CCSS Analytic Concept Proposal

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STUDY TITLE: The risk of breast and thyroid cancer after radiotherapy for Hodgkin's Lymphoma: Can reconstructed dosimetry data be used to predict secondary malignancies?

WORKING GROUP AND INVESTIGATORS:

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BACKGROUND AND RATIONALE

Improvements in treatment have contributed to a significant increase in the proportion of pediatric patients surviving Hodgkin lymphoma (HL). This improvement in initial cure rate, however, has also been accompanied by an increasing recognition of the morbidity and mortality associated with second cancers, largely attributed to radiation therapy.

A major limitation of our current understanding of second cancers is that published risk estimates are based on outdated radiation therapy doses and techniques. Consequently, currently available data are of limited usefulness when counselling contemporary patients about the risks associated with modern therapy. The development of a robust model that helps to quantify second cancer risk based on normal tissue dosimetry would be of considerable clinical use for optimizing patient treatment, counselling patients regarding side effects, and developing individualized follow-up care plans.

Models of second cancer risk related to normal tissue dosimetry (so-called "radiobiologic models") have been developed by different investigators, including ours.[1-3] None of the existing models, however, are specific for pediatric cancer patients/survivors, and none have been validated against a cohort of patients for whom both normal tissue dosimetry *and* long-term follow-up are available.

Risk of Secondary Breast and Thyroid Cancer in Hodgkin's Lymphoma Survivors

Objective(s)

The objectives of this study are as follows:

1. Refine the predictive estimates of breast and thyroid second cancer risk obtained from radiobiologic models that are based primarily on normal tissue dosimetry so that they correspond with the observed risk of CCSS patients for whom both normal tissue dosimetry and observed risk estimates are available.
    a. Quantify the observed risk of second breast and thyroid cancers among CCSS HL survivors as described below.
    b. Utilize existing radiobiologic models based on reconstructed normal tissue dosimetry to estimate the risks of breast and thyroid cancer among the same cohort of patients.
    c. Compare the resulting risk estimates from the model with actual observed second cancer risk.
    d. Refine the radiobiologic models to improve correspondence with observed risk.

2. Estimate the second breast and thyroid cancer risk of patients treated on contemporary Children's Oncology Group (COG) protocols using the refined radiobiologic models.

METHODOLOGY

Study Design and Settings

This study will employ a case-cohort design. This study design is similar to the case-control design insofar as it increases efficiency by collecting detailed data only from cases and a subset of the source cohort, rather than the entire cohort. As we intend on estimating the excess relative risk (ERR) of developing the aforementioned secondary malignancies based on the mean dose of radiation received by normal tissues using reconstructed dosimetry data, this approach represents the most efficient way of conducting our study. Dose reconstruction represents a rate-limiting step in the conduct of this study.

CCSS Study Population

The source population of our study is comprised of all individuals in the Childhood Cancer Survivor Study (CCSS) database that were of age 13-20 at the time treatment of HL between 1970 and 1986 and who received mediastinal RT (N = 761) or chemotherapy alone (N = 60)

We have already reconstructed dosimetry data on cases with second cancers of the breast and thyroid from the source population who had mediastinal RT (N = 74).

We then drew a random of sample of 300 patients from the source cohort who had mediastinal RT. This was done without regard for whether or not these subjects ultimately developed a secondary cancer. This sampling will allow us to analyze the data like a case-cohort study (which is similar to a case-control study but arguably better suited for handling censored- time-to-event data).

Among these sampled patients, 67 were lacking sufficient data to reconstruct normal tissue dosimetry. From the remaining patients we again randomly sampled patients for dose reconstruction, aiming to do this on a sample size 2x larger than the number of second cancers. We have reconstructed data on 134 of these patients with useable RT data.

Statistical Analysis

As our study population has been randomly sampled from the larger CCSS database, we will examine important confounding variables (i.e. age, gender, malignancy, age at exposure, radiation therapy prescribed) to validate that our sample is truly representative of the patient population of interest.

The first analytic step will then be to describe the incidence of breast and thyroid cancer in the current study population. Specifically, we will calculate standardized incidence ratios (SIR) as the ratio of observed to expected cases, where the number of cases will be based on incidence rates from the Surveillance, Epidemiology and End Results (SEER) cancer registries. To estimate relative risks (RR) and their respective 95% confidence intervals, Poisson regression analysis will be used. Given the case-cohort nature of this study, appropriate weighting will be assigned to cases, members of the subcohort, and study subjects that have been oversampled[8].

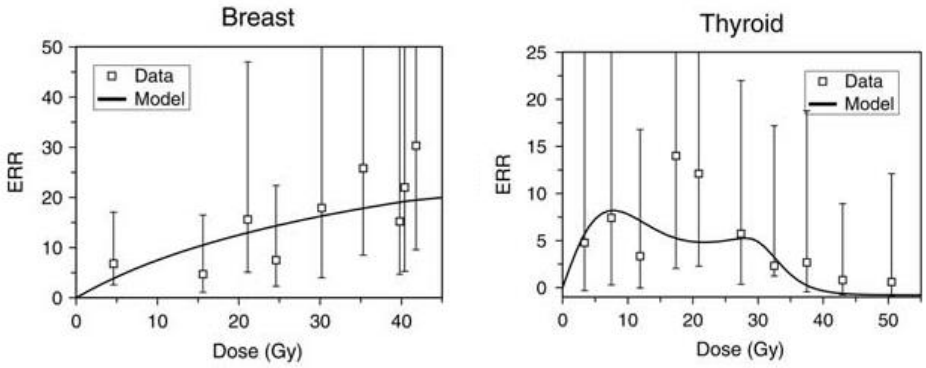
Regression analysis will performed to explore the effects of time since RT receipt, treatment age, and the reconstructed mean RT dose delivered to the breast and thyroid tissues on the ERRs.

The second step will be to produce second cancer risk estimates for the same patients using established radiobiologic models based on breast and thyroid radiation dose exposure[9], which we have reconstructed. These models operate under the assumption that target cells for radiation carcinogenesis are organ-specific stem or progenitor cells. These cells are subject to inactivation, repopulation and initiation. These inactivation, initiation, proliferation (IIP) processes are modeled stochastically following the approach of Sachs et al.[4] Some improvements relative to previous IIP models are introduced: in mathematical approach, by using analytic solutions for stochastic birth–death processes in place of Monte-Carlo simulations; and in biological assumptions, by emphasizing pre-malignant niches and clones, rather than individual pre-malignant cells. all of which are short-term mechanisms described in detail by Shuryak et al.[3]

The long-term formalism, into which short-term mechanisms are embedded, describes timescales of years or decades. It approximates carcinogenesis by a two-stage process, where normal stem cells can be initiated to become pre-malignant cells, which can clonally expand and mutate into fully malignant cells, which then give rise to cancer after some lag period. The basic assumptions are similar to those of the two stage clonal expansion (TSCE) model. However, the long-term formalism differs from the TSCE model in two main ways: (1) Normal and pre-malignant stem cells are considered as localized in distinct stem cell niches or compartments, where the number of such niches per organ, and/or the number of stem cells per niche, are homeostatically regulated, (2) Pre-malignant cells in all niches are assumed to lose their carcinogenic potential with age, so that at old age they have a progressively smaller probability of being transformed to malignant cells.

Eventual cancer risk is assumed to be proportional to the number of pre-malignant cells, shifted by lag time (i.e. 10 years) needed for a fully malignant cell to grow into a clinically detectable tumour.These models, which have been established for both breast and thyroid disease sites (Figure 1), have parameters to account for age at exposure, attained age, latency, radiation dose, and alkylator exposure, in addition to several other radiobiologic parameters. The parameters were estimated by fitting the models to data on background cancers, Japanese atomic bomb survivors, and second cancers in cancer radiotherapy patients. These models will be compared to the observed risks in the cohort that are developed as described above.

Figure 1. Best-fit model second breast and thyroid risk predictions for high-dose fractionated radiotherapy.[3]



The ability of the models to fit the data will be assessed, both in absolute terms (i.e. how well does a given model version describe the data), and in relative terms (i.e. how do the fits of different model versions to the data compare with each other). Absolute goodness of fit (GOF) assessment is a complicated problem, with ongoing active debate. [5] Our approach will be guided by the following measures of goodness of fit: (1) the X^2 test (ideally non-significant at the type I error threshold of 0.05), (2) the standardized root mean square residual (SRMR, ideally below 0.09). Ranking of models in terms of relative GOF, taking into account sample size and the number of adjustable parameters, will be performed based on the Akaike information criterion with correction for finite sample sizes (AICc), which has gained widespread popularity for this purpose. Comparison of a mechanistic model with a descriptive (e.g. polynomial) dose response

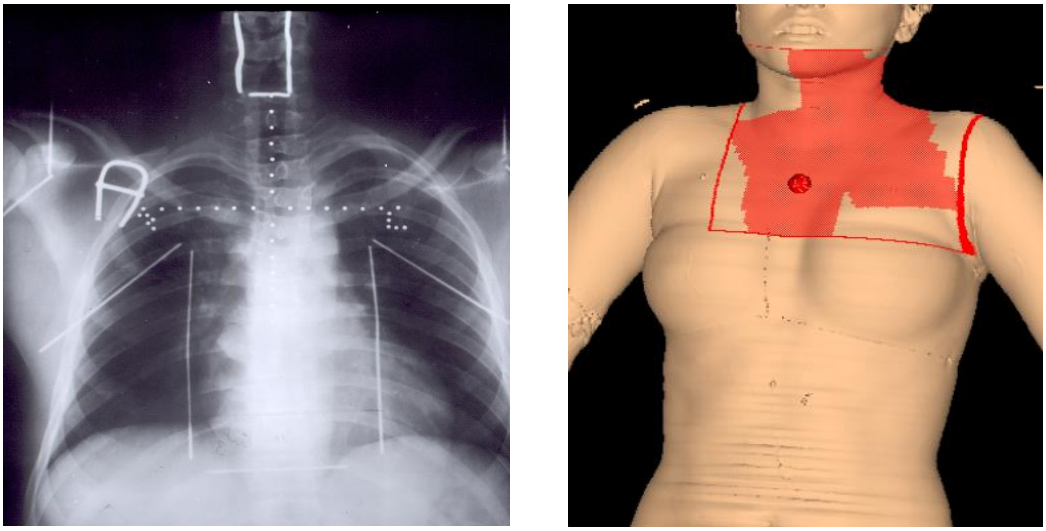
function with the same number of adjustable parameters by AICc will also be performed to supplement the absolute GOF assessment. If the mechanistic model fits the data similarly to the descriptive function (i.e. the AICc score difference between them is ≤6 units), this suggests that the mechanistic model describes the data almost as well as any simple functional form could do.

Nonparametric bootstrapping will be performed to establish the robustness of the findings and generate confidence intervals for model predictions and parameter values. Having refined the radiobiologic models, they will then be applied to 190 patients recently treated with radiotherapy in the COG 0031 and COG 0831 trials, to estimate the ERRs and cumulative incidence of breast and thyroid malignancies associated with contemporary therapy.

Evaluation of Second Cancer Risk among Contemporary Patients

In response to emerging data on the increased risk of second cancer in HL survivors, attributable in part to the receipt of radiation therapy, the use of extended-field radiation therapy (i.e. mantle, extended mantle or subtotal nodal RT fields that include grossly enlarged lymph nodes and surrounding lymph nodes) [10] has been largely discontinued in favor of involved field radiation therapy (IFRT) administered following chemotherapy [10] and involved site radiation therapy (ISRT). Reduced-dose IFRT (20 Gy) appears to produce comparable early disease control for selected favorable and intermediate risk patients [10].

Figure 2. Comparison of historical (left) and modern (right) radiation therapy planning.



As such, given that most published estimates of second cancer risks after radiotherapy in HL survivors are based on results from patients treated with extended-field RT, upon refining predictive model estimates of second cancer risk using CCSS observed risk data (objective 1), we will estimate the second breast and thyroid cancer risk of patients treated on contemporary

Children's Oncology Group (COG) protocols using the refined models. For this study objective, the dosimetry data on 191 patients treated on two recent COG studies has been obtained. This includes 68 patients from the AHOD 0031 study with intermediate risk HL [11], and 123 patients from the AHOD 0831 study with high risk HL [12]. Compared to the CCSS cohort, COG study participants received a considerably lower mean dose (Gy) to normal tissues, at all stages of disease (Figure 3a/b)

Figure 3a. Mean dose to normal tissues in stage I/II HL CCSS versus COG patients.

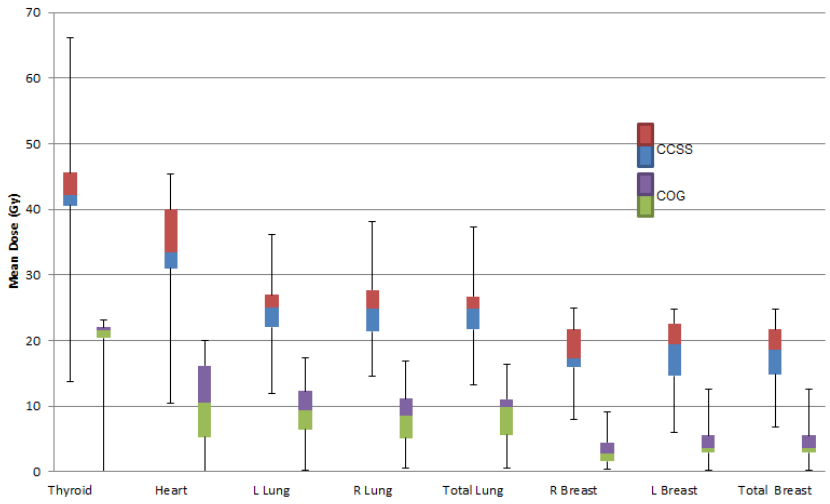
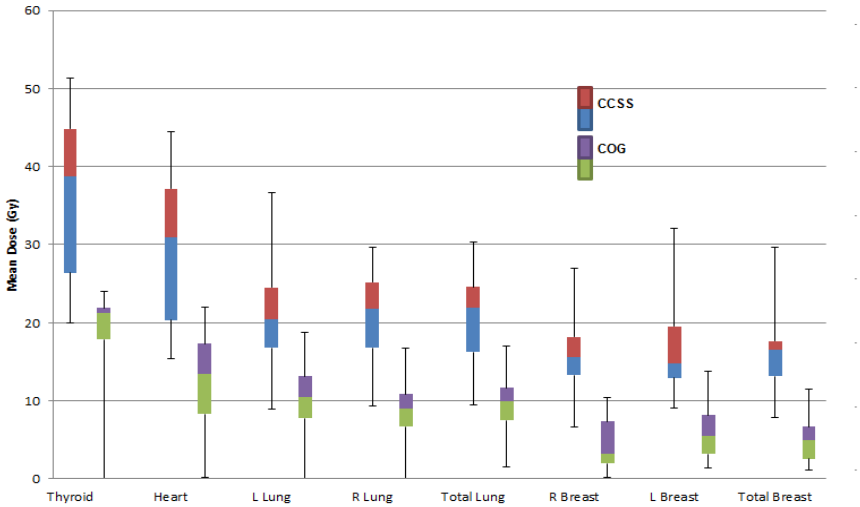


Figure 3b. Mean dose to normal tissues in stage III/IV HL CCSS versus COG patients.



APPENDIX

PROPOSED TABLES

Table 1. Comparison of patient and treatment-related characteristics between source cohort and subcohort

	Source cohort (n = 761)	Subcohort (n = 168)	P-value
Attained age, mean (SD)			
Age at RT received, mean (SD)			
Gender: Male, % (No.)			
Ever smoked, % (No.)			
RT dose (Gy), mean (SD)			
Chemotherapy receipt, % (No.)			
Cyclophosphamide dose, mean (SD)			
Anthracycline score, mean (SD)			
Follow-up duration (PY), mean (SD)			

Table 2. Standardized breast and thyroid cancer incidence ratios (stratified by demographic and treatment-related factors)

Characteristic	PY/10,000	BC cases	SIR (95% CI)	Thyroid cases	SIR (95% CI)
Overall					
Sex					
Male					
Female					
Age at RT, years					
<17 years					
≥ 17 years					
Type of treatment					
RT and chemotherapy					
RT only					
Chemotherapy only					
Smoking history					

Table 3. Breast cancer relative risks (RR) for demographic and treatment-related factors resulting from univariate and multivariate Poisson regression analyses

	Univariate		**Multivariate**	
	RR (95% CI)	P-value	RR (95% CI)	P-value
Attained age				
Gender (Male)				
Ever smoked				
RT Dose (Gy)*				
Chemotherapy receipt (y/n)				
Cyclophosphamide dose				
Alkylator score				

*****Mean dose to breasts only.

Table 4. Thyroid cancer relative risks (RR) for demographic and treatment-related factors resulting from univariate and multivariate Poisson regression analyses

	Univariate		**Multivariate**	
	RR (95% CI)	P-value	RR (95% CI)	P-value
Attained age				
Gender (Male)				
Ever smoked				
RT Dose (Gy)*				
Chemotherapy receipt (y/n)				
Cyclophosphamide dose				
Alkylator score				

*****Mean dose to thyroid gland only.

Table 5. Secondary cancer excess relative risks (ERR) for HL patients treated with mantle RT, stratified by time since RT (0-5, 5-15, >15)

	5-15 years	**>15 years**
Breast cancer		
Thyroid cancer		

Table 6. Secondary cancer excess relative risks (ERR) for HL patients treated with mantle RT, stratified by age at which treatment was received

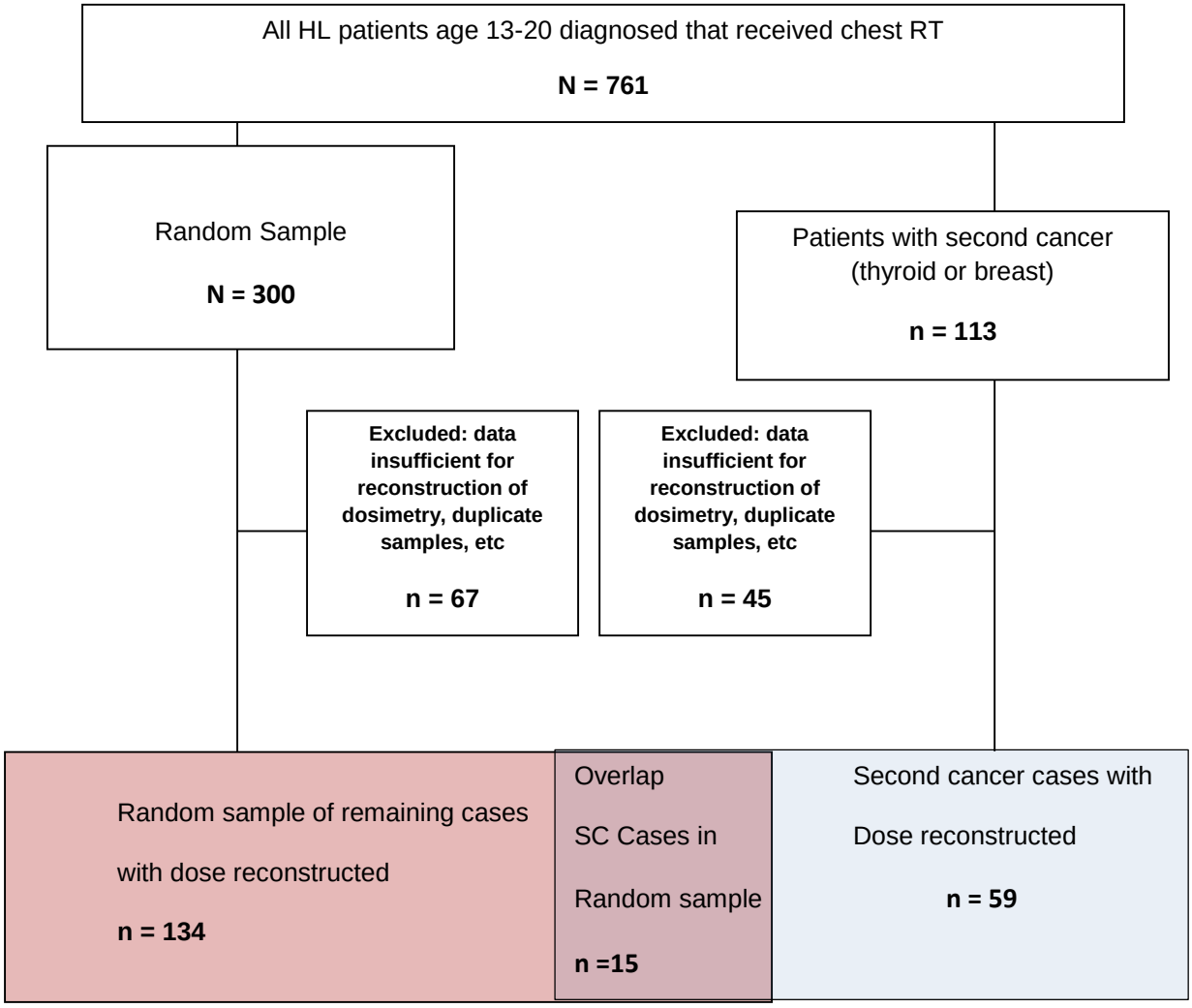
	RT < 17	**RT ≥ 17**
Breast cancer		
Thyroid cancer		

Table 7. Secondary cancer excess relative risks (ERR) for HL patients treated with mantle RT, stratified by prescription dose

	Mantle (<45Gy)	**Mantle (≥45 Gy)**
Breast cancer		
Thyroid cancer		

PROPOSED FIGURES

Figure 2. CONSORT – cohort selection diagram for reconstruction of Dosimetry*



*****There are 60 additional patients treated with chemotherapy alone. We will evaluate SC in all chemo only patients (not a random sample) due to small numbers.

Figure 3. Cumulative incidence curves for breast cancer.

- This would consist of Figure 1a, 1b, 1c, corresponding to different doses (i.e. <20 Gy, 20-30, >30 for example)
- In each Figure 1a-c, also showing 2 curves for RT received at age above or below median age (17).

Figure 4. Cumulative incidence curves for thyroid cancer (same concept as above)

Figure 5a. Graphic representation (box-plot) of overall observed and radiobiologic model ERR estimates for breast cancer.

Figure 5b. Graphic representation (box-plot) of overall observed and radiobiologic model ERR estimates for thyroid cancer.

Figure 6a. Graphic representation (box-plot) of 5-15 and >15 year observed and radiobiologic model ERR estimates for breast cancer.

Figure 6b. Graphic representation (box-plot) of 5-15 and >15 year observed and radiobiologic model ERR estimates for thyroid cancer.

Figure 7a. Graphic representation (box-plot) of observed and radiobiologic model ERR estimates for breast cancer in patients that received RT before and after age 17 (median age), respectively.

Figure 7b. Graphic representation (box-plot) of observed and radiobiologic model ERR estimates for thyroid cancer in patients that received RT before and after age 17 (median age), respectively.

Figure 8a. Graphic representation (box-plot) of observed and radiobiologic model ERR estimates for breast cancer in patients stratified by prescription dose (<45Gy or ≥45 Gy).

Figure 8b. Graphic representation (box-plot) of observed and radiobiologic model ERR estimates for thyroid cancer in patients stratified by prescription dose (<45Gy or ≥45 Gy).

References

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