CHILDHOOD CANCER SURVIVOR STUDY
Gastrointestinal Sequelae in Adult Survivors of Childhood Cancer
Analysis Concept Proposal

Working Group and Investigators

Chronic Disease Working Group

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Background and Rationale

Current treatments have dramatically increased survival rates for children with cancer. While various disease specific combinations of chemotherapy, radiation and surgery have improved survival, these treatment modalities have the potential to cause significant gastrointestinal complications. Abdominal radiation often results in several acute toxicities, including enteritis and dysmotility of the intestinal tract. Chemotherapy is associated with many gastrointestinal toxicities, including nausea, vomiting, diarrhea, constipation and susceptibility to infections while patients are undergoing treatment. Surgery is responsible for structural and mechanical changes to the gastrointestinal system that are problematic in the initial surgical recovery. However, there is a paucity of data regarding the long-term gastrointestinal complications.

It has been reported in the literature that survivors of childhood cancers have an increased risk of developing severe or life-threatening conditions, in general, as late effects of the treatment. Patients treated with abdominal radiation had 8.8 times relative risk for developing severe or life threatening conditions. In particular, combination therapies such as abdominal radiation with alkylating chemotherapy were associated with at least a 10 fold increase in expected risk for any severe or life-threatening condition.[2] However, the incidence of specific gastrointestinal late effects related to childhood cancer therapy is not well known.

The Childhood Cancer Study Survey (CCSS) includes 10,397 adult survivors who were diagnosed between 1970 and 1986 with a childhood cancer, and survived 5 years after diagnosis. Of these survivors, 2,259 patients received abdominal radiation. Additionally, at least 2,425 patients had abdominal surgery related to their initial cancer treatment (i.e. needle biopsy, excisional biopsy, tumor excision, or tumor debulking (ICD 9 codes 42-46, 50-52, 54) and 7,012 received chemotherapy, either alone or in conjunction with surgery and/or radiation.

While acute gastrointestinal toxicities during childhood cancer treatment are well known, there is a paucity of information about the late gastrointestinal complications. The CCSS database offers a unique opportunity to study the gastrointestinal late effects and the associated risk factors in childhood cancer survivors. We propose a study to assess abdominal outcomes in adult survivors of childhood cancer identified in the CCSS cohort. We hypothesize that adverse outcomes will be higher in survivors who have had abdominal radiation, especially those who received radiation in combination with chemotherapy or surgery.

Specific Aims

Primary

1. To describe the incidence of adverse abdominal conditions in survivors of childhood cancer as well as make comparison to participating siblings
2. To evaluate the impact of therapy(such as radiation treatment, GI-toxic chemotherapies, surgeries, hematopoietic stem cell transplant, etc.) among childhood cancer survivors in the cohort.

Secondary

1. To evaluate the effect of other risk factors such as age, gender, primary disease location, disease type, surgery, chemotherapy utilized, and time from treatment on the risk of developing late gastrointestinal sequelae in survivors of childhood cancer.

Hypotheses

1. Survivors of childhood cancer will have increased risk of gastrointestinal issues compared to sibling controls.
2. Survivors of childhood cancer treated with abdominal radiation will have the highest risk of adverse gastrointestinal conditions, when compared with survivors not treated with abdominal radiation therapy, as well as sibling controls
3. Survivors treated with higher doses of radiation therapy at a younger age will have the greatest risk of adverse gastrointestinal sequelae.
4. Chemotherapy and surgery will enhance this risk.

Analysis Framework

Outcome variables: Three types of gastrointestinal outcomes will be considered: Upper Gastrointestinal (GI) Complications, Liver Conditions, Lower Gastrointestinal Complications.

a. Upper Gastrointestinal (GI) Complications: Upper intestinal problems include reported ulcer (H7), esophageal disease (H8), indigestion (H9), heartburn (H10), and other upper GI trouble (from H11 and H6). ICD9 codes for other stomach (H11) and other

b. Liver Conditions: Liver complications include gallstones (H1, H2), liver cirrhosis (H3), jaundice (H5), other liver trouble (H6), and surgical procedures including post-treatment liver biopsy (ICD9 CODES 5010-5012, 5019) (I21). ICD9 codes for other liver problems (H6) were reviewed and placed into one of the three categories. Included in "liver complications" (see Attachment A) were reports of secondary malignancies of the liver, hepatitis, and other liver problems. An aggregate variable for "any liver complications" will be derived from the responses listed above.

c. Lower Gastrointestinal Complications: Lower intestinal problems includes intestinal polyps (H12), diverticular disease (H13), colitis (H14), constipation (H15), diarrhea (H16), rectal/anal fistula (H17), and rectal/anal stricture (H18), and surgical procedures including surgery for intestinal obstruction (I11), colostomy/ileostomy (I12), takedown of colostomy/ileostomy (I13). Some responses to H11 (other stomach trouble) were included in the data for lower intestinal problems (see Attachment A). These diagnoses include secondary neoplasms of the intestines, peritoneal adhesions and peritonitis and other lower intestinal problems. An aggregate variable for "any lower intestinal dysfunction" will be composed of responses listed above.

For each of these three outcome variables, a "yes" response to any component of an aggregate variable will constitute a "yes" for that variable. For the outcomes that can be accompanied by an age (upper intestinal, liver complications, lower intestinal dysfunction), if a "yes" response was recorded without an accompanying age at first occurrence, the feasibility of imputing the age at first occurrence will be imputed using multiple imputation methodology employed for event-time imputations and along with appropriate methods for incorporating imputed values into the analyses will be evaluated.

b. Subject population
- Cases: 10,397 adult survivors in the CCSS cohort.
- Controls: 3,034 adult siblings in the CCSS cohort.

c. Data to be used in analyses:
- Outcome variables: see above.
- Explanatory Variables:
    - Exposure variables:
        - Abdominal surgery, specifically intra-abdominal procedures from MRAF (ICD 9 codes 42-46, 50-52, 54)
        - Radiation to chest, abdomen, and pelvis
            - Include subjects who received radiation within 5 years from diagnosis.
        - Chemotherapy agents & dose range

        - Alkylating agent score (as done in the fecundity of males abstract – ASCO 2007)
        - Anthracycline (cumulative dose >,< 450mg/m2)
        - Vincristine (yes or no)
      - Relapse
      - Bone marrow transplant (or HSCT)
  - Potential confounders and effect modifiers
      - Gender
      - Ethnicity
      - Current age
      - Age at diagnosis
      - Time interval between cancer diagnosis and late-effect occurrence

d. Analyses

Three separate outcome variables are defined based on aggregate variables as described above and have an associated age at first event (upper intestinal, liver complications, lower intestinal dysfunction). We will summarize proportions of subjects experiencing each event and will summarize the timing of onset of the outcomes. Cumulative incidence curves will be calculated to illustrate when various abdominal sequelae occur, stratified by abdominal radiation dosage if any, surgery, and chemotherapy exposure. Additionally, we will analyze the cumulative incidence of GI late effects, and will determine the number of patients reporting 2 or more late GI effects compared to those report only one. As radiation is predicted to influence GI outcomes and can affect growth, we propose to evaluate the impact of abdominal radiation on reported height and weight, within gender stratum, using linear models, adjusted for potential confounding variables such as age (Table 5).

Poisson regression will be used to calculate incidence rates and Poisson or Cox proportional hazards regression will be utilized to estimate relative risk estimates for the comparison of survivors to siblings and to evaluate the impact of the variables listed above under "Explanatory Variables" on each outcome among survivors. A priori, we expect to adjust all analyses for age at diagnosis and gender at a minimum. The 3,034 siblings who agreed to participate will be included as controls. Sandwich variance estimates will be utilized to account for the intra-family correlation between siblings and survivors included in the analysis. All above formal statistical analyses will focus on events occurring during the time period more than 5 years after diagnosis since the survivor cohort is defined from this time point forward. In addition, the number of events and prevalence of survivors who have experienced an event in the first 5 years after diagnosis will be summarized and compared to a similar age adjusted proportion among siblings to form a prevalence ratio.

Specific Tables/Figures

Table 1. Clinical Characteristics

Characteristics	Survivors (N=) No. (%)	Siblings (N=3899) No. (%)	P-Value
Age at Interview			
<20			
20-29			
30-39			
≥40			
Patient Sex			
Male			
Female			
Race/Ethnicity			
White, NH*			
Black, NH*			
Hispanic/Latino			
Asian/Pacific Islander			
Other			

*NH = Non-Hispanic

Characteristics	Survivors (N=) No. (%)	P-Value
Vital Status at interview		
Alive		
Dead		
Age at Diagnosis		
<3		
3-9		
≥10		
Diagnosis		
ALL		
AML		
Other Leukemia, NOS		
Astrocytoma		
Medulloblastoma/PNET		
Other CNS Tumor		
Hodgkin's Disease		
Non-Hodgkin's Lymphoma		
Kidney Tumor		
Neuroblastoma		
Soft Tissue Sarcoma		
Ewing Sarcoma		
Osteosarcoma		
Other Bone Tumor		
Abdominal Therapy		
None		
Radiation Only		
Surgery Only		
Chemotherapy Only		
Radiation + Chemotherapy		
Radiation + Surgery		
Surgery + Chemotherapy		
All Treatments		
Recurrence		
Yes		
No		
Bone Marrow Transplant		
Yes		
No		

Table 2. Incidence Rates and Relative Risks by Time Period of Onset of Adverse Gastrointestinal Outcomes

	Condition	Reported Outcome	Yes #	Yes %	Sibs Yes #	Sibs Yes %	Dx to 5 Years	Yes	PR§	95% CI	Dx after 5 Years	Yes	Rate‡	95% CI	RR§	95% CI
Upper GI Complications	Ulcer															
	Esophageal Disease															
	Indigestion/ Heartburn															
	Nausea/ Vomiting															
	Other Upper GI Trouble															
Liver Conditions	Gallstones & Other Gall Bladder Issues															
	Liver Cirrhosis															
	Jaundice															
	Liver Biopsy															
	Other Liver Trouble															
Lower Intestinal Complications	Intestinal Polyps/ Diverticular Disease															
	Colitis															
	Constipation															
	Diarrhea															
	Rectal/Anal Fistula/Stricture/ Other Obstruction Surgery															
	Colostomy/ Ileostomy															
	Other Lower Intestinal Trouble															

Abbreviation: PR, Prevalence Ratio; RR, relative risk.
*Excludes conditions prior to diagnosis.
†Includes "not sure" and missing responses.
‡Rate per 1,000 person-years.
§Adjusted for sex and age; relative to siblings.
_*P* _ .0001.

Table 3. Analysis of Factors that May Influence Gastrointestinal Complications

	Upper GI Complication		Liver Complications		Lower GI Complication	
	RR (95% CI)	P-value	RR (95% CI)	P-value	RR (95% CI)	P-value
Age at Diagnosis						
<3						
3-9						
10+						
Abdominal Primary Tumor						
Yes						
No						
Abdominal Radiation						
Yes						
No						
Abdominal Radiation Dose						
Unknown						
> Median						
<Median						
None						
Chemotherapy						
Yes						
No						
Alkylating Agents Score						
1st quartile						
2nd quartile						
3rd quartile						
4th quartile						
Vincristine						
Yes						
No						
Anthracycline						
none						
≥450 mg/m2						
<450 mg/m2						
Abdominal Surgery						
Yes						
No						
Surgery + XRT						
Surgery + Chemotherapy						
Chemotherapy + XRT						
Combined Therapy Surgery/Chemo/XRT						
Recurrence						
Yes						
No						
Bone marrow transplant						
Yes						
No						

Table 4. Radiation Site and Dose on Risk of Late Onset GI Complications

	Thoracic Dose		Abdominal Dose		Pelvic Dose	
	< Median	> Median	< Median	> Median	< Median	> Median
Upper Intestinal Disease						
Liver Complications						
Lower Intestinal Dysfunction						

Table 5. Reported Height and Weight of Cohort Based on Abdominal Radiation Exposure

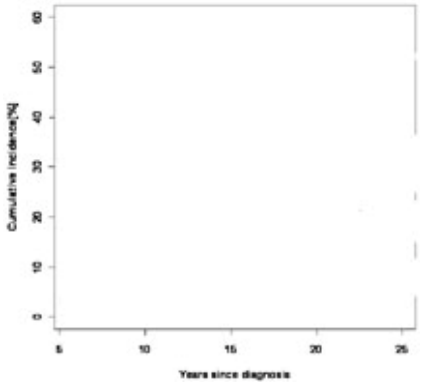
	Childhood Cancer Survivors				Sibling Controls	
	Radiation Therapy		No Radiation Therapy			
	Male	Female	Male	Female	Male	Female
Height						
Weight						
BMI						

Table 6. Occurrence of Multiple Adverse GI Outcomes

Conditions	**Upper GI Complications**		**Liver Complications**		**Lower GI Complications**		**All GI Complications**	
	Any	**2 or More**	**Any**	**2 or More**	**Any**	**2 or More**	**Any**	**2 or More**
Reported Outcome								
Yes*								
No†								
5 Years after Dx								
Yes*								
Rate‡								
95% CI								
RR**								
95% CI								

*Excludes conditions prior to diagnosis.
†Includes "not sure" and missing responses.
‡ Rate per 1,000 person-years.
** Relative rate, adjusted for age, sex and race; relative to siblings.
P < .001.

Figures
Cumulative incidence figures



References

1. Dickerman J The Late Effects of Childhood Cancer Therapy. *Pediatrics* 2007 Mar; 119(3)554-68.
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3. Guerin S et al. Concomitant chemo-radiotherapy and local dose of radiation as risk factors for second malignant neoplasms after solid cancer in childhood: A case-control study. *Int J Cancer* 2006;120, 96-102
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