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Nutritional Status and Clinical Outcomes in Pediatric Solid Tumor Patients: A Systematic Review of the Literature

Lenat Joffe, MD^a, Sarah Dwyer, MS^b, Julia L. Glade Bender, MD^c, A. Lindsay Frazier, MD^d, and Elena J. Ladas, PhD^{e,*}

^aDepartment of Pediatric Hematology, Oncology and Stem Cell Transplant, Morgan Stanley Children's Hospital, Columbia University Medical Center, 3959 Broadway, CHN 10-03, New York, New York 10032; lv2351@cumc.columbia.edu

^bInstitute of Human Nutrition, Columbia University Medical Center, 630 West 168th Street, New York, New York 10032; sadwyer24@gmail.com

^cDepartment of Pediatrics, Memorial Sloan Kettering Cancer Center, 1275 York Avenue, New York, New York 10065; gladebej@mskcc.org

^dDana-Farber/ Boston Children's Cancer and Blood Disorders Center, 450 Brookline Avenue, Boston, Massachusetts 02215; lindsay_frazier@dfci.harvard.edu

^eDepartment of Pediatric Hematology, Oncology and Stem Cell Transplant, Morgan Stanley Children's Hospital, Columbia University Medical Center, 3959 Broadway CHN 10-06A, New York, NY 10032; Telephone: (212) 305-7835; Fax: (212) 305-5848

Abstract

Introduction: Nutritional status (NS), defined by undernutrition (body mass index (BMI) <5th percentile) or overnutrition (BMI ≥85th percentile), is a poor prognostic indicator in pediatric oncology patients. The impact of NS has been primarily studied in hematologic malignancies. This review is intended to summarize literature reporting on the association of NS and treatment-related outcomes in pediatric solid tumors.

Methods: We searched four electronic databases from inception through August, 2018 without language restriction, and included studies of children with cancers arising from renal, bone, liver, eye, muscle, vascular, germ cell, and neural crest tissues, reporting on NS as a predictor for toxicity, survival or relapse. Due to data heterogeneity and limited availability of studies, formal statistical analysis was not achievable. Descriptive statistics were summarized in table format.

*Corresponding Author: Elena Ladas PhD, RD, ejd14@cumc.columbia.edu.

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Results: Of 8991 reports identified, 75 full-text articles were evaluated, 10 of which met inclusion criteria. Up to 62% of patients were over- or undernourished at diagnosis. Abnormal BMI was associated with worse overall survival (OS) in Ewing sarcoma (hazard ratio (HR): 3.46, $P = 0.022$), osteosarcoma (HR: 1.6, $P < 0.005$), and a trend towards poorer OS in rhabdomyosarcoma (HR: 1.70, $P = 0.0596$). High BMI in osteosarcoma was associated with increased nephrotoxicity (odds ratio: 2.8, $P = 0.01$) and post-operative complications. NS was not a significant predictor of outcomes in other included disease categories.

Conclusions: Existing literature supports the prognostic significance of NS in pediatric solid tumor patients, and underscores the need for prospective studies to better elucidate underlying physiologic changes in this population.

Keywords

nutritional status; pediatric solid tumors; outcomes

Introduction

Many of the most common pediatric solid tumors achieve a 5-year overall survival of only 60–70%, with relatively little advances in therapy for the past several decades.[1] Severe, even fatal, toxicity has been observed in up to 80% of patients treated for high-risk disease. [2] With the growing global double-burden of malnutrition, the co-existence of both undernutrition (body mass index (BMI) $< 5^{\text{th}}$ percentile) and overnutrition (BMI 85^{th} percentile) have been used to describe nutritional status.[3, 4] There is a growing body of evidence suggesting that nutritional status can affect treatment outcomes in children and adolescents with cancer. Nutritional status has been linked to diminished tolerance to chemotherapy, treatment delays, increased rates of infection, impaired prognosis, and poorer quality of life.[5–8] In pediatrics, this area has been best studied in hematologic malignancies. In a meta-analysis exploring this association in pediatric leukemia, high BMI was associated with 56% increased risk of mortality. Reduced survival was observed in both lymphoid and myeloid malignancies, and across all ages. The authors hypothesized that this adverse association may be due to greater treatment-related mortality in overweight/obese children rather than diminished therapeutic efficacy and relapse.[9]

Investigations evaluating the role of nutritional status in pediatric solid tumors are lacking. While a prevalence of undernutrition as high as 50% has been reported in this population, data on overnutrition is sparse.[5, 7, 8] Patients with solid tumors undergo multimodal therapy, including dose-intense antineoplastic agents, surgery, and radiotherapy. Oftentimes, this multimodality therapy results in a constellation of serious adverse effects that further potentiate poor nutrition.[8] Consequently, in recent years, the focus on treatment advances has shifted to the development of targeted therapies. Many of these agents are currently under evaluation in phase I and II trials and have been noted to demonstrate significant gastrointestinal toxicity.[10, 11] Enhancing nutritional status in this patient population has the potential to improve tolerance to both traditional and novel therapies, and thereby play a key role in increasing survival and quality of life.

The purpose of this review is to reconcile the controversial findings published on this topic. Our objective is to summarize data reporting the association of nutritional status with treatment-related toxicity (TRT), event-free survival (EFS), cumulative incidence of relapse (CIR), and overall survival (OS) in children and adolescents diagnosed with a solid tumor. To the authors' knowledge, this is the first comprehensive review evaluating nutritional status and outcomes in this population.

Methods

Literature Search

Our search methodology utilized the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (PRISMA). With the aid of a library scientist, we systematically searched the electronic databases of MEDLINE, Ovid Medline, the Cochrane Library, and Embase from inception through August, 2018. Our search was limited to studies of human subjects and had no language restriction. Our strategy included MeSH terms and text relating to childhood malignancies originating from renal, bone, liver, eye, muscle, vascular, germ cell, and neural crest tissues; anthropometric measures of nutritional status (weight, BMI); and treatment outcomes (survival, relapse, toxicities). Search strategies for each of the databases are outlined in Supplemental Table 1. References were compiled in EndNote (X7) for review by title and abstract by two independent authors (SD, LJ). Subsequent manual review of citations was conducted to include additional manuscripts meeting eligibility criteria. Any lack of consensus was resolved via consultation with a third independent author (EJL).

Eligibility Criteria

Included in the review were published manuscripts reporting on the association of nutritional status and treatment outcomes (OS, EFS, CIR, TRT) in pediatric patients with an extracranial solid tumor, wherein at least 80% of participants were between birth and 21 years of age (inclusive), or the mean/median study population age was under 21 years. Only patients treated in high-income countries, as categorized by the World Bank [12], were included. Studies reporting on patients whose treatments were not reflective of modern-day therapy, *all participants* treated on protocols prior to 1990, were omitted. Case reports, case series, reviews, and reports investigating nutritional status in cancer survivors were also excluded. Search strategy results are detailed in Figure 1.

Data Extraction

Extracted data was comprised of country of publication, year, study design, sample size, primary and secondary outcomes, demographic data (age, gender, race, ethnicity), tumor type, treatment consortium and regimen, definition and categorization of anthropometric data (weight, BMI; underweight, normal, overweight, obese), TRT (chemotherapy-associated targeted toxicity, protocol-specific graded toxicity), indications of treatment efficacy (tumor necrosis, number of full drug dose infusions, completeness of surgical resection), treatment-related complications (in-hospital days; post-surgical wound infection, thrombosis, hemorrhage, or hematoma), OS (time from enrollment to death from any cause),

EFS (time from enrollment to disease recurrence, progression, or death), and CIR (time to post-remission relapse). Within these categories, we extracted statistical information including incidence of under- and overnutrition, measures of association (odds ratio (OR), risk ratio (RR), hazard ratio (HR)), *P*-values, confidence intervals (CI), and adjustment variables used in multivariate analyses. Data was extracted by two authors (SD, LJ) and independently verified by one author (EJL).

Statistical Synthesis and Analysis

Due to heterogeneity of the data and the small number of clinical trials evaluating a single diagnosis, formal statistical analysis was not feasible. Descriptive statistics were extracted from each study and summarized in Table 2. Studies were further classified by disease type, as well as study strengths, weaknesses, and outcomes.

Results

Search Results and Study Descriptions

Following removal of duplicates, 8969 manuscripts met initial search criteria. Twenty-two additional abstracts were identified via citation review. A full-text review was conducted on 75 articles, 10 of which met eligibility criteria and were included in the analysis (Ewing sarcoma, *n* = 3; osteosarcoma, *n* = 2; mixed Ewing sarcoma and osteosarcoma, *n* = 1; rhabdomyosarcoma, *n* = 2; Wilms tumor, *n* = 1; neuroblastoma, *n* = 1). Study characteristics are detailed in Table 1. NIH quality score assessment [13] for all eligible studies was calculated by three independent authors (EJL, SD, LJ), and revealed all reports to be of fair or good quality (scoring 8/14) in design and reporting (Supplemental Table 2). Included studies reported on a total of 4109 patients treated for an extracranial solid tumor between 1978 and 2011.

Results by Disease Group

Ewing sarcoma

Three studies addressed the impact of nutritional status on outcomes in Ewing sarcoma (Table 1, Table 2).[14–16] One study of good quality (*N* = 71) found that of the 11 patients who developed symptomatic cardiotoxicity during therapy, 9 were underweight at diagnosis. While low BMI was associated with increased risk of cardiotoxicity on univariate analysis (*P* = 0.034), this was not confirmed by multivariate models (*P* = 0.347).[14] In contrast, a study of fair quality (*N* = 142) showed no relationship between nutritional status and TRT. [16] In a third study, also of fair quality (*N* = 50), abnormal BMI (high and low collapsed into one category) was significantly associated with poor histologic response (tumor necrosis <90%) (OR: 4.33, 95% CI: 1.12–19.14, *P* = 0.034), as well as worse OS (HR: 2.76, 95% CI: 1.19–9.99, *P* = 0.022).[15] The available studies suggest an association of BMI with TRT and survival in Ewing sarcoma. However, in interpreting these findings it is critical to recognize that all three studies were derived from retrospectively collected data centered in one or two institutions, and that the sample sizes in each study are limited.

Osteosarcoma

Two studies evaluated the effects of nutritional status on outcomes in osteosarcoma (Table 1, Table 2).[17, 18] Both studies were performed on prospectively collected data obtained from a single Children's Oncology Group (COG) data set. One study of good quality (N = 498) showed that in the post-operative period those with high BMI had significantly increased odds of developing arterial thrombosis (OR: 9.4, $P=0.03$), while those with low BMI had a twofold increased risk of developing wound infection and slough (OR: 2.0, $P=0.07$).[18] A fair quality study (N = 710) showed a significant association between high BMI and grade III-IV nephrotoxicity (OR: 2.8, $P=0.01$). High BMI was also associated with worse OS (69.7% versus 80.5%) (HR: 1.6, 95% CI: 1.14–2.24, $P<0.005$) and a notable difference in EFS (HR: 1.3, 95% CI: 1.0–1.8, $P=0.05$).[17] Taken together, these studies demonstrate a relationship between nutritional status, treatment-related complications, TRT, and survival in osteosarcoma. Though these findings are limited by virtue of their being derived from the same data pool, their legitimacy is reinforced by the fact that they were obtained from a meticulously conducted clinical trial.

Rhabdomyosarcoma

Two studies of good quality examined the role of nutritional status in rhabdomyosarcoma outcomes (Table 1, Table 2).[19, 20] Here too, both studies were based upon prospective data obtained from a single COG data set. One study (N = 468) focused on the impact of weight changes during therapy. Nutritional status was not prognostic for infection rates, TRT or survival in this group. However, patients who experienced >10% weight loss had significantly increased number of hospitalization days (OR: 1.24, 95% CI: 1.00–1.54, $P=0.0463$).[19] The second study (N = 370) utilized a recursive partitioning algorithm to compare the prognostic significance of tumor volume and patient weight on EFS with known factors such as age and greatest tumor dimension. Algorithm results revealed that tumor volume ($>20\text{ cm}^3$), histology, and patient weight ($<50\text{ kg}$), had the strongest association with EFS (overall $P<0.001$).[20] Overall, these studies support an association between nutritional status and survival in rhabdomyosarcoma. Despite the limited data source, results of these studies are strengthened by the rigor of the data collection as part of a COG therapeutic trial.

Other

A good quality study including both Ewing sarcoma and osteosarcoma patients (N = 139) found that 2 years following initiation of treatment, 43.4% of osteosarcoma and 25.5% of Ewing sarcoma patients exhibited an abnormal BMI. Ultimately, however, altered nutritional status was not associated with survival outcomes.[21] There were two single, good quality studies that reported on the association of nutritional status and outcomes in children with neuroblastoma (N = 154) and Wilms tumor (N = 1,532).[22, 23] No statistically significant association was observed between nutritional status and survival in either study (Table 1, Table 2).

Discussion

Survival outcomes in pediatric solid tumors, with the notable exception of the positive impact of immunotherapy in neuroblastoma, have remained fairly stagnant since the 1990s. [1, 24] Nutritional status represents a modifiable risk factor long suggested to affect survival and TRT in both adult and pediatric malignancies.[7, 9, 25–28] Our review indicates that up to 62% of pediatric solid tumor patients are either over- or undernourished at diagnosis.[14] Four of the ten included studies identify abnormal BMI as a poor prognostic indicator in this group.[15, 17, 18, 20] One mechanism by which nutritional status may be influencing outcomes is its contribution to underlying body composition makeup. Variations in lean tissue and fat mass are thought to impact chemotherapy volume of distribution, metabolism, and thereby modify clearance of hydrophilic and/or lipophilic drugs from systemic circulation.[29–34] While it is evident that traditional methods of dosing by body surface area do not accurately predict chemotherapy pharmacokinetics, our understanding of the underlying differences between individuals and disease populations is limited.[35] This is especially true of the pediatric cancer population, and additional research is warranted to explore this critical factor in the care of solid tumor patients.

Our findings must be interpreted within a limited clinical framework. Malnutrition in childhood cancer is a complex, multifactorial process. Currently, there is no uniform measure to identify those at nutritional risk.[8, 36–39] While BMI is often relied upon due to its ease of collection, inference is limited. Those categorized as “normal” may still be malnourished.[7, 8, 21, 36, 40] These limitations likely contribute to the conflicting results reported in the literature. More recently, sarcopenia, defined as severe depletion of skeletal muscle, and sarcopenic obesity, defined as muscle depletion in the setting of excess fat, have been found to be more sensitive indicators of TRT, post-operative complication rates / hospital length of stay, and survival in adult cancer patients.[29, 31, 35, 41–44] In fact, literature shows that visceral-to-subcutaneous fat area ratio and lean body mass are significant predictors for disease-free survival and dose limiting toxicities, respectively.[29, 30] The role of body composition in pediatric solid tumors is a highly understudied area and is critical to advancing our understanding of the mechanisms by which nutritional status may be adversely impacting outcomes in this patient population.

Our review is not without its limitations. First, there are very few solid tumor studies in which nutritional anthropometrics were collected and reported upon in a systematic fashion. This is compounded by the small sample sizes within each study, and is particularly evident in osteosarcoma and rhabdomyosarcoma. The reported upon study populations in each of these disease categories were derived from single clinical trials. Additionally, there is a profound lack of studies looking at fluctuations in nutritional status. Yet, in pediatric leukemia variations in nutritional status during therapy have emerged as a more important prognostic factor than weight at diagnosis alone.[45]

Another limitation is the inconsistent methodology by which included studies were conducted. Half of the reported upon publications were based upon retrospective chart reviews, three of which spanned over several decades of data collection. Though four of these reported on patients treated as per national or international protocols, their analyses

were performed on a subset of the original study population. Therefore, their results may not be generalizable. The other half of included publications were post hoc analyses of COG clinical trials. Here anthropometric data was previously collected in a prospective fashion; however, these secondary analyses were not part of the original set of aims. Lastly, by the nature of their design, all of these studies are limited in their ability to evaluate causality. Given the low incidence of solid tumors, a limited availability of randomized controlled trials is inherent to supportive care studies aimed at this population. Advocating for cooperative groups and societies to collect anthropometric data in a prospective, longitudinal fashion will enhance our understanding of the influence of nutritional status, and shed new light on cause and effect relationships.

This review of the literature strongly supports the need to better understand the role of nutritional status in pediatric solid tumors. Given that nutritional status is a potentially modifiable condition and there is a window of opportunity to appropriately adjust dosing of cancer therapeutics to better reflect underlying individual metabolism, the role of body composition is a priority for future study. Prospective, modernized studies are necessary in order to fully recognize the mechanistic changes occurring beneath the surface. Understanding these transformations will allow for earlier intervention, and improved outcomes in this population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Vitae

Lenat Joffe, MD, MS

Dr. Lenat Joffe completed her pediatric hematology, oncology, and stem cell transplant fellowship training at Columbia University Medical Center in June, 2018, and is currently a Postdoctoral Clinical Research Fellow funded by an NIH/NCI T32-Cancer-Related Population Sciences Training Grant at the Columbia University Mailman School of Public Health. As a clinician scientist, her research interests are focused on cancer control and supportive care in pediatric oncology. Dr. Joffe is Children's Oncology Group (COG) Young Investigator, and was invited to presented her research at an NIH-supported State-of-the-Science meeting to address nutrition at this year's COG Fall Group Meeting.

Sarah Dwyer, MS

Ms. Sarah Dwyer is currently a first-year medical student at Geisinger Commonwealth School of Medicine, and she received her Master's Degree in Human Nutrition from Columbia University Medical Center in 2017. Sarah's research interests include health outcomes in oncology as well as genomics and synthetic biology. During her undergraduate career at Davidson College, she co-directed a multi-institutional food system symposium and co-founded a community nutrition education program.

Julia Glade Bender, MD

Dr. Julia L. Glade Bender is the Vice Chair of Clinical Research in the Department of Pediatrics at Memorial Sloan Kettering Cancer Center. Dr. Glade Bender's clinical practice revolves around patients with sarcoma and other high-risk solid tumors. On a national level, she provides scientific leadership for early phase and precision oncology clinical trials for children with resistant cancers, sponsored by the National Cancer Institute, the Children's Oncology Group, smaller disease-oriented consortia and pharmaceutical industry. Dr. Glade Bender's primary translational work has been on the clinical development of targeted agents which inhibit growth pathways and manipulate the tumor microenvironment.

A. Lindsay Frazier, MD, ScM

Dr. A. Lindsay Frazier is an Associate Professor of Pediatrics at Harvard Medical School and of Epidemiology at the Harvard T.H. Chan School of Public Health. In clinical practice, Dr. Frazier is the national expert on pediatric germ cell tumors (GCTs), and serves as Chair of the Children's Oncology Group Germ Cell subcommittee in Rare Tumors. Dr. Frazier's research focuses on cancer prevention in adolescents, colorectal cancer screening, and treatment of pediatric GCTs. Dr. Frazier served as the co-director of the Growing Up Today Study, a national cohort study of 27,000 offspring of the women in the Nurses Health Study.

Elena Ladas, PhD, RD

Dr. Elena J. Ladas is a Sid and Helaine Lerner Associate Professor for Global Integrative Medicine in the Department of Pediatric Hematology, Oncology, and Stem Cell Transplant (in Epidemiology and in the Institute of Human Nutrition) at the Columbia University Medical Center (CUMC). Dr. Ladas serves as Co-Director of the Center for Comprehensive Wellness at CUMC, as well as the Chair of the Nutrition Committee of Children's Oncology

Group. Dr. Ladas is an NIH funded clinical investigator, and an international leader in the area of nutrition and supportive care research in pediatric oncology.

Abbreviations

BMI	body mass index
CIR	cumulative incidence of relapse
EFS	event-free survival
EMM	estimated marginal mean
ES	Ewing sarcoma
NR	not reported
OS	overall survival
TRT	treatment-related toxicity
WFA	weight for age

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Figure 1.
Results of Search Strategy

Table 1

Characteristics of Studies Included in the Systematic Review^a

Study, Country	Consortium	Treatment Regimens	Study Dates	Tumor Type (Participants, n)	Ages at Diagnosis, y	Anthropometric Data Collection	Anthropometric Data Category Definition	Main Findings
Ewing Sarcoma								
Brown 2013 [14], Canada	CCG/POG/ COG ^b	NR ^c	1978–2006	Localized and metastatic (n=71)	Median: 11 Range: 2.2–16.1	Retrospective review of medical records	BMI (CDC)	<ul style="list-style-type: none">● At diagnosis: 54% overweight; 8% overweight● By univariate analysis <i>alone</i> low BMI was associated with Grade III–V cardiotoxicity (<i>P</i>=0.034)
Goldstein 2015 [15], Israel	EURO EWING	NR ^d	2000–2011	Localized and metastatic (n=50)	Median by BMI: <i>Normal</i> : 13.9 <i>Abnormal</i> : 14.3 Range: 9.7–20.1	Retrospective review of medical records	BMI (CDC/ COG ^e)	<ul style="list-style-type: none">● BMI at diagnosis: 16% low; 20% high● Abnormal BMI significantly associated with poor histologic response (OR=4.33, <i>P</i>=0.034) and worse OS (HR=2.76, <i>P</i>=0.022)● BMI not prognostic of EF
Sharib 2012 [16], United States	COG	NR ^f	1980–2010	Localized and metastatic (n=142)	NR ^g	Retrospective review of medical records	BMI (cohort divided into tertiles)	<ul style="list-style-type: none">● BMI not associated with TRT
Osteosarcoma								
Hingorani 2011 [18], United States	COG/CCG/ POG	INT-0133 (CCG-7921, POG-9351)	1993–1997	Localized (n=498)	Mean: 14 Range: 3.7–30	Prospectively on clinical trial	BMI (CDC)	<ul style="list-style-type: none">● BMI at diagnosis: 14.7% low; 8.6% high● Increased risk of arterial thrombosis associated with high BMI (OR=9.4, <i>P</i>=0.03)● Wound infection/slough more common in low BMI (OR=2.0, <i>P</i>=0.07)
Altat 2013 [17], United States	COG/CCG/ POG	INT-0133 (CCG-7921, POG-9351)	1993–1997	Localized and metastatic (n=710)	Median by BMI: <i>Low</i> : 12.9 <i>Normal</i> :14 <i>High</i> : 14 Range: 2–20	Prospectively on clinical trial	BMI (CDC/ COG ^e)	<ul style="list-style-type: none">● BMI at diagnosis: 10.4% low; 26.6% high● High BMI associated with:<ol style="list-style-type: none">1. Increased nephrotoxicity in course 2 (OR=2.8, <i>P</i>=0.01)2. Decreased OS (69.7% vs 80.5%) (HR =1.6, <i>P</i><0.005)3. Impaired EFS (66.2% vs 75.5%) (HR=1.3, <i>P</i>=0.05)
Neuroblastoma								
Snall 2015 [22], Australia	NR	NR	1985–2005	Stage 1–4, 4s (n=129)	Median: 1.2 Range: 0–10.6	Retrospective review of medical records	Weight/BMI zscores (British 1990 Growth Reference Data and LMS Growth Program)	<ul style="list-style-type: none">● At diagnosis: 24% overweight; 11.6% overweight● All, except 4s patients, had significant decrease in BMI at 6 months (EMM 0.73, <i>P</i><0.001) and increase from baseline by 24 months (EMM 0.81, <i>P</i>=0.007)● BMI not predictive of OS

Study, Country	Consortium	Treatment Regimens	Study Dates	Tumor Type (Participants, n)	Ages at Diagnosis, y	Anthropometric Data Collection	Anthropometric Data Category Definition	Main Findings
Wilms Tumor								
Fernandez 2009 [23], Canada	NWTS	NWTS-5	1995–2002	Stage I-IV favorable histology (n=1532)	NR ^h	Prospectively on clinical trial	Age < 2y: WFA Age (CDC) 2y: BMI	● BMI/WFA at diagnosis: low 15% / 15.8%; high 13% / 15.2% ● NS not predictive of EFS
Rhabdomyosarcoma								
Burke 2013 [19], United States	COG	D9803	NR ⁱ	Intermediate risk (n=468)	Median: NR Range: 2–20	Prospectively on clinical trial	Weight (percent change from baseline); BMI (CDC)	● At diagnosis: 9.8% underweight; 12.8% overweight; 11.5% obese ● By week 24, 19% of patients lost > 10% baseline weight. Loss associated with increased hospitalization days (OR=1.24, P=0.0463); trend towards more grade III-IV TRT (P=0.06) ● NS not predictive of infection rates or survival
Rodeberg 2011 [20], United States	COG	D9803	1999–2005	Intermediate risk (n=370)	Mean/Median by Clinical Group: I: 7.39 / 6.08 II: 7.24 / 6.92 III: 7.22 / 5.23 Range: 0.07–41.86	Prospectively on clinical trial	<50 kg or 50 kg/ ^j	● Patients with larger tumor volumes (< 20cm ³) and weight >50kg had poorest EFS (47%; 95% CI: 0.330.60) of 4 risk groups identified. ● Tumor volume/patient weight are superior to greatest tumor dimension /age as predictors for EFS
Mixed Solid Tumor								
Tenardi 2012 [21], Germany	EURO EWING/ EURAMOS / COSS	Euro EWING 99; COSS-96; EURAMOS1	2001–2009	Localized and metastatic ES (n=62) and osteosarcoma (n=77)	Median: 14 Range: 1–27	Retrospective review of medical records	Weight/BMI zscores (European children and adolescents reference data)	● At diagnosis: 10.1% underweight; 17.2% overweight/obese ● Extreme weight changes overall (30% to +44%). Most notable in osteosarcoma (P<0.05). ● By 24 months 43.4% of osteosarcoma and 25.5% of ES patients had abnormal BMI, increased 13.5% / 1.3% from baseline, respectively ● NS not associated with outcome

^aBMI, body mass index; CCG, Children’s Cancer Group; CDC, Centers for Disease Control and Prevention; CI, confidence interval; COG, Children’s Oncology Group; COSS, Cooperative German-Austrian-Swiss Osteosarcoma Study Group; EFS, event-free survival; EMM, estimated marginal mean; ES, Ewing sarcoma; EURAMOS, European and American Osteosarcoma Study Group; Euro EWING, European Ewing Consortium; HR, hazard ratio; NR, not reported; NWTS, National Wilms Tumor Study Group; NS, nutritional status; OR, odds ratio; OS, overall survival; POG, Pediatric Oncology Group; TRT, treatment-related toxicity; WFA, weight for age.

^b91% of patients, rest unspecified.

^cAll received doxorubicin (none dextrazoxane). Radiotherapy (n=54). Autologous transplant (n=14).

^dAll received vincristine, ifosfamide, doxorubicin, etoposide. Then, standard risk: vincristine, actinomycin, ifosfamide; high risk: autologous transplant, radiotherapy.

^eCOG Nutrition Committee criteria.

Due to differences in treatment over time, single cumulative/dose-intensity chemotherapy scores given to normalize data to interval compressed arm of COG AEW50031.
 f_j
 g_j
85% of patients had income data information applicable only to those under 21y.
 N_j
NWTS-5 was limited to patients under 16y.[46]
 D_j
[20]
 f_j
Cutoffs determined by recursive partitioning algorithm.

Table 2

Outcomes and Methodology of Studies Included in the Systematic Review^a

Study, Country	Outcomes of Interest	Statistical Methodology	Adjustment Variables	Duration or Time-points of Follow-up	Strengths & Weaknesses ^b
Ewing Sarcoma					
Brown 2013 [14], Canada	Primary: Cardiac toxicity (ejection fraction <40%) for low vs normal vs high BMI Secondary: OS	Univariate/multivariate analyses for cardiotoxicity predictors; Kaplan-Meier methodology for survival	Age, BMI, anthracycline intravenous bolus/48hour infusion	Median: 88 months; Range: 8–304 months	S: Pediatric patients only; prolonged follow up; examines toxicities and survival W: Study spans 28y period, nonuniform patient treatment; OS analysis doesn't include BMI
Goldstein 2015 [15], Israel	Primary: Tumor necrosis for abnormal (<5%; >85%) vs normal (5–85%) BMI Secondary: OS, EFS abnormal vs normal BMI	Multivariate logistic regression for BMI as a predictor of histologic response; Kaplan-Meier method, log-rank test, multivariate Cox regression for OS/EFS	BMI, age, gender, metastatic status, disease site	Median: 42 months; Range: 9–149 months	S: Pediatric patients only; patients uniformly treated W: Adherence to regimen after surgery not accounted for
Sharib 2012 [16], United States	Primary: Grade III-IV nonhematologic TRT	Fisher's exact test for toxicity predictors; Logistic regression for independent contribution of bivariate predictors	Age, ethnicity, income, clinical trial status ^c	Range: 1.3–30.7 months ^d	S: Chemotherapy dosing normalized for uniform comparison W: Study spans 30y period, nonuniform patient treatment; BMI cutoffs not specified; multivariable analysis doesn't include BMI
Osteosarcoma					
Hingorani 2011 [18], United States	Primary: Post-operative wound complications for low (<10%) vs middle (11–94%) vs high (>95%) BMI	Logistic regression/Fisher's exact test for BMI as a predictor	Treatment arm, surgical site	Within 30 days of surgery	S: Large cohort W: BMI cutoffs group overweight (85–94%) into "middle" category; BMI right before surgery unknown; includes adult patients
Altat 2013 [17], United States	Primary: TRT for high (>85%) vs normal (5–85%) vs low (<5%) BMI Secondary: OS, EFS high vs normal vs low BMI	Logistic regression for BMI as predictor of TRT- stratified into hematologic toxicity, infection, nephrotoxicity; Cox proportional hazards for OS/EFS	Primary tumor location, sex, treatment regimen, metastatic status ^e	Toxicity analysis at 10 weeks (following induction chemotherapy); 5-y OS, 3-y EFS analysis	S: Large cohort; pediatric patients only; examines toxicities and survival W: TRT data only for first 10 weeks and limited to grade III-IV
Neuroblastoma					
Small 2015 [22], Australia	Primary: Height, weight, BMI trajectories Secondary: OS for underweight (<15%; z-score < -1.040) vs normal (15–85%; z-score > -1.036 & < 1.030) vs overweight (>85%; z-score > 1.036)	Chi-squared, Kruskal-Wallis, Mann-Whitney U for anthropometric trajectories; Linear mixed models for predictors of anthropometric measures; Kaplan-Meier method, Logrank test, multivariable Cox regression for OS	Age, sex, disease stage, time after diagnosis, stage/time interaction for anthropometric trajectories; Age, diagnostic BMI/weight, disease stage for OS	0, 3, 6, 12, 24 months; Median: 5.6y; Range: 3–7y; 5-y survival analysis	S: Measures anthropometrics longitudinally; pediatric patients only W: Study spans 30y period; treatment regimens not described; didn't evaluate impact of weight fluctuation on OS
Wilms Tumor					
Fernandez 2009 [23], Nova Scotia	Primary: EFS for low (<10%) vs normal	Stratified by age (<2y, 2y). Log-rank test for univariate analysis; Cox	Disease stage, chemotherapy protocol	Median: 4.9y; 5-y survival analysis	S: Very large cohort; pediatric patients only W: Outcomes limited to EFS

Study, Country	Outcomes of Interest	Statistical Methodology	Adjustment Variables	Duration or Time-points of Follow-up	Strengths & Weaknesses ^b
	(10–89.9%) vs high (>90%) WFA/BMI	proportional hazards for WFA or BMI as predictors for EFS			
Rhabdomyosarcoma					
Burke 2013 [19], United States	Primary: TRT, days hospitalized, and number of infections for weight loss (<5%) vs (5–10%) vs (>10%) Secondary: OS for 1. Weight loss (<5%) vs (5–10%) vs (>10%) 2. Baseline BMI - underweight (<5%) vs normal (5–85%) vs overweight (85–94%) vs obese (>95%)	Negative binomial regression for predictors of TRT and hospital days; Logistic regression for predictors of infection; Cox regression models, Kaplan-Meier method, log-rank test for OS	Race, risk group, baseline weight	0, 12, 24, 42 weeks	S: Large cohort; measure anthropometrics longitudinally; pediatric patients only; examines toxicities and survival W: Relationship between TRT and Baseline BMI not analyzed
Rodeberg 2011 [20], United States	Primary: EFS for 1. Tumor volume/ patient weight vs tumor size/patient age 2. Tumor volume/ patient weight ratio vs tumor volume alone Secondary: EFS for clinical group by weight/tumor volume ratio	Recursive partitioning method for risk group identification; Kaplan-Meier method for survival distribution; Cox regression model, likelihood-ratio test for EFS	Age, disease stage, clinical group, tumor classification, lymph node status, histology, primary site, greatest tumor dimension, tumor volume, height, weight, body surface area, treatment regime	Median: 4.4y; Range: 0.1–8.2y; 4-y survival analysis	S: Large cohort; innovative methodology W: Includes adult patients
Mixed Solid Tumor					
Tenardi 2012 [21], Germany	Primary: Trajectory of height/weight Secondary: 1. Weight change for A. Days hospitalized (108) vs (109–139) vs (140–169) vs (170) B. Number of medications received (27) vs (28–36) vs (3742) vs (43) 2. EFS, OS	Linear regression/ analysis of covariance, stratified by cancer type, for predictors of anthropometrics over time	Tumor location, volume, resection status, regression, chemotherapy type, quantity/type of antiemetics and analgesics	0, 3, 6, 9, 12, 24 months	S: Measures anthropometrics longitudinally; weight of implanted prosthesis considered in calculation of growth parameters W: Short follow-up interval; limited information on survival analysis

^aBMI, body mass index; EFS, event-free survival; NR, not reported; OS, overall survival; TRT, treatment-related toxicity, WFA, weight for age.

^bWeaknesses throughout literature: No prospective studies, supportive care not addressed, longitudinal BMI assessment understudied, underreporting nutritional interventions.

^cBMI not included in the model because not identified as a predictor in bivariate analysis.

^dRange for lengthiest protocol included.

^eMetastatic disease included in toxicity analysis but excluded from OS/EFS analysis