may also impact weight loss in this population and were not studied here. Additionally, this study is subject to confounding by indication: higher-grade malignancies require higher intensity treatment. Patients cannot be randomized to treatment so there may be confounded effects of the underlying malignancy in addition to the intensity of the treatment. Given that all groups were below the 50th percentile and then experienced a decrease in weight-for-age z-score after treatment initiation, there is an evident impact specifically of treatment intensity causing weight loss. While this study examined the difference between brain tumors and non-brain tumors, the numbers were not sufficient to examine within group differences between different diagnoses. Future prospective studies should be powered to identify differences between specific diagnoses in order to better understand interventions needed for individual treatment regimens. Finally, this study is limited by the lack of consensus around the most appropriate marker for nutritional status, particularly in infants and young children. While weight-for-age z-scores were used in this study, additional anthropomorphic measurements

have been argued to be more appropriate in pediatrics, possibly limiting the generalizability for this particular study. Several published studies have used weight-for-age z-scores as markers of nutritional status and it is specifically more sensitive and specific than body mass index, which is used in adolescents and adults.

The identified limitations of this study offer prime opportunities for future study and direction. Performing a similar study and collecting retrospective data on older children, adolescents, and young adults could offer understanding of the patients in these groups at highest risk for significant weight loss. Additionally, identifying high-risk patient populations will create opportunity to develop prospective, interventional studies key to creating the most effective and beneficial nutritional interventions. For example, delivery of nutrition consultation in resource limited settings, understanding the benefit of proactive percutaneous or nasoenteral feeding tubes, and proactively supplementing nutrition are key areas to improve nutritional outcomes in this vulnerable population. Understanding the impact of these interventions on health care cost, patient experience, family perception, and overall morbidity and mortality will assist in balancing the risks and benefits of intervention and dramatically improve supportive care in pediatric oncology.

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G. TABLES/FIGURES

Figure 1: Consort Diagram for Patient Eligibility and Inclusion

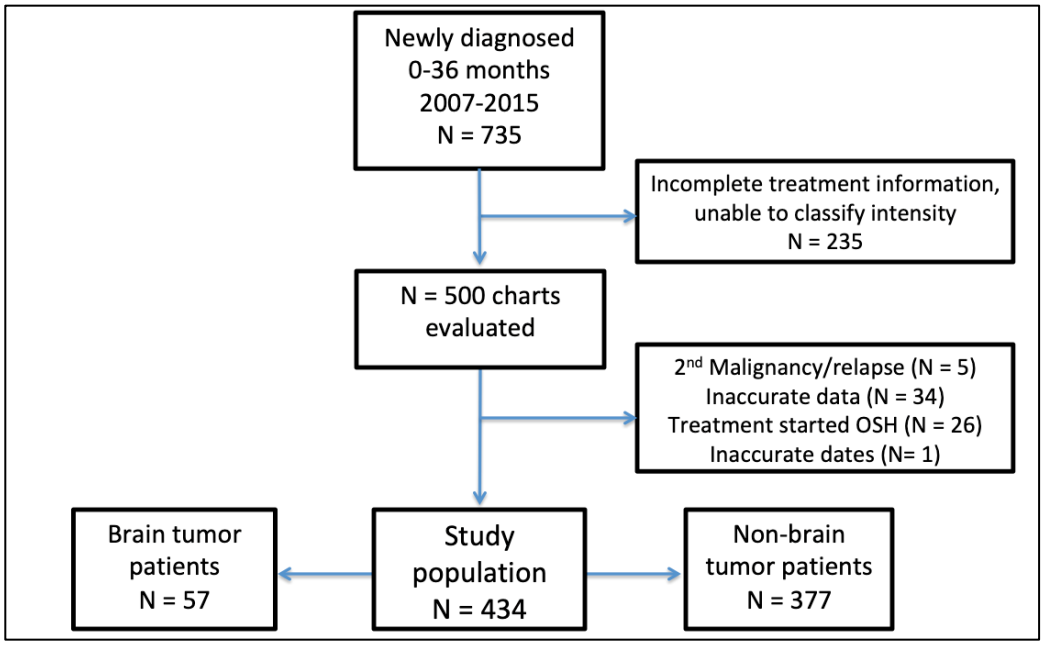

Table 1: Patient Demographics

Variable	N = 434	(100%)
Sex		
Male	221	(50.9%)
Female	213	(49.1%)
Race		
White	256	(59.0%)
Black	146	(33.6%)
Other	32	(7.4%)
Ethnicity		
Non-Hispanic	366	(84.3%)
Hispanic	63	(14.5%)
Unknown	5	(1.2%)
Treatment Intensity Rating		
1	21	(4.8%)
2	171	(39.4%)
3	186	(42.9%)
4	56	(12.9%)
Mean age in years at diagnosis (SD)	1.49	(0.88)
Age group at diagnosis		
0 – 0.99 years	146	(33.6%)
1 – 1.99 years	131	(30.2%)
2 – 2.99 years	157	(36.2%)
Mean Weight-for-age Z-score at diagnosis (SD)	-0.14	(1.35)
Mean Height-for-age Z-score at diagnosis (SD)	-0.26	(1.24)
Hematologic malignancy	155	(35.7%)
ALL	105	(24.2%)
AML	39	(9.0%)
JMML	6	(1.4%)
Lymphoma	3	(0.7%)
Other	2	(0.5%)
Solid Tumor (non-brain)	222	(51.2%)
Neuroblastoma	82	(18.9%)
Retinoblastoma	44	(10.1%)
Nephroblastoma	42	(9.7%)
Skin/Tissue Sarcoma	25	(5.8%)
Hepatoblastoma	21	(4.8%)
Germ cell tumor	8	(1.8%)
Brain Tumor	57	(13.1%)
Astrocytoma	17	(3.9%)
Medulloblastoma	10	(2.3%)
Ependymoma	9	(2.1%)
ATRT	8	(1.8%)
Glioma	4	(0.9%)
Glioblastoma	3	(0.7%)
Pineoblastoma	2	(0.5%)
PNET	2	(0.5%)
Germinoma	2	(0.5%)

Table 2: Mean Weight-for-Age Z-Scores (SD) at Evaluated Time Points

Variable	Initiation	p	6 mo	p	12 mo	p	24 mo	p
Tumor Type								
Brain Tumor	-0.22 (1.37)	0.79 *	-0.59 (1.33)	0.94 *	-0.44 (1.35)	0.71 *	-0.37 (1.14)	0.18 *
Non-brain tumor	-0.27 (1.22)		-0.57 (1.20)		-0.35 (1.26)		-0.04 (1.27)	
Intensity Group								
Low	-0.27 (1.23)	0.94 *	-0.45 (1.27)	0.13 *	-0.13 (1.24)	<0.01 *	0.09 (1.16)	0.03 *
High	-0.26 (1.22)		-0.67 (1.16)		-0.58 (1.27)		-0.26 (1.34)	
Age at Diagnosis								
0-0.99 years	-0.32 (1.35)	0.13 +	-0.91 (1.30)	<0.01 +	-0.87 (1.31)	<0.001 +	-0.70 (1.53)	<0.001+
1-1.99 years	-0.38 (1.08)		-0.62 (1.09)		-0.34 (1.15)		0.03 (0.97)	
2-2.99 years	-0.11 (1.24)		-0.28 (1.19)		-0.06 (1.24)		0.25 (1.11)	

* Two-sample independent t-test; +One way ANOVA, F test

Figure 2: Differences in Weight-for-Age Z-score by Diagnosis Age at Initiation

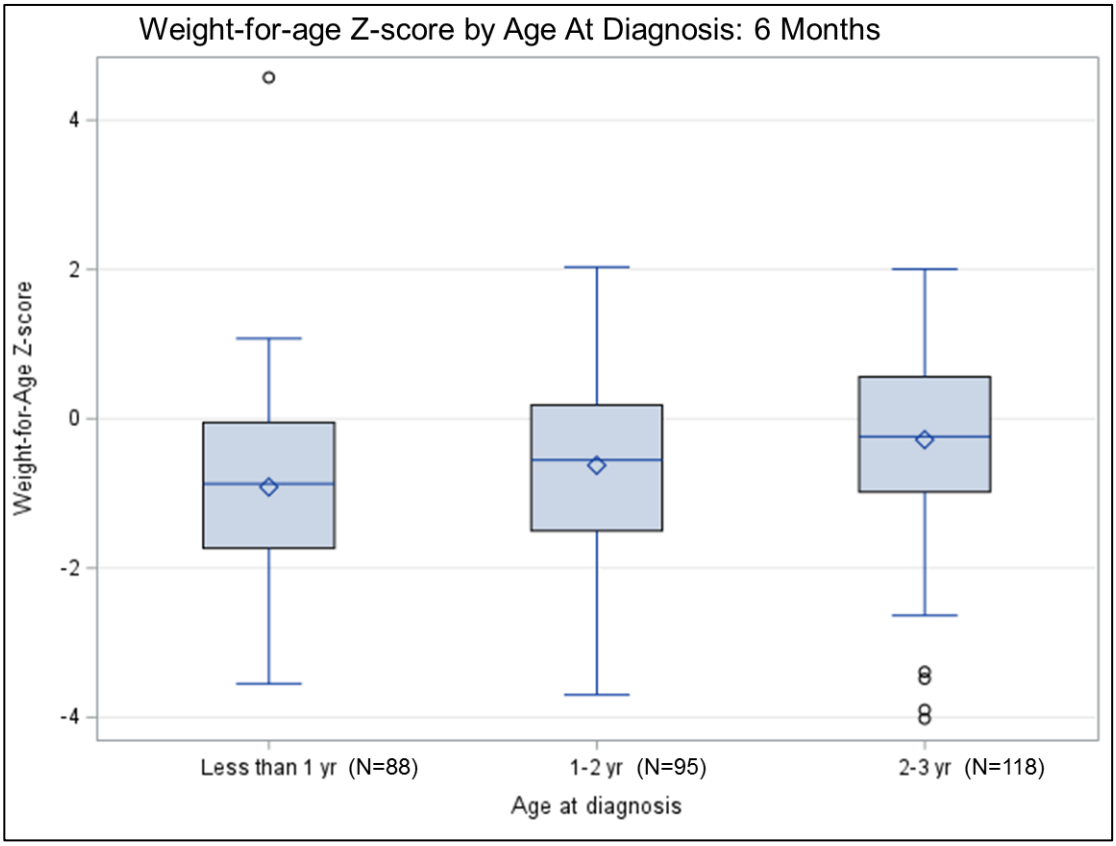

Figure 3: Differences in Weight-for-Age Z-score by Diagnosis Age at 6 Months

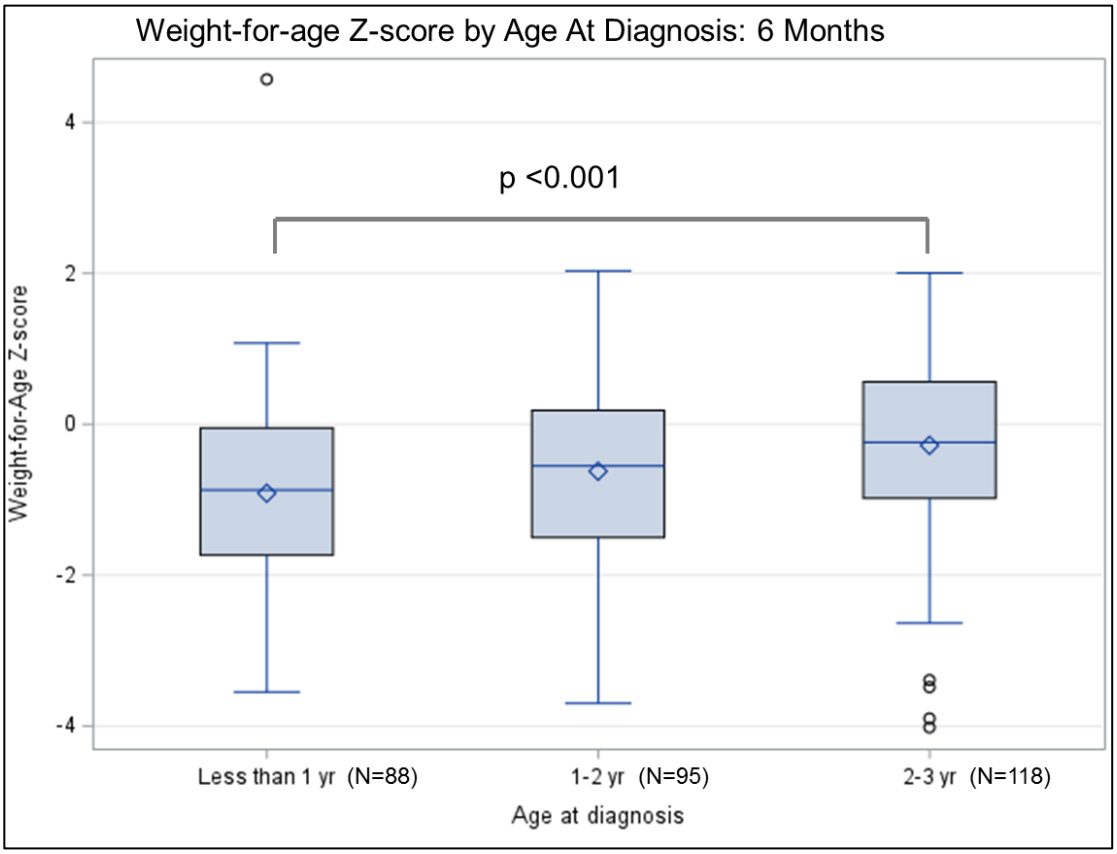

Figure 4: Differences in Weight-for-Age Z-score by Diagnosis Age at 12 Months

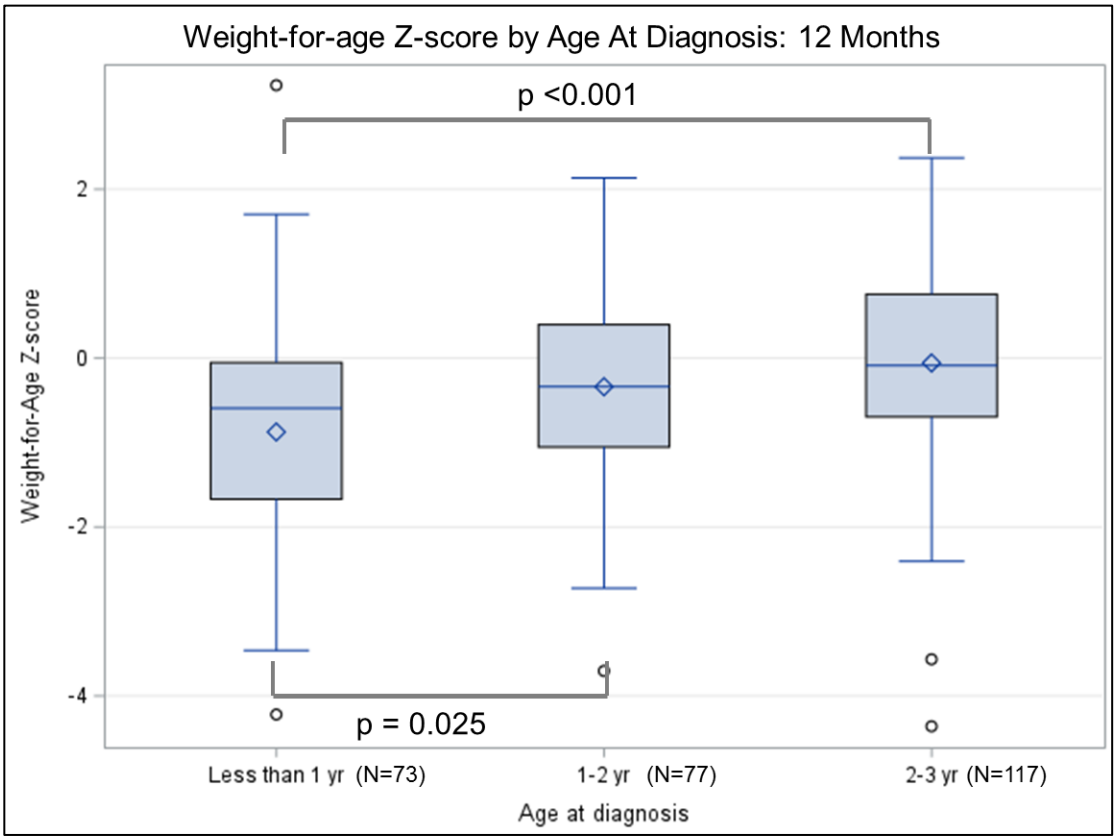

Figure 5: Differences in Weight-for-Age Z-score by Diagnosis Age at 24 Months

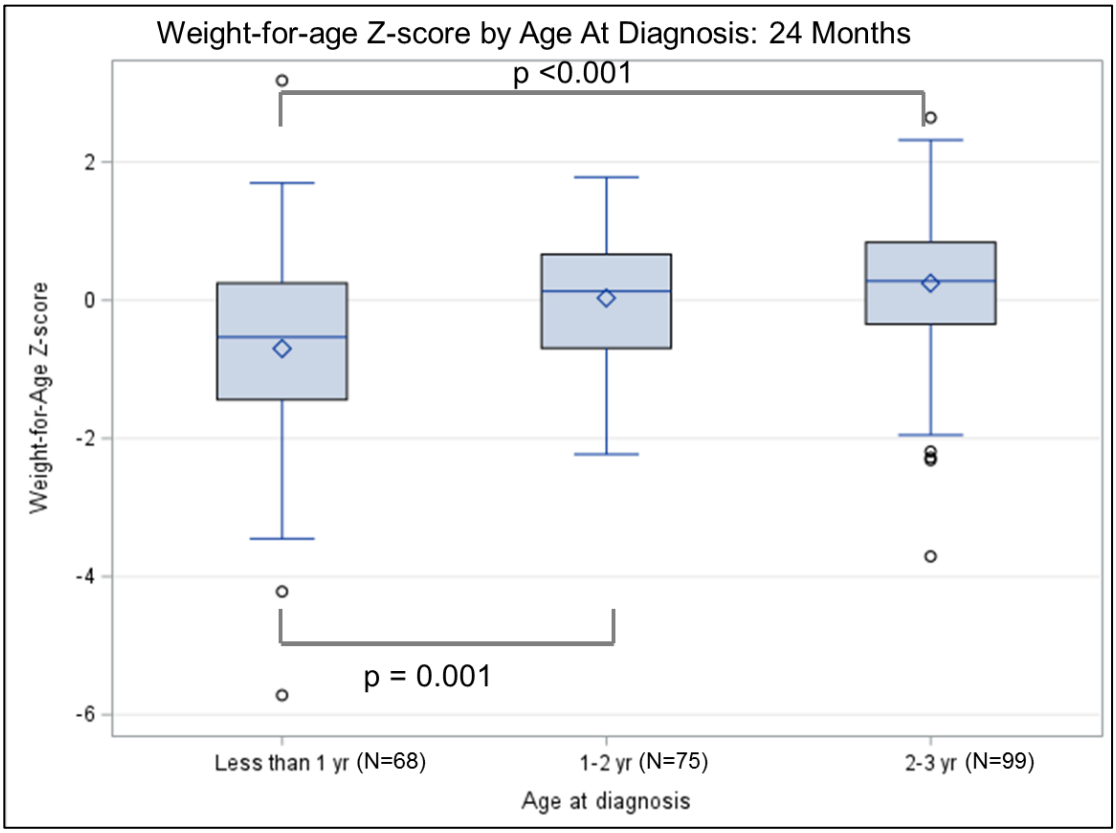

Table 3: Proportion of Patients Experiencing Clinically Significant Weight Loss

Variable	None	Significant weight loss	p-value*
Tumor Type			
Brain Tumor	34 (59.6%)	23 (40.4%)	0.75
Non-brain tumor	233 (61.8%)	144 (38.2%)	
Intensity Group			
Low	143 (74.5%)	49 (25.5%)	<0.001
High	124 (51.2%)	118 (48.8%)	
Age at Diagnosis			
0-0.99 years	69 (47.3%)	77 (52.7%)	<0.001
1-1.99 years	91 (69.5%)	40 (30.5%)	
2-2.99 years	107 (68.2%)	50 (31.8%)	

*Chi-square p value

Table 4: Univariate logistic regression analysis

Variable	OR	95% CI	p-value
White (vs Non-White Race)	1.00	0.62-1.61	0.999
Non-Hispanic Ethnicity (vs Hispanic)	1.01	0.91-1.13	0.642
Age Group (0v1)	2.39	1.50-3.81	<0.0001
Age Group (0v2)	2.53	1.55-4.12	<0.0001
Male Sex (vs Female)	0.96	0.65-1.42	0.850
Tumor Type	0.91	0.52-1.61	0.756
High Intensity Group (vs Low)	2.78	1.84-4.19	<0.0001
ITR (2v1)	2.21	0.62-7.85	0.151
ITR (3v1)	5.39	1.54-18.91	0.005
ITR (4v1)	6.92	1.83-26.17	0.001

Age group 0 = Patients diagnosed 0-0.99 years of age; Age group 1 = Patients diagnosed 1.00-1.99 years, Age group 2 = Patients diagnosed 2.00-2.99 years; ITR = Intensity of Treatment Rating Score

Table 5: Multivariate Logistic Regression

Variable	aOR	95% Wald CI	p-value*
Intensity Group			
High intensity (vs. Low)	2.83	1.85-4.31	<0.001
Age at Diagnosis			
<1 year (vs. 1-2yo)	2.73	1.63-4.54	<0.001
<1 year (vs. 2-3yo)	2.27	1.40-3.68	<0.001
1-2 year (vs. 2-3yo)	0.83	0.50-1.40	0.011

*Multivariate logistic regression confidence interval p value

Figure 6: Time to First Significant Weight Loss

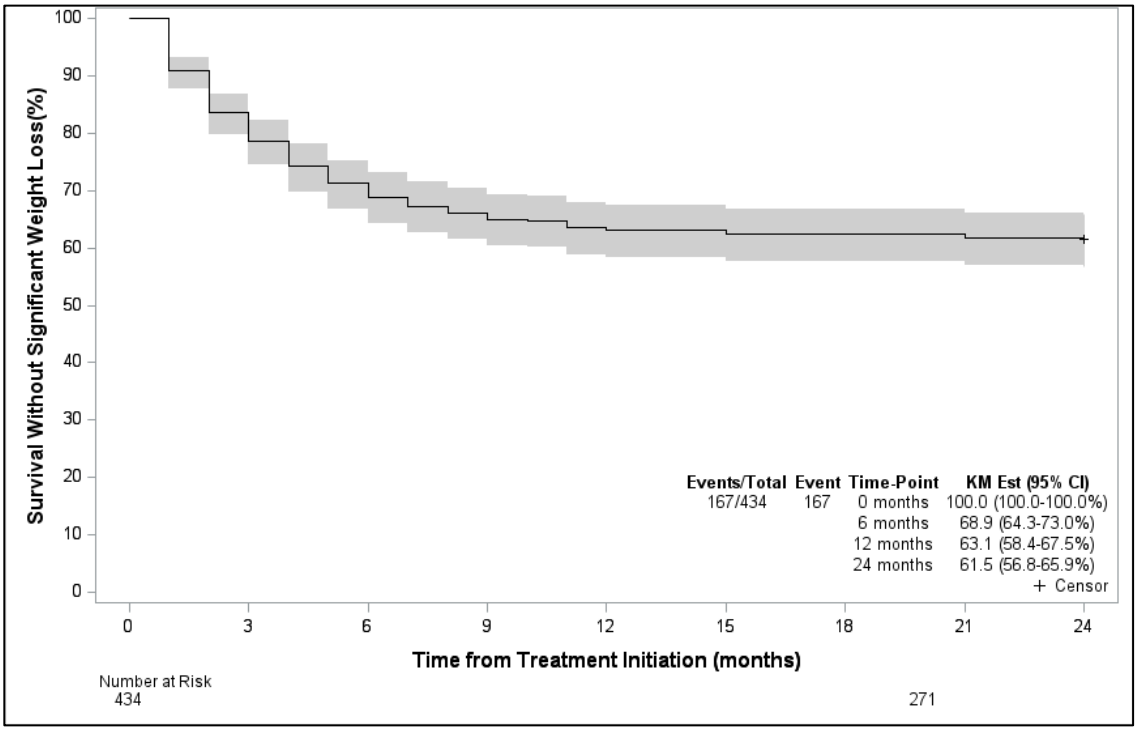

Figure 7: Time to First Significant Weight Loss by Tumor Type

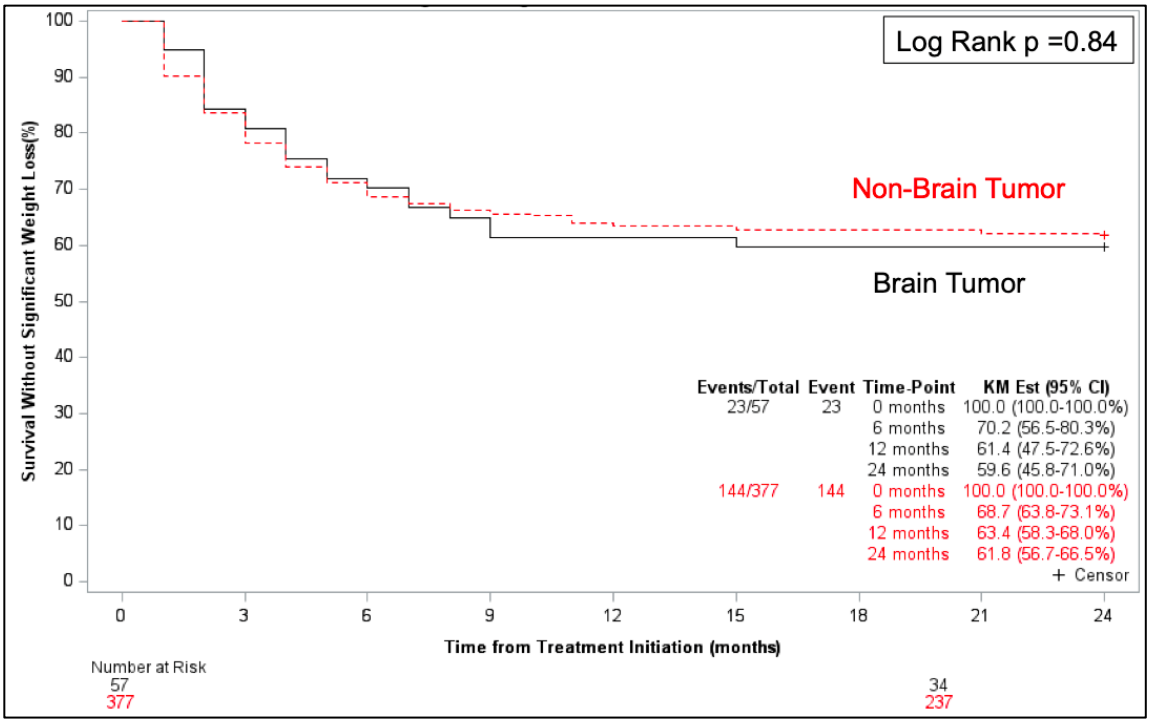

Figure 8: Time to First Significant Weight Loss by Treatment Intensity Group

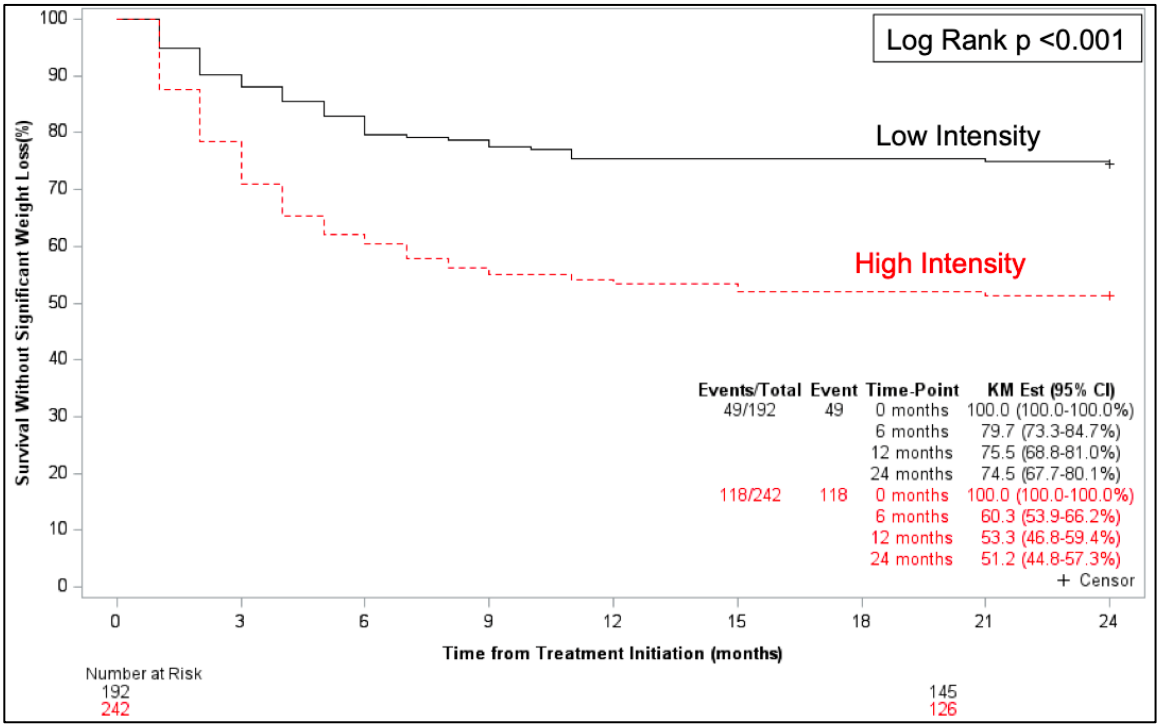

Figure 9: Time to First Significant Weight Loss by Age at Diagnosis

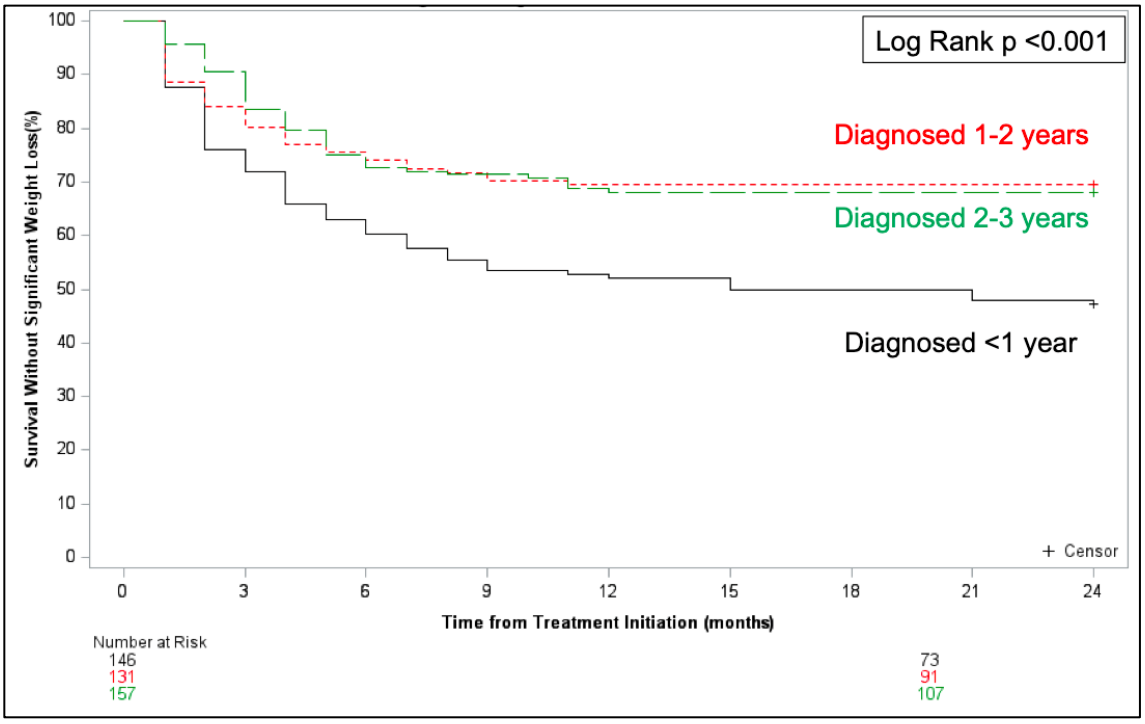

Table 6: Kaplan Meier Estimates for Time to Weight Loss by Age at Diagnosis

Age Group	Events/Total	Time Point	KM Estimate	95% CI
<1 year	77/146	0 Months	100.0%	-
		6 Months	60.3%	51.9-67.7%
		12 Months	52.1%	43.7-59.8%
		24 Months	47.3%	39.0-55.1%
1-2 year	40/131	0 Months	100.0%	-
		6 Months	74.0%	65.6-80.7%
		12 Months	69.5%	60.8-76.6%
		24 Months	69.5%	60.8-76.6%
2-3 year	50/157	0 Months	100.0%	-
		6 Months	72.6%	64.9-78.9%
		12 Months	68.2%	60.2-74.8%
		24 Months	68.2%	60.2-74.8%