1. Study title

Risk factors for intestinal obstruction requiring surgical intervention among patients with primary abdominal tumors in childhood

2. Working group and investigators

This proposed project will be undertaken with the assistance of the Childhood Cancer Survivor Study (CCSS) Chronic Disease Working Group, with secondary assistance of the CCSS Epidemiology and Biostatistics Working Group. Proposed investigators include the following members:

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3. Background and rationale

Children with primary abdominal tumors possess a heightened risk of intestinal complications in the years and decades following therapy.[1] Post-resection surgical adhesions, chemotherapy, irradiation, and tumor recurrence may lead to intestinal obstruction.[2] As 5-year survival rates of all major childhood cancers have increased over the past decades,[3] long-term effects of therapy become of paramount importance, especially among children who are followed for decades. However, no study has documented and characterized the incidence of and risk factors for intestinal obstruction in this population.

Long-term intestinal obstruction among children diagnosed with intra-abdominal tumors has not been thoroughly characterized. Specifically, the effects of risk factors including cancer treatments such as surgery, radiotherapy, and chemotherapy remain unknown. Surgical resection and radiotherapy may reduce the acute risk of obstruction by decreasing tumor burden, however they may also lead to increased long-term risk of obstruction due to bowel adhesions[9] and fibrosis[4]. The most likely mechanism by which radiation causes intestinal obstruction entails full thickness damage to the bowel wall.[10] Chemotherapy possesses several short- and long-term gastrointestinal toxicities,[11] however it remains unknown whether chemotherapy affects the risk of obstruction. Knowledge regarding risks and benefits of treatment on intestinal obstruction would be useful in guiding clinical decisions for children with abdominal primary tumors.

Information regarding intestinal obstruction is of particular importance given the severity of sequelae in this at-risk population. For example, chemotherapy or radiotherapy may predispose patients to more severe obstruction with further complications such as bowel perforation.[4] The impact of intestinal obstruction may be substantial, as over 80% of children with adhesive small bowel obstruction undergo operative intervention with either adhesiolysis or small bowel resection.[5] Unfortunately, as with cumulative incidence and risk factors, implications of intestinal obstruction on children with intra-abdominal tumors likewise remain unknown.

Existing data are sparse and largely limited to single-institution retrospective analyses with inherent biases. One single-institution retrospective analysis by Aguayo et al. in 2010 reported that intestinal obstruction may afflict up to 3.7% of pediatric patients diagnosed with intra-abdominal Wilms' tumor, rhabdomyosarcoma, neuroblastoma, and Hodgkin's and non-Hodgkin's lymphoma.[2] However, it is unclear if this number represents an accurate long-term estimate, given that mean follow-up time was limited to 3.6 years (median follow-up time was not reported, with a potential to over-estimate the overall follow-up due to right-skewedness). Additionally, the study was limited by the retrospective nature of the data collection and lacked several important clinical fields such as details of cancer treatment including surgery, chemotherapy, and radiation. The authors found that younger, male patients with Wilms' tumor, rhabdomyosarcoma, or Burkitt's lymphoma were at higher risk of intestinal obstruction compared to other malignancies.[2] The study was not designed to assess the impact of clinical factors such as tumor size and modifiable risk factors on obstruction. A 2010 systematic review by Bolling et al. compiled the results of case reports regarding late effects of radiotherapy on abdominal complications among pediatric patients. The authors found a potential association between small bowel obstruction and surgical resection but not radiotherapy.[9]

The purpose of the present study is to characterize and identify specific risk factors for intestinal obstruction among childhood cancer survivors with primary abdominal tumors.

4. Specific aims/objectives/research hypotheses

A. Specific aim 1

To describe the incidence of late (≥5 years post-diagnosis) intestinal obstruction requiring surgery among childhood cancer survivors with primary abdominal tumors.

Hypothesis: Late intestinal obstruction requiring surgery occurs significantly more frequently among childhood cancer survivors with primary abdominal tumors than survivors with primary non-abdominal tumors or siblings of survivors.

B. Specific aim 2

To characterize and compare the influence of specific demographic and treatment risk factors on late (≥5 years post-diagnosis) intestinal obstruction requiring surgery among childhood cancer survivors with primary abdominal tumors.

Hypothesis: Late intestinal obstruction requiring surgical intervention occurs significantly more frequently among patients with demographic and treatment risk factors, including treatment with chemotherapy, treatment with radiation therapy, prior surgery, and open (vs. minimally invasive) surgical approach.

C. Specific aim 3

To characterize the clinical severity of late (≥5 years post-diagnosis) intestinal obstruction requiring surgery among childhood cancer survivors with primary abdominal tumors.

Hypothesis: Overall survival is significantly decreased among childhood cancer survivors with primary abdominal tumors who have undergone surgery for late intestinal obstruction, compared with childhood cancer survivors with primary abdominal tumors who have not undergone surgery for late intestinal obstruction.

5. Analysis framework

A. Outcomes of interest

Outcomes of interest for this study will be established from CCSS surveys of survivors and siblings (Original Cohort). We will employ any CCSS survey completed by each survivor or sibling that captured relevant information prior to and including the 2007 follow-up questionnaire. Time to first occurrence of each outcome will be used.

Primary endpoint (time dependent, if available):

- Surgery for intestinal obstruction, occurring ≥5 years after enrollment. Defined as time (calculated based upon reported age at surgery for intestinal obstruction) from diagnosis of cancer (baseline #I-11, FU2007 #J-14).

Secondary endpoints (time dependent):

- Overall survival. Defined as time from diagnosis of cancer to all-cause mortality. The relationship between surgery for intestinal obstruction and overall survival will be evaluated among survivors with primary abdominal tumors.

B. Subject population

1. Childhood cancer survivors holding the diagnosis of primary abdominal tumor (including abdominal lymphomas, kidney tumors, neuroblastoma, and soft tissue sarcomas). In the preliminary query, 782 survivors with abdominal primary cancers were identified. Of these, 48 patients underwent surgery for intestinal obstruction after cohort entry.

2. Childhood cancer survivors holding the diagnosis of primary non-abdominal tumor. In the preliminary query, 13,168 survivors with non-abdominal primary cancers were identified. Of these, 262 patients underwent surgery for intestinal obstruction after cohort entry.

3. All siblings included in the CCSS database.

C. Exploratory variables of interest

- Sociodemographic variables
    - Sex
    - Race/ethnicity
    - Age at response to relevant question
    - Household income (most recently reported value)
    - Education (most recently reported value)

    - Health insurance coverage (most recently reported value)
- Disease variables
    - Age at diagnosis
    - Year of diagnosis
    - Type of cancer
    - Intra-abdominal site of tumor
- Treatment variables (MRAF)
    - Chemotherapy
        - Specific agent
        - Class of agent (alkylating agent, antimetabolite, anti-tumor antibiotic, topoisomerase inhibitor, mitotic inhibitor, corticosteroids, immunotherapy, other)
    - Abdominal or pelvic radiation treatment
        - Continuous (Gy)
        - Dose: < 10 Gy vs. 10 – 45 Gy vs. > 45 Gy (subject to change)
    - Surgery ICD-9 CM Procedure Code
        - Abdominal or pelvic surgery

D. Statistical methods

For survivors (with abdominal primary tumors and non-abdominal primary tumors) and siblings, we will tabulate demographic and clinical characteristics. For initial univariable analyses, categorical variables will be compared between groups (Abdominal tumor vs. non-abdominal tumor and within those, intestinal surgery vs. no intestinal surgery) using the Chi-square test or Fisher's exact test, when appropriate. Continuous variables will be compared between groups using the two-sample t-test (ANOVA for >2 groups) or Mann-Whitney *U* test (Wilcoxon rank-sum test for >2 groups), for non-parametrically distributed variables.

In the overall cohort (survivors and siblings), cumulative incidence curves of surgery for intestinal obstruction will be displayed for survivors with abdominal primary cancers, survivors with non-abdominal primary cancers, and siblings. The number of such surgeries is very small for siblings, so we will not carry out formal comparisons. Among survivors (excluding siblings), we will perform Cox proportional hazards modeling to compare hazard of surgery for intestinal obstruction between survivors with abdominal primary cancers and survivors with non-abdominal primary cancers.

Among survivors (excluding siblings), we will perform Cox proportional hazards modeling to assess hazard ratios of surgery for intestinal obstruction based on risk factors including the following: year of diagnosis, gender, age at cohort entry, primary cancer type (abdominal versus non-abdominal primary), chemotherapy, radiation therapy, and surgery. Adjustment for other predictors and/or confounders will be made to the hazard ratios in a multivariable analysis. We will evaluate whether it is necessary to stratify analysis by primary cancer location status or by surgical treatment status. Care will be taken to understand the relationship between treatment variables and primary cancer location in this exercise.

Among survivors with abdominal primary tumors (excluding siblings and survivors with non-abdominal primary tumors), we will perform Cox proportional hazards models to assess hazard ratios of death based on risk factors including intestinal obstruction requiring surgery as a time-dependent covariate. Adjustment for other predictors and/or confounders will be made to the hazard ratios in a multivariable analysis.

All models will take one of two approaches to account for age: 1) adjustment by including age in a multivariable model, using time since diagnosis as the time scale for the model or 2) adjustment by using age as the time-scale. Both approaches will be evaluated. The number of person-years at risk for intestinal obstruction requiring surgery will be designated beginning at five years after entrance into the CCSS database until most recent follow-up or intestinal obstruction requiring surgery. When age is used as the time scale, survivors will enter the risk set for the analysis at the age at which they reach 5 years after diagnosis. Death will be treated as a competing risk to intestinal obstruction requiring surgery and cumulative incidence curves of death will also be plotted. Multiple imputation methodology for age-at-event will be used for patients among whom surgery for intestinal obstruction was reported, but the participant did not report the year or age at which the surgery occurred. All analyses will also be adjusted for race and sex.

E. Examples of tables and figures

Table 1. Baseline characteristics of patients with and without abdominal tumors

Variable	*Abdominal tumor*	*Non-abdominal tumor*	*Siblings*
Primary cancer			
Lymphoma			
Neuroblastoma			
Sarcoma			
Wilms' tumor			
Surgical intervention			
Chemotherapy			
Radiation therapy			
Caucasian race			
Male			
Age at diagnosis			
Duration of follow-up			
Clinical Status			
Alive, NED			
Alive, disease			
Deceased			
Intestinal obstruction [N (%)]			
Years from surgery to intestinal obstruction			
Age at intestinal obstruction			

NED, no evidence of disease.

Table 2A-B. A comparison of patients who do and do not require surgery for intestinal obstruction, among patients with abdominal tumors (Table 2A) and non-abdominal tumors (Table 2B).

Table 2A

Variable	*Abdominal tumor*		P
	Intestinal obstruction	*No intestinal obstruction*	
Primary cancer			
Lymphoma			
Neuroblastoma			
Sarcoma			
Wilms' tumor			
Surgical intervention			
Chemotherapy			
Radiation therapy			
Caucasian race			
Male			
Age at diagnosis			
Duration of follow-up			
Clinical Status			
Alive, NED			
Alive, disease			
Deceased			
Intestinal obstruction [N (%)]			
Years from surgery to intestinal obstruction			
Age at intestinal obstruction			

NED, no evidence of disease

Table 2B

Variable	*Non-abdominal tumor*		P
	Intestinal obstruction	*No intestinal obstruction*	
Primary cancer			
Lymphoma			
Neuroblastoma			
Sarcoma			
Wilms' tumor			
Surgical intervention			
Chemotherapy			
Radiation therapy			
Caucasian race			
Male			
Age at diagnosis			
Duration of follow-up			
Clinical Status			
Alive, NED			
Alive, disease			
Deceased			
Intestinal obstruction [N (%)]			
Years from surgery to intestinal obstruction			
Age at intestinal obstruction			

NED, no evidence of disease

Table 3. Multivariable model(s) of factors associated with intestinal obstruction requiring surgery among survivors*

Variable	*Adjusted hazard ratio*	*95% Confidence Interval*	P
Abdominal primary cancer (vs. non-abdominal)			
Male			
Age at diagnosis			
Surgical resection			
Chemotherapy			
Radiotherapy			

***Separate models for primary diagnosis variables and treatment variables will likely be fit, adjusted for demographic variables.**

Figure 1. Cumulative incidence curves of intestinal obstruction requiring surgery
Curve A: no tumor (siblings)
Curve B: non-abdominal primary tumor
Curve C: abdominal primary tumor

Figure 2. Effect of multiple abdominal surgeries* on cumulative incidence of intestinal obstruction requiring surgery among survivors
Curve A: non-abdominal primary tumor
Curve A: abdominal primary tumor, no surgery
Curve B: abdominal primary tumor, one abdominal surgery
Curve C: abdominal primary tumor, two abdominal surgeries
Curve D: abdominal primary tumor, three or more abdominal surgeries
*Multiple abdominal surgeries defined as metachronous interventions carried out as part of the primary treatment period or at any point during follow-up.

Figure 3. Cumulative incidence of intestinal obstruction requiring surgery among survivors
Curve A: non-abdominal primary tumor
Curve A: abdominal primary tumor, no chemotherapy or radiotherapy
Curve B: abdominal primary tumor, chemotherapy
Curve C: abdominal primary tumor, radiotherapy
Curve D: abdominal primary tumor, chemotherapy and radiotherapy

Figure 4. Effect of chemotherapy type on incidence of intestinal obstruction requiring surgery among patients with abdominal tumors
Curve A: no chemotherapy
Curve B: chemotherapy class 1
Curve C: chemotherapy class 2
Curve D: chemotherapy class 3

Figure 5. Dose-response curve of radiation therapy on cumulative incidence of intestinal obstruction requiring surgery among patients with abdominal tumors
Curve A: no radiotherapy
Curve B: low-dose radiotherapy (< 10 Gy)
Curve C: medium-dose radiotherapy (10 – 45 Gy)
Curve D: high-dose radiotherapy (> 45 Gy)

References

1. Goldsby R, Chen Y, Raber S, et al. Survivors of childhood cancer have increased risk of gastrointestinal complications later in life. *Gastroenterology.* May 2011;140(5):1464-1471 e1461.

2. Aguayo P, Ho B, Fraser JD, Gamis A, St Peter SD, Snyder CL. Bowel obstruction after treatment of intra-abdominal tumors. *Eur J Pediatr Surg.* Jul 2010;20(4):234-236.

3. Jemal A, Siegel R, Ward E, et al. Cancer statistics, 2008. *CA Cancer J Clin.* Mar-Apr 2008;58(2):71-96.

4. Shafi MA, Bresalier RS. The gastrointestinal complications of oncologic therapy. *Gastroenterol Clin North Am.* Sep 2010;39(3):629-647.

5. Lautz TB, Raval MV, Reynolds M, Barsness KA. Adhesive small bowel obstruction in children and adolescents: operative utilization and factors associated with bowel loss. *J Am Coll Surg.* May 2011;212(5):855-861.

6. Peyvasteh M, Askarpour S, Javaherizadeh H, Taghizadeh S. Ileus and intestinal obstruction--comparison between children and adults. *Pol Przegl Chir.* Jul 2011;83(7):367-371.

7. Aslar AK, Ozdemir S, Mahmoudi H, Kuzu MA. Analysis of 230 cases of emergent surgery for obstructing colon cancer--lessons learned. *J Gastrointest Surg.* Jan 2011;15(1):110-119.

8. Birgisson H, Pahlman L, Gunnarsson U, Glimelius B. Adverse effects of preoperative radiation therapy for rectal cancer: long-term follow-up of the Swedish Rectal Cancer Trial. *J Clin Oncol.* Dec 1 2005;23(34):8697-8705.

9. Bolling T, Willich N, Ernst I. Late effects of abdominal irradiation in children: a review of the literature. *Anticancer Res.* Jan 2010;30(1):227-231.

10. Coia LR, Myerson RJ, Tepper JE. Late effects of radiation therapy on the gastrointestinal tract. *Int J Radiat Oncol Biol Phys.* Mar 30 1995;31(5):1213-1236.

11. Di Fiore F, Van Cutsem E. Acute and long-term gastrointestinal consequences of chemotherapy. *Best Pract Res Clin Gastroenterol.* 2009;23(1):113-124.

12. Tsai MS, Liang JT. Surgery is justified in patients with bowel obstruction due to radiation therapy. *J Gastrointest Surg.* Apr 2006;10(4):575-582.

13. Wong TH, Tan YM. Surgery for the palliation of intestinal obstruction in advanced abdominal malignancy. *Singapore Med J.* Dec 2009;50(12):1139-1144.