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Obesity is a Risk Factor for Renal Toxicity and Wound Complications among a Cohort of Pediatric Cancer Patients at a Single Tertiary Care Institution

Jennifer H Aldrink[1]*, Catherine Paris[2], Wei Wang[3], Erin Teeple[4], Aaron Wilcox[5], Kasi Eastep[1], Sarah H O'Brien[6] and Marc P Michalsky[1]

[1]*Department of Surgery, Division of Pediatric Surgery, Ohio State University College of Medicine, USA*
[2]*Department of Surgery, Division of Pediatric Surgery, Sherbrooke University Hospital Center, Canada*
[3]*Department of Biostatistics, Nationwide Children's Hospital, USA*
[4]*Department of General Surgery, Brigham and Women's Hospital, USA*
[5]*Department of General Surgery, Mount Carmel Health System, USA*
[6]*Department of Pediatrics, Division of Pediatric Hematology/Oncology/Bone Marrow Transplantation, Nationwide Children's Hospital, USA*

Abstract

Background: Evidence exists in the adult literature linking obesity to an elevated risk for the development of certain malignancies, and to an increase in treatment-related complications. Little information is available examining this relationship in the obese pediatric oncology population.

Methods: We performed a retrospective analysis for all patients with a malignancy and treated at our institution between January, 2005 and December, 2009. Body mass index (BMI) was calculated, categorizing them as obese or nonobese based upon their BMI percentile. Stratification by tumor type (leukemia/lymphoma, solid tumor) was performed. Data on the incidence of fifteen potential complications were recorded.

Results: Sixty-three patients (17%) were classified as obese, and 302 (83%) as nonobese. Wound complications occurred more frequently in obese patients with leukemia/lymphoma compared to nonobese patients (13.2% vs. 1.6%, p=0.0075). Renal toxicity occurred more frequently in the obese patients than in the nonobese patients (38.1% vs. 26.2% (p=0.06).

Conclusions: In a growing population of obese pediatric patients, certain malignancy-related treatment complications may occur at an increased incidence, including higher rates of renal toxicity and wound complications. This report highlights early treatment-related complications by BMI in pediatric patients with cancer, and demonstrates the need for an individualized approach in treating this population.

Keywords: Cancer; Obesity; Renal toxicity; Wound complications

Introduction

Obesity is a growing public health concern that currently affects approximately one-third of adults and nearly 17% of children and adolescents in the United States [1]. Recent data has demonstrated that the prevalence of obesity has increased over the past several decades to epidemic proportions in both the adult and pediatric populations in the U.S. with a nearly four-fold rise in the prevalence of overweight and obesity in the pediatric population. Of particular concern are recent reports estimating that approximately 4-7% of the of the affected pediatric population has a body mass index (BMI) percentile greater than 99 [2]. While long-term obesity-related health concerns such as type 2 diabetes mellitus and cardiovascular disease are well-established [3-5], recent literature has highlighted the increased risk for the occurrence of certain malignancies, including those arising from the gastrointestinal tract, kidney, breast, and endometrium, among obese adults [6-10]. In addition to increasing reports highlighting the apparent link(s) between chronic obesity and the development of cancer, numerous investigations have reported an increased incidence of documented treatment-related morbidity following the associated surgical and medical management of malignancies among obese adults when compared to individuals with a lean body habitus [11-17].

While data exists describing long-term sequelae of childhood neoplasms, including the risk of developing obesity in adult survivors [18-21], only one study has evaluated the relationship between weight at diagnosis and treatment-related complications for patients [22]. Despite the strong evidence linking obesity with a higher incidence of various neoplasms and a correspondingly increase in the risk of treatment-related complications in adults, there is currently a paucity of data examining this relationship in the obese pediatric population. The purpose of this retrospective analysis was to evaluate a cohort of pediatric cancer patients undergoing treatment at a single tertiary care institution in order to determine if obese children demonstrate an increased incidence of treatment-related morbidity and mortality.

Materials and Methods

After obtaining approval from the Institutional Review Board at Nationwide Children's Hospital, Columbus, Ohio, a retrospective analysis of the institutional patient cancer registry was conducted for all patients diagnosed with any malignancy and treated at our institution between January, 2005 and December, 2009. Patients were evaluated as an entire cohort, and also subgrouped into two broad categories: solid tumors (including brain tumors, soft tissue sarcomas, abdominal tumors, bone tumors) and leukemia/lymphoma (including acute lymphoblastic leukemia, acute myelogenous leukemia, Hodgkin lymphoma, non-Hodgkin lymphoma). Collected data points were

***Corresponding author:** Jennifer H. Aldrink, M.D., FACS, FAAP, Assistant Professor of Clinical Surgery, Nationwide Children's Hospital, Division of Pediatric Surgery, 700 Children's Drive, ED320, Columbus, Ohio 43205, USA, Tel: 614-722-0440; Fax: 614-722-3903; E-mail: Jennifer.aldrink@nationwidechildrens.org

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obtained from our institutional cancer registry as well as electronic medical records, and included patient age, sex, cancer diagnosis, tumor histology, patient weight (kg) and height (cm) at the time of initial diagnosis, initial vital signs (resting heart rate, systolic and diastolic blood pressure), calculated body mass index (BMI) percentile (weight (kg)/[height (m)]^2) per age and gender, and vital status. In addition, information regarding specific therapeutic interventions (chemotherapy, radiation therapy, bone marrow transplantation, cyto-reductive surgery) was collected, as well as data regarding treatment-related complications during the entire course of therapy. Specific documentation of complications including sepsis, urinary tract infection (UTI), venous thromboembolic event (VTE), disseminated intravascular coagulation (DIC), graft versus host disease (GVHD), varicella zoster, clostridium difficile, postoperative wound infection and other nonsurgical wound complications, tumor lysis syndrome, cardiac toxicity, renal toxicity, liver toxicity, pancreatitis, and acute respiratory failure requiring ventilation support were recorded.

Given the retrospective nature of this study, real-time urine output data was not available. Renal toxicity was therefore defined as any creatinine increase above normal range for age, and generally considered to be reflective of a decrease in glomerular filtration rate. Liver toxicity was defined by Hy's rule for drug-induced liver injury [23]. Pancreatitis was defined as serum lipase levels above normal value, abdominal pain, and, if available, the presence of pancreatic inflammation as documented by radiological imaging including ultrasound (US), computed tomography (CT) and/or magnetic resonance imaging (MRI).

Statistical Analysis

For the purposes of analysis, subjects were stratified by BMI percentile, using the U.S. Centers for Disease Control and Prevention (CDC) classifications as obese (BMI greater than or equal to 95th percentile for age) or non-obese (BMI less than 95th percentile for age and gender) [24]. An analysis was also performed separately comparing the underweight (<5th percentile for age) to the non-obese and obese groups. Tumor histology was classified broadly into two categories: solid tumor and leukemia/lymphoma. The groups were then compared for incidence of morbidity and mortality.

Categorical data were compared between the groups by using appropriate likelihood ratio Chi-Square test or Fisher's exact test. Continuous data were compared using either Student's t-test or nonparametric method Wilcoxon two-sample test when appropriate. Binary complication variables were also compared between groups using univariate logistic regression. Multivariate logistic regression

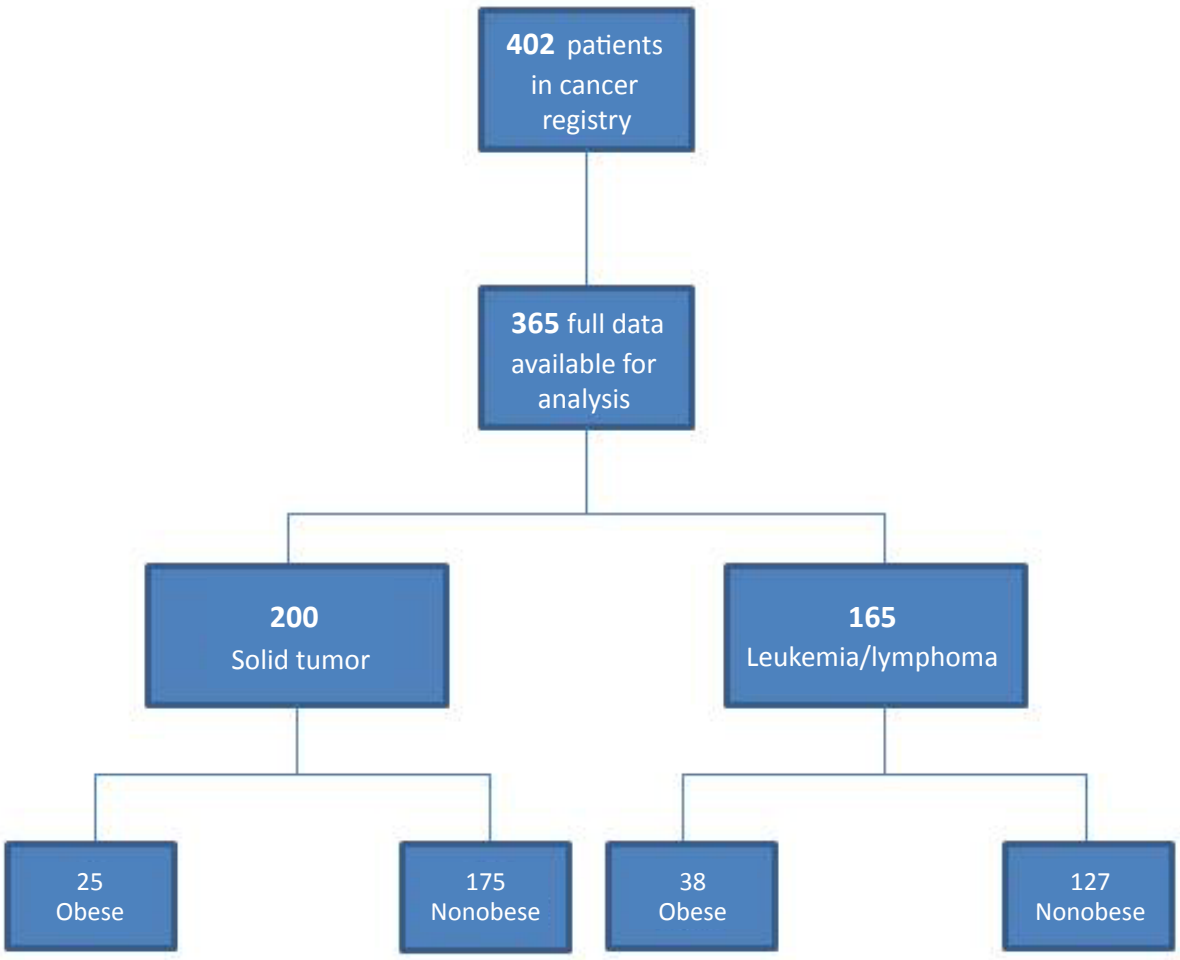

Figure 1: Patient distribution by tumor type and BMI classification.

analysis was performed evaluating the relationship between obesity and death related to specific complications. All statistical analysis was conducted using SAS 9.3 (by SAS Institute Inc., Cary, NC, USA). Statistical significance was considered to be P<0.05.

Demographic	Total Number	Nonobese % (n) (BMI < 95%ile)	Obese % (n) (BMI ≥ 95%ile)	p-value
Age (mean ± SD, yrs)	365	10.7 ± 4.7	12.5 ±4.4	**0.0089**
Sex				
M	184	47.4% (143)	65.1% (41)	**0.01**
F	181	52.6% (159)	34.9% (22)	
Race				
White	302	82.8 (250)	82.5 (52)	0.679
Black	44	11.3 (34)	15.9 (10)	
Hispanic	8	2.3 (7)	1.6 (1)	
Asian	7	2.3 (7)	0 (0)	
Other	4	1.3 (4)	0 (0)	

Table 1: Baseline patient demographics (Chi square).

Complication Variable	Nonobese % (n)	Obese % (n)	p-value
Sepsis	25.5 (77)	28.6 (18)	0.6157
Pneumonia	17.9 (54)	27 (17)	0.1081
UTI	13.2 (40)	15.9 (10)	0.5873
VTE	7.6 (23)	7.9 (5)	1
DIC	1.3 (4)	1.6 (1)	1
GVHD	2.6 (8)	1.6 (1)	1
Zoster	3 (9)	0 (0)	0.3682
C difficile	10.6 (32)	7.9 (5)	0.5129
Wound infection	4.3 (13)	7.9 (5)	0.2123
Cardiac toxicity	5 (15)	3.2 (2)	0.7476
Renal toxicity	26.2 (79)	38.1 (24)	0.0613
Liver toxicity	52.6 (159)	49.2 (31)	0.619
Pancreatitis	10.9 (33)	7.9 (5)	0.4659
Acute respiratory failure	11.6 (35)	9.5 (6)	0.6304
Death	17.2 (52)	17.5 (11)	0.9632

UTI, urinary tract infection; VTE, venous thromboembolism; DIC, disseminated intravascular coagulopathy

Table 2: Incidence of complications, obese vs nonobese (Univariate logistic regression).

Complication Variable	Nonobese % (n)	Obese % (n)	p-value
Sepsis	21 (37)	16 (4)	0.5409
Pneumonia	13 (23)	12 (3)	1
UTI	13 (23)	20 (5)	0.3587
VTE	4 (7)	8 (2)	0.3127
DIC	0 (0)	0 (0)	n/a
GVHD	0 (0)	0 (0)	n/a
Zoster	2 (3)	0 (0)	1
C difficile	9 (15)	12 (3)	0.4769
Wound infection	7 (12)	0 (0)	0.3686
Cardiac toxicity	5 (8)	0 (0)	0.5993
Renal toxicity	20 (35)	28 (7)	0.3728
Liver toxicity	37 (65)	20 (5)	0.0803
Pancreatitis	7 (13)	0 (0)	0.3775
Acute respiratory failure	9 (16)	4 (1)	0.7011

Table 3: Incidence of complications, obese vs nonobese for solid tumors (Fisher's exact test).

Complication Variable	Non-obese % (n)	Obese % (n)	p-value
Sepsis	32 (40)	37 (14)	0.5406
Pneumonia	24 (31)	37 (14)	0.1392
UTI	13 (17)	13 (5)	0.971
VTE	13 (16)	8 (3)	0.5682
DIC	3 (4)	3 (1)	1
GVHD	6 (8)	3 (1)	0.686
Zoster	5 (6)	0 (0)	0.3379
C difficile	13 (17)	5 (2)	0.2482
Wound infection	2 (2)	13 (5)	0.0075
Cardiac toxicity	6 (7)	5 (2)	1
Renal toxicity	35 (44)	45 (17)	0.2621
Liver toxicity	74 (94)	69 (26)	0.5014
Pancreatitis	16 (20)	13 (5)	0.6921
Acute respiratory failure	15 (19)	13 (5)	0.7801

Table 4: Incidence of complications, obese vs nonobese for leukemia/lymphoma. (Fisher's exact test).

Results

Of the 402 patients with documented malignancies entered into the institutional cancer registry between January, 2005 and December, 2009, complete data were available for 365 patients (90.8%). As seen in Figure 1, 200 children (54.7%) presented with a solid tumor diagnosis and 165 children (45.3%) presented with leukemia/lymphoma. Sixty-three (17%) patients were classified as obese (BMI percentile >95th percent), and 302 (83%) patients were nonobese (BMI percentile <95th percent). The distribution of weight category between the tumor types (solid versus leukemia/lymphoma) is depicted in Figure 1. This revealed 25 obese patients and 175 nonobese in the solid tumor group; and 38 obese and 127 nonobese in the leukemia/lymphoma group. There were 16 (4%) patients in the entire cohort who were underweight (BMI<5%ile for age and gender). Since these patients represented such a small portion of the entire cohort, they were grouped with the nonobese patients for analysis.

Baseline demographics of the investigational cohort are depicted in Table 1. The mean age of obese children was 12.5 years (SD ± 4.4 years; median 14 years), which was significantly older than the mean age of the nonobese children at 10.7 years (SD ± 4.7 years; median 11 years) (p=0.0089). In addition, results demonstrate a higher proportion of males in the obese cohort compared to females (22% males, 12% females were obese; p=0.0100). No other baseline demographic differences were detected.

Table 2 displays the incidence of complications by BMI category among the entire cohort. Renal toxicity was more likely to occur in obese patients with an incidence of 38.1% compared to non-obese patients with an incidence of 26.2% (p=0.0600), although this was not statistically significant.

Analysis of complication incidence stratified by histologic subgroup in relation to BMI categorization is shown in Tables 3 and 4. There was a higher rate of soft tissue complications (including both postoperative and nonsurgical) among obese patients being treated for leukemia/lymphoma (5/38; 13.2%) compared to their non-obese counterparts (2/127; 1.6%) (p=0.0075). A similar relationship for soft tissue complications was not seen in the solid tumor patients. However, of the soft tissue complications that occurred in the leukemia/lymphoma group, only 3 (57%) were surgical wounds, with the others being decubital ulcers that became infected (n=2), infection of a foot

Complication Variable	Odds Ratio	CI	p-value
Obesity (BMI ≥ 95%)	1.023	0.498-2.101	0.95
Tumor histology (Solid tumor vs leuk/lymph)	1.761	1.016-3.055	0.044
Sepsis	3.26	1.883-5.643	<0.0001
Pneumonia	2.531	1.401-4.572	0.002
UTI	2.357	1.221-4.552	0.011
VTE	2.733	1.208-6.184	0.016
DIC	7.336	1.201-44.794	0.031
GVHD	5	1.405-17.791	0.013
Zoster	0.581	0.072-4.728	0.612
C difficile	1.937	0.914-4.104	0.084
Wound infection	1.187	0.384-3.669	0.767
Cardiac toxicity	4.61	1.709-12.436	0.003
Renal toxicity	2.319	1.342-4.006	0.003
Liver toxicity	2.193	1.258-3.824	0.006
Pancreatitis	2.152	1.035-4.474	0.04
Acute respiratory failure	15.435	7.490-31.807	<0.0001

UTI, urinary tract infection; VTE, venous thromboembolism; DIC, disseminated intravascular coagulopathy; GVHD, graft versus host disease.

Table 5: Univariate logistic regression analysis of the effect of BMI and variable complications on mortality.

laceration from an injury sustained at home (n=1), and a paronychial infection involving a toe (n=1). Patients with a diagnosis of solid tumor demonstrated no significant differences in the incidence of specific complications as they related to associated classification of obesity.

Mortality was not influenced by BMI status (Table 5). Patients with solid tumor histologies had a higher rate of death compared to those with leukemia/lymphoma histologies (p=0.0400). The incidence of mortality was significantly related to many of the evaluated complications, including sepsis, pneumonia, UTI, VTE, DIC, GVHD, cardiac toxicity, renal toxicity, liver toxicity, pancreatitis, and acute respiratory failure. Multivariate logistic regression analysis found no significant relationships between obesity and specific complications with mortality.

Discussion

With a continuously expanding body of evidence demonstrating that a significant proportion of the pediatric and adolescent populations are affected by the growing obesity epidemic and corresponding data demonstrating an increased incidence of obesity-related co-morbid disease, careful patient evaluation is required to ensure the ongoing optimization of clinical treatment algorithms related to the affected sub-population being treated for various documented malignancies. As demonstrated in the current review, 17% of our study cohort was defined as obese at the time of diagnosis (BMI percentile >95), consistent with the National Health and Nutrition Examination Survey (NHANES 2009-2010) definition [1].

The physiology of excess weight and the pharmacokinetics of drugs in obese patients play a role in the effective delivery of chemotherapy agents [25]. The amount of free drug available for therapeutic effect as well as the amount of drug to be cleared from the body is dependent upon binding to serum proteins [25]. Alkaline drugs, frequently utilized as chemotherapeutic agents, are bound by alpha-1 acid glycoprotein which occurs at an increased rate in obese patients, potentially resulting in less free drug available and consequently less pharmacologic effect. In addition, excretion of the unbound portion of the drug may be slower, resulting in a prolonged effect [25-27]. These metabolic subtleties may have implications in the incidence of drug-related organ toxicity in the obese.

We found that renal toxicity more commonly occurred in the obese patients. Obesity-related co-morbid disease states, including the development of chronic renal disease, type 2 diabetes mellitus, atherosclerosis, and malignancy, are strongly associated with an accompanying systemic low-grade inflammatory state. However, even when excluding co-existing morbidities such as hypertension and diabetes, obesity remains an independent risk factor for the development of chronic renal disease [28-30]. In a recent multivariate analysis, the relative risk for the development of chronic renal disease strongly correlated with the severity of obesity [31]. Adipose tissue is now recognized as an active endocrine organ, secreting hormones (i.e. adipokines) and inducing macrophage-derived cytokines that act as mediators of renal cellular damage [30]. While many of these inflammatory markers and cytokines have been identified in animal models of obesity, they remain largely investigational and their clinical utility at this time is unknown. More clinically relevant, the impact of obesity on renal dysfunction has evolved with the identification of urinary cystatin C (Cys-C) as a correlate marker for glomerular filtration rate (GFR) [32,33]. While markers of inflammation including Cys-C were not evaluated in our cohort, we did identify an increased risk of renal toxicity based upon serum creatinine values in the obese patients. Future investigations related to chronic renal disease and obesity will likely focus on counteracting the detrimental effects caused by these inflammatory markers.

In addition to demonstrating a higher risk for renal toxicity, the current study also identified a higher rate of soft tissue complications, including postoperative wound problems in obese patients with leukemia/lymphoma, but not in solid tumor patients. Several adult studies have provided conflicting data regarding the incidence of postoperative surgical site infection in obese patients with malignancy [12,15,17,34,35]. In a review of 150 patients undergoing surgery for rectal cancer, Balentine et al. [35] identified an elevated BMI to be significantly associated with increased wound complications in both minimally invasive and open surgical resection, a trend they speculated may be attributed to prolonged operative time in obese patients [17]. Similarly, an analysis of the American College of Surgeons National Surgical Quality Improvement Project (ACS NSQIP) dataset demonstrated that severely morbidly obese patients had a higher rate of surgical site infection and wound dehiscence compared to normal weight patients [12]. Additional reports for patients undergoing surgical resection of pancreatic and hepatic malignancies have also shown increased rates of wound infection or intraabdominal abscess in obese patients [14,36]. However, others report that despite the increased technical difficulty, longer operative times, and increase in intraoperative blood loss, obesity does not portend a higher rate of postoperative wound complications [5,34,37].

There have also been reports relating obesity with the development of pressure ulcers [38]. A recent review by Rana et al. evaluating a large cohort of pediatric trauma patients identified decubital ulcers to occur more frequently in obese trauma patients compared to nonobese ones [39]. While we did not specifically evaluate pressure or decubital ulcers as a separate complication, several of the wound problems we identified were related to infection of pressure ulcers. In our study, despite few occurrences we did detect a significant difference in wound infection rates in obese leukemia/lymphoma patients but not in solid tumor resection, generally associated with larger surgical wounds, longer operative times, and increased surgical stress in the latter group. Taken

together, these observations suggest that other factors such as patient disease, chemotherapy profile, or other contributing factors may have contributed to this finding.

This study represents the first attempt to evaluate the incidence of various complications in pediatric patients with malignancies and the relationship(s) to the patient's degree of obesity at diagnosis as determined by BMI. We acknowledge significant limitations of this type of review. This was a retrospective review, prone to the flaws and biases inherent to this type of analysis. The population studied included diverse malignancies, making this an extremely heterogeneous cohort with complex treatment regimens, many of which could have contributed to the toxicity findings. However, given the variability in the therapeutic plans, it is unlikely that one dominant treatment regimen accounted for the findings we observed of increased renal toxicity and wound complication rate in the obese subset. This was a single institution study, and the small numbers of the variable complications may have made it difficult to discern differences. In addition, the study was not designed to address cancer relapse rates as they relate to obesity as others have done, demonstrating a disease-free disadvantage for the obese in certain malignancies [40]. Finally, the complications reported are admittedly generalized from the patient's clinical records, and future analysis of specific makers of cardiac or renal toxicity may allow for more insightful conclusions.

In conclusion, this study provides the first comprehensive report of various complications among pediatric cancer patients in relation to BMI stratification at diagnosis. In doing so, the study addresses the general paucity of data related to this important topic. Future areas of study include further exploration of pharmacokinetics for specific chemotherapeutic agents in obese children, validation of predictors of renal function thereby recognizing and preventing renal toxicity, surgical and nonsurgical wound complications management and prevention, and investigations examining the impact of obesity on pre-existing cardiac disease and the implication of dosing cardiotoxic drugs. These future areas will be of great benefit in improving longitudinal clinical outcomes.

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