CONCEPT PROPOSAL

STUDY TITLE: Impact of Radiation Dose and Volume to the Pancreas on Subsequent Risk of Diabetes Mellitus in Long-term Survivors of Childhood Cancer Treated with Abdominal Radiation: A Report from the Childhood Cancer Survivor Study

WORKING GROUP: This report will be written within the Chronic Disease Working Group. Proposed investigators include:

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BACKGROUND AND STUDY RATIONALE:
Due to improved curative therapies for childhood cancer, five-year survival rates now exceed 80% [1]. As of January 2010, more than 370,000 survivors of childhood cancer were estimated to live in the United States [2]. Improved survival, however, has led to increased recognition of survivors' excess risk of morbidity and mortality due to treatment-related late effects [3-8]. By the age of 50, more than 50% of childhood cancer survivors will have experienced a severe, life-threatening, disabling or fatal chronic condition [9]. While many chronic conditions impact survivors shortly after therapy, others may not become apparent until survivors mature into adulthood. The long-term follow-up of large cohorts of childhood cancer survivors, such as the Childhood Cancer Survivor Study (CCSS), allows identification of these conditions.

Radiation therapy as a predictor of adverse outcomes: Radiation therapy has been associated with a variety of long-term adverse health outcomes, which are related to individual patient factors as well as radiation site, cumulative radiation dose, and age at exposure [10]. In addition to the well-documented risk of radiation-induced second neoplasms [11-18], survivors treated with radiation are

also at risk for a number of endocrine and metabolic derangements [19-24], including diabetes mellitus (DM) [25, 26].

DM as a chronic condition: DM is a metabolic disorder resulting from defects in insulin secretion, insulin action, or both, which increases both cardiovascular and all-cause mortality [27, 28]. Type 1 DM results from autoimmune destruction of the pancreatic β cells and leads to insulinopenia, while type 2 DM is characterized by an initial period of insulin resistance and compensatory hyperinsulinemia, with subsequent progression over time to β cell failure. Chronic hyperglycemia, which characterizes both types of DM, results in long-term end-organ damage [29, 30].

The link between radiation therapy and DM: The diabetogenic effect of radiation therapy was first noted in small preclinical studies on the rat and primate pancreas [31, 32]. Similar findings were reported in humans in 1995 when Teinturier at al described a cohort of 121 patients treated with abdominal radiation in which 6.6% developed "pancreatic DM," or a non-autoimmune insulinopenic form of DM [33]. Concerns about a possible link between abdominal radiation and β cell dysfunction followed in other brief reports [21, 34].

In 2009, a CCSS analysis of 8,599 survivors, and 2,936 sibling comparisons, DM was reported in 2.5% of survivors (n=218) and 1.7% of siblings [35]. Survivors were 1.8 times more likely than siblings to report DM, after adjusting for age, sex, race/ethnicity, household income, and insurance status. This excess risk was most pronounced in those previously treated with total body or abdominal irradiation. After stratifying by diagnosis, survivors of neuroblastoma were 6.9 times more likely, and survivors of Wilms tumor and Hodgkin lymphoma were 2.1 times more likely, to develop DM if they had previously received abdominal radiation. Unlike the general population, the excess risk of DM demonstrated in CCSS survivors appeared to be independent of body mass index (BMI) or a sedentary lifestyle [35].

While precise radiation doses were not examined in the CCSS report, a large, retrospective analysis of 2,520 survivors of childhood cancer treated in France and the UK explored the relationship between pancreatic radiation dose and the subsequent development of DM [25]. Using radiation dosimetry, radiation dose estimates were determined for different regions of the pancreas for **1,632 survivors treated with abdominal radiation** (65% of the overall cohort). Excess rates of both type 1 *and* type 2 DM in young adulthood were evident in those previously treated with abdominal radiation; a dose-response relation between radiation exposure to the tail of the pancreas, where insulin-producing islet cells reside, and subsequent risk of DM was evident with doses up to 20-29 Gy. Younger age at treatment (<2 years) was a significant risk. While DM rarely occurred before 20 years of age, the incidence increased sharply thereafter and the cumulative incidence of DM was 5.5% by age 45 in survivors treated with abdominal radiation.

More recently, an analysis of 2,264 Hodgkin lymphoma survivors treated from 1965-1995 in the Netherlands (median age at diagnosis = 27 years; median duration of follow-up = 21.5 years; **1,083 (48%) treated with para-aortic radiation**) reported an overall 30-year cumulative incidence of 8.3% for DM [26]. Those treated with para-aortic radiation doses ≥ 36 Gy had a significantly increased risk of DM, when compared with: a) patients not treated with para-aortic radiation (HR 2.28; 95% CI, 1.53 to 3.38) and b) with those treated with 10 to 35 Gy to the para-aortic field (HR 2.04; 95% CI, 1.20 to 3.44). In contrast to the findings of the French/UK study, the risk of DM increased with increasing mean dose to the pancreatic tail without an evident plateau.

In addition to the delivered radiation dose, the volume of irradiated tissue is an important determinant of late radiation-related organ toxicity [36, 37]. While dose-volumetric parameters have been studied for many organs [38], such as the heart, lung, or the parotid gland, these relationships are not yet established for the pancreas. Recently, a study of radiation-related thyroid dysfunction demonstrated that the percentage of thyroid volume exceeding 30 Gy (also known as the V30) predicted the risk of

long-term thyroid dysfunction in Hodgkin lymphoma survivors [39]. Similarly, we plan to account for dose-volumetric factors in the current study by considering the percentage of pancreatic volume receiving a minimum of a specific radiation dose (eg, V20 = percentage of the pancreas receiving 20 Gy or more; V30 = percentage of the pancreas receiving 30 Gy or more) in relation to long-term risk of diabetes in CCSS survivors treated with abdominal radiation.

The current proposal will thus determine whether a dose-volume response relationship is evident in CCSS survivors treated with abdominal radiation in the overall CCSS cohort. **Using data from participants in the original and expansion cohorts, we plan to describe the risk of DM in CCSS survivors treated with abdominal radiation, without radiation exposure impacting the whole brain or total body irradiation, in relation to pancreatic radiation dose and volume, and identify modifying risk factors.** Survivors previously exposed to whole brain radiation or total body irradiation (TBI) will be excluded as these exposures are also implicated in DM risk, independent of abdominal radiation. The potential modifying effects of age at irradiation, time since irradiation, chemotherapy, and BMI will be evaluated. This study will include the largest number of abdominally irradiated childhood cancer survivors studied to date. Given the elapsed time since the last CCSS analysis in which 218 survivors reported taking a medication for DM [35], a greater number of cases will be described in the present study. Additional cases are expected in the expansion cohort as well.

The current proposal seeks to: (1) provide updated prevalence rates of DM in the overall CCSS cohort treated with abdominal radiation and (2) clarify the dose-volume response relationship between radiation dose and volume to the pancreas and DM risk. The study specific aims include:

Aim 1: Among survivors in the original and expansion cohorts, determine the prevalence of DM in CCSS survivors treated with abdominal radiation and compare it to the prevalence of DM in: (1) survivors not treated with abdominal radiation (or whole brain radiation or TBI) and (2) siblings (original cohort only).
Hypothesis: CCSS survivors treated with abdominal radiation will exhibit an increased risk of DM when compared to: (1) survivors not treated with abdominal radiation (or whole brain radiation or TBI) and (2) siblings.

Aim 2: Identify treatment-related and demographic risk factors for DM in CCSS survivors treated with abdominal radiation.
Hypothesis: Survivors treated with abdominal radiation at an early age will have a greater risk of DM independent of BMI.

Aim 3: Examine the dose-volume response relationship, using radiation dosimetry, between pancreatic radiation dose, volume, and risk of DM in CCSS survivors exposed to abdominal radiation.
Hypothesis: Cancer survivors treated with abdominal radiation exhibit a linear dose response-relation between radiation dose to the tail of the pancreas and prevalence of DM, without plateau in risk. Survivors exposed to higher pancreatic radiation volume will demonstrate higher risks for DM.

ANALYSIS FRAMEWORK:
Study Population: Study participants will include: (1) any patient in the original or expansion CCSS survivor cohorts treated with abdominal radiation, without documented radiation exposure impacting the whole brain and/or TBI, as these exposures are also implicated in DM risk, independent of abdominal radiation; (2) any patient in the original or expansion CCSS cohort not treated with abdominal radiation (or whole brain radiation or TBI) and (3) the sibling comparison group from the original cohort (expansion cohort siblings not yet available). Treatment analyses will be limited to those survivors who consented to medical record abstraction.

Outcome of Interest: The primary outcome of interest is the prevalence of DM in childhood cancer

survivors treated with abdominal radiation in the overall cohort, when compared to: (1) survivors not treated with abdominal radiation (or whole brain radiation or TBI) and (2) siblings. Demographic and treatment-related factors, including pancreatic radiation dose and volume, that impact DM risk will be assessed as well.
Exclusion criteria: CCSS survivors treated with abdominal radiation with additional documented radiation exposure impacting the whole brain and/or total body irradiation will be excluded. Additionally, those with a late recurrence > 5 years after diagnosis will be excluded as well.

Explanatory variables to be analyzed:
General variables:

A. Primary cancer diagnosis
B. Age at primary cancer diagnosis
C. Attained age at assessment (DOB – assessment)
D. Length of follow-up
E. Sex (Baseline A2, Baseline – expanded A2)
F. Race/ethnicity (Baseline A4, A4.a, Baseline – expanded A5, A5.a)
G. BMI (Calculated from Height/Weight on: Baseline A10, A11; FU 2003 7-8; FU 2007 A1-A2; Expansion A3-A4)
H. Household Income (Baseline <18 Q8; Baseline Q8, Q9; FU 2003 S1-S3; FU 2007 A6-A8; Expansion T1-T3)
I. Insurance (Baseline Q2, Q3, Q3.a, Q3.b; FU 2000 16; FU 2003 M1; FU 2007 B9; Expansion U2, U3, U3.a, U3.b)
J. Education level (Baseline O1; FU 2000 1; FU 2003 1; FU 2007 A3; Expansion R1)
K. Employment (Baseline <18 O6, O7; Baseline O5-O11; FU 2000 3; FU 2003 4-5; FU 2007 A4, A5; Expansion S1-S2)

Treatment variables:

L. History of chemotherapy [yes/no; if yes, alkylating agents (CED score); corticosteroids; anthracyclines (mg/m2)]
M. Age at abdominal radiation
N. Abdominal radiation dose (medical record abstraction)
O. Pancreatic radiation dose (head, body, tail). Radiation dosimetry records will be reviewed for all cases in order to reconstruct exact radiation doses to the head, body and tail of the pancreas.
P. Pancreatic radiation volume; volume receiving ≥ 20 Gy (V20), ≥ 30 Gy (V30) using radiation dosimetry records
Q. Additional sites of radiation

Outcomes variables:
In accord with the criteria used by Meacham et al in their 2009 analysis [35], eligible cases will include those who listed an oral DM medication and/or a form of insulin as a medication taken regularly on the baseline or follow-up (FU) questionnaires. Those who respond in the affirmative to any of the following questions will be included:

A. Medication for Diabetes (Baseline B8.7; FU 2002 6g)
B. Pills for Diabetes (FU 2003 Q4) and/or Insulin Injections for Diabetes (FU 2003 Q5)
C. Pills or Insulin for Diabetes (FU 2007 C8.4)
D. Pills or Insulin for Diabetes (Expansion B8.4)

This methodology may be modified depending on the quality of responses.

Statistical analysis:
Summary statistics and graphical methods will be used to explore the data. Prevalence will be estimated and compared between groups using a marginal regression framework. Models will use DM

as the outcome and include data from all of the relevant questionnaires. Models will be fit using generalized estimating equations assuming a Poisson distribution with a log link function and using the Huber-White sandwich variance estimate to obtain robust standard errors. This approach will allow us to estimate adjusted prevalence ratios, include data assessed at multiple time points, and account for both the within-participant and within-family correlation. All models will be adjusted for age at survey completion. Models comparing the three different groups [(1) childhood cancer survivors treated with abdominal radiation; (2) childhood cancer survivors not treated with abdominal radiation; (3) siblings] will include indicator variables for group status. Potential treatment-related risk factors, including anthracycline exposure, alkylating agent exposure (CED score), and corticosteroid exposure, will be evaluated in this regression framework. Demographic risk factors, BMI, and length of follow-up will be determined from each questionnaire and included in the models.

The dose-volume response relationship will be assessed with separate models using either (1) the dose for the whole pancreas (2) the dose to the tail of the pancreas, or (3) the volume of the pancreas irradiated, by including the relevant dose as a covariate in a marginal Poisson regression model with DM as the outcome. We will carefully consider the appropriate functional form for each measure of radiation dose by several means including plotting the raw data, considering transformations of the continuous dose and plotting covariate values against model residuals.

Model diagnostics will be used to evaluate the model assumptions of all the models described above, including the overall goodness of fit of the models and whether the functional forms of the different variables in the model are appropriate. Different functional forms for the covariates (e.g. using a logarithmic transformation or a squared term) may be used if the linear term does not appear to be the best fit. For a sensitivity analysis, we may also compare the results of these models to log-binomial models.

TABLES/FIGURES

Table 1. Characteristics of Childhood Cancer Survivors and Siblings

Characteristic	Survivors Treated with Abdominal Radiation	Survivors Not Treated with Abdominal Radiation†	Siblings	P value*	P value**
Sex Male Female					
Race White Black Other Unknown					
Age at Treatment, years Mean (SD) Median (Range)					
Age at Interview, years Mean (SD) Median (Range)					
Cancer Diagnosis Neuroblastoma					

Wilms tumor Hodgkin lymphoma Other					
Chemotherapy Alkylating agents Anthracyclines Corticosteroids					
BMI at interview <18.5 18.5-24.9 25.0-29.9 ≥ 30					
Median age at last follow up, years (Range)					
Median duration of follow-up, years (Range)					
Vital Status Alive Deceased					

Abbreviations: † comparison group excludes CCSS survivors treated with whole brain radiation and/or total body irradiation; * comparison between CCSS survivors treated with abdominal radiation and siblings; ** comparison between CCSS survivors treated with abdominal radiation and CCSS survivors not treated with abdominal radiation, whole brain radiation, or total body irradiation

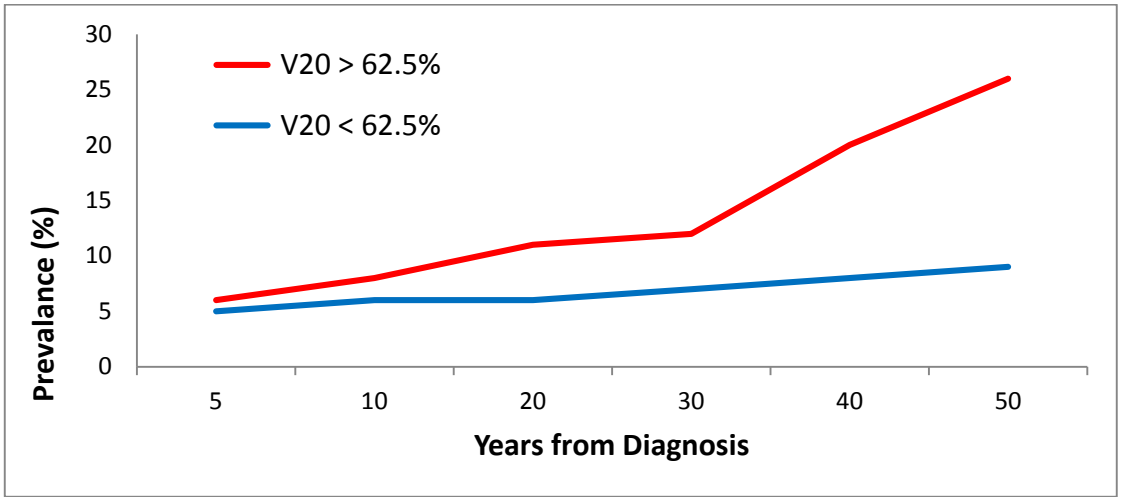
Figure 1. Prevalence of diabetes mellitus in childhood cancer survivors (CCS) exposed to abdominal radiation (vs prevalence in CCS not treated with abdominal radiation, cranial radiation or TBI vs siblings)

Figure 2. Prevalence of diabetes mellitus by maximal dose of abdominal radiation

Table 2. Prevalence and relative risk of diabetes according to radiation dose to the tail of the pancreas

Dose to the tail of the pancreas (Gy)	**Prevalence**	**Relative risk (95% CI)**
Zero		
> 0 – 0.9		
1 – 9.9		
10 – 19.9		
20 – 29.9		
30 – 39.9		
≥40		

Figure 3. Prevalence of diabetes mellitus at two different levels of pancreatic radiation volume



Abbreviation: V20 = the percentage of pancreatic volume exposed to a radiation dose exceeding 20 Gy

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