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REPETITIVE, PRE-ANESTHETIC FASTING AND MALNUTRITION IN A PEDIATRIC ONCOLOGY POPULATION UNDERGOING RADIATION THERAPY

Laura P. Santibáñez

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REPETITIVE, PRE-ANESTHETIC FASTING AND MALNUTRITION IN A PEDIATRIC
ONCOLOGY POPULATION UNDERGOING RADIATION THERAPY

A DISSERTATION SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR
THE DEGREE OF DOCTOR OF PHILOSOPHY IN NURSING

THE UNIVERSITY OF TEXAS HEALTH SCIENCE CENTER AT HOUSTON
SCHOOL OF NURSING

BY

LAURA P. SANTIBÁÑEZ, PhD(c), MSN

August 2016

The University of Texas Health Science Center at Houston
School of Nursing
Houston, Texas

06/07/2016

Date

To the Dean for the School of Nursing:

I am submitting a dissertation written by Laura P. Santibáñez and entitled "Repetitive, Pre-Anesthetic Fasting and Malnutrition in a Pediatric Oncology Population undergoing Radiation Therapy." I have examined the final copy of this dissertation for form and content and recommend that it be accepted in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Nursing.



Cathy L. Rozms, RN, PhD, Committee Chair

We have read this dissertation
and recommend its acceptance:

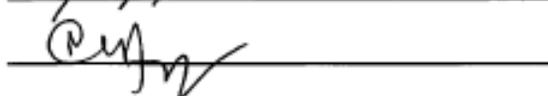
Penelope Z. Strauss, PhD



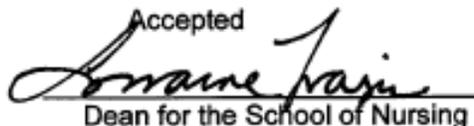
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Accepted



Dean for the School of Nursing

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Laura P. Santibáñez, PhD(c), MSN, RN, CRNA

Repetitive, Pre-Anesthetic Fasting and Malnutrition in a Pediatric Oncology
Population undergoing Radiation Therapy

August 2016

Abstract

Background: Pediatric oncology patients often experience nutritional status changes, particularly malnutrition, which may adversely affect their outcomes. Although the consequences of malnutrition are elucidated, its causes remain unclear. A possible cause of malnutrition in pediatric oncology patients is repetitive, pre-anesthetic fasting prior to non-invasive procedures and treatments, such as anesthesia-assisted radiation therapy (AART). This exploratory study investigated the association between repetitive, pre-anesthetic fasting and non-fasting days and malnutrition in pediatric oncology patients receiving AART.

Procedure: A retrospective cohort of 138 pediatric oncology patients (≤ 10 years of age) who received any type of radiation therapy (RT) with or without anesthesia between 2006 and 2015 in a tertiary care hospital was evaluated for nutritional status changes from the start to the end of RT using three primary indicators for malnutrition (weight gain velocity $< 75\%$ of expected weight gain, deceleration in weight for length/height z-score ≥ 1 , and percent weight loss $\geq 5\%$). Univariate and multivariate regression analyses were conducted to evaluate the association between fasting and non-fasting days and malnutrition.

Results: The number of fasting and non-fasting days was not significantly associated with malnutrition by the end of AART. However, after adjusting for age, patients who received concurrent chemotherapy had higher odds of becoming malnourished (odds

ratio [OR] = 3.48; $p = 0.024$). Furthermore, after adjusting for concurrent chemotherapy, patients 2 years of age and older had lower odds of becoming malnourished (OR = 0.23, $p = 0.018$ for patients ≥ 2 to < 5 years; OR = 0.26, $p = 0.047$ for patients ≥ 5 years).

Conclusions: In pediatric oncology patients receiving AART, malnutrition status is not associated with repetitive, pre-anesthetic fasting, but with young age and concurrent chemotherapy. Further research is needed to corroborate these findings.

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Summary of Study

The primary goal of this research study was to investigate the malnutrition status of pediatric oncology patients undergoing anesthesia-assisted radiation therapy, which requires intermittent repetitive fasting. The completed study summarized in the manuscript did not include or analyzed several of the outcome measures originally outlined in the research proposal, which included the following:

1. Deceleration in weight for length/height z-scores for all children were not obtained. Z-score tables for this primary indicator were only available for lengths/heights < 121.5 cm.
2. Cancer grade and stage, secondary diagnoses, chemotherapy treatment, and protocol information was not available for significant number of included cases, therefore it was unable to be analyzed.
3. No documented diagnosis of nutritional deficiencies based on ICD-9 codes during radiation therapy dates were found.
4. Data for discharge time of recovery unit after each anesthetic administration after radiation therapy was not available during chart review, therefore these data were not abstracted.
5. Start and end of anesthesia, cumulative intravenous fluid administration, lab values, and radiation type and site were not analyzed because of significant missing values or disparity in data abstracted (for example, lab values available or disparity in timing during radiation therapy).

Research Proposal

A. Specific Aims

Approximately 43% of children in the US are chronically ill.(Bethell et al., 2011) One chronic illness is cancer, which is the leading cause of death by disease in children after infancy. In the US, 1 in 285 children is diagnosed with cancer before 20 years of age.(American Cancer Society, 2014) Pediatric oncology patients undergo multiple diagnostic and therapeutic procedures that require anesthesia during their course of illness, often to ensure immobility during non-invasive procedures.(Latham, 2014) This is the case for pediatric oncology patients under 10 years of age receiving radiation therapy, who require daily anesthesia for up to 6 consecutive weeks.(Buchsbaum et al., 2013; McFadyen, Pelly, & Orr, 2011; Scheiber, Ribeiro, Karpienski, & Strehl, 1996) These children undergo pre-anesthetic fasting prior to *each* administration of anesthesia,(American Society of Anesthesiologists Committee, 2011) which may place them at risk for malnutrition. Malnutrition in pediatric oncology patients has been associated with poor clinical outcomes including a higher incidence of treatment-related mortality.(Antillon et al., 2013; Brinksma et al., 2015; Ethier et al., 2012; Inaba et al., 2012; Loeffen, Brinksma, Miedema, de Bock, & Tissing, 2015; Orgel et al., 2014; Sala et al., 2012) However, the association between repetitive pre-anesthetic fasting and malnutrition in pediatric oncology patients has not been investigated. This gap in knowledge poses a substantial problem in this population because healthcare providers are unable to assess the potential effect of repetitive pre-anesthetic fasting on patients' nutritional status.

Our long-term goal is to identify factors that place chronically ill pediatric patients at risk for worse outcomes and to develop interventions to improve outcomes. The overall objective of this exploratory study, which is the first step in pursuit of our goal, is to

determine the association between repetitive pre-anesthetic fasting and malnutrition in a population of pediatric oncology patients who received anesthesia-assisted radiation therapy (AART) for up to 6 weeks. Our central hypothesis is that repetitive pre-anesthetic fasting negatively affects the nutritional status of pediatric patients. Our hypothesis is formulated on the basis that the nutritional requirements of chronically ill children are frequently unmet,(Groleau et al., 2014; Hendricks et al., 1995; Huysentruyt et al., 2013; Joosten & Hulst, 2008; Mara et al., 2014; Silva et al., 2013) and that fasting creates various adverse metabolic effects (e.g., depletion of hepatic glycogen reserves, increased protein catabolism, higher energy expenditure at rest).(Awad, Constantin-Teodosiu, Macdonald, & Lobo, 2009; Awad & Lobo, 2012; Nygren, 2006) The rationale for the proposed research is that establishing the association between repetitive fasting and nutritional status in this population will enable the study of the underlying metabolic mechanisms of *repetitive* pre-anesthetic fasting on nutritional status (e.g., post-treatment insulin resistance) and subsequent long-term outcomes (e.g., treatment response, event-free survival rate). We expect this to result in the development of new interventions to improve outcomes in chronically ill pediatric patients.

We plan to test our central hypothesis with the following two specific aims:

1. ***Determine the association between total pre-anesthetic fasting days and primary indicators for nutritional status (weight gain velocity in patients < 24 months age; weight loss in patients ≥ 24 months age; deceleration in weight for length/height z-scores in all patients) in pediatric patients under 10 years of age during a radiation therapy (RT) cycle.*** We hypothesize that a higher number of pre-anesthetic fasting days during an RT cycle will be associated with worse nutritional status.

2. ***Determine the association between total non-fasting days (i.e., treatment off days during AART or treatment days without AART) and primary indicators for nutritional status in pediatric patients under 10 years of age during a RT cycle.*** We anticipate, based on our hypothesis, that a higher number of non-fasting days during an RT cycle will be associated with better nutritional status.

With respect to outcomes, we expect to determine the associations between repetitive pre-anesthetic fasting and nutritional status changes in pediatric patients over a specified treatment period. The findings are anticipated to advance the fields of pediatric anesthesia, clinical nutrition, and radiation oncology by identifying modifiable factors that will inform the development of new interventions for nutritional pre-anesthetic evaluation, management, and follow-up. Additionally, these findings are anticipated to have a positive translational impact because the determined associations will provide the preliminary data to support the study of various nutrition-related long-term outcomes, which are discussed in the Significance section.

B. Research Strategy

Significance

Current practice guidelines for pre-anesthetic fasting recommend that children abstain, at minimum, from breast milk for 4 hours, from clear liquids for 2 hours, and from nonhuman milk or solid foods for 6 hours prior to anesthesia. (American Society of Anesthesiologists Committee, 2011) In actual practice, anesthetic providers use their clinical judgment to determine the appropriate minimum fasting time prior to *each* anesthetic administration; therefore, reported pre-anesthetic fasting times are usually much longer than the minimum recommendations. (Arun & Korula, 2013a; Hancock,

Cresci, & Martindale, 2002; Williams et al., 2014) It is important to note that parent-reported pre-anesthetic fasting times may not be accurate in some cases.(Adudu, Egwakhide, & Adudu, 2008; Cantellow, Lightfoot, Bould, & Beringer, 2012; Kushnir, Djerassi, Sofer, & Kushnir, 2015) Despite the varying length of time that children fast prior to each anesthetic, repetitive pre-anesthetic fasting may place pediatric patients at risk for malnutrition. Malnutrition in pediatric oncology patients has been associated with worse health-related quality of life, increased occurrences of febrile neutropenia, higher incidence of treatment-related mortality, and lower event-free survival rates. (Antillon et al., 2013; Brinksma et al., 2015; Ethier et al., 2012; Inaba et al., 2012; Loeffen et al., 2015; Orgel et al., 2014; Sala et al., 2012) However, it is unknown whether repetitive pre-anesthetic fasting is associated with nutritional status in these patients. Our expected contribution is to determine the extent to which repetitive pre-anesthetic fasting is associated with malnutrition. *This contribution is significant because it will provide a positive translational impact on the assessment and improvement of long-term clinical outcomes in chronically ill pediatric patients.* Specifically, interventions to improve nutritional outcomes based on identified risk factors can be developed and tested. For example, pediatric anesthesiologists will have empirical evidence to develop new protocols to evaluate nutritional status during their pre-anesthetic assessment in order to identify patients at high risk for malnutrition, who should be referred to clinical nutritionists. Clinical nutritionists could then develop individualized diet plans, while radiation oncologists could consider modifying treatment cycle schedules for high-risk patients to minimize the amount or length of time of pre-anesthetic fasting. Thus, important advances in clinical practice and multidisciplinary collaboration are expected. It is also expected that this exploratory study will provide the basis for investigating the relationship between repetitive pre-anesthetic fasting and malnutrition with subsequent long-term outcomes, such as treatment-related toxicity, quality of life, and event-free

survival, in order to improve overall outcomes. Furthermore, this exploratory study is significant because it will contribute to the broader understanding of iatrogenic-related clinical malnutrition.

Innovation

To date, most research in the area of pre-anesthetic fasting in pediatric patients has been limited to *single* instances of fasting and has focused on the prevention of pulmonary aspiration,(Andersson, Zaren, & Frykholm, 2015; Arun & Korula, 2013b; Brady, Kinn, O'Rourke, Randhawa, & Stuart, 2005; Buehrer et al., 2014; Campbell, 2011; Castillo-Zamora, Castillo-Peralta, & Nava-Ocampo, 2005; Chen, Toung, Haupt, Hutchins, & Cameron, 1984; Engelhardt, 2015; Gombar, Dureja, Kiran, Gombar, & Chhabra, 1997; Goudsouzian & Young, 1987; Henderson, Spence, Clarke, Bonn, & Noel, 1987; Jabbari Moghaddam, Seyedhejazi, Naderpour, Yaghooblu, & Golzari, 2014; D. A. Kelly, 1994; Kemmotsu et al., 1991; Kraus, Braun, Gotz, Raithel, & Danner, 1990; Luce et al., 2014; Maekawa, Mikawa, Yaku, Nishina, & Obara, 1993a; Maekawa, Nishina, Mikawa, Shiga, & Obara, 1998; Muhammad, Wadood, Haroon, Khan, & Shah, 2012; Patino et al., 2015; Poulton, 2012; Schmidt et al., 2015; Schmitz et al., 2011; Schmitz, Kellenberger, Liamlahi, Studhalter, & Weiss, 2011; Schmitz et al., 2012; Scrimgeour, Leather, Perry, Pappachan, & Baldock, 2015) management of intravenous fluids,(Gawecka & Mierzewska-Schmidt, 2014a; Hashimoto, Fujii, & Serada, 2011; Murat & Dubois, 2008; Sumiyoshi, 2013) evaluation of complications,(Andersson et al., 2015; C. J. Kelly & Walker, 2015; Ribeiro de Amorim et al., 2015; Robertson-Malt et al., 2008; Scarlett, Crawford-Sykes, & Nelson, 2002) and assessment of immediate short-term outcomes.(Klemetti et al., 2010; Yurtcu, Gunel, Sahin, & Sivrikaya, 2009) In the relatively few studies that have focused on pediatric nutritional outcomes, researchers investigated the tolerance of carbohydrate oral solutions preoperatively or depletion of

blood glucose postoperatively.(Adenekan, 2014; Gawecka & Mierzewska-Schmidt, 2014b; Huang et al., 1993; Jensen, Wernberg, & Andersen, 1982; Maekawa, Mikawa, Yaku, Nishina, & Obara, 1993b; Shah, Zahooreullah, Haq, & Akhtar, 1990; Somboonviboon & Kijmahatrakul, 1996) *The proposed research is innovative, in our opinion, because it represents a fundamental and significant departure from the status quo by shifting the focus from single instances of pre-anesthetic fasting to repetitive instances, and because it evaluates nutritional status changes as an outcome for the first time.* We expect that results from this exploratory study will open new avenues in pediatric research by providing the preliminary data to support future research on the underlying metabolic and nutritional effects associated with repetitive pre-anesthetic fasting and their subsequent long-term outcomes. For example, research investigating the benefits of caloric restriction in reducing oxidative stress and improving cancer treatment responses is emerging.(Champ et al., 2013; Dan, Wright, & Simone, 2014; Habermann et al., 2015; Jin et al., 2014; Klement, 2013; Klement & Champ, 2014; Kowaltowski, 2011; Oliai & Yang, 2014; Saleh et al., 2013; Seyfried, Flores, Poff, D'Agostino, & Mukherjee, 2015; Simone et al., 2013; Yoshida, Hirabayashi, Watanabe, Sado, & Inoue, 2006) In addition, the associations between the metabolic responses from a single episode of pre-anesthetic fasting with baseline characteristics (e.g., malnutrition preoperatively) and postoperative outcomes (e.g., length of stay) have begun to be studied in adult patients.(Awad et al., 2009; Awad & Lobo, 2012; Nygren, 2006) However, it is unclear how repetitive pre-anesthetic fasting indirectly affects treatment responses through caloric restriction or how metabolic derangements induced by repetitive pre-anesthetic fasting affect pharmacogenetic responses to radiation or chemotherapy in pediatric patients. We expect that the preliminary data collected in this study will support future investigations into the metabolic effects of repetitive pre-

anesthetic fasting and subsequent long-term outcomes that have not been evaluated in chronically ill children.

Approach

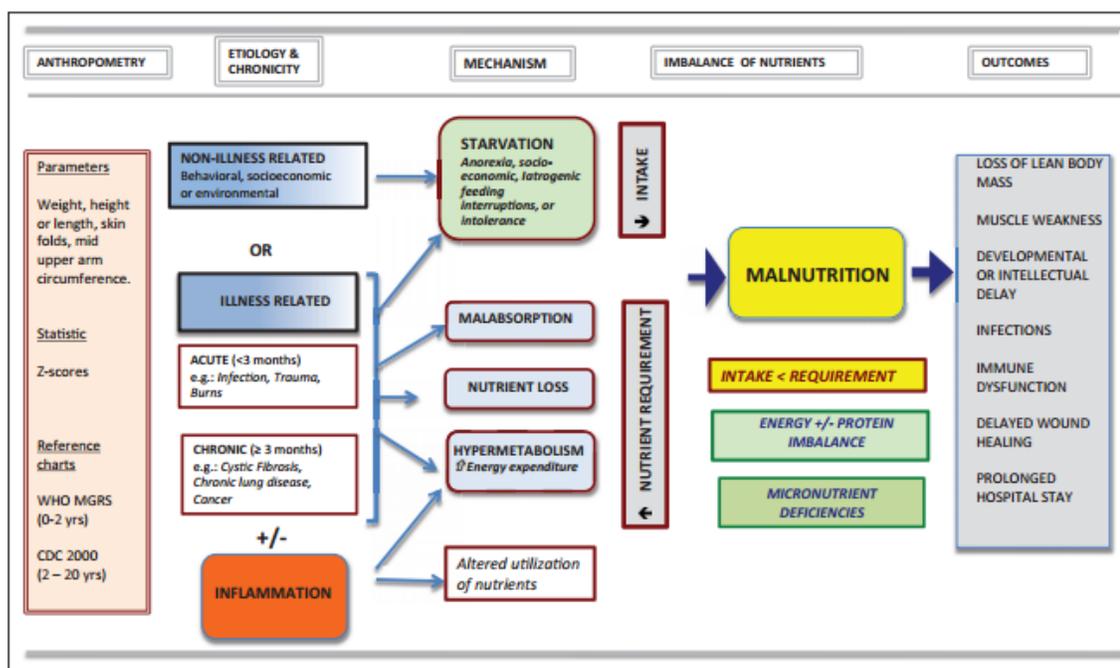
Introduction and Rationale

We propose to test our *central hypothesis* that repetitive pre-anesthetic fasting negatively affects the nutritional status of pediatric patients with two specific aims. This hypothesis is based on a model for child malnutrition, the underlying mechanisms produced by fasting that lead to metabolic changes, and research findings describing the nutritional requirements that are often unmet in chronically ill children.

Pediatric malnutrition model. An interdisciplinary working group of nurses, physicians, dietitians, and pharmacists, under the direction of the American Society of Parental and Enteral Nutrition (ASPEN), developed a definition and a key concept model of malnutrition using the best available evidence (Figure 1). (Mehta et al., 2013) Five domains were identified to describe pediatric malnutrition, which included anthropometric parameters and growth, etiology and chronicity, mechanisms, imbalance of nutrients, and outcomes. Pediatric malnutrition, related to undernutrition, was defined as the “imbalance between nutrient requirement and intake, resulting in cumulative deficits of energy, protein, or micronutrients that may negatively affect growth, development and other relevant outcomes.” (Mehta et al., 2013) The model and definition of malnutrition developed by the ASPEN group should be used for hospitalized children, but the working group emphasized that the model and definition addresses children in all settings, with the exception of malnutrition observed in the developing world or in neonates. Type and severity of disease were identified as two important variables that dictate nutrient requirements and a child’s ability to absorb and utilize nutrients. Conceptually, pediatric oncology patients undergoing RT may already be at risk for

malnutrition because of their diagnosis (etiology) and treatment (mechanism involving altered nutrient utilization and hypermetabolism). In addition, the subset of children undergoing AART may be placed at a higher risk for malnutrition because of the additional burden of intermittent, but repetitive, starvation periods (mechanism) resulting from pre-anesthetic fasting.

Figure 1. Key concepts of malnutrition in hospitalized children^a



^aReproduced from Mehta *et al.*, 2013.(Mehta et al., 2013) CDC, Centers for Disease Control and Prevention; MGRS, Multicenter Growth Reference Study; WHO, World Health Organization.

Metabolic derangements of fasting. The metabolic effects of fasting have been described in the literature. Generally, fasting, or starvation, occurs when energy requirements exceed energy intake over a prolonged period of time.(Nygren, 2006) The body energy stored as carbohydrates, or hepatic glycogen, generally lasts for less than 24 hours during a period of fasting, whereas protein and fat stores last much longer, approximately 21 days and 55 days, respectively.(Nygren, 2006) In adults, a 10%–15% weight loss in body weight typically does not lead to any significant functional derangements, but weight loss in the range of 30%–45% of body weight can become

life-threatening.(Nygren, 2006) In children, weight loss, or deceleration in weight gain, may result in significant metabolic derangements or death, depending on the underlying conditions present (e.g., illness), age and stage of development, and baseline energy stores.(Browning et al., 2006; Freemark, 2015; Ugochukwu, 2006) In sustained fasting conditions, or prolonged periods of time with decreased energy intake, metabolic adaptation occurs to decrease the rate of protein store depletion. However, as insulin and glucose concentrations decrease, both proteolysis (primarily in muscle) and lipolysis occurs.(Awad et al., 2009) Energy expenditure at rest increases as a result of gluconeogenesis and ketogenesis.(Awad et al., 2009; Webber & Macdonald, 1994) Additionally, even brief periods of fasting results in a significant decrease in insulin sensitivity.(Awad et al., 2009; Nygren, 2006) The development of insulin resistance has been associated with an increase in postoperative morbidity and mortality.(Awad & Lobo, 2012) Overall, pre-anesthetic fasting has been associated with an overall induction of metabolic stress and subsequent insulin resistance, which has been hypothesized to affect mitochondrial cellular processes as well as protein and gene expression.(Awad & Lobo, 2012)

Nutritional status of chronically ill children. Close to 25% of hospitalized children are acutely malnourished, while close to 30% can be classified as being chronically malnourished.(Hendricks et al., 1995; Joosten & Hulst, 2008) Among hospitalized children, those with chronic medical conditions and younger than 2 years of age have a higher prevalence of protein-energy malnutrition.(Hendricks et al., 1995) Malnutrition is often unrecognized by clinicians, leading to approximately only one-third of undernourished hospitalized children receiving nutritional support.(Huysentruyt et al., 2013; Silva et al., 2013) A recent study evaluating hospitalized children receiving nutritional support reported that even when ill children receive nutritional support, protein

and energy requirements are met in only about 38% and 33% of pediatric patients, respectively. (Mara et al., 2014) Fasting, including pre-anesthetic fasting, and fluid restrictions imposed for clinical reasons were the two most commonly cited reasons for not meeting nutritional target goals in the remaining group of children. (Mara et al., 2014)

Research Design

A retrospective cohort design will be employed to test our specific aims. Chart reviews will be conducted to abstract demographic, covariate, and outcome data. This proposed study design has been employed successfully in previous studies investigating both pre-anesthetic fasting and nutritional status changes in chronically ill children.

Participants and Procedure Patients treated at a large, 500+ bed academic and research cancer center, The University of Texas MD Anderson Cancer Center (MDACC), will be screened for study eligibility. Inclusion criteria will be limited to pediatric oncology patients (a) who are under 10 years of age as of October 1, 2015, and (b) who received any type of RT at MDACC between January 1, 2006, and October 1, 2015, either with or without anesthesia. Patients with all cancer diagnoses will be included. Exclusion criteria will include (a) patients without a charted weight or length/height within 14 days of the start of radiation treatment, and (b) patients without a charted weight or length/height within 14 days after the completion of radiation treatment. After institutional review board (IRB) approval, a medical record database query request will be submitted to the MDACC Clinical Analytics and Informatics Department. A list of medical record numbers for patients who meet the preliminary age and treatment inclusion criteria will be obtained. Electronic medical charts will be accessed and reviewed for inclusion criteria using the medical record numbers obtained from the MDACC Clinical Analytics and Informatics Department. Convenience, consecutive sampling of eligible patients will be performed, starting with the inclusion of

patients who were most recently treated until a sufficient sample size for each included group is obtained for analytical purposes.

Variables and Data Collection/Abstraction Variables that will be abstracted from the electronic medical charts of patients are listed in Table 1. Data abstracted from charts will be entered into an electronic study database provided by the MDACC Biostatistics Department.

Table 1. Study variables to be abstracted

Demographic/ Patient characteristics	Covariate	Outcome
Ethnicity and/or nationality	Date of radiation simulation	Height/length measure within 14 days of start of RT (most recent to first day of RT)
Sex	Date of first and last day of RT	Height/length measure within 14 days of completion of RT (most recent to last day of RT)
Date of birth	Dates of RT	All height/length measures during RT
Primary cancer diagnosis	Dates of anesthetic administrations during RT (including simulation)	All weight measures during RT
Cancer grade and stage	Start and end time of anesthesia billing time for each anesthetic administration during RT	Weight measure within 14 days of start of RT (most recent to first day of RT)
Secondary diagnoses	Discharge time from recovery unit after each anesthetic administration during RT	Weight measure within 14 days of completion of RT (most recent to last day of RT)
Radiation site	Dates of anesthetic administration to include any anesthetics within 1 month prior to start of radiation	

	treatment or during radiation treatment cycle	
Total radiation dose	Documented referral/consult to clinical nutrition or ongoing management by clinical dietician	
Protocol	Documented diagnosis of nutritional deficiencies (ICD-9 Codes 260-269.9)	
Radiation type	Dose and type of prescribed dietary supplements	
Baseline nutritional status (weight for height z-score or BMI for age z-score)	Type, duration, amount of enteral/tube feedings during RT cycle or within 14 days of start or end of RT cycle	
	Dates of prescribed steroid therapy to include up to 3 months prior to beginning of treatment, during or up to 14 days after last day of treatment cycle	
	Cumulative intravenous fluid administration during AART (type and total volume)	
	Cumulative TIVA anesthetic dose (propofol) during AART	
	Dates, doses and type of chemotherapy treatment to include any treatment within 1 month prior to start of RT or during RT cycle (concomittant chemotherapy)	

	<p>All lab result values available from 14 days prior to start of RT up to 14 days after last date of RT including:</p> <ul style="list-style-type: none"> - Total protein - Serum albumin - Pre-albumin - Ferritin - Hemoglobin - Hematocrit - Lipid profile - Liver function tests Pancreatic enzymes - White blood count - Total lymphocyte count - Bicarbonate - Lactic acid - Glucose - A1c 	
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Instruments Growth can be defined as the development into maturity, which can be observed as an increase in physical size.(Becker et al., 2015) Growth charts that allow the comparison of standard deviations (SD) from the norms in various reference age groups, that is, z-score comparisons, have been recommended for the evaluation and tracking of nutritional status in children.(Becker et al., 2015)

World Health Organization Growth Standards, 0–24 months of age. The Centers for Disease Control and Prevention (CDC) recommends the use of World Health Organization (WHO) growth standards to evaluate infants and children from birth to 2 years of age.(CDC National Center for Health Statistics, 2010) The WHO charts provide growth standards for infants who were predominantly breastfed during the first 4 months of life and continued to be breastfed until 12 months of age. The WHO charts present the rate at which small children should grow when provided with optimal alimentary conditions. In contrast, CDC charts identify how children in the US grew during a specific time period, which may not represent ideal growth patterns. Thus, the WHO standards

are better than the CDC standards for assessing physiological growth in early life. The methods and development of the most recent WHO growth standards have been published.(WHO Multicentre Growth Reference Study Group, 2009)

Centers for Disease Control and Prevention Growth Standards, ≥ 24 months of age. The CDC recommends the use of the CDC growth standards to monitor the growth of children in the US who are 24 months of age or older.(CDC National Center for Health Statistics, 2010) The methods and development of the most recent CDC growth charts have been published(Kuczmarski, Ogden, Guo, & et al, 2002)

Outcome Measures In their 2014 Pediatric Malnutrition Consensus Statement,(Becker et al., 2015) the Academy of Nutrition and Dietetics and the ASPEN recommended the use of various primary indicators as criteria for identifying and diagnosing malnutrition related to undernutrition when two or more anthropometric data points are available in children. The primary indicators that will be used to measure malnutrition in this exploratory study are shown in Table 2.

Table 2. Included primary indicators for the assessment of malnutrition in children^b

Primary indicators	Subject Age	Mild malnutrition	Moderate malnutrition	Severe malnutrition
Weight gain velocity(World Health Organization, 2015b)	< 24 months of age	$50 \leq x < 75\%$ of the norm for expected weight gain	$25 \leq x < 50\%$ of the norm for expected weight gain	<25% of the norm for expected weight gain
Weight loss	≥ 24 months of age	$5 \leq x < 7.5\%$ baseline body weight	$7.5 \leq x < 10\%$ baseline body weight	$\geq 10\%$ baseline body weight
Deceleration in weight for length/height z-score(World	All ages	Decline of 1-1.9 z-score	Decline of 2-2.9 z-scores	Decline of ≥ 3 z-scores

Health Organization, 2015a)				
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^b Adapted from Becker *et al.*, 2015.(Becker et al., 2015)

Weight gain velocity in children < 24 months of age and weight loss in children ≥ 24 months of age. Growth velocity is defined as the rate of change over time in weight or length/height.(Becker et al., 2015) The rate of change in growth can be used to assess a child's health and nutritional status over time.(Iannotti, Zavaleta, Huasaquiche, Leon, & Caulfield, 2015) Average rates of weight gain during periods of growth enable a child to maintain a stable rate of growth as determined by age and stage of development and evaluated by using the WHO growth standards. An example of a weight gain velocity chart depicted in 1-month weight increments for boys from birth to 12 months is included (Figure 2). Low weight gain velocities that may occur during time periods with insufficient rates of weight gain or weight loss in children have been independently related to higher mortality more closely than other malnutrition indicators.(O'Neill, Fitzgerald, Briend, & Van den Broeck, 2012)

Figure 2. 1-month weight increments percentiles (weight increase in grams) for boys, birth to 12 months^c

1-month weight increments BOYS

Birth to 12 months (percentiles)



Interval	L	M ^a	S	δ	Percentiles (weight increment in g)										
					1st	3rd	5th	15th	25th	50th	75th	85th	95th	97th	99th
0 – 4 wks	1.3828	1423.0783	0.22048	400	182	369	460	681	805	1023	1229	1336	1509	1575	1697
4 wks – 2 mo	0.7241	1596.3470	0.19296	400	528	648	713	886	992	1196	1408	1524	1724	1803	1955
2 – 3 mo	0.6590	1215.3989	0.19591	400	307	397	446	577	658	815	980	1071	1228	1290	1410
3 – 4 mo	0.7003	1017.0488	0.20965	400	160	241	285	403	476	617	764	845	985	1041	1147
4 – 5 mo	0.7419	921.6249	0.22790	400	70	150	194	311	383	522	666	746	883	937	1041
5 – 6 mo	0.7668	822.1842	0.24854	400	-17	61	103	217	287	422	563	640	773	826	927
6 – 7 mo	0.7688	756.5306	0.26783	400	-76	0	42	154	223	357	496	573	706	758	859
7 – 8 mo	0.7624	715.6257	0.28677	400	-118	-43	-1	111	181	316	457	535	671	724	827
8 – 9 mo	0.7620	684.7459	0.30439	400	-153	-77	-36	77	148	285	429	508	646	701	806
9 – 10 mo	0.7659	658.5809	0.32154	400	-183	-108	-66	48	120	259	405	486	627	683	790
10 – 11 mo	0.7713	643.4374	0.33882	400	-209	-132	-89	27	100	243	394	478	623	680	791
11 – 12 mo	0.7761	639.4743	0.35502	400	-229	-150	-106	15	91	239	397	484	635	695	811

^a The L, M, S values provided are estimated based on the modelling of the shifted observations (i.e. by the addition of delta to the actual increment) which explains the difference (equals to delta) in value between the "M" and the 50th centile values.

^cReproduced from WHO weight velocity child growth standards, 2015(World Health Organization, 2015b)

Deceleration in weight for length/height z-scores in all patients. Deceleration of

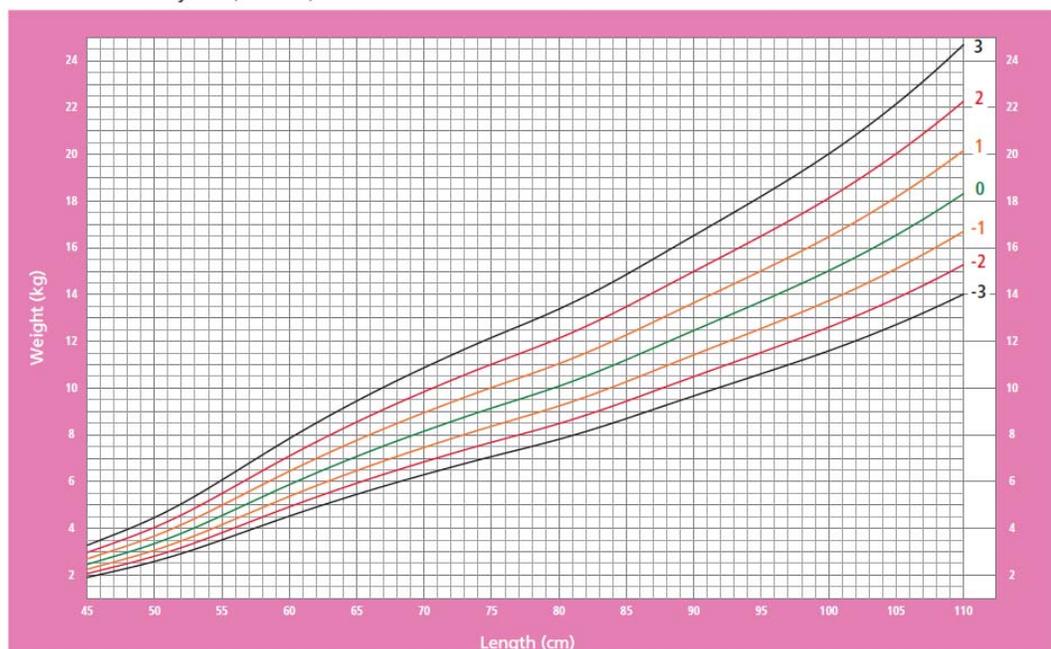
weight over time is one of the terms used to define malnutrition.(Eskedal et al., 2008)

The Academy of Nutrition and Dietetics and the ASPEN recommend the use of z-scores, namely, the decline in z-scores when comparing weight deceleration for length/height, to identify and evaluate malnutrition in children.(Becker et al., 2015) An example of a deceleration in weight for length chart for girls from birth to 24 months is included (Figure 3).

Figure 3. Weight-for-length z-scores for girls, birth to 24 months^d

Weight-for-length GIRLS

Birth to 2 years (z-scores)



WHO Child Growth Standards

^dReproduced from WHO z-score growth standards charts for girls, 2015 (World Health Organization, 2015a)

Covariates Variables that may (a) influence the growth (weight/length or height) pattern of a child such as steroid treatment therapy, (Couluris et al., 2008; Muller et al., 2003) (b) contribute to malnutrition status such as concomitant chemotherapy, (Groot-Loonen, Otten, van't Hof, Lippens, & Stoelinga, 1996; Ladas et al., 2005; Sacks et al., 2014) or (c) may reflect metabolic derangements from repetitive fasting (Ilhan, Sari, Eren, & Tacyildiz, 2015; Ong, Han, Wong, & Lee, 2014) or anesthetic administration (Bhukal, Thimmarayan, Bala, Solanki, & Samra, 2014; Chauhan, Garg, & Bharadwaj, 2013; Ture, Mercan, Koner, Aykac, & Ture, 2009) (e.g., albumin or triglyceride results) will be abstracted as covariate data and controlled statistically.

Cumulative anesthetic dose. The majority of the children undergoing AART at MDACC receive total intravenous anesthetic (TIVA) administration. (Owusu-Agyemang et al., 2014) Propofol is the anesthetic of choice for TIVA at MDACC. Propofol is an anesthetic that is formulated in a 10% intravenous fat emulsion, (Mirtallo, Dasta, Kleinschmidt, & Varon, 2010) and provides 1.1 kcal/mL. (Lowrey, Dunlap, Brown, Dickerson, & Kudsk, 1996) The cumulative anesthetic dose (mg/kg) that each patient receives during AART will be abstracted and total calories received through propofol infusions calculated. The total number of calories provided by propofol will be used as a covariate in subsequent analyses.

Cumulative intravenous fluid administration. Children receiving TIVA during AART also receive intravenous fluids (IVFs). Intravenous fluids containing dextrose provide calories. For example, a 5% dextrose solution on average provides 170kCal/L while a Plasma-Lyte R solution provides 17kCal/L. (Lutz, Litch, Mazur, STAT!Ref, & Teton Data Systems, 2015) The type of IVF administered for each anesthetic in every patient and the total volume of intravenous fluid administered during AART will be abstracted. The total number of calories provided by IVFs will be used as a covariate in subsequent analyses.

Experimental Approach

Specific Aim 1. Determine the association between total pre-anesthetic fasting days and primary indicators for nutritional status in pediatric patients under 10 years of age during an RT cycle. *Hypothesis: Higher number of pre-anesthetic fasting days during an RT cycle will be associated with worse nutritional status.* The length of RT cycles varies based on cancer diagnosis, tumor location, treatment protocol, and RT type, among other things. Radiation treatment cycles at MDACC for pediatric oncology patients range

from approximately 2 to 6 weeks. Children under the age of 10 years receiving RT with and without anesthesia will be included to test Specific Aim 1. A varying number of total pre-anesthetic fasting days during an RT cycle will be included. Most children under 6 years of age receive AART, whereas those over 6 years of age may or may not receive AART, depending on their ability to remain immobile during treatment. We anticipate that the total number of pre-anesthetic fasting days during an RT cycle will range from 0–30 days in children over 6 years of age (Table 3), whereas the total number of pre-anesthetic fasting days will range from 10–30 days in children under 6 years of age (Table 3). Outcome measures used differ for children < 24 months (weight gain velocity, deceleration in weight for length/height z-score) and those \geq 24 months (weight loss, deceleration in weight for length/height z-score). Outcomes (dependent variables) will be coded as dichotomous (no malnutrition/malnutrition) or ordinal (mild, moderate, or severe malnutrition), depending on the statistical approach. Risk for malnutrition will be evaluated by using the total number of pre-anesthetic fasting days as an independent variable while controlling for covariates. Among patients with an outcome of malnutrition status, risk factors will be determined for worse outcome.

Specific Aim 2. Determine the association between total non-fasting days and primary indicators for nutritional status in pediatric patients under 10 years of age during an RT cycle. *Hypothesis: Higher number of non-fasting days during an RT cycle will be associated with better nutritional status.* The length of RT cycles varies based on various factors, as mentioned previously. Children under the age of 10 years receiving RT with and without anesthesia will be included to test Specific Aim 2. A varying number of total non-fasting days during an RT cycle will be included. We anticipate that the total number of non-fasting days during an RT cycle will range from 2–40 days in children over 6 years of age (Table 3), whereas the total number of non-fasting days will range from 2–

10 days in children under 6 years of age (Table 3). Additionally, we anticipate that the total number of non-fasting days will vary slightly within each group from those estimated for clinical (e.g., febrile child where AART is cancelled) and non-clinical (e.g., treatment day falling on a weekday holiday) reasons. Outcome measures used differ for children < 24 months (weight gain velocity, deceleration in weight for length/height z-score) and those \geq 24 months (weight loss, deceleration in weight for length/height z-score). Outcomes will be coded as dichotomous (no malnutrition/malnutrition) and ordinal (mild, moderate, or severe malnutrition), depending on the statistical approach. Risk for malnutrition will be evaluated by using total non-fasting days as an independent variable while controlling for covariates. Among patients with an outcome of malnutrition status, risk factors will be determined for worse outcome while controlling for non-fasting days.

Table 3. Estimated number of total pre-anesthetic fasting and non-fasting days

Length of RT (range, estimated shortest to longest)	AART*		RT without Anesthesia ^α	
	FD	NFD	FD	NFD
2 weeks <ul style="list-style-type: none"> • 10 weekdays • 4 weekend days, inclusive 	10	2–4	0	12–14
6 weeks <ul style="list-style-type: none"> • 30 weekdays • 12 weekend days, inclusive 	30	10–12	0	40–42

AART, Anesthesia-Assisted Radiation Therapy; FD, pre-anesthetic fasting days; NFD, non-fasting days; RT, Radiation Therapy; * = Most children under 6 years of age will receive AART; ^α = Some children over 6 years of age will be capable of receiving RT without anesthesia.

Expected Outcomes We expect that this exploratory study will determine the associations between repetitive pre-anesthetic fasting and nutritional status changes in pediatric patients over an RT period. We expect to determine the effect that an increasing number of total pre-anesthetic fasting days has on the development of

malnutrition. Findings will be confirmed by then determining whether an increasing number of non-fasting days is found to decrease the risk for malnutrition. Additionally, among those children found to be malnourished at the end of RT, risk factors will be evaluated for varying levels of malnutrition (mild, moderate, and severe) while controlling for covariates.

Statistical Approach Data will be analyzed in consultation with an assigned biostatistician from the MDACC Biostatistics Department. Descriptive statistics will be used to evaluate patient characteristics of the study sample. Chi-square tests will be used to compare the distribution of baseline nutritional status across primary cancer diagnoses. Differences in groups regarding the presence or absence of malnutrition at the end of RT will be estimated by using univariate and multivariate binary logistic regression, yielding odds ratios (ORs) and 95% confidence intervals (95% CI). Ordinal logistic regression will be used to evaluate risk factors for mild, moderate, and severe malnutrition. Significance levels will be established at $p < 0.05$. The recommended sample size estimates for regression models vary, but a sample size of at least 5–10 cases per variable is acceptable. (Findley & Daum, 1989; Harrell, Lee, Matchar, & Reichert, 1985; Hsieh, Bloch, & Larsen, 1998; Sackett, Haynes, Guyatt, & Tugwell, 1991) A minimum of 120 patients will be included in this exploratory study, which is our estimated required sample size for statistical analyses.

Specific Aim 1. Univariate analysis will be used to examine the relationship between total number of pre-anesthetic fasting days and malnutrition status at the end of RT. Age will be categorized and divided into ranges so that trends within age groups can be identified. Multivariate logistic regression will be used to evaluate if a higher number of pre-anesthetic fasting days is associated with malnutrition status at the end of RT.

Specific Aim 2. Univariate analysis will be used to examine the relationship between total number of non-fasting days and malnutrition status at the end of RT. Age will be categorized and divided into ranges so that trends within age groups can be identified. Multivariate logistic regression will be utilized to evaluate if a higher number of non-fasting days is associated with non-malnutrition status at the end of RT.

Potential Problems and Alternative Approaches

Missing data due to incomplete documentation because of the nature of retrospective chart reviews is the main potential challenge for the proposed study. All data will be abstracted from electronic medical records, which were incorporated into the MDACC system starting in 2006. Patients will be excluded if height/length or weight have not been captured in the medical record prior to and after RT. Rules and a study protocol regarding the management of missing data for covariates or demographic variables will be devised prior to data collection. Whenever possible, missing data points will be imputed through statistical analysis.(Dworkin, 1987; Worster & Haines, 2004) In cases when data imputation cannot be done, the entire case will be excluded from statistical analyses. To account for potential exclusion or deletion of cases, oversampling by 15% will occur. Data will be abstracted from a total of 138 electronic medical charts from eligible patients. Another potential challenge is ensuring that we have access to the minimum number of medical records of for eligible patients. However, based on a recently published study investigating AART at MDAAC,(Owusu-Agyemang et al., 2014) we estimate that at least 180 charts from patients who meet the inclusion criteria are available for review. These charts are for pediatric oncology patients under 10 years of age who received anesthesia-assisted proton therapy between January 1, 2006, and January 1, 2014. We anticipate that the number of eligible patients is actually much higher given that we expect to also recruit patients who (a) received RT other than

proton therapy, (b) received RT without anesthesia, and (c) received RT after January 1, 2014.

Protection of Human Subjects

We expect that the IRB will waive informed consent requirements because of the retrospective research design of this study. No direct risk will be imposed on patients. All data will be de-identified upon abstraction from medical records. All electronic data will be encrypted and password-protected using institutional standards. Laptops and files (hard and soft copy) will be physically secured in a designated location at the UTHealth School of Nursing or at MDACC, as established by the primary researchers. Only key personnel (i.e., data collectors or primary researchers) will have access to study data, and only to data necessary to complete assigned tasks. Data will be destroyed after IRB approval expiration or minimum amount of time required for data retention has elapsed (whichever is longer). To ensure proper data destruction, physical files will be shredded while electronic files will be overwritten at the file and block level with specialized software.

Future Directions

This exploratory study will broaden our understanding of iatrogenic-related malnutrition by providing knowledge regarding the association between repetitive pre-anesthetic fasting and nutritional status changes and, if found, the strength of this association. We also expect to determine the extent to which non-fasting days or breaks from intermittent, repetitive fasting may ameliorate worse nutritional status changes. This work builds upon a conceptual model of malnutrition for ill children. We expect that the preliminary data collected in this study will support future research on the metabolic effects of repetitive pre-anesthetic fasting and subsequent long-term outcomes that have

not yet been evaluated in pediatric oncology patients, in particular, or chronically ill children, in general.

In future studies, we plan to investigate the potential indirect benefits of caloric restriction produced by repetitive pre-anesthetic fasting and cancer treatment responses in pediatric oncology patients undergoing AART. We also plan to investigate the interactions between the metabolic responses (e.g., insulin resistance) from repetitive pre-anesthetic fasting, along with baseline characteristics (e.g., malnutrition preoperatively) and subsequent long-term, post-treatment outcomes (e.g., length of stay, event-free survival).

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LETTER TO THE EDITOR

July 6, 2016

Peter E. Newburger, MD
Editor-in-Chief, *Pediatric Blood & Cancer*
205 Shannon Oaks Circle
Cary, NC 27511

Dear Dr. Newburger:

Attached, please find our manuscript, "Repetitive, pre-anesthetic fasting and malnutrition in a pediatric oncology population undergoing radiation therapy" for your consideration for publication as an original research article in *Pediatric Blood & Cancer*. We believe our study makes an important contribution to the growing literature on malnutrition in pediatric oncology patients. Specifically, it is the first study to examine the relationship between repetitive pre-anesthetic fasting and malnutrition. Thus, it will be of special interest to your readers who are actively involved in the treatment and care of very young pediatric oncology patients given that these patients are more likely to receive repetitive anesthesia-assisted diagnostic or therapeutic procedures. Our findings indicate that, among a cohort of pediatric oncology patients receiving anesthesia-assisted radiation therapy, malnutrition status was not associated with repetitive, pre-anesthetic fasting, but with young age and concurrent chemotherapy. Therefore, identified subgroups of pediatric oncology patients who are susceptible to malnutrition should be closely monitored for significant nutritional status changes during anesthesia-assisted radiation therapy.

This manuscript has not been published previously and is not under consideration by another journal. All authors have contributed to this manuscript, have reviewed and agreed upon the manuscript content, and are aware that it is being submitted to *Pediatric Blood & Cancer*. Furthermore, none of the authors have any potential conflicts of interest to disclose.

Potential reviewers for this manuscript include Adam J. Esbenshade, MD; Eva Cignacco, PhD; and Aeltsje Brinksma, PhD. These reviewers are considered experts in the field of malnutrition in pediatric oncology, and have published articles on related topics in *Pediatric Blood & Cancer* within the past 5 years. Lastly, these reviewers are not affiliated with our institutions and, to our knowledge, have no potential conflicts of interest.

Thank you for your time and consideration. If you have any questions, please feel free to contact me, as I am serving as the corresponding author for this manuscript. We look forward to hearing from you.

Sincerely,

Laura P. Santibanez, PhD, CRNA

Co-authors: Cathy L. Rozmus, PhD; Penelope Z. Strauss, PhD; Joya Chandra, PhD; Pascal Owusu-Agyemang, MD; Mike Hernandez, MS

MANUSCRIPT

Introduction

In the United States, pediatric cancers are rare, representing only 1% of all newly diagnosed cancers (American Cancer Society, 2014), but they are the leading cause of death by disease in children after infancy. Each year, 1 in 285 children are diagnosed with cancer before 20 years of age (American Cancer Society, 2014), with leukemia, brain and central nervous system tumors, and lymphoma being the most common pediatric cancers. Due to advances in treatment, the overall prognosis for children with cancer has improved greatly over the past several decades (*Cancer incidence and survival among children and adolescents: United states SEER program 1975-1995*, 1999). For example, the 5-year survival rate of children diagnosed with cancer before 20 years of age was 50% in 1975, compared with more than 80% in 2004–2010 (*SEER cancer statistics review, 1975-2012*). However, in conjunction with this improvement in survival, there has been an increase in the incidence of pediatric cancers, which means that pediatric oncology patients will remain a considerable population both as patients and survivors.

In addition to type and severity of disease, nutritional status is an important determinant of outcomes in pediatric oncology patients during both treatment and survivorship (Brinksma et al., 2015). In these patients, malnutrition may result from the disease as well as its treatment. Although the etiology and prevalence of malnutrition remain unclear (Brinksma et al., 2012; Co-Reyes, Li, Huh, & Chandra, 2012), its consequences are clear. Specifically, malnutrition has been associated with more treatment complications, higher relapse rates, and lower survival rates among pediatric oncology patients (Brinksma et al., 2012). Thus, correctly identifying and adequately treating malnutrition in pediatric oncology patients is critical for ensuring positive short-term and long-term outcomes. To this end, an interdisciplinary working group of nurses,

physicians, dietitians, and pharmacists, under the direction of the American Society of Parental and Enteral Nutrition (ASPEN), has developed a definition and a key concept model of malnutrition using the best available evidence (Mehta et al., 2013). The ASPEN working group identified five domains to describe pediatric malnutrition, which include (1) anthropometric parameters and growth, (2) etiology and chronicity, (3) mechanisms, (4) imbalance of nutrients, and (5) outcomes. The ASPEN working group also identified type and severity of disease as two important variables that dictate a child's nutrient requirements and his or her ability to absorb and utilize nutrients, which, in turn, directly affects his or her nutritional status. Pediatric malnutrition, which is primarily related to undernutrition, is defined as the "imbalance between nutrient requirement and intake, resulting in cumulative deficits of energy, protein, or micronutrients that may negatively affect growth, development and other relevant outcomes (Mehta et al., 2013)." The ASPEN working group's model and definition of malnutrition apply to children in all settings, with the exception of malnutrition observed in the developing world or in neonates. Although malnutrition has been defined and conceptualized and is recognized as resulting in serious consequences, its causes in this population require further elucidation.

A possible cause of malnutrition in pediatric oncology patients is fasting prior to undergoing anesthesia. Pediatric oncology patients undergo multiple diagnostic and therapeutic procedures during their course of illness that require anesthesia to ensure immobility during non-invasive procedures (Buchsbaum et al., 2013; Latham, 2014; McFadyen, Pelly, & Orr, 2011; Scheiber, Ribeiro, Karpienski, & Strehl, 1996). Current practice guidelines for pre-anesthetic fasting recommend that children abstain, at a minimum, from breast milk for 4 hours, from clear liquids for 2 hours, and from nonhuman milk or light meal for 6 hours prior to anesthesia (American Society of Anesthesiologists Committee, 2011). In actual practice, however, anesthetic providers

use their clinical judgment to determine the appropriate minimum fasting time prior to each anesthetic administration, so reported pre-anesthetic fasting times are usually much longer than the minimum recommendations (Arun & Korula, 2013; Hancock, Cresci, & Martindale, 2002; Williams et al., 2014). Pediatric oncology patients receiving radiation therapy (RT) may already be at risk of malnutrition because of their diagnosis (etiology) and treatment (mechanism involving altered nutrient utilization and hypermetabolism). Moreover, the subset of children undergoing anesthesia-assisted RT (AART) may be placed at an even higher risk of malnutrition because of the additional burden of intermittent, but repetitive, starvation periods (mechanism) resulting from pre-anesthetic fasting. Despite these gaps in knowledge and the clinical implications of malnutrition in pediatric radiation oncology patients, no studies have examined repetitive instances of pre-anesthetic fasting or evaluated anesthesia-related nutritional status changes as an outcome in pediatric patients; specifically, no studies have investigated the association between repetitive pre-anesthetic fasting and malnutrition in pediatric oncology patients undergoing RT.

Accordingly, in the current study, the association between repetitive fasting and nutritional status in pediatric oncology patients under 10 years of age who received any type of RT with or without anesthesia at a tertiary care hospital was investigated. Based on a model for child malnutrition, the underlying mechanisms produced by fasting that lead to metabolic changes (Awad, Constantin-Teodosiu, Macdonald, & Lobo, 2009; Awad & Lobo, 2012; Nygren, 2006), and research indicating that nutritional requirements are often unmet in chronically ill children (Groleau et al., 2014; Hendricks et al., 1995; Huysentruyt et al., 2013; Joosten & Hulst, 2008; Mara et al., 2014; Silva et al., 2013), it was hypothesized that repetitive pre-anesthetic fasting negatively affects the nutritional status of these patients and that non-fasting mitigates the risk for malnutrition. To test this hypothesis, (1) the association between pre-anesthetic fasting days and primary

indicators for malnutrition, and (2) the association between non-fasting days and primary indicators for malnutrition in children undergoing AART during an RT cycle were investigated. Research findings could advance the study of the underlying metabolic mechanisms of repetitive, pre-anesthetic fasting on nutritional status (e.g., post-treatment insulin resistance) and subsequent long-term outcomes (e.g., treatment response, event-free survival rate) in pediatric oncology patients.

Methods

Study Population

After approval by The University of Texas MD Anderson Cancer Center Institutional Review Board and The University of Texas Health Science Center at Houston (UTHealth) Committee for the Protection of Human Subjects, a retrospective cohort was assembled of pediatric oncology patients (≤ 10 years) who received any type of RT with or without anesthesia at a tertiary care hospital between January 1, 2006, and October 1, 2015. Eligible subjects were patients who had a charted height and weight within 14 days of both the start date and end date of RT. Consecutive screening of eligible patients was performed, starting with the inclusion of patients who were most recently treated until 138 eligible patients were identified. The recommended sample size estimates for regression models vary, but a sample size of at least 10 cases per variable is acceptable (Findley & Daum, 1989; Harrell, Lee, Matchar, & Reichert, 1985; Hsieh, Bloch, & Larsen, 1998; Sackett, Haynes, Guyatt, & Tugwell, 1991). A minimum of 120 patients was estimated for statistical analysis, but to account for potential exclusion or deletion of cases, oversampling by 15% was performed.

Data Collection and Extraction

The medical record of each eligible patient was reviewed to extract data on demographics, diagnostics, and anesthetic history. Data were extracted, when

available, on anthropometric (length/height and weight) measurements, anesthetic administration, and laboratory values from up to 14 days before the start of RT to 14 days after the end of RT. For each patient, a baseline and a final charted weight (kilograms) and length/height (centimeters) to the nearest tenth were recorded. Final charted heights < 2 cm from baseline heights were considered invalid and attributed to equipment or operator error; thus, final charted heights in 3 patients were changed manually to the next most recently charted height near the end of RT. When a measured height was missing for a corresponding weight on the same day, the previous or next available charted height (whichever was closest to the day when the charted weight was recorded) was used if both the charted height and weight fell within 14 days of the start (for baseline values) or end (for final values) of RT. Time intervals between baseline and final anthropometric values ranged from 9 to 64 days for RT cycles lasting between 8 and 54 days, respectively.

Assessment of Malnutrition

Because anthropometric data were available, three primary indicators were used for malnutrition (low weight gain velocity, weight loss, and deceleration in weight for length/height z-score) that are recommended in the 2014 Pediatric Malnutrition Consensus Statement(Becker et al., 2015) by the Academy of Nutrition and Dietetics and ASPEN to assess malnutrition at baseline and at the end of RT. As recommended by the U.S. Centers for Disease Control and Prevention (CDC)(Grummer-Strawn, Reinold, Krebs, & Centers for Disease Control and Prevention (CDC), 2010), z-scores were derived using the 2006 World Health Organization (WHO) growth standards(World Health Organization, 2006) for patients younger than 2 years and the 2000 CDC growth standards(Kuczmarski et al., 2002) for patients 2 years of age and older. Z-scores were calculated using a medical calculator for clinical providers (www.peditools.org)(Chou, 2015). For patients younger than 2 years, the percentile rank of their weight increment

was estimated using the 2009 WHO Child Growth Standards (WHO Multicentre Growth Reference Study Group, 2009) weight velocity percentile charts.

To assess malnutrition at baseline, weight for length/height z-score or body mass index (BMI) for age z-score was used as the primary malnutrition indicator because one anthropometric data point was available (length/height and weight at start of RT). For patients with length/height < 121.5 cm, weight for length/height z-scores were used; for patients with length/height > 121.5 cm, BMI for age z-scores were used. Malnutrition at baseline was defined as either a weight for length/height z-score or a BMI for age z-score ≤ -1 .

To analyze the correlations between malnutrition indicators and variables of interest, percent weight change from baseline (continuous variable), differences between baseline and final z-scores (continuous variable), and weight gain velocity percentiles (ordinal variable) were used. Weight gained between the start and end of RT was unable to be used as a continuous variable for weight gain velocity because these values are only meaningful when interpreted using weight gain velocity percentile charts according to a patient's gender, age, and the time interval when growth was measured. Therefore, for weight gain velocity, patients < 2 years of age were coded as "0," not malnourished ($\geq 75\%$ expected weight gain); "1," mildly malnourished ($50\% \leq x < 75\%$ expected weight gain); "2," moderately malnourished ($25\% \leq x < 50\%$ expected weight gain); or "3," severely malnourished ($< 25\%$ expected weight gain).

Logistic regression models were then constructed to assess malnutrition at the end of RT. Low weight gain velocity, weight loss, and deceleration in weight for length/height z-score as the primary malnutrition indicators were used because two anthropometric data points were available (baseline and final length/height and weight). Malnutrition at end of RT was defined as (1) weight loss $\geq 5\%$ of baseline weight in

patients ≥ 2 years of age, (2) weight for length/height z-score decline ≥ 1 z-score in patients ≤ 121.5 cm in length/height, and (3) weight gain velocity $< 75\%$ of the expected weight gain in patients < 2 years of age.

Cumulative malnutrition, used as the outcome in the logistic regression models, was coded as a dichotomous variable: "1" for malnutrition or "0" for absence of malnutrition. Patients with a weight for length/height z-score or BMI for age z-score ≤ -1 at the start of RT were coded as malnourished at baseline. Cumulative malnutrition at baseline was derived by combining results from the two malnutrition indicators used (weight for length/height and BMI for age z-scores). At baseline, there was no overlap in malnutrition assessment between these two indicators. Patients with an expected weight gain velocity $< 75\%$ (age < 2 years), a decline of ≥ 1 z-score in weight for length/height (length/height < 121.5 cm), or weight loss $\geq 5\%$ (age ≥ 2 years) from baseline were coded as malnourished at the end of RT. Cumulative malnutrition at the end of RT was derived by combining results from the three malnutrition indicators used (weight gain velocity, z-score, and percent weight changes). Patients were coded as malnourished at end of RT if they met the criteria for malnutrition according to any indicator. There was a discrepancy of malnutrition indicator coding between patients ≥ 2 years of age but ≤ 121.5 cm in height and patients < 2 years of age. At the end of RT, 102 patients between the ages of 2 and 10 years of age had both calculated weight for length/height z-score and percent weight loss changes. Of these patients, 10 were coded as malnourished by percent weight loss, but not by declines in z-scores, whereas 2 were coded as malnourished by declines in z-scores, but not by percent weight loss. These 12 patients were coded as malnourished when scores were combined in cumulative malnutrition (Supplemental Table I). Furthermore, at the end of RT, 18 patients younger than 2 years had both calculated weight gain velocity and weight for

length/height z-score changes. Of these patients, 9 were coded as malnourished by low percentile weight gain velocities, but not by declines in z-scores. These 9 patients were coded as malnourished when scores were combined in evaluating cumulative malnutrition (Supplemental Table I).

Statistical Analyses

After verifying data for accuracy and completeness and analyzing distribution of continuous variables for assumptions of normality, non-parametric tests were used to analyze data that did not meet statistical assumptions. Descriptive statistics were used to summarize patient characteristics. Chi-square tests (χ^2) were used to compare differences in the proportion of patients with malnutrition at baseline and at end of RT; between RT cohorts (AART vs. non-AART); and among age groups (< 2 years vs. 2–5 years vs. > 5 years) in the AART cohort, which is the cohort of patients who underwent repetitive, pre-anesthetic fasting. Pearson's correlation, or if more appropriate, Spearman rank correlation (r_s), was used to assess the strength of correlations between the number of fasting or non-fasting days, along with other select covariates of interest, and malnutrition at the end of AART. Primary indicators were: (1) percent weight change, (2) weight for height/length z-score differences as continuous variables, and (3) weight gain velocity as an ordinal variable (on an ordinal scale coded from absence of malnutrition to severe malnutrition).

To further assess the relationship between patient characteristics and malnutrition, logistic regression models were constructed to examine pre-anesthetic fasting and non-fasting days as predictors for malnutrition at the end of AART, while adjusting for select patient and treatment-related variables of interest. For logistic regression models, malnutrition status both at baseline and at the end of RT was dichotomized by combining the results of the primary indicators. All statistical analyses were performed using IBM SPSS Statistics Version 23 (IBM Corp., Armonk, NY).

Results

Patient Characteristics

Patient characteristics are shown in Table I. The median age (interquartile range [IQR]) at baseline was 5 years (3.25–7.13). Most patients were male (58.0%) and white (62.3%); diagnosed with either brain (52.9%) or extracranial solid (44.9%) tumors; and received AART (66.0%) with concurrent chemotherapy (63.0%). In terms of age, patients in the AART cohort (median age = 3.8 years, IQR = 2.6–5.1) were younger than those in the non-AART cohort (median age = 7.8 years, IQR = 6.1–8.9). All patients < 2 years received AART as did the vast majority (96%) of patients aged 2–5 years. The duration of RT cycles between the AART (median duration = 40 days, IQR = 29–43) and non-AART (median duration = 39 days, IQR = 29–42) cohorts were similar (Supplemental Table II). The cumulative propofol and intravenous fluid received by the AART cohort are shown in Supplemental Table III.

Malnutrition at Baseline and at End of Radiation Therapy

Overall, the prevalence of cumulative malnutrition at baseline was 18.8%, which increased to 26.8% at the end of RT, and the cumulative incidence of malnutrition was 28.6% over a maximum RT cycle duration of 56 days (N = 138, Supplemental Table IV and Supplemental Table V). Malnutrition at baseline did not differ significantly among age groups in the AART cohort [χ^2 (2, N = 91) = 1.93, p = 0.38] or between the AART and non-AART cohorts [χ^2 (1, N = 138) = 0.004, p = 1.0]. However, at the end of AART, patients < 2 years had a significantly higher rate of malnutrition (n = 10/18, 55.6%) than those aged 2–5 years (n = 13/47, 27.7%) [χ^2 (1, N = 65) = 4.43, p = .046]. Furthermore, at the end of RT, patients who received AART (n = 31/91, 34.1%) had a significantly higher rate of malnutrition than those who did not receive AART (n = 6/47, 12.8%) [χ^2 (1, N = 138) = 7.17, p = 0.008].

Correlations between Malnutrition Indicators and Number of Fasting and Non-Fasting Days

In the AART cohort, which comprised patients who experienced repetitive, pre-anesthetic fasting, a significant correlation was found between weight gain velocity and the number of non-fasting days ($r_s = -0.49$, $p = 0.039$), that is, as number of non-fasting days increased, the presence and severity of malnutrition decreased. No other significant correlations were found between primary malnutrition indicators and fasting or non-fasting days.

Univariate Logistic Regression Analyses

Number of fasting and non-fasting days, which were analyzed in 5-day increments because of consecutive weekday RT treatment schedules, were not significant predictors of malnutrition status at the end of AART (Table II). Other potential predictors of malnutrition were also examined, such as primary cancer diagnosis, concurrent chemotherapy, malnutrition at baseline, age, and gender. Of these, only age was found to be a significant predictor of malnutrition. Specifically, patients 2–5 years of age had lower odds than those younger than 2 years of age of becoming malnourished by the end of AART (odds ratio [OR] = 0.31, $p = 0.04$). Concurrent chemotherapy trended towards significance as a predictor of malnutrition at the end of AART (OR = 2.62, $p = 0.055$). Lastly, when all RT patients (both AART and non-AART cohorts) were included in the analysis, receiving AART was a significant predictor of malnutrition when compared to not receiving AART (OR = 3.531, $p = 0.01$).

Multivariate Logistic Regression Analyses

Given the results of the univariate regression analyses, age and concurrent chemotherapy were tested as predictors for malnutrition in a multivariate regression model. When considered together, age and concurrent chemotherapy were significant predictors of malnutrition at the end of AART (Table III, Model 1). Specifically, after

adjusting for age, patients who received concurrent chemotherapy had higher odds than those who did not receive concurrent chemotherapy of becoming malnourished by the end of AART (OR = 3.48; $p = 0.024$). In addition, after adjusting for concurrent chemotherapy status, patients 2 years of age and older had lower odds than those younger than 2 years of age of becoming malnourished by the end of AART (OR = 0.23, $p = 0.018$ for patients ≥ 2 to < 5 years; OR = 0.26, $p = 0.047$ for patients ≥ 5 years). Furthermore, concurrent chemotherapy and older age remained significant predictors of malnutrition at the end of AART, even after adjusting for pre-anesthetic fasting days and non-fasting days (Table III, Models 2 and 3). Lastly, after adjusting for concurrent chemotherapy status and age, patients who received AART did not have higher odds than those who did not receive AART of becoming malnourished by the end of RT (Table III, Model 4).

Discussion

In this exploratory study, the association between pre-anesthetic fasting days and primary indicators for malnutrition, as well as the association between non-fasting days and primary indicators for malnutrition in patients receiving AART were examined. It was found that the number of pre-anesthetic fasting days was not significantly associated with any primary indicators of malnutrition. However, the number of non-fasting days was significantly correlated with the absence of malnutrition as determined by weight gain velocity for patients younger than 2 years in the AART cohort. By the end of AART, neither the number of pre-anesthetic fasting days nor the number of non-fasting days was a significant predictor for presence of malnutrition. Collectively, these findings do not support the hypothesis that repetitive, pre-anesthetic fasting negatively affects the nutritional status of pediatric oncology patients receiving AART or that an increasing number of non-fasting days during an AART cycle mitigates the risk of malnutrition.

In addition, it was found that the rates of malnutrition by the end of RT differed significantly by RT cohort (AART vs. non-AART). Specifically, patients in the AART cohort had a significantly higher rate of malnutrition than patients in the non-AART cohort. However, on multivariate logistic regression analysis, receiving AART was not a significant predictor of malnutrition, after controlling for age and concurrent chemotherapy administration. This finding suggests that age and/or concurrent chemotherapy and receiving AART are correlated. When analyzed, there was multicollinearity between receiving AART and age. The multicollinearity between AART and age can be explained by the fact that the AART cohort was mainly composed of younger patients (< 5 years) compared with the non-AART cohort. Because most young patients tend to receive AART to ensure immobility during RT, when age was controlled for, receiving AART no longer made a significant contribution to the model prediction.

Within the AART cohort, patients younger than 2 years of age had significantly higher rates of malnutrition than those 2–5 years of age. This finding was corroborated by univariate and multivariate logistic regression analysis, which revealed that patients 2 years of age and older had lower odds than those younger than 2 years of age of becoming malnourished at the end of AART. This finding suggests that younger patients are more vulnerable than older patients to disease and/or treatment effects that may lead to malnutrition. It also suggests that growth impairment as operationalized by weight gain velocity is a more sensitive indicator of malnutrition than deceleration in weight for length/height z-scores in patients younger than 2 years of age. Specifically, of the 10 total cases of malnutrition in children under 2 years of age, 9 were identified by weight gain velocity only, whereas 1 case was identified by both weight gain velocity and deceleration in weight for length/height z-score at the end of AART. However, the high detection rate of malnutrition by low weight gain velocity, along with a small sample size

of patients younger than 2 years of age ($n = 18$), may have falsely driven the rate of malnutrition higher in this age group compared with that in the other two age groups.

The possible implication of the relative sensitivity of the indicators of malnutrition used in the current study is important for two reasons. First, there is no agreement on which indicators should be used to evaluate malnutrition in pediatric oncology patients (Brinksma et al., 2012; Loeffen, Brinksma, Miedema, de Bock, & Tissing, 2015), so studies generally use different indicators. Second, even when studies use the same indicators, different criteria are used to categorize or analyze malnutrition (Altaf et al., 2013; Esbenshade et al., 2011; Ethier et al., 2012; Orgel et al., 2014; Withycombe et al., 2015). Briefly, the following indicators of malnutrition with different cutoff values have been used: the Netherlands BMI for age z-scores (Loeffen et al., 2015), CDC BMI for age percentiles (Altaf et al., 2013; Esbenshade et al., 2011; Ethier et al., 2012; Orgel et al., 2014; Withycombe et al., 2015), CDC BMI for age z-scores (Esbenshade et al., 2011), CDC weight for length z-scores (Esbenshade et al., 2011; Orgel et al., 2014), United Kingdom adjusted BMI z-scores (Aldhafiri, McColl, & Reilly, 2014), United States National Health and Nutritional Examination Survey (NHANES) 1971-1974 triceps skin fold thickness percentiles (Antillon et al., 2013; Sala et al., 2012), NHANES 1971-1974 mid upper arm circumference percentiles (Antillon et al., 2013; Sala et al., 2012), weight loss (Loeffen et al., 2015), and albumin lab values (Sala et al., 2012). To help improve the overall quality of studies evaluating malnutrition in pediatric oncology patients, cutoff scores must be determined and standardized according to their clinical relevance (Loeffen et al., 2015). In their review of the prevalence of malnutrition in pediatric oncology patients, Brinksma et al. (Brinksma et al., 2012) recommended that the WHO growth standards be used in conjunction with BMI cutoff scores derived from an international survey (Cole, Flegal, Nicholls, & Jackson, 2007), which would enable comparisons among studies evaluating malnutrition in pediatric oncology patients.

Brinksma et al. also recommended that weight loss and body composition changes (e.g., fat free mass and fat mass) be included. To date, however, Brinksma et al.'s recommendations have not been evaluated against those of the 2014 Pediatric Malnutrition Consensus Statement (Becker et al., 2015) by the Academy of Nutrition and Dietetics and ASPEN, which were followed in this study. Thus, more research is needed to determine which malnutrition indicator(s), as well as cutoff score(s), is the most clinically relevant when evaluating malnutrition in pediatric oncology patients, in general, and in those undergoing RT, in particular.

This study has some important limitations that should be considered when interpreting its findings. First, this exploratory study has a retrospective observational design. Thus, limited control existed over (1) the quality or completeness of data entered into medical records, (2) patient assessment and follow up between and within cohorts, and (3) construction of cohorts. Second, the sample size was small, which decreased the precision of the significant findings (i.e., generated wide confidence intervals); however, it is comparable to those of other studies investigating AART-related outcomes (Buchsbaum et al., 2013). Third, anthropometric measurements were extracted from medical records, limiting their reliability, accuracy, and completeness. For example, 3 cases with negative values for height over time, which were attributed to equipment or operator error, were manually adjusted. Fourth, the study findings cannot be compared with those of other studies because of the paucity of existing data on nutritional status changes related to repetitive pre-anesthetic fasting in pediatric patients, in general, and in pediatric oncology patients undergoing RT, in particular. Fifth, most of the study cohort received proton therapy, so study findings may only be generalized to patients at tertiary care hospitals that deliver this specialized type of RT. Sixth, the broad categorization of diagnoses and low number of hematological malignancies may have masked a disease-specific effect on malnutrition. Finally, malnutrition at the end of

RT was evaluated using three malnutrition indicators: low weight gain velocity, deceleration of weight for length/height z-scores, and percent weight loss. Data comparing the different criteria for the three malnutrition indicators with clinical outcomes after RT, such as event-free survival rates or treatment response, are needed to evaluate the clinical implications of nutritional status changes in this patient population. Despite these limitations, a major strength of this exploratory study is that it provides preliminary data to support the continued study of various nutrition-related short-term and long-term outcomes in pediatric oncology patients. Another strength of this exploratory study is that it identifies a subgroup of pediatric oncology patients who are susceptible to malnutrition and, thus, should be closely monitored for significant nutritional status changes during RT (i.e., patients aged < 2 years receiving AART with concurrent chemotherapy).

In conclusion, this exploratory study found that pediatric oncology patients younger than 2 years of age receiving AART are more likely than those who do not receive AART to be malnourished by the end of treatment; however, malnutrition status is not associated with repetitive, pre-anesthetic fasting, but with young age and concurrent chemotherapy. Further research is needed to corroborate these findings and to explore the underlying adverse metabolic effects (e.g., depletion of hepatic glycogen reserves, increased protein catabolism, higher energy expenditure at rest, post-treatment insulin resistance)(Awad et al., 2009; Awad & Lobo, 2012; Nygren, 2006). that may predispose or exacerbate negative nutritional status changes in younger pediatric oncology patients.

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CONFLICT OF INTEREST

We have no potential or actual conflicts of interest to declare.

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TABLE I. Patient Characteristics

	Total	AART Cohort	Non-AART Cohort	P-value
Characteristic, no. (%)	N = 138 (100)	n = 91 (66)	n = 47 (34)	
Age at start of RT				<0.001*
< 2 years	18 (13.0)	18 (19.8)	0	
≥ 2 to < 5 years	49 (35.5)	47 (51.6)	2 (4.3)	
≥ 5 years	71 (51.5)	26 (28.6)	45 (95.7)	
Gender				0.717
Male	80 (58.0)	54 (59.3)	26 (55.3)	
Female	58 (42.0)	37 (40.7)	21 (44.7)	
Race/Ethnicity				0.148
White	86 (62.3)	54 (59.3)	32 (68.1)	
African American	13 (9.4)	10 (11.0)	3 (6.4)	
Hispanic	24 (17.4)	19 (20.9)	5 (10.6)	
Asian	7 (5.1)	2 (2.2)	5 (10.6)	
Unknown/not reported	8 (5.8)	6 (6.6)	2 (4.3)	
Primary diagnosis				0.012*
Hematological malignancies	3 (2.2)	3 (3.3)	0	
Brain tumors	73 (52.9)	55 (60.4)	18 (38.3)	
Extracranial solid tumors	62 (44.9)	33 (36.3)	29 (61.7)	
Type of RT				0.541
Proton	102 (73.9)	69 (75.8)	33 (70.2)	
IMRT or conventional XRT	36 (26.1)	22 (24.2)	14 (29.8)	
Concurrent chemotherapy	87 (63.0)	58 (63.7)	29 (61.7)	0.854

Clinical nutrition referral^a	41 (29.7)	34 (37.4)	7 (14.9)	0.006*
Enteral feeds^b	29 (21)	23 (25.3)	6 (12.8)	0.122
Recent or concurrent steroid therapy^c	25 (18.1)	18 (19.8)	7 (14.9)	0.642

AART, anesthesia-assisted radiation therapy; non-AART, non-anesthesia-assisted radiation therapy; RT, radiation therapy; IMRT, intensity-modulated radiation therapy; XRT, external-beam radiation therapy; * $P < 0.05$. ^aReferral within 7 days before or during RT cycle; ^bEnteral feeds started 14 days before or during RT; ^cSteroid therapy within 3 months before or during RT.

TABLE II. Univariate Analysis of Predictors of Malnutrition at the End of Radiation Therapy in the AART Cohort (n = 91)^a

Variables	Presence of malnutrition at end of RT (%)	OR (95% CI)	P
Number of fasting days in RT cycle			
5-day increments	—	1.13 (0.84–1.51)	0.420
Number of non-fasting days in RT cycle			
5-day increments	—	0.93 (0.59–1.46)	0.743
Cumulative Propofol dose (mg/kg/day) ^{b,c,d}	—	1.00 (0.93–1.08)	0.988
Cumulative Kilocalories from propofol (Kcal/kg/day) ^{b,c,d}	—	1.01 (0.52–1.96)	0.988
Cumulative IVF (mL/kg/day) ^{b,c,e}	—	1.06 (0.93–1.21)	0.364
Concurrent chemotherapy			
No (n = 33)	7 (21.2)	Reference	
Yes (n = 58)	24 (41.4)	2.62 (0.98–7.02)	0.055
Primary diagnosis			
Non-brain tumor (n = 36)	13 (36.1)	Reference	
Brain tumor (n = 55)	18 (32.7)	0.86 (0.36–2.08)	0.739
Age			
< 2 years (n = 18)	10 (55.6)	Reference	
≥ 2 to < 5 years (n = 47)	13 (27.7)	0.31 (0.10–0.95)	0.040*
≥ 5 years (n = 26)	8 (30.8)	0.36 (0.10–1.24)	0.104
Malnutrition at baseline			
No (n = 74)	25 (33.8)	Reference	
Yes (n = 17)	6 (35.3)	1.07 (0.35–3.23)	0.906
Gender			
Male (n = 54)	18 (33.3)	Reference	
Female (n = 37)	13 (35.1)	1.08 (0.45–2.61)	0.859
Enteral feeding			
No (n = 68)	22 (32.4)	Reference	
Yes (n = 23)	9 (39.1)	1.34 (0.51–3.58)	0.554

Steroid therapy			
No (n = 73)	26 (35.6)	Reference	
Yes (n = 18)	5 (27.8)	0.70 (0.22–2.17)	0.531
Race/ethnicity			
White, non-Hispanic (n = 54)	21 (38.9)	Reference	
Non-Whites (n = 37)	10 (27)	0.58 (0.24–1.44)	0.243
Dietary supplements			
Yes (n = 12)	2 (16.7)	Reference	
No (n = 79)	29 (36.7)	2.90 (0.59–14.16)	0.188
Nutritional consult			
Yes (n = 34)	9 (26.5)	Reference	
No (n = 57)	22 (38.6)	1.75 (0.69–4.43)	0.240
Type of RT			
IMRT or conventional XRT (n = 22)	6 (27.3)	Reference	
Proton therapy (n = 69)	25 (36.2)	1.52 (0.53–4.37)	0.442
AART receipt ^f			
Yes (n = 91)	31 (34.1)	3.53 (1.35–9.22)	0.010
No (n = 47)	6 (12.8)	Reference	

OR, odds ratio; CI, confidence interval; * P < 0.05; RT, radiation therapy; IMRT, intensity-modulated radiation therapy; XRT, external-beam radiation therapy; ^aExcept where specified; ^bCalculated average weight used to calculate dose per kilogram. Average weight was calculated by averaging baseline and final weight, ^cCumulative dosing was divided by subject's total number of radiation treatment days to adjust for varying lengths of radiation treatments between subjects, ^dn = 88, subjects who had partial AART treatment were excluded from analysis since they did not receive all radiation treatments under anesthesia, ^en = 71, Twenty subjects had >40% missing values for intravenous fluid administration during AART were excluded from analysis. ^fWith both AART and non-AART cohorts combined for comparison, n = 138.

TABLE III. Multivariate Model of Predictors of Malnutrition at the End of Radiation Therapy

Model	OR (95% CI)	P
Model 1: AART cohort (n =91)		
Concurrent chemotherapy		
No	Reference	
Yes	3.48 (1.18–10.23)	0.024*
Age		
< 2 years	Reference	
≥ 2 to < 5 years	0.23 (0.07–0.77)	0.018*
≥ 5 years	0.26 (0.07–0.98)	0.047*
Model 2: AART cohort (n = 91)		
Number of fasting days in RT cycle		
5-day increments	1.22 (0.88–1.70)	0.231
Concurrent chemotherapy		
No	Reference	
Yes	3.97 (1.31–12.08)	0.015*
Age		
< 2 years	Reference	
≥ 2 to < 5 years	0.22 (0.06–0.76)	0.017*
≥ 5 years	0.27 (0.07–1.04)	0.058
Model 3: AART cohort (n = 91)		
Number of non-fasting days in RT cycle		
5-day increments	1.01 (0.62–1.67)	0.96
Concurrent chemotherapy		
No	Reference	
Yes	3.49 (1.17–10.43)	0.025*
Age		
< 2 years	Reference	
≥ 2 to < 5 years	0.23 (0.07–0.77)	0.018*
≥ 5 years	0.26 (0.07–0.99)	0.047*
Model 4: AART and non-AART cohort (n = 138)		
AART		
No	Reference	
Yes	3.078 (0.94–10.04)	0.062
Concurrent chemotherapy		
No	Reference	
Yes	4.528 (1.62–12.64)	0.004*
Age		
< 2 years	Reference	
≥ 2 to < 5 years	0.20 (0.06–0.70)	0.012*
≥ 5 years	0.25 (0.06–0.95)	0.042*

OR, odds ratio; CI, confidence interval; * P < 0.05; RT, radiation therapy; AART, anesthesia-assisted radiation therapy; non-AART, non-anesthesia-assisted radiation therapy

APPENDIX

Supplemental Table I. Cumulative Malnutrition Coding Discrepancies When Indicators

Study ID	Age at start of RT (yr)	Height at end of RT (cm)	Percent Weight loss from baseline (Patients > 2 years)	Weight for Length/Height z-score difference (Patients < 121.5 cm height)	Expected weight gain percentile (Patients < 2 years)	Cumulative Malnutrition Final coding
003	1.08	70.0	–	-0.39 NM	<25% M	M
004	1.58	75.7	–	-0.76 NM	<25% M	M
011	4.42	110.0	-0.05 M	-0.51 NM	–	M
016	1.42	76.6	–	-0.47 NM	<25% M	M
025	4.08	104.0	-0.06 M	-0.80 NM	–	M
038	1.50	90.0	–	-0.33 NM	<25% M	M
039	4.50	103.5	-0.04 NM	-1.24 M	–	M
057	1.08	74.5	–	-0.17 NM	<25% M	M
069	4.00	101.0	-0.05 M	-0.09 NM	–	M
070	3.17	99.7	-0.07 M	-0.97 NM	–	M
071	5.67	104.0	-0.07 M	-0.43 NM	–	M
077	1.83	81.5	–	-0.63 NM	25≤x<50% M	M
081	4.25	103.5	-0.08 M	-0.99 NM	–	M
095	1.50	75.0	–	-0.11 NM	<25% M	M
098	1.83	85.0	–	-0.80 NM	<25% M	M
104	3.50	91.0	-0.07 M	-0.87 NM	–	M
118	1.58	79.6	–	-0.23 NM	<25% M	M
126	3.08	96.0	-0.06 M	-0.70 NM	–	M
133	3.75	114.0	-0.05 M	-0.70 NM	–	M
134	3.50	99.0	0.06 NM	-2.02 M	–	M

138 5.50 109.0 -0.05 M -0.56 NM – M

Yr, years; cm, centimeters; M, Malnourished as defined by malnutrition indicator used; NM, Not malnourished as defined by malnutrition indicator used; RT, Radiation therapy.

Supplemental Table II. Radiation Therapy Treatment Regimens

	Total	AART Cohort	Non-AART Cohort
	Mean, Median (IQR)	Median (IQR)	Median (IQR)
Number of fasting days during RT	15.9, 20 (0–29)	28 (20–30)	0 (0)
Number of non-fasting days during RT	18.9, 13 (10–30)	12 (9–13)	38 (29–42)
Duration of RT cycle, days	35.1, 40 (29–43)	40 (29–43)	39 (29–42)
Number of RT treatments	24.3, 28 (20–30)	28 (20–30)	28 (20–30)

Supplemental Table III. Anesthetic Administration in AART Cohort

	Mean, Median (IQR)
Cumulative Propofol dose (mg/kg/day) ^{a,b,c}	12.57, 12.52 (8.89–15.11)
Cumulative Kilocalories from propofol (Kcal/kg/day) ^{a,b,c}	1.38, 1.38 (0.98–1.66)
Cumulative IVF (mL/kg/day) ^{a,b,d}	13.51, 12.97 (10.67–15.72)

AART, anesthesia-assisted radiation therapy; IVF, intravenous fluid; Kcal, Kilocalories; kg, kilogram; mg, milligrams; RT, radiation therapy. ^aCalculated average weight used to calculate dose per kilogram. Average weight was calculated by averaging baseline and final weight, ^bCumulative dosing was divided by subject's total number of radiation treatment days to adjust for varying lengths of radiation treatments between subjects, ^cn = 88, subjects who had partial AART treatment were excluded from analysis since they did not receive all radiation treatments under anesthesia, ^dn = 71, Twenty subjects had >40% missing values for intravenous fluid administration during AART were excluded from analysis.

Supplemental Table IV. Malnutrition at Baseline

Malnutrition Indicator	Total	AART Cohort	Non-AART Cohort
Weight for length/height z-score ^{a,b}	19 (13.7)	15 (16.5)	4 (8.5)
BMI for age z-score ^{a,c}	7 (5.1)	2 (2.2)	5 (10.6)
Cumulative ^d	26 (18.8)	17 (18.7)	9 (19.1)

BMI, Body Mass Index; ^az-score ≤ -1 ; ^bn = 102; ^cn = 36; ^dOutcomes from all malnutrition indicators at baseline combined (Weight for length/height z-score plus BMI for age z-score).

Supplemental Table V. Malnutrition at the End of Radiation Therapy

Malnutrition Indicators	Total	AART Cohort	Non-AART Cohort
Low weight gain velocity ^a	10	10	n/a
Deceleration weight for length/height z-score ^{b,c}	15	12	3
Weight loss ^d	25	19	6
Cumulative ^e	37 (26.8)	31 (34.1)	6 (12.8)

^aPatients < 2 years of age with < 75% weight gain for gender and age, n = 18; ^bn = 102;

^cDeceleration z-score ≥ 1 in patients ≤ 121.5 cm in length/height; ^dWeight loss $\geq 5\%$ from baseline weight in patient ≥ 2 years of age, n = 120; ^eOutcomes from all malnutrition indicators at the end of RT combined (Low weight gain velocity plus deceleration weight for length/height z-score plus weight loss);

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Professional Memberships

12/2013–Present Southern Nursing Research Society
08/2010–Present American Association of Nurse Anesthetists
08/2010–Present Texas Association of Nurse Anesthetists
06/2007–Present Sigma Theta Tau International, Zeta Pi Chapter
08/2008–08/2010 International Transplant Nurses Society
10/2009–11/2011 American Association of Critical-Care Nurses
06/2006–08/2007 Association of Pediatric Hematology Oncology Nurses

Publications

05/2013 "Learning to be 'CRNA Strong': My 2013 AANA Mid-Year Assembly experience." *TANA Newsletter*, 2013 Summer Issue, Vol. 66, No. 2, pp. 13-14.
03/2013 "From the OR to the Texas State Capitol." *TANA Newsletter*, 2013 Spring Issue, Vol. 66, No. 1, p. 5.
08/2012 "I left (a part of) my heart in San Francisco." *TANA Newsletter*, 2012 Fall Issue, Vol. 65, No. 3, p. 8.

Media Products

01/2015 "2015 CRNA Week Campaign Video." Project coordinator, principal writer and content expert. Texas Association of Nurse Anesthetists. (DVD, RSS formats).
<https://www.youtube.com/watch?v=siUdgdY-Lb8>

Presentations

06/2016 "Signal Transduction and Second Messengers," [Guest Speaker] Advanced Anatomy, Physiology, Pathophysiology, and Biochemistry for Nurse Anesthetists I, UTHealth School of Nursing, Houston, TX
08/2015 "Neurocognitive Outcomes in Pediatrics After Anesthetic Exposure," [Speaker] American Association of Nurse Anesthetists, 2015 Nurse Anesthesia Annual Congress, Salt Lake City, UT
03/2015 "Geriatric pharmacology: A focus on postoperative cognitive dysfunction," [Speaker] Texas Association of Nurse Anesthetists, 2015 Spring Meeting, San Antonio, TX

- 12/2012 "Fetal & neonatal pulmonary anatomy and physiology," [Guest speaker] Advanced Anatomy, Physiology, Pathophysiology, and Biochemistry for Nurse Anesthetists I, UTHealth School of Nursing, Houston, TX
- 09/2012 "Understanding the thromboelastogram tracing and its use in goal-directed transfusion therapy," [Poster presentation] Texas Association of Nurse Anesthetists, 2012 Fall Annual Convention, San Antonio, TX
- 09/2012 "Mitochondrial myopathies in children," [Student presentation] Role Practicum I, UTHealth School of Nursing, Houston, TX
- 05/2012 "Neuro & endocrine physiology," [Student presentation] Clinical Practicum II, UTHealth School of Nursing, Houston, TX
- 12/2011 "Interventions to improve cost-related health outcomes in the geriatric population with low-literacy: A systematic review," [Student presentation] Evaluation and Application of Research in Advanced Nursing Practice, UTHealth School of Nursing, Houston, TX
- 11/2011 "Justification for proposed tuition increases at the UTHealth School of Nursing," [Student leadership presentation] Town Hall Student Meeting, UTHealth School of Nursing, Houston, TX
- 11/2011 "The U.S. nursing shortage: A concise update," [Student presentation] Professional Aspects, UTHealth School of Nursing, Houston, TX
- 2010–2011 "Student InterCouncil introduction and overview," [Student leadership presentation] Undergraduate and graduate student orientations, UTHealth School of Nursing, Houston, TX
- 09/2011 "Student orientation to SRNA blackboard pages," [Guest speaker] Incoming nurse anesthesia student orientation, UTHealth School of Nursing, Houston, TX
- 03/2011 "CPR and first aid training for the lay rescuer," [Guest speaker] Seniors' Ministry, Calvary Houston, Friendswood, TX
- 03/2009 "Diabetes: Symptoms, diagnosis, treatment and management," [Guest speaker] Seniors' Ministry, Calvary Houston, Friendswood, TX
- 02/2009 "Overview of organ donation: From brain death to procurement" &
"Nursing care for patients with left ventricular assist devices," [Guest speaker] Health Occupations Students of America, Sam Rayburn High School Chapter, Pasadena, TX
- 04/2008 "Pursuing nursing as a career," [Guest speaker] Health Occupations Students of America, Sam Rayburn High School Chapter, Pasadena, TX
- Awards**
- 08/2013 Memorial Hermann Accelerated PhD Scholar, UTHealth School of Nursing

05/2013	Nurse Anesthesia Program Director's Award, UTHealth School of Nursing
03/2013	AANA 2013 Annual Mid-Year Assembly Meeting Scholarship, Texas Association of Nurse Anesthetists
08/2012, 08/2010	Advanced Education Nursing Traineeship Scholarship, American Association of Colleges of Nursing
08/2012	AANA 2012 Annual Meeting Scholarship, Texas Association of Nurse Anesthetists
08/2012	Dawn Gross Endowed Scholarship, UTHealth School of Nursing